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CARACTERIZAÇÃO DOS MECANISMOS ENVOLVIDOS NO DESENVOLVIMENTO E PIGMENTAÇÃO DA PELAGEM DE MAMÍFEROS UTILIZANDO REDES DE INTERAÇÕES MOLECULARES

Porto Alegre
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Pontifícia Universidade Católica do Rio Grande do Sul
Escola de Ciências
Programa de Pós-Graduação em Biologia Celular e Molecular

Fernanda de Jesus Trindade
Orientador: Prof. Dr. Eduardo Eizirik

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RESUMO

Apesar de as bases genéticas da pigmentação em mamíferos terem sido extensamente estudadas, as complexas interações entre rotas e genes que afetam esta característica não foram completamente caracterizadas. Além disso, as bases moleculares do desenvolvimento de padrões periódicos de pelagem, como listras e pintas, um importante fenótipo em diversos aspectos da biologia dessas espécies, ainda não são completamente compreendidos. Essas questões podem ser exploradas por meio de abordagens de biologia de sistemas, avaliando interações previamente conhecidas entre proteínas e revelando outras novas, além do uso de propriedades de redes para caracterizá-las. Ao explorar um fenótipo como sistema, ao invés dos genes isoladamente, podemos melhor compreender e caracterizar características complexas, como a pelagem de mamíferos. Aqui, aplicamos esta estratégia sobre processos que compõem a pelagem de mamíferos e construímos uma rede de interações utilizando um conjunto de genes relacionados à pigmentação e ao desenvolvimento de pelo em camundongo. Além disso, também buscamos separadamente por interatores de dois loci (*Lvrn* e *Alx3*) conhecidos por participar do mecanismo de desenvolvimento de padrões periódicos em felinos e roedores, respectivamente, e fusionamos essas duas redes com àquela relacionada a processos que compõem a pelagem de mamíferos. Sobre essas redes, realizamos analises de centralidade e exploramos suas conexões. Nossos resultados indicaram que genes pertencentes à rota Wnt têm papel particularmente importante nesses fenótipos, juntamente com outros envolvidos em sinalização por endotelinas, imunidade, adesão celular, angiogênese, fatores de crescimento, apoptose e sobrevivência, bem como pró-opiomelanocortina. Este resultado ilustra a complexidade de interações entre diversas rotas que têm papel no desenvolvimento da pelagem. Com relação aos padrões periódicos, observamos que o *Alx3* e o *Lvrn* se conectam aos mecanismos de pigmentação e desenvolvimento da pelagem em posições diferentes, o que apoia a inferência de que eles agem através de mecanismos distintos. Além disso, identificamos genes que atuam sobre fenótipos de pelagem, como *Ets1* e *Sfn*, que potencialmente conectam as rotas de pigmentação com o mecanismo de padronização induzido por Lvrn, fornecendo assim novos candidatos para estudos experimentais desde fenótipo intrigante.

ABSTRACT

Although the genetic bases of mammalian pigmentation have been extensively studied, the complex interactions among the pathways and genes that affect this trait have not been fully characterized. Furthermore, the molecular bases of periodic coat patterning, such as stripes and spots, an important phenotype in several aspects of species biology, are still incompletely understood. These questions can be explored with systems biology approaches, by assessing known and predicting new interactions among proteins along with using network properties to characterize them. By exploring a given trait as a system, instead of isolated genes, we can better understand and characterize complex phenotypes such as the mammalian coat. Here, we applied this strategy to mammalian pelage features and constructed an interaction network using a dataset of mouse pigmentation and hair growth genes. In addition, we also specifically searched for genes interacting with two loci (*Lvrn* and *Alx3*) that are known to participate in the mechanism of coat periodic patterning in cats and rodents, respectively, and merged their networks with the main coat-related network. On these networks, we performed centrality analyses and explored their connections. Our results indicated that genes belonging to the Wnt pathway play particularly important roles in these phenotypes, along with endothelin signaling, immunity, cell adhesion, angiogenesis, growth factors, apoptosis and cell survival, and proopiomelanocortin. This result illustrates the complex interplay among the diversity of pathways that affect the mammalian coat. With regard to periodic patterning, we observed that *Alx3* and *Lvrn* connect to pigmentation pathways at distinct positions, supporting the inference that they act via distinct mechanisms. Furthermore, we identified genes playing a role in pelage phenotypes, such as *Ets1* and *Sfn*, that potentially connect mammalian pigmentation pathways with those related to *Lvrn*-based patterning, thus providing novel candidates for experimental assessments of this intriguing phenotype.

SUMÁRIO

CAPÍTULO I. INTRODUÇÃO GERAL

I.I. COLORAÇÃO DOS ANIMAIS

A coloração dos animais é um fenômeno que, inclusive por questões sociais, culturais e econômicas, movimenta diversos focos de pesquisa. Em Metazoa, há diferentes estratégias, tipos celulares e pigmentos que são responsáveis por gerar a coloração. São três as principais formas de produção de cor: por meio de estruturas que podem, conforme diferente incidência de luz, refletir cores; por bioluminescência, geralmente gerada por meio de organismos simbiontes; e por síntese de pigmentos, os quais absorvem e refletem diferentes comprimentos de onda (Booth, 1990). Alguns desses mecanismos, que envolvem informação genética, são conservados entre diferentes grupos. Nos vertebrados, observamos uma variedade grande de coloração em todos os grupos tradicionalmente reconhecidos (peixes, anfíbios, répteis, aves e mamíferos). Dependendo do grupo e de suas características morfológicas, os pigmentos que expressam essa coloração podem estar presentes em diferentes tipos celulares e estruturas (Protas e Patel, 2008). Adicionalmente, os fenótipos de pigmentação podem ser afetados por diversos fatores externos, como o ambiente e variações hormonais. A coloração é um tema abordado em diferentes áreas da ciência, como em modelos matemáticos sobre a síntese dos pigmentos (Øyehaug *et al.*, 2002) e o estudo da organização dos folículos pilosos em mamíferos (Sick *et al.*, 2006). Dentre estes temas, a formação de padrões do tegumento (presença de marcas/manchas, periódicas ou não) é um interessante tópico de estudo sobre o qual ainda se tem muitas questões em aberto (Eizirik *et al.*, 2010; Kondo, 2017).

Em vertebrados, a pele é formada por três camadas: epiderme, derme e hipoderme. A origem embrionária das células que as compõem é a ectoderma, sendo as células pigmentares oriundas da crista neural (Hou, Panthier e Arnheiter, 2000). Apesar de cada grupo de animais possuir características diferenciadas na pele, como escamas, glândulas, penas e pelos, a pigmentação tende a se dar de forma geral a partir de células especializadas presentes na mesma. Dentre elas, estão os cromatóforos (ou cromatócitos), em peixes, anfíbios e répteis, e os melanócitos, em aves e mamíferos (Protas e Patel, 2008). Nos cromatóforos há divisão de diferentes células de acordo com a cor do pigmento que produzem. Os melanócitos, por outro lado, produzem apenas um tipo de pigmento, a melanina. Ainda assim, é possível observar uma variedade de cores e tons devido à síntese de uma melanina mais clara (feomelanina) ou

mais escura (eumelanina), a qual é depositadas de formas variadas na pele e/ou pelos (Barsh *et al.*, 2000).

O valor adaptativo dos fenótipos de pigmentação é uma questão bastante explorada (Caro, 2005; Hubbard *et al.*, 2010), mas ainda pouco compreendida. Eles podem estar relacionados à comunicação entre os indivíduos da mesma espécie, afetando, por exemplo, a escolha de parceiros para reprodução. Também tem função na interação com indivíduos de outras espécies, como no mimetismo para evitar predadores, e na camuflagem com o ambiente, utilizada tanto para proteção como para a caça. Pode também ter papel em processos fisiológicos, como a fotoproteção e termorregulação, devido às características físico-químicas das moléculas do pigmento, e até resistência a microrganismos (Caro, 2005). Na área da genética evolutiva, a formação de padrões de pigmentação constitui um interessante sistema de estudo, visto que muitos genes relacionados a este fenótipo já são conhecidos e que frequentemente parecem estar sob forte pressão seletiva (Hoekstra, 2006). Entretanto, o valor adaptativo de alguns fenótipos de pelagem, bem como os mecanismos moleculares por trás destes, ainda não foram explorados e, portanto, não são compreendidos.

Em alguns grupos de animais, ocorre variação da coloração e da formação de padrões de forma intraespecífica. As mudanças ontogenéticas na coloração dos animais, ou seja, variações associadas ao desenvolvimento dos indivíduos de uma espécie sendo afetadas ou não por condições externas (Booth, 1990), incluem diferenças entre fêmea e macho (Hill, 1990), jovem e adulto (Creer, 2005; Hawlena *et al.*, 2006), ou variação em resposta ao ambiente (Nilsson Sköld, Aspengren e Wallin, 2013). Isso pode se dar por fatores diretos, como acúmulo de pigmentos da dieta, simbiontes, ou degradação das moléculas do pigmento; ou possivelmente pela regulação da expressão dos genes relacionados à pigmentação, potencialmente em resposta a mudanças hormonais ou a fatores bióticos e abióticos do ambiente (Booth, 1990). Em algumas espécies de peixes, por exemplo, já foi verificada relação da variação na pigmentação com hormônios sexuais e comportamento (Cardwell e Liley, 1991; Korzan *et al.*, 2008). Em mamíferos, um fenômeno interessante que envolve prováveis efeitos adaptativos de padrões de pigmentação na pelagem é a mudança de coloração durante o crescimento do filhote até a fase adulta que ocorre em Cervidae, Suidae, Tapiridae e Felidae. Nos três primeiros grupos, os filhotes apresentam manchas mais claras em relação ao fundo e à pelagem adulta sem manchas (Padilla e Dowler, 1994; Sempere, Sokolov e Danilkin, 1996). Por outro lado, em certos felinos, os filhotes apresentam um padrão de manchas mais escuras do que a pelagem de fundo, o qual esmaece até praticamente

desaparecer na fase adulta (Currier, 1983; Haas, Hayssen e Krausman, 2005; Pocock, 1907). As bases moleculares deste tipo de fenômeno são ainda desconhecidas, o que dificultar a análise aprofundada de sua relevância adaptativa. Para iniciar a caracterização deste tipo de processo, é necessária a identificação do maior número possível de genes envolvidos na formação de padrões periódicos na pelagem de mamíferos, e investigar sua conexão funcional com o processo de síntese de melanina, conhecido como melanogênese.

I.II. MELANOGÊNESE EM MAMÍFEROS

A melanogênese é o processo bioquímico de síntese da melanina (Figura 1A), um biopolímero que apresenta diversas propriedades fisicoquímicas, as quais fornecem a este papel em diferentes funções. Conforme sua estrutura final, a melanina pode ser de três tipos: neuromelanina, encontrada no cérebro; e eumelanina e feomelanina, encontradas principalmente na pele (Slominski, 2004). O primeiro substrato da via de síntese é a L-fenilalanina, a qual é transformada em L-tirosina pela fenilalanina hidroxilase (Pah). O aminoácido é então hidroxilado pela tirosinase (Tyr) em $_{L}$-dihidroxifenilalanina ($_{L}$-DOPA), que por sua vez é convertida em dopaquinona, a qual será a molécula precursora dos dois tipos de melanina associadas à pigmentação da pele e pelos – eumelanina (de cor marrom ou preta) e feomelanina (de cor avermelhada ou amarelada). Na eumelanogênese, há a transformação da dopaquinona em mais um intermediário para resultar na eumelanina, enquanto que na feomelanogênese, a dopaquinona faz um conjugado com cisteína, para posteriormente resultar na feomelanina. Entretanto, apesar de se conhecer suas vias gerais de síntese, ainda há lacunas de conhecimento quanto à completa caracterização de enzimas atuantes e da estrutura dos pigmentos. Em mamíferos, esse processo ocorre nos melanócitos, células que estão distribuídas na epiderme e nos folículos pilosos. Essas células possuem uma organela chamada melanossomo, a qual é construída de forma regulada para a síntese de cada tipo de melanina (Slominski, 2004; Tobin e Kauser, 2005).

Os melanócitos são células dendrídicas que se diferenciam a partir dos melanoblastos, que por sua vez têm origem da crista neural e são desprovidas de pigmentos. Essas células migram para diferentes partes do corpo, durante o desenvolvimento, após o fechamento do tubo neural. Quando diferenciadas em melanoblastos, antes de serem melanócitos funcionais, podem ser encontradas tanto na epiderme como na derme, além do ouvido interno e coroide (Hou, Panthier e Arnheiter, 2000). Existem alguns marcadores expressos especificamente em

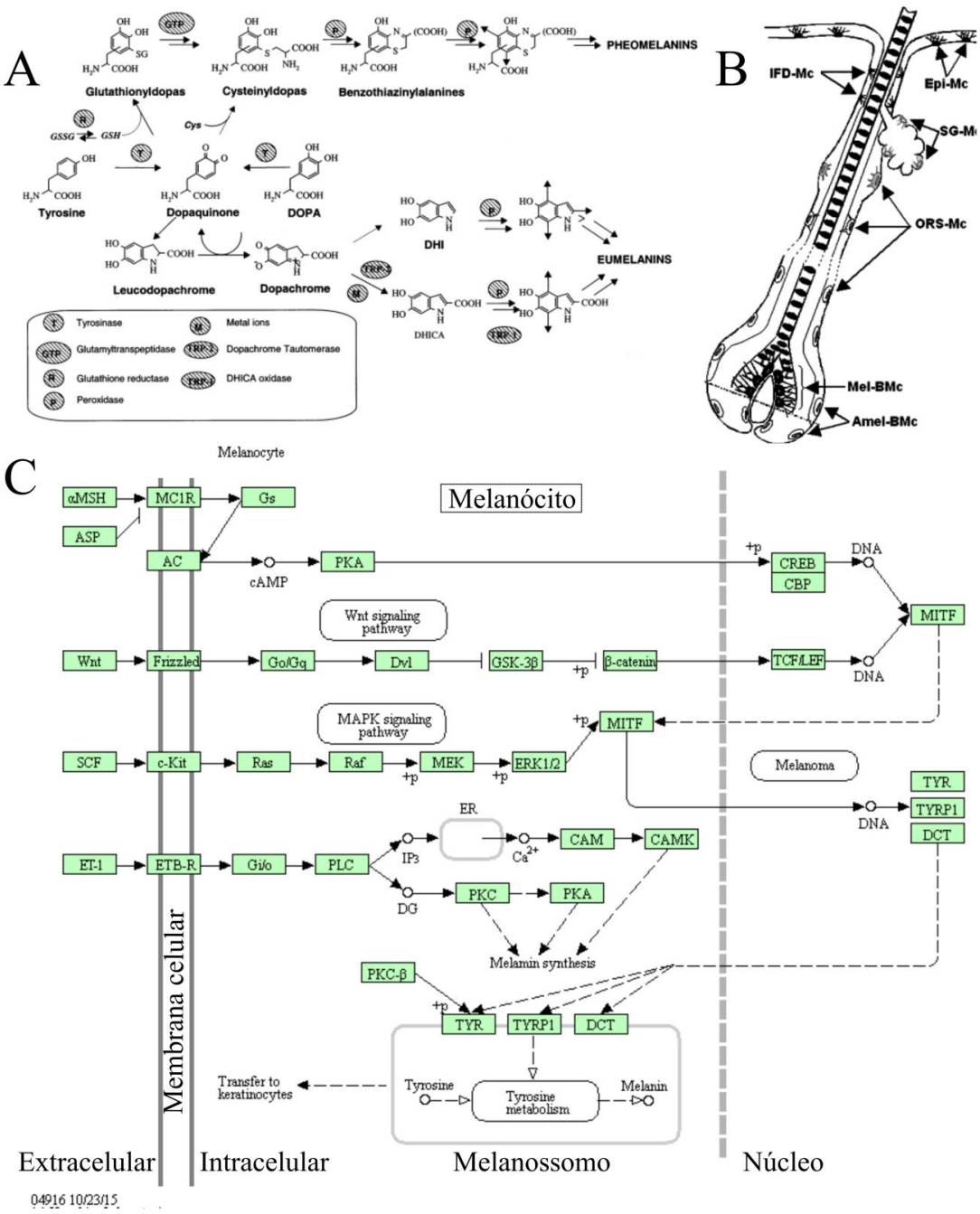

Figura 1. A) Esquema da síntese da melanina. Figura adaptada de Prota (2000). B) Folículo piloso em esquema, com setas apontando para diferentes melanócitos. Somente os do bulbo são os que produzem melanina ativamente no ciclo do crescimento do pelo. Figura adaptada de Slominski *et al.* (2005). C) Rota da melanogênese, com enzimas/proteínas (retângulos verdes) e outras moléculas (círculos vazados) atuando em cada parte do melanócito (meio extracelular, membrana celular, citoplasma, núcleo, melanossomo). Adaptado de KEGG ko04916 (Kanehisa *et al.*, 2016). Epi-Mc, melanócitos da epiderme; IFD-Mc, melanócitos do infundíbulo; SG-Mc, melanócitos das glândulas sebáceas; ORS-Mc, melanócitos da bainha externa da raiz; Mel-BMc, melanócitos melanogênicos do bulbo; Amel-BMc, melanócitos amelanogênicos do bulbo; DP, papila dérmica. Tirosinase (em A) = TYR (em C); Dopacroma tautomerase (em A) = DCT (em C).

melanócitos, como a tirosinase (Tyr) e o fator de transcrição associado à microftalmia (Mitf), os quais estão relacionados à sua função primária (D'Mello *et al.*, 2016).

No folículo piloso (Figura 1B), a síntese de melanina pelos melanócitos do bulbo ocorre somente durante a fase anágena, ou seja, quando o pelo está em crescimento (Slominski *et al.*, 2005). A pigmentação do pelo vai depender da interação entre os melanócitos foliculares, queratinócitos e fibroblastos localizados na papila dérmica (Slominski *et al.*, 2005; Slominski e Paus, 1993). A síntese de melanina pelo melanócito folicular é independente da dos melanócitos da pele, sendo os foliculares mais sensíveis à influência da idade (Tobin e Paus, 2001). Além disso, outras diferenças são vistas entre essas células: os melanócitos do folículo piloso são maiores, mais dendrídicos, com melanossomos maiores e com complexo de Golgi e retículo endoplasmático mais desenvolvidos (D'Mello *et al.*, 2016; Slominski *et al.*, 2005). A melanogênese é um processo que pode ser regulado a partir de pelo menos quatro diferentes vias de sinalização: por Mc1r/α-Msh (via AMP cíclico), Scf/c-kit (via quinase Mapk/Erk), Wnt/β-catenina e endotelina (Pillaiyar, Manickam e Jung, 2017). Estes processos estimulam a produção do fator de transcrição Mitf, que por sua vez induz a expressão de enzimas melanogênicas (Figura 1C). Além disso, outras moléculas e vias de sinalização também tem papel na regulação desse processo, como Pi3k/Akt, oxido nítrico (NO), citocinas, proteínas de choque térmico (Hsp), colesterol, além de outros fatores de transcrição, como Nf-κβ e Pax3 (Pillaiyar, Manickam e Jung, 2017).

O controle da alternância entre a produção de eumelanina e feomelanina vem de fora do melanossomo, sendo regulado de forma temporal e local-específica (Kaelin e Barsh, 2013). Este se dá principalmente pela atividade de sinalização do receptor de melanocortina 1 (Mc1r), uma proteína de membrana do melanócito acoplada a proteínas G (Barsh, 1996; Mountjoy *et al.*, 1992). Quando o MC1R interage com seu agonista, o hormônio estimulante de melanócitos (α-Msh) (Barsh *et al.*, 2000), é disparada sinalização via o segundo mensageiro cAMP, o que leva ao aumento da expressão de *Tyr* e *Tyrp2/Dct*, acarretando o aumento da síntese de eumelanina. O hormônio α-Msh é produzido pela clivagem da pro-opiomelanocortina (Pomc), a qual é sintetizada pelos queratinócitos da epiderme, havendo, assim, uma regulação parácrina da síntese de eumelanina (Slominski, 2004). Por outro lado, baixos níveis de cAMP devido à ligação do antagonista 'proteína sinalizadora agouti' (Asip) ao Mc1r (Barsh *et al.*, 2000), causa um aumento na expressão de um transportador de cisteína (*Slc7a11*) e redução do *Tyrp2/Dct*, acarretando no aumento da síntese de feomelanina (D'Mello *et al.*, 2016). Após a melanogênese, o melanossomo é transportado para os dendritos do melanócito com o auxílio de uma miosina (Myo5a), uma proteína ligada a GTP

(Rab27a) e uma proteína adaptadora (Mlph) (Kaelin e Barsh, 2013). Por fim, a melanina é transferida para os queratinócitos.

Mutações nos genes citados acima são conhecidas por afetar o fenótipo de pigmentação de mamíferos de diferentes formas. Curiosamente, diferentes mutações em diferentes genes podem acarretar em fenótipos semelhantes, como, por exemplo, nos casos de melanismo. O melanismo, processo de hiperpigmentação da pelagem de fundo devido ao excesso de produção de eumelanina, é um fenótipo recorrente em felinos. Em onça-pintada, ele ocorre devido a uma deleção no gene *Mc1r* (Eizirik *et al.*, 2003), acarretando provavelmente em um receptor resistente à inativação por Asip, o que leva à síntese somente de eumelanina por essa via. Em leopardos, por outro lado, esse fenótipo ocorre devido a uma mutação no gene *Asip* (Schneider *et al.*, 2012), afetando a mesma rota. Além disso, mutações diferentes em um mesmo gene podem acarretar em fenótipos completamente opostos. O lobo-marinho-antártico (*Arctocephalus gazella*) é uma espécie cuja pelagem mais comum é marrom escura, porém, alguns indivíduos apresentam cor creme (Peters *et al.*, 2016). Isso se deve a um processo de hipopigmentação caracterizado pela diminuição na produção de eumelanina. Nesses animais, foi observada uma mutação no gene *Mc1r* como responsável por esse fenótipo (Peters *et al.*, 2016). Além desses exemplos, o *Mc1r* também está relacionado a variações de tons de pelagem em pequenos roedores, em vários casos com impactos adaptativos demonstrados (Hoekstra *et al.*, 2006).

Como dito anteriormente, o papel do Asip está relacionado à produção de feomelanina ao invés de eumelanina. Dependendo da espécie, essa produção pode ocorrer por todo o crescimento do pelo ou em pulsos, resultando em um pelo bandeado de pigmentos claros e escuros. Além da presença de bandas, o tamanho e a quantidade das mesmas podem variar, resultando em diferentes tons de pelagem (Linnen *et al.*, 2009). No fenótipo comum da pelagem de fundo, logo no início do crescimento do pelo ocorre uma deposição inicial de feomelanina, e posteriormente passa-se a produzir eumelanina. Isso resulta em um pelo bandeado com a região distal mais clara e o restante mais escuro. Essa troca entre a síntese de diferentes tipos de pigmentos, porém, também pode ser regulada por outros meios, como pela via de sinalização Wnt/β-catenina (Enshell-Seijffers *et al.*, 2010). Esta é uma via famosa por estar relacionada a diversos processos de desenvolvimento, incluindo a formação dos folículos pilosos (Schmidt-Ullrich e Paus, 2005). A β-catenina parece agir como um bloqueador da Asip, resultando que, na presença da mesma, o antagonista não consegue se ligar ao *Mc1r*, o que leva à produção de eumelanina. Além disso, a β-catenina parece

estimular *Corin*, um gene cujo produto interage com Asip impedindo-a de se ligar ao *Mc1r* (Enshell-Seijffers, Lindon e Morgan, 2007), o que também resulta na produção de eumelanina. Em alguns grupos de mamíferos que apresentam padrão de marcas na pelagem, pelos bandeados podem ocorrer tanto em regiões de marcas como no fundo, mas em proporções muito diferentes. Isso ilustra uma regulação diferente da produção de melanina pelos melanócitos dos folículos pilosos de cada região – mancha a fundo.

A regulação parácrina da síntese de cada tipo de melanina resulta no fenótipo de coloração da pelagem que vemos nos mamíferos. E esta, por sua vez, é frequentemente expressa no folículo piloso de acordo com o prévio estabelecimento de um padrão espacial sobre a pele.

I.III. FORMAÇÃO DE PADRÕES DE PELAGEM

Os mamíferos apresentam não somente uma variedade de cores de pelagem, mas também de padrões de manchas ocorrentes em várias linhagens. Esses padrões incluem marcas com formatos específicos e organizados (periódicos), ou irregulares e desorganizados (não-periódicos), mais claros ou mais escuros em relação à pelagem de fundo (Figura 2). Apesar de já existirem alguns estudos em mamíferos e aves (Eizirik *et al.*, 2010; Haupaix *et al.*, 2018; Kaelin *et al.*, 2012; Manceau *et al.*, 2011), as bases genéticas da formação desses padrões são ainda muito pouco conhecidas.

Figura 2 Padrões de pelagem em mamíferos.

Um padrão bastante comum em animais é a diferenciação entre a coloração do ventre e do dorso. Esse fenótipo parece ser potencialmente importante para a camuflagem, visto que funcionaria como uma forma de neutralizar a claridade do sol vinda de cima; entretanto, isso possivelmente se aplica menos a espécies terrestres. Proteção contra UV, padrão de pelagem

dorsal para se camuflar no ambiente e economia de energia na produção de pigmento no ventre são outras potenciais funções deste fenótipo discutidas na literatura (Caro, 2005; Kiltie, 1988). Em espécies de camundongos selvagens, foi demonstrado que a expressão do gene *Asip* em áreas específicas durante o desenvolvimento do animal tem relação com o fenótipo de diferenciação ventre-dorso no adulto. O fenótipo branco no ventre se dá pela inibição da maturação do melanócito nessa região, causada pelo aumento da concentração da proteína Asip durante o desenvolvimento do folículo piloso (Manceau *et al.*, 2011).

Além da diferenciação entre ventre e fundo, há os mecanismos relacionados à determinação do padrão de pigmentação. O gato doméstico (*Felis catus*) é uma espécie de felino que em especial apresenta uma grande variação de fenótipos de padrão periódico. Esta espécie apresenta quatro padrões herdáveis de pelagem: *ticked*, *mackerel*, *blotched* e *spotted*. Por serem animais domesticados e de mais fácil manipulação do que espécies silvestres, estudos de padrões de herança fenotípica, com várias gerações, associados a fatores genéticos se tornaram viáveis (Eizirik *et al.*, 2010). A partir deste estudo inicial, foi proposto que o padrão da pelagem de mamíferos é resultado de dois processos distintos, com mecanismos genéticos diferentes. Primeiramente, há um processo de orientação espacial do pré-padrão, o qual irá ditar os padrões de diferenciação celular. Posteriormente, há um mecanismo de orientação da deposição diferencial da pigmentação, o qual utiliza o pré-padrão como guia para os processos de síntese da melanina (Eizirik *et al.*, 2010). Essa hipótese veio a ser reforçada com a identificação de alguns dos genes e mecanismos por trás desses processos não apenas em mamíferos.

Recentemente, em aves, esse mecanismo de dois passos foi verificado (Haupaix *et al.*, 2018). Foi relatado que espécies de galiformes, com padrão de listras longitudinais, têm o pré-estabelecimento do mesmo durante o desenvolvimento do somito. Está é uma estrutura que se forma no início do desenvolvimento embrionário, com células de origem do mesoderma; dispõe-se aos pares ao longo de ambos os lados do tubo neural. As células do somito delimitam a posição da expressão do gene *Asip*, cujo local exato e de forma dose dependente vai delinear a posição e largura das listras mais claras, fazendo com que nos demais espaços sejam desenvolvidas listras escuras (Haupaix *et al.*, 2018). Esse resultado demonstra que o sinal inicial para o estabelecimento das listras longitudinais dessas espécies de galiformes não tem origem do tubo neural, do qual os melanócitos são derivados, mas sim de células que darão origem à derme.

Os pequenos roedores do grupo dos arvicantíneos são membros da da família Muridae, e consistem de espécies com grande diversidade de padrões periódicos, variando e mesclando entre pintas e listras longitudinais (Johnson, Barsh e Mallarino, 2018). Em uma das espécies deste grupo, o rato africano listrado (*Rhabdomys pumilio*), foi identificado o gene *Alx3* como direcionador deste fenótipo, além da regulação parácrina para pelos pretos e bandeados (Mallarino *et al.*, 2016). A espécie apresenta um padrão que consiste em sete linhas longitudinais dorsais, intercalando claro e escuro (Figura 3A). A proporção de pelos claros, pretos e bandeados de cada região (Figura 3B) resulta no fenótipo observado da pelagem e essa coloração é definida por dois mecanismos diferentes. O fator de transcrição *aristaless-like homeobox 3* (Alx3) atua se ligando na região promotora do *Mitf*, bloqueando a sua expressão e resultando na interferência da diferenciação dos melanócitos do folículo piloso e consequente ausência de pigmentação dos pelos (Figura 3C). Por outro lado, onde não há atuação do Alx3, há regulação parácrina da síntese de cada tipo de pigmento a ser produzido pelos melanócitos do folículo, com a endotelina 3 (Edn3) e Asip estimulando a produção de eumelanina e feomelanina, respectivamente (Figura 3C). Entretanto, ainda não é conhecido o mecanismo responsável pela regulação da expressão de *Alx3* e dos fatores parácrinos para cada uma das regiões específicas.

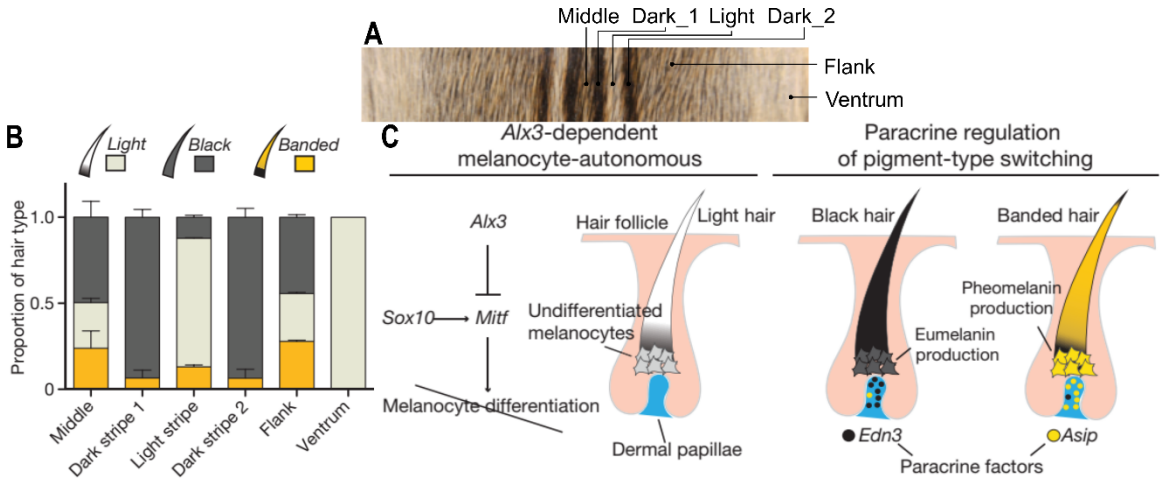

Figura 3 Mecanismo do Alx3 no desenvolvimento de padrões de listras em roedores. (A) Padrão de listras longitudinais da espécie *Rhabdomys pumilio*, visão ventre-dorso-ventre em corte transversal. (B) Proporção de cor de pelos encontrados em cada uma das áreas indicadas, conforme posição em (A). (C) Esquema que dirige o aparecimento das listras: Alx3 impedindo a diferenciação dos melanócitos, acarretando em pelos brancos, predominantes nas listras claras e ventre; Edn3 estimulando a produção de eumelanina, acarretando em pelos escuros, predominantes nas listras pretas; e Asip indiretamente estimulando em pulsos a produção de feomelanina, resultando em pelos bandeados, em maior ocorrência na listra mediana e flanco. Figura editada de Mallarino *et al.* (2016).

Em Felidae, família que inclui todas as espécies de felinos, é observada uma diversidade muito grande de padrões, apresentando tanto espécies com pelagem lisa como outras com variados padrões de manchas não-periódicos e periódicos (Sunquist e Sunquist, 2002). Estudos genéticos e moleculares sobre mecanismos de pigmentação desses animais constituem uma linha de pesquisa bem estabelecida, havendo dois genes já caracterizados com fenótipos associados (Kaelin e Barsh, 2013). Foi verificado que o gene *laeverin* (*Lvrn*), conhecido também por *aminopeptidase transmembrana Q* (*Taqpep*), é um dos principais responsáveis pela variação de padrões nesse grupo (Kaelin *et al.*, 2012). O fenótipo *mackerel* de gato doméstico, por exemplo, o qual consiste em listras transversais (Figura 4A), é expresso de acordo com o estabelecimento do pré-padrão durante o desenvolvimento da pele do feto (7-8 semanas de gestação) promovido pela enzima Lvrn funcional (Figura 4B), com posterior elevação da expressão de Edn3 nessas áreas do pré-padrão, dando coloração escura à mancha (Figura 4C). Mutações no gene *Lvrn* acarretam a perda da periodicidade deste padrão, causando o fenótipo *king cheetah*, por exemplo, no qual as pintas normalmente bem definidas e separadas dos guepardos se aglomeram em formas irregulares (Kaelin *et al.*, 2012).

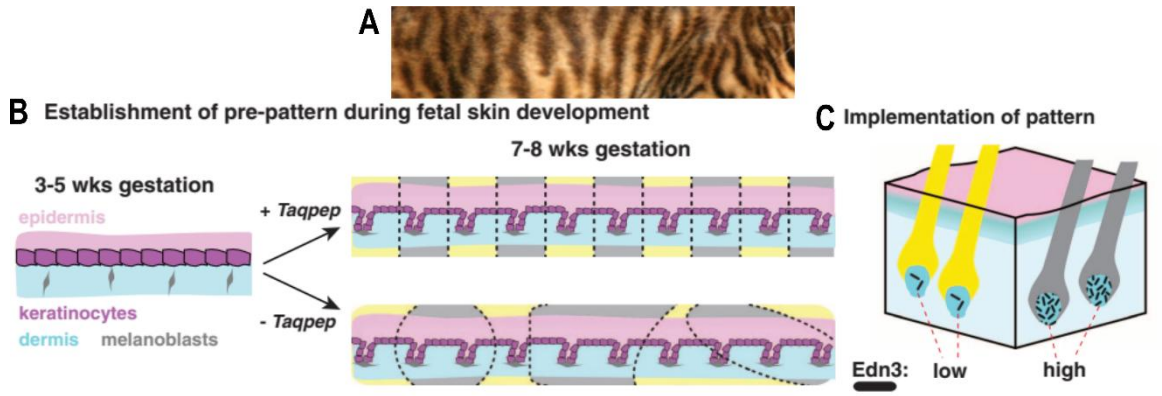

Figura 4 Mecanismo da proteína Lvrn (Taqpep) no desenvolvimento de padrões em felinos. (A) padrão de pelagem mackerel de gato doméstico (visão do flanco). (B) Esquema do estabelecimento de pré-padrão durante o desenvolvimento da pele: na presença da enzima funcional, há periodicidade do local onde as marcas escuras aparecerão, enquanto que, quando a proteína está mutada, essa periodicidade é perdida e a marcação para futura pigmentação escura se dá em áreas de formatos irregulares. (C) Conforme o pré-padrão, onde há marcação para pigmentação escura, há maior expressão de Edn3, responsável por estimular a produção de eumelanina. Figura editada a partir de Kaelin *et al.* (2012).

Entretanto, não se sabe como a proteína Lvrn, conhecidamente com papel importante na placentação (Fujiwara *et al.*, 2004), atua nesse processo de estabelecimento de padrão na pele. Além disso, também não se sabe como o seu papel pode, posteriormente, resultar na

alteração dos níveis de *Edn3* nos locais de mancha. Adicionalmente, como citado anteriormente, Felidae possui duas espécies (leão e puma) que apresentam um fenótipo interessante de perda do padrão de pelagem durante o desenvolvimento, cujos filhotes pintados culminam em adultos de pelagem lisa (Pocock, 1907). Isto sugere que é possível 'desacoplar' os processos de estabelecimento/manutenção do padrão espacial e pigmentação diferencial de áreas delimitadas pelo padrão, mesmo após o nascimento do indivíduo.

Explorar e caracterizar esses mecanismos utilizando um organismo-modelo, por se ter mais informação genética e fenotípica associadas, seria importante para sugerir mecanismos candidatos em outros organismos próximos filogeneticamente ou em fenótipos de pigmentação semelhantes e ainda não caracterizados. Portanto, uma opção interessante no contexto deste tema é utilizar como organismo-modelo o camundongo (*Mus musculus*), do qual se tem uma vasta quantidade de informação genética sobre fenótipos de pigmentação, de forma a investigar como tais genes e suas interações com outros podem regular a variedade de fenótipos de pigmentação observados em mamíferos.

I.IV. BIOLOGIA DE SISTEMAS

A Biologia de Sistemas consiste na caracterização de redes complexas de interações, por meio da qual conhecimentos obtidos isoladamente por métodos experimentais podem ser integrados, com o objetivo de explorar o conjunto de participantes (que podem ser proteínas, células, indivíduos, dependendo do tipo de interações que se está estudando) de determinado sistema, ao invés de apenas caracterizar cada um separadamente (Hood, 2003). Assim, essa abordagem permite a identificação de potenciais novas conexões baseadas em bases de dados curadas, obtendo novas informações sobre o papel de cada participante – bem como do sistema como um todo (Mering, von *et al.*, 2005). Considerando um trabalho de caracterização molecular de um fenótipo, os participantes seriam genes/proteínas que estão envolvidos, em diferentes níveis, na formação deste fenótipo.

Para fazer um levantamento de proteínas associadas a determinados fenótipos, como o desenvolvimento de pelo e coloração, há diversas bases de dados com grande densidade de informações gênicas com funções/fenótipos associados, especialmente para animais-modelo. A ferramenta web BioMart, gerenciada pelo Ensembl (Zerbino *et al.*, 2018), por exemplo, permite extrair e exportar informações provenientes de diferentes dados biológicos oriundos de bases de dados acessadas pelo Ensembl. Neste caso, são utilizadas o *Mouse Genome*

Informatics (MGI), um consórcio que visa a integrar informações genéticas e genômicas de linhagens de camundongos (Smith *et al.*, 2018), e o *International Mouse Phenotyping Consortium* (IMPC), semelhantemente um catálogo de funções gênicas (Dickinson *et al.*, 2016). A extração de informações destas pode ser realizada por meio de buscas quanto ao fenótipo, recorrendo a termos contendo pigmentação e pelagem, por exemplo. Associados a essas características, é possível obter os nomes e descrição dos genes, termos GO (*gene ontology*), entre outros. Além desta, há também o *Kyoto Encyclopedia of Genes and Genomes* (KEGG), a qual mantém uma coleção de bancos com informações biológicas funcionais, entre elas mapas de diversas vias metabólicas caracterizadas. Sobre pigmentação, recentemente foi publicada uma lista curada de 650 genes associados à pigmentação do tegumento em zebrafish (*Danio rerio*), camundongo e humanos (Baxter *et al.*, 2018). Estas são importantes fontes de informações genéticas sobre desenvolvimento de pelagem, as quais podem ser usadas de forma integrada para melhor caracterizar o fenótipo por meio da identificação das interações existentes e análises de rede.

Uma rede de interações é representada na forma de que as interações entre duas proteínas são as arestas e as próprias proteínas são os vértices (também chamados de ‘nós’). A base de dados mais utilizada para realizar levantamento de interações entre proteínas é o STRINGdb (*Search Tool for the Retrieval of Interacting Genes/Proteins*), a qual busca diferentes tipos de evidências de interação e calcula um *score* de confiança relativo à interação encontrada entre duas proteínas (Mering *et al.*, 2003; Szklarczyk *et al.*, 2017). Estes sinais de interação podem ser classificados como diretos, por interação física, ou indiretos, pertencentes ao mesmo processo metabólico ou rota molecular. Além disso, também é realizada associação *de novo*, identificando novas interações, baseando-se em métodos computacionais de predição e transferência entre organismos, cujos alvos sejam ortólogos. As associações, diretas ou indiretas, são derivadas de ensaios experimentais, bases de dados de rotas metabólicas, contexto genômico e artigos científicos (Mering, von *et al.*, 2005). Essa é uma interessante fonte de informação, não apenas para construções de redes de interação, mas para poder explorar potenciais caminhos funcionais de proteínas ainda pouco caracterizadas ou de espécies não-modelo.

Há diversos algoritmos desenvolvidos para caracterizar os nós de acordo com propriedades de topologia de rede (Seebacher e Gavin, 2011), como os vértices com mais ligações, cuja ausência comprometeria a rede, representando a relevância do nó para a estabilidade e funcionalidade da mesma (Poloni *et al.*, 2014). Esses algoritmos se dividem

entre métodos de locais, os quais consideram os conectores diretos a determinado nó sendo avaliado; e métodos globais, os quais se baseiam em caminhos mais curtos entre todos os nós e métricas de conectividade (Chin *et al.*, 2014). Dentre os métodos locais, se tem o 'grau de nó', ou *degree*, o qual quantifica nós adjacentes diretamente conectados (Figura 5A), sendo então utilizado para identificar *hubs* (nós com elevado grau de nó). Visto sua alta conectividade, *hubs* são proteínas importantes para o funcionamento da rede, potencialmente indicando que a sua remoção pode comprometer a estrutura do sistema afetando a atividade das proteínas com as quais interage (Jeong *et al.*, 2001). Por outro lado, dentre os métodos globais, se tem a 'intermediação', ou *betweenness*, a qual avalia o número de caminhos mais curtos que passam por determinado nó em relação à rede como um todo (Figura 5B). Elevado valor de intermediação aponta nós conhecidos como gargalos. Em se tratando de uma rede de proteínas, um gargalo pode representar uma proteína com papel de sinalização, por exemplo, e são apontados como importantes conectores cujo papel parece ser especialmente crítico em redes regulatórias (Yu *et al.*, 2007). Por fim, é utilizado o termo *hub*-gargalo, ou *hub-bottleneck*, para apontar aqueles nós que apresentam ambas as características de apresentar muitas conexões e de ser como importantes "pontes" entre nós (Figura 5C).

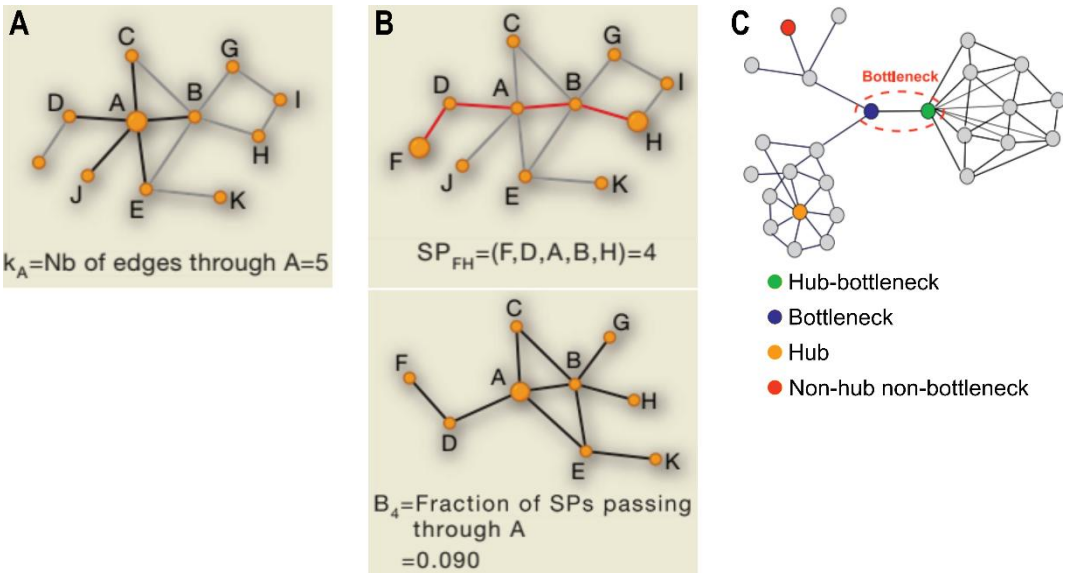

Figura 5 Métricas de análise de redes que definem *hubs*, gargalos e *hub*-gargalos. (A) Representação do cálculo de grau de nó, que equivale ao número de arestas saindo de determinado nó. (B) Representação do cálculo de caminhos mais curtos (superior), que seriam os caminhos com menor quantidade de nós entre dois nós, utilizado para o cálculo de intermediação (inferior), o qual representa uma fração de quantos SPs (*shortest paths*) atravessam determinado nó. (C) Rede ilustrativa apontando nós que são *hubs*, gargalos e *hub*-gargalos. k: degree; SP: *shortest paths*; B: betweenness. (A) e (B) adaptados de Seebacher & Gavin (2011). (C) adaptado de Yu *et al.* (2007).

A utilização de redes de interações e suas propriedades tem sido aplicada a diversas perguntas biológicas, como a busca por alvos terapêuticos (Li *et al.*, 2017; Makondi *et al.*, 2018), o estudo de doenças (Barabási, Gulbahce e Loscalzo, 2011) e a caracterização de tecidos (Quigley *et al.*, 2009). Caracterizar o desenvolvimento e papel do melanócito como sistema, devido a sua alta complexidade, regulação, interação com outras células e sinalização, seria idealmente realizada por meio de abordagem de redes, visto que ela enfoca o sistema como um todo e não apenas o papel de proteínas específicas. Isso seria importante para melhorar a compreensão do seu funcionamento, bem como do desenvolvimento de resposta a fatores externos e internos (Baxter, Loftus e Pavan, 2009). Além disso, visto a ocorrência de doenças por funcionamento celular incorreto, como o desenvolvimento de melanoma, abordagens de biologia de sistemas podem auxiliar na investigação de mutações e suas consequências, bem como identificar potenciais alvos para terapia (Smalley, 2010). Entretanto, essa abordagem foi até agora aplicada apenas para a exploração de fenótipos específicos e rotas metabólicas relacionadas à pigmentação e pelos (Baxter *et al.*, 2010; Nigenda-Morales *et al.*, 2018; Raghunath *et al.*, 2015; Severin *et al.*, 2017; Wang *et al.*, 2017). Até o momento, nenhum estudo integrou o desenvolvimento de pelo e a pigmentação, aplicando esta abordagem para melhor compreender o processo de formação de padronização da pelagem.

Abordagens *in silico*, como as de biologia de sistemas, têm a competência de tratar diversas questões provenientes de diferentes tipos de dados biológicos. Estas são importantes na exploração de grandes conjuntos de dados, especialmente provenientes de tecnologias de alto desempenho. A capacidade de prever uma nova conexão funcional entre proteínas, ou identificar a potencial participação de novos genes em determinado fenótipo (que até então não havia sido sugerida) é um uso bastante relevante dessas abordagens. A análise de dados pode servir de orientação, direcionando as respostas a um problema biológico para serem confirmados por uma abordagem experimental, o que torna as abordagens *in silico, in vitro* e *in vivo* complementares.

Assim, neste trabalho almejamos caracterizar os mecanismos moleculares relacionados ao desenvolvimento e pigmentação da pelagem de mamíferos como sistema, com foco no mecanismo de padrões periódicos via *Lvrn* e *Alx3*, por meio da integração de redes de genes relacionados a esses fenótipos. Com este intuito, construímos uma rede de interações, utilizando bases de dados de *Mus musculus* e predição de novas interações, contendo genes relacionados a fenótipos de desenvolvimento/crescimento de pelo e de

pigmentação. Da mesma forma, também construímos redes de interações de dois genes recentemente caracterizados como participantes do fenótipo de formação de padrões periódicos da pelagem em mamíferos, *Lvrn* e *Alx3*. Com isso, foi possível verificar como os processos moleculares associados a esses genes de formação de padrões periódicos da pelagem se conectam com o mecanismo de pigmentação e/ou como podem ser regulados para exercerem seu papel no fenótipo, além de identificar proteínas essenciais para o correto funcionamento e estrutura das redes dos genes de formação de padrões periódicos e de desenvolvimento de pelo e pigmentação.

I.V. OBJETIVO GERAL

Caracterizar os mecanismos moleculares relacionados ao desenvolvimento e pigmentação da pelagem de mamíferos como sistema, com foco no mecanismo de padrões periódicos via *Lvrn* e *Alx3*.

I.VI. OBJETIVOS ESPECÍFICOS

- Realizar um levantamento de genes que possuam relação funcional com fenótipos de pelagem e de pigmentação via melanina em *Mus musculus*;
- Construir uma rede de associação molecular dos genes levantados acima, utilizando bases de dados de interação direta e indireta de *Mus musculus*;
- Construir uma rede de associação molecular do gene *laeverin* (*Lvrn*) e interatores identificados, utilizando bases de dados de interação direta e indireta de *Mus musculus*;
- Construir uma rede de associação molecular do gene *aristaless-like homeobox 3* (*Alx3*) e interatores identificados, utilizando bases de dados de interação direta e indireta de *Mus musculus*;
- Caracterizar, com base nas redes construídas, os genes mais importantes para o correto funcionamento e estabilidade da rede, apontando potenciais genes mais relevantes para o fenótipo de pelagem e pigmentação;
- Avaliar as potenciais vias de interação entre os mecanismos Lvrn-pigmentação e Lvrn-Alx3, visando melhor compreender o processo de estabelecimento de padrão periódico de pelagem em mamíferos.

CAPÍTULO II. ARTIGO CIENTÍFICO

Manuscript, Pigment Cell & Melanoma Research
Original Research Article

Systems biology of mammalian pigmentation and hair development genes reveals essentiality of Wnt signaling and insights into periodic coat patterning

Running Title: Systems biology of mammalian coat genes.

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ABSTRACT

Although the genetic bases of mammalian pigmentation have been extensively studied, the complex interactions among the pathways that affect this trait have not been fully characterized. Furthermore, the molecular bases of periodic coat patterning (stripes, spots) are still incompletely understood. These questions can be explored with systems biology by assessing interactions among proteins using network properties. We applied this strategy to mammalian pelage features using a dataset of mouse pigmentation and hair growth genes. We also specifically searched for genes interacting with two loci (*Lvrn* and *Alx3*) known to affect mammalian periodic patterning, merged their networks with the main pigmentation-related network, and performed centrality analyses. Our results indicated that genes belonging to the Wnt pathway play particularly important roles in these phenotypes. With regard to periodic patterning, we observed that *Alx3* and *Lvrn* connect to pigmentation pathways at distinct positions, supporting the inference that they act via distinct mechanisms. Furthermore, we identified genes playing a role in coloration and hair phenotypes that potentially connect mammalian pigmentation pathways with those related to *Lvrn*-based patterning, thus providing novel candidates for experimental assessments of this intriguing phenotype.

SIGNIFICANCE

This study describes the most comprehensive systems biology analysis of mammalian hair and pigmentation genes performed to date. We demonstrate that several genes belonging to the Wnt signaling pathway play critical roles in the networks that regulate these phenotypes, highlighting their

importance as drivers of hair development and pigmentation, and potential targets for empirical research on pigmentation disorders and/or melanoma biology. In addition, our results also provided novel insights into the poorly known molecular basis of mammalian coat patterning (e.g. stripes and spots), with the identification of genes that connect pattern formation and pigmentation pathways, providing new avenues for empirical research.

KEYWORDS

Hair color; Biological Evolution; Body Patterning; Protein Interaction Networks.

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INTRODUCTION

Mammals exhibit a wide variety of skin and hair pigmentation phenotypes, which play critical roles in diverse processes, such as UV protection, thermoregulation and other physiological mechanisms, as well as social communication, concealment, and inter-species advertisement (Caro, 2005; Solano, 2014). Genetic and molecular mechanisms underlying these phenotypes have been extensively investigated (e.g. G. Barsh, Gunn, He, Schlossman, & Duke-Cohan, 2000; G. S. Barsh, 1996; Millar, 2002; Pawelek & Korner, 1982; Slominski et al., 2005). As a result, some of these aspects are now relatively well understood, such as melanogenesis, which is regulated by paracrine compounds, especially the α-melanocyte stimulating hormone (α-MSH) and endothelin-1 (Edn1), both of which stimulate the expression of the *microphthalmia-associated transcription factor* (*Mitf*). However, other genes involved in developmental, immune and inflammatory systems can also affect melanogenesis (D'Mello, Finlay, Baguley, & Askarian-Amiri, 2016; Pillaiyar, Manickam, & Jung, 2017). Considering such a diversity of regulators and the variety of biochemical events influencing melanin synthesis, this phenotype is expected to have a complex dynamics, with potentially important drivers that are still incompletely characterized.

Other aspects of mammalian pigmentation are still in their infancy with respect to knowledge of underlying molecular mechanisms, such as the formation of periodic pelage patterns (i.e. regular stripes and spots). These patterns have been proposed to derive from processes acting at two different stages during development, an early one creating a spatially-oriented pattern on the embryo's skin, and a later one using the pre-established areas to differentially regulate melanogenesis (Eizirik et al., 2010). This two-stage concept was also recently proposed for pigment pattern formation in bird

feathers (Haupaix et al., 2018), suggesting that this may be a broadly applicable concept for vertebrates. In the cat family (Felidae), which harbors extensive variation of periodic coat patterns, the molecular basis of these processes has begun to be identified with the discovery of one of the implicated genes, *transmembrane aminopeptidase Q* (*Taqpep*), also known as *laeverin* (*Lvrn*) (Kaelin et al., 2012). Although previously the main known function of this gene was to regulate placentation-related peptides at the embryo-maternal interface (Maruyama et al., 2007), mutations at this locus in wild and domestic cats were found to lead to irregular coat patterns, with less periodicity. The connection between the pre-established pattern and hair pigmentation was found to involve *endothelin 3* (*Edn3*) signaling, although the details of this interaction (including the full suite of implicated genes) have so far not been completely characterized.

A different gene, *aristaless-like homeobox 3* (*Alx3*), which encodes a transcription factor involved in cell-type differentiation and development, was recently implicated in the generation of periodic dorsal stripes in the wild mouse *Rhabdomys pumilio* (Mallarino et al., 2016), with analogous function to Edn3-driven pattern implementation in felids. That study proposed that, in rodents with such periodic patterns, Alx3 interacts with the *Mitf* promoter, blocking its expression and thus its function in melanocyte development, resulting in a stripe of light hair. However, the factors that regulate *Alx3* expression at that exact position are still poorly understood (Johnson, Barsh, & Mallarino, 2018). Therefore, exploring this interaction in more detail, along with investigating the relationship between this process and *Lvrn*-related mechanisms, are promising avenues to better understand the biology of coat pattern formation.

When analyzing complex networks of gene and/or protein interaction, knowledge gathered with experimental methods can be complemented, expanded and integrated with the use of new computational analyses. Among these, systems biology approaches are often quite informative, consisting of the joint exploration of all the implicated players, instead of studying them separately (Hood, 2003). This allows the identification of potential new connections based on curated databases, and may reveal novel information regarding the relative role of each protein as well as of the system as a whole (Albert, Jeong, & Barabási, 2000; Szklarczyk et al., 2017; von Mering et al., 2005). There are several network metrics developed to score nodes (genes/proteins) according to their topological and neighborhood features (Chin et al., 2014; Seebacher & Gavin, 2011), representing their essentiality to network stability and functionality. Among them, we focus on each node's 'degree' and 'betweenness'. Nodes with the highest 'degree' (indicating how many other nodes it interacts with directly) are identified as 'hubs', whose removal could compromise network structure (Jeong, Mason, Barabási, & Oltvai, 2001). Nodes with the highest 'betweenness' (indicating how many of the shortest estimated paths go through it) are identified as 'bottlenecks', i.e. key connectors whose role is especially critical in regulatory networks (Yu, Kim, Sprecher, Trifonov, & Gerstein, 2007).

Assessments of interaction networks and their properties have been applied to a variety of biomedical problems (Barabási, Gulbahce, & Loscalzo, 2011; Ho et al., 2010; Z. Li et al., 2017; Makondi et al., 2018; Quigley et al., 2009). In the context of mammalian pigmentation, the application of these approaches to understand melanocyte biology has been advocated previously (Baxter, Loftus, & Pavan, 2009), as was its use for the investigation of mutations and their downstream consequences in melanoma signaling pathways, potentially providing improvements in cancer therapy (Smalley, 2010). In spite of these early recommendations, it has still been rarely applied to pigmentation-related problems, having so far been mostly restricted to specific components of pathways or phenotypes (Baxter, Moreland, Nguyen, Wolfsberg, & Pavan, 2010; Nigenda-Morales et al., 2018; Raghunath, Sambarey, Sharma, Mahadevan, & Chandra, 2015; Severin, Li, Qian, Mueller, & Petukhova, 2017; N. Wang et al., 2017). Therefore, an integrative assessment of all molecular players involved in hair phenotypes has so far not been performed, and no study has employed this approach to investigate genes implicated in periodic coat patterning.

To address this issue, here we perform systems biology analyses of mammalian pigmentation and hair-growth pathways, based on curated databases of mouse (*Mus musculus*) genes, complemented by two genes identified in other species (so far the only ones for mammals) that affect periodic coat pattern formation. We characterized the interactions among these genes using network metrics, specifically targeting the following objectives: (i) to create a complete interaction network of currently known hair color/growth genes in the mouse; (ii) to create interaction networks focused on the recently identified periodic coat patterning genes *Alx3* and *Lvrn*; (iii) to assess how the processes of periodic patterning and hair pigmentation may connect; (iv) to identify essential proteins in these networks as assessed by centrality scores. Our results demonstrate the usefulness of systems biology approaches in pigmentation research, and open up new avenues for experimental investigation that should be relevant in the context of comparative and biomedical applications.

MATERIALS AND METHODS

We searched for genes that had been previously associated with hair color and/or growth in mammals, by employing three complementary approaches (see Figure 1). The first one was based on the *Mus musculus* Ensembl dataset (GRCm38.p5, release 67), employing the R package biomaRt (Durinck, Spellman, Birney, & Huber, 2009). We searched for phenotypes (and associated genes) using the keywords ‘pigment’, ‘color’, ‘melanin’, ‘melanogenesis’ and ‘hair’, and subsequently filtered out phenotypes that were not related to hair coloration/development or melanin-related pathways. These phenotypes were retrieved from the Mouse Genome Informatics (MGI) (Smith, Blake, Kadin, Richardson, & Bult, 2018) and International Mouse Phenotyping Consortium (IMPC) (Dickinson et al., 2016) databases. The second approach was based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa, Sato, Kawashima, Furumichi, & Tanabe, 2016), by

compiling genes comprising the mouse melanogenesis pathway (mmu04916). The third approach was to merge the results from both searches described above, along with those provided by the most recent list of vertebrate integument pigment cell genes (Baxter, Watkins-Chow, Pavan, & Loftus, 2018), keeping loci that affect these phenotypes in mammals and/or that exhibit orthology with the mouse. Finally, we filtered out duplicated genes, creating our baseline dataset.

We employed this baseline dataset as the input to construct a network using STRING (Szklarczyk et al., 2017) and searching *Mus musculus* databases. We considered the following sources (types of evidence) of protein-protein interactions: literature mining (i.e. pair of genes reported in the same papers), experiments (laboratory assays such as genetic interactions from BioGRID), databases (e.g. KEGG pathways), coexpression (e.g. both genes being expressed in the same microarray experiment) and neighborhood (a genomic context attribute related to physical proximity). Individual scores from each type of evidence were used to compute a final interaction score among genes/proteins. To focus on interactions for which there was high confidence, the minimum required interaction score was 0.7. We then used the top interaction scores from the STRING analysis to append 10 new proteins (not present in our baseline dataset) in the first round (shell) of analysis, and 10 others in the second shell. From the resulting STRING network, we focused on the main compartment only (henceforth referred to as 'Main' network), as defined by Cytoscape v3.6.1 (Shannon et al., 2003), which implies removing nodes that formed small and isolated networks.

To investigate the association between hair development/pigmentation and the establishment of periodic coat patterning (e.g. stripes, spots), we explored two genes shown to be related to these phenotypes in cats and wild rodents (*Lvrn* and *Alx3*, respectively [Kaelin et al., 2012; Mallarino et al., 2016]). We constructed independent networks for each of them, also using the STRING *M. musculus* databases. The sources of interactions were the same as described above. However, the minimum required interaction score was 0.4 to keep interactions of medium confidence, since STRING did not find interactions when higher stringency levels were applied. We then allowed appending of $\leq$ 50 new proteins in the first and $\leq$ 20 new proteins in the second shell. Finally, these networks were merged with the 'Main' compartment of the hair color/growth network using the 'merge' tool in Cytoscape. We will refer to this composite result as the 'coat color/growth/patterning (CGP) network'.

We characterized the estimated networks (separate networks and the final CGP network) using Cytoscape plugins. To identify important elements of the topology of each network, we calculated two centrality scores (betweenness and degree) using cytoHubba v0.1 (Chin et al., 2014). To be conservative regarding hubs and bottlenecks, we considered the 10% top values of degree to be hubs, and the 10% top values of betweenness to be bottlenecks (Chen, Tripathi, & Mizuguchi, 2016). Among these nodes, those that presented top degree and top betweenness were considered 'hub-bottlenecks' (Yu et al., 2007). Finally, to perform an overrepresentation analysis (ORA) in the hubs,

bottlenecks and hub-bottlenecks within the CGP network, we used the WebGestalt web tool database 6.7 (J. Wang, Vasaikar, Shi, Greer, & Zhang, 2017).

RESULTS AND DISCUSSION

Construction and Characterization of Networks

Our baseline dataset included 1156 unique mouse genes associated with pigmentation and/or hair growth (Table S1). After applying our search parameters, we obtained a network comprising 823 connected proteins. Of these, 764 comprised the main compartment and were used in subsequent analyses. For this network ('Main' network, as defined above), our centrality metrics identified 37 hubs, 37 bottlenecks and 39 hub-bottlenecks (Figure S1, Table S2).

When we assessed the two separate networks containing interactors with *Alx3* and *Lvrn*, we observed that they comprised 33 and 52 nodes, respectively. The *Alx3*-related network contained one hub, one bottleneck and two hub-bottlenecks (Figure 2A), while the *Lvrn*-related network contained five hub-bottlenecks (Figure 2B). Finally, by merging the 'Main', *Alx3*–related and *Lvrn*–related networks, we formed the Coat Color/Growth/Patterning (CGP) network, which comprised 842 nodes, including 43 hubs, 43 bottlenecks and 41 hub-bottlenecks (Table S3).

Important Pathways in Coat Color/Growth/Patterning

Upon assessing overrepresented pathways in the set of essential nodes within our CGP network, we detected several processes for hubs and hub-bottlenecks, but none for bottlenecks (Figure 3). This is likely because top betweenness scores (which define bottlenecks) define nodes that are important connectors among different points of the network, so it would be expected that they perform such different molecular roles that no overrepresented pathway would be detected. In contrast, for the degree score, the most connected nodes in the CGP topology were in dense regions containing several nodes connected with each other, which led to the observation of hubs and hub-bottlenecks belonging to the same pathways. All the hubs/hub-bottlenecks from the 'Main' network were also retrieved in the larger CGP network, except for two hub-bottlenecks in 'Main' that were classified as hubs in CGP (Tables S2, S3).

We then assessed patterns of functional enrichment in hubs and hub-bottlenecks of the CGP network, and detected a particularly prominent role for the Wnt signaling pathway (Figure 3). Twenty five hubs (out of 43) included genes from the Wnt, dishevelled, frizzled, Gnaq, and Plcb families, all of which are part of this pathway. In addition, 13 hub-bottlenecks (out of 41) included Wnt, dishevelled, frizzled, β-catenin and Gsk3b genes, also belonging to this pathway. Many of these loci are part of the KEGG melanogenesis pathway, with some being implicated in 'dilute coat color' (MGI:2387667 [Y. Wang, Huso, Cahill, Ryugo, & Nathans, 2001]) and 'abnormal hair follicle orientation' in the mouse (MGI:108474 [Guo, Hawkins, & Nathans, 2004]). The Wnt pathway is

known to affect various developmental processes (Clevers, 2006), including hair follicle development (Schmidt-Ullrich & Paus, 2005). It also plays a role in pigment-type switching through β-catenin (Ctnnb1), a canonical Wnt protein, by blocking agouti activity and stimulating the transmembrane serine protease Corin, which also blocks agouti (Enshell-Seijffers, Lindon, Wu, Taketo, & Morgan, 2010). Regarding melanocyte development and stimulation of melanogenesis, the Wnt pathway enhances *Mitf* expression via one of its members, the lymphoid enhancing factor-1/T-cell factor (LEF-TCF) transcription factor, which is activated by β-catenin (Pillaiyar et al., 2017). In addition, the Wnt pathway has also been found to be enriched in genes related to hair follicle integrity (Severin et al., 2017). In spite of these previously reported roles for the Wnt pathways in specific phenotypes related to pigmentation or hair development, up to now there had been no network analyses encompassing both processes from a broad perspective, and our results indicate that this approach holds potential for further dissection of these interactions.

Among CGP hub-bottlenecks, we also observed several genes belonging to the Akt signaling pathway, which seems to play an important role in this network in spite of not having been retrieved as significantly overrepresented. This pathway plays a role in melanogenesis by improving binding affinity of Mitf to tyrosinase-related gene promoters (Khaled et al., 2002; Pillaiyar et al., 2017). Further, it participates in melanoma progression (Smalley, 2010), was reported as essential for skin pigmentation in response to ultraviolet radiation (Raghunath et al., 2015), and participates in hair follicle development, regeneration and integrity (Di-Poi et al., 2005; Qiu et al., 2017; Severin et al., 2017).

An interesting observation was that two CGP hub-bottlenecks (Gart and Pfas), both of which are required for purine biosynthesis (Bønsdorff et al., 2004), were also retrieved as hub-bottlenecks in the separate analysis of the *Lvrn*-related network (Figure 2B), indicating that they play important roles in the pattern-formation component of this system. In addition, these nodes were found to connect the 'Main' and *Lvrn*-related networks within the broader CGP network, which highlights their potential roles in the regulation of pattern development.

The endothelin signaling pathway, centered around genes that were originally characterized as vasoconstrictors (Davenport et al., 2016), was found to be enriched among both hubs and hub-bottlenecks. This pathway is well known to participate in pigmentation, having a role in melanogenesis in response to UV radiation (Imokawa, Kobayashi, Miyagishi, Higashi, & Yada, 1997), development of iridophore-based stripes in zebrafish (Krauss et al., 2014), and implementation of coat patterning in domestic and wild cats (Kaelin et al., 2012). In addition, we also retrieved enriched pathways that are related to immunity, cell adhesion, angiogenesis, growth factors (epidermal, vascular, endothelial and fibroblast), apoptosis and cell survival, and proopiomelanocortin (Figure 3). These results provide a comprehensive view of the complex interplay among diverse pathways in the context of mammalian coat development.

Although there was no detected enrichment of pathways among CGP bottlenecks, some interesting patterns could be discerned when assessing individual nodes that were retrieved using this metric. This may be particularly interesting since bottlenecks can be considered bridges between separate points of a network, thus being key connectors with important functional roles (Yu et al., 2007). As the main CGP bottleneck gene, we retrieved *Mitf* (Table S3), a well-known melanogenesis regulator and an important transcription factor in melanocytes (Levy, Khaled, & Fisher, 2006), also found to be essential in skin pigmentation in response to UV radiation (Raghunath et al., 2015). Further, we also retrieved Alx3 and Lvrn as bottlenecks, which would be expected within their own networks, but it is noteworthy that even in a broader context (CGP network) they maintained this status. Other interesting examples of nodes retrieved as bottlenecks were Myo5a, which is associated with melanosome transport (Barral & Seabra, 2004), and Edn1, which is associated with melanogenesis stimulated by UV (Imokawa et al., 1997). Such congruence between the network-based results and known functional roles supports the validity of the systems biology approach, and thus its inferences regarding poorly known portions of the assessed networks. Finally, we found CGP network bottlenecks that are responsible for the connection between the 'Main' network and the two periodic patterning networks: Sfn and Ets1 for the *Lvrn*-related network, and Mitf for the *Alx3*-related network. Their particular roles will be discussed in the next section.

Insights into the Establishment of Periodic Coat Patterning and its Implementation

The *Alx3*-related network connected to the 'Main' network only via the Mitf node (Figure 4A). In this context, it is noteworthy that our STRING search did not retrieve the empirically demonstrated interaction between Alx3 and Mitf (Mallarino et al., 2016), which we had to add to our analyses manually. This missing link illustrates the potential effects of gaps in empirical knowledge and/or in existing databases, or sparse information generated for distinct species, on the completeness of the results generated by such a search algorithm. In this case, the algorithm assigns high scores for proteins cited simultaneously several times in abstracts and/or full texts (Szklarczyk et al., 2017), which would not be the case for this connection. This is because the connection was only recently discovered, and reported in a single paper for a species that is not *M. musculus*, the focal taxon of our curated databases.

Still regarding the *Alx3*-related network, it was interesting to note the presence of seven genes belonging to the transmembrane receptor tyrosine kinase signaling pathway, including Eph/ephrin genes reported to be involved in organizing neural crest cell migration streams. Both Alx3 and Eph/ephrin have been described to be involved in neural crest cell migration associated with development of skeletal structures (Minoux & Rijli, 2010). This suggests that Eph/ephrin genes may also be involved in periodic pattern formation on the mammalian skin, which would be connected to pigmentation-related phenotypes via Alx3-related signaling.

In the case of the *Lvrn*-related network, its connection to the 'Main' network occurred at seven nodes/genes: *Dlat*, *Ets1*, *Ets2*, *Gart*, *Paics*, *Pfas* and *Sfn*. These seven genes connected directly to several players within the CGP network (Figure 4B). This observation may imply that the laeverin mechanism of action is more intrinsic (i.e. more connected to 'core' processes) in hair development and pigmentation than that of Alx3. With respect to the known functions of individual connecting nodes, Dlat is a component of the pyruvate dehydrogenase complex, while Gart and Paics are enzymes acting in purine biosynthesis, and all three are associated with pigmentation phenotypes in zebrafish, such as abnormally increased or decreased pigmentation granules (Baxter et al., 2018). The link between Lvrn and Dlat is indirect, with Gart acting as the intermediate between them. The connection of Gart and Paics with Lvrn, however, is based on a predictive association between putative homologs, which poses challenges to our interpretation concerning their roles in pigmentation.

Other connectors between the *Lvrn*-related network and the 'Main' network are Ets2, a transcription factor, and Sfn, an adapter protein, both of which were verified to be associated with hair follicle and hair morphology abnormalities in the mouse (Q. Li, Lu, Estepa, & Verma, 2005; Yamamoto et al., 1998). The STRING-predicted association between Lvrn and Ets2 was supported by empirical results reporting a transactivation role of Ets2 on a laeverin homolog (Meadows, Myers, & Krieg, 2011). In addition, Ets2 also connects to nodes related to the melanogenesis pathway (e.g. Hras and Mapk3 [KEGG mmu04916]) and hair morphology (Runx3 [Raveh, Cohen, Levanon, Groner, & Gat, 2005]). Regarding Sfn, its link with Lvrn was based on the predicted composition of a complex associated with cytoplasmic vesicle membranes, identified by R-MMU-1445129 in the Reactome database (Ramm, Larance, Guilhaus, & James, 2006). As an adapter protein, Sfn regulates the activity of other proteins. When it interacts with keratin 17 (Krt17), for example, it regulates protein synthesis and stimulates the Akt/mTOR pathway affecting epithelial cell growth (Kim, Wong, & Coulombe, 2006). Likewise, when associated with calmodulin-like 5 (Calml5), it participates in epidermis differentiation (Sun et al., 2015). Furthermore, Sfn has predicted association to at least eight nodes participating in hair follicle development and pigmentation (Figure 4B), one of them being Akt1. This protein has been shown to increase *Mitf* expression via interaction with the endothelin pathway (Kadekaro et al., 2005). Concerning this pathway, it is particularly noteworthy that Edn3 has been implicated in the implementation of the periodic patterning of cat coloration (Kaelin et al., 2012), which makes Sfn an especially interesting target for further investigation.

The final pair of connectors between the *Lvrn*-related network and the 'Main' network are Ets1 (a transcription factor) and Pfas (a required enzyme in the synthesis of inosine monophosphate), both of which are associated with white spotting phenotypes in mouse (Baxter et al., 2018). The connection between Pfas and Lvrn is difficult to interpret, since their STRING-predicted interaction is mainly based on putative homologs in other species. For Ets1, however, it was based on co-expression with laeverin in extravillous trophoblast cells (Apps et al., 2011), and we note that there are additional

lines of evidence for this interaction. For example, the 'variable spotting' mouse phenotype arose due to an *Ets1* mutation, and later this gene was discovered to enhance *Sox10* expression, such interaction being essential to properly develop the melanocyte (Betancur, Bronner-Fraser, & Sauka-Spengler, 2010; Saldana-Caboverde et al., 2015). Furthermore, a correct interaction between Sox10 and Ednrb/Edn3 is also necessary for normal melanocyte development (Stanchina et al., 2006). Therefore, our findings suggest that in initial stages of development, Lvrn and Ets1 may jointly play a role in pre-pattern establishment. Later in melanocyte differentiation, Ets1 and Sox10 may interact to define those cells in which the pigmentation pattern should appear and, finally, Sox10 and Edn3 would jointly induce the pigmentation stage of pelage markings. This hypothetical scenario for a cascade producing periodic pattern formation can be assessed with experimental essays such as those suggested by Johnson et al. (2018), which should allow the dissection of the roles of each of these putatively involved genes.

Interestingly, the *Alx3*-related and *Lvrn*-related networks joined the 'Main' network at separate locations, without any overlapping genes. Although both of them have been empirically implicated in periodic coat patterning, the Alx3 mechanism affects pattern implementation by blocking *Mitf* expression, resulting in undifferentiated melanocytes and light hair. In contrast, Lvrn affects pattern establishment likely through a signaling cascade that drives the shape of the resulting coat markings (Kaelin et al., 2012). The two processes thus seem to be unrelated, perhaps occurring at different developmental stages and cell types, and so far have been demonstrated to occur in different groups of mammals. Our results indicate that both could independently act in species whose patterns include areas with lighter hair. Furthermore, it is noteworthy that Lvrn has a known role in human placentation, being hypothesized to be associated with preeclampsia when misfolding or when presenting defects in glycosylation (Nystad et al., 2016). If such a role is widespread across all mammals, mutations such as those found in cats and cheetahs, leading to loss of periodic pattern (Kaelin et al., 2012), should be strongly deleterious given their implied impact on placentation. Since there is no evidence of such an impact in terms of the fecundity or viability of these animals (although data on this topic are scarce), it is possible that genes involved in patterning work differently in distinct groups. This highlights the need for broader comparative assessments of the structure and function of *Lvrn* across multiple groups of mammals.

With respect to laeverin's role in pigmentation, the mechanism through which it drives the formation of pattern on the mammalian coat remains uncertain. In this context, our identification of its potential functional relationships with proteins such as Ets1 and Sfn may be quite relevant, as they may underlie the connection between the processes of pre-pattern establishment and pigmentation. Further exploration of Edn3 network, along with assessments of tissue- and stage development-specific gene expression networks, could help improve this characterization. Therefore, our results open up new avenues for both *in silico* and experimental studies focusing on the mechanisms driving

and regulating the formation of periodic patterning on the mammalian coat.

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FIGURES AND LEGENDS

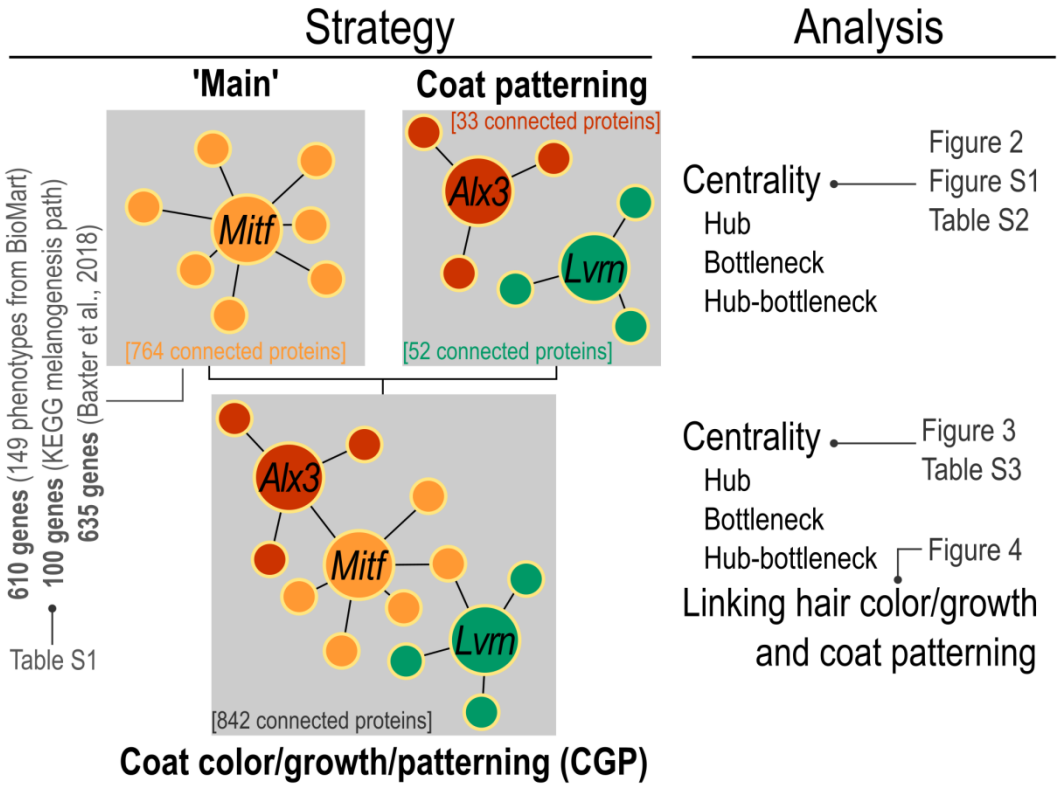

Figure 1. Schematic representation of our methodological approach. Our strategy included: the search for genes associated with pigmentation or hair growth phenotypes in BioMart databases, KEGG melanogenesis pathway and pigment gene list from Baxter et al. (2018), leading to the formation of the 'Main' network, represented by *Mitf* and its interactors (orange circles). In parallel, we built two coat patterning networks based on two focal genes (*Alx3* and *Lvrn*) and their respective interactors (red and green circles, respectively). Lastly, we merged these three networks into the final coat color/growth/patterning (CGP) network. The right-hand panel indicates the analyses that were performed with each network, along with the figures and tables in which their results are presented.

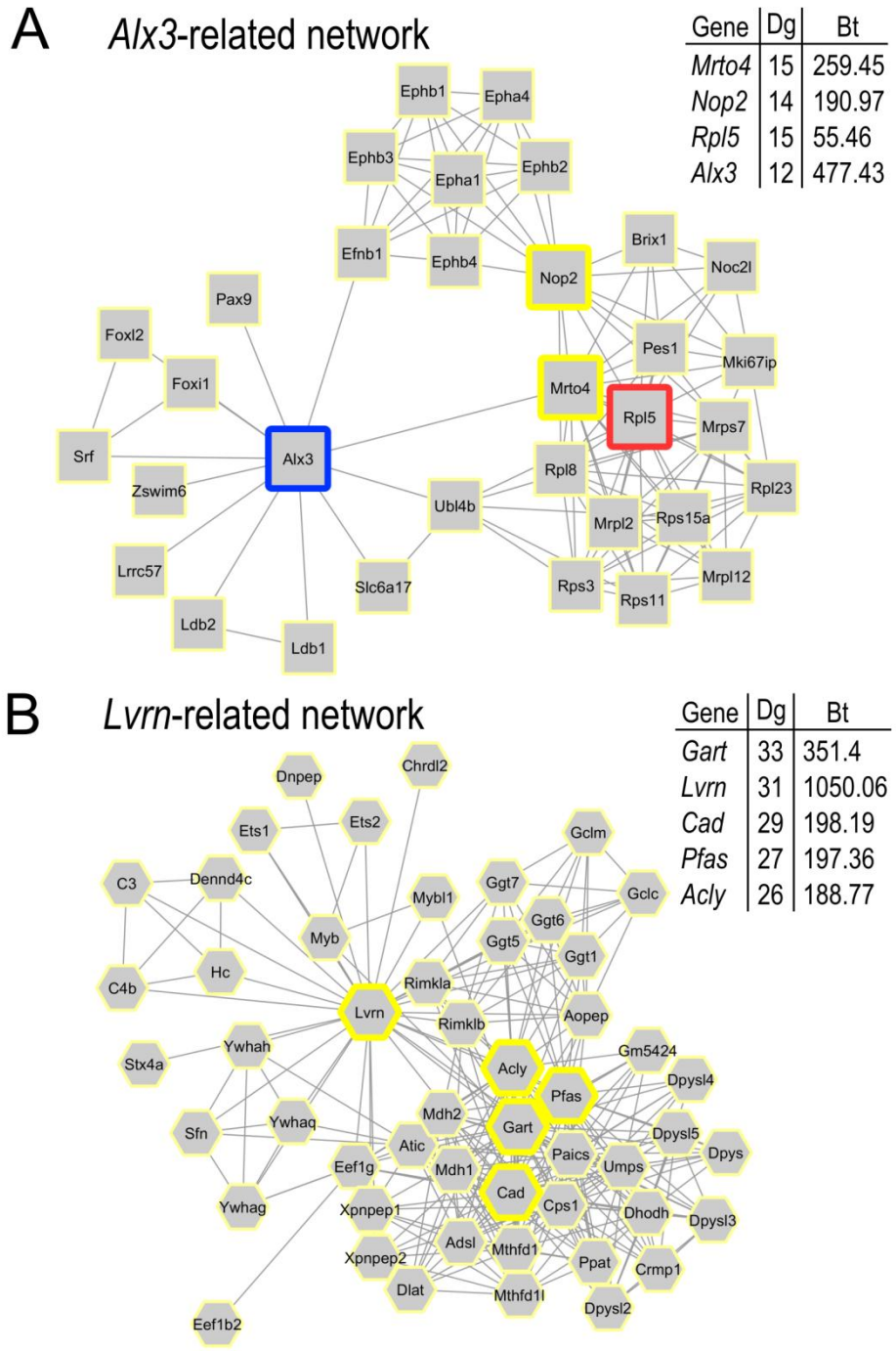

Figure 2. Networks constructed on the basis of interactions with periodic coat patterning genes *Alx3* (A) and *Lvrn* (B), including centrality scores (Dg: degree; Bt: betweenness) of highlighted nodes (genes). The polygon with a red border is a hub, the one with a blue border is a bottleneck, and those with thick yellow borders are hub-bottlenecks.

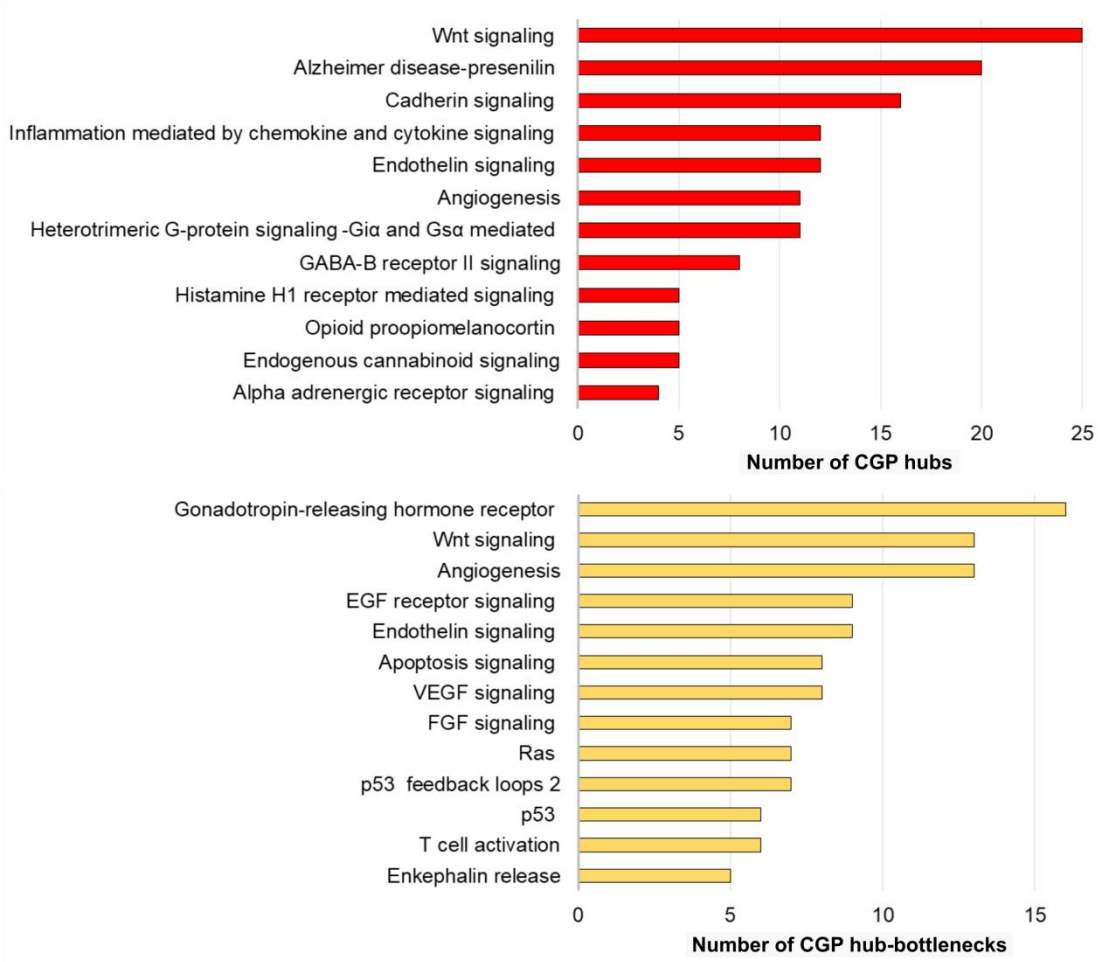

Figure 3. Overrepresented pathways among CGP hubs and hub-bottlenecks. Pathways are derived from the Panther database with FDR < 0.01. See Table S3 for a full list of hubs, bottlenecks and hub-bottlenecks from the CGP network, including their respective degree and betweenness scores.

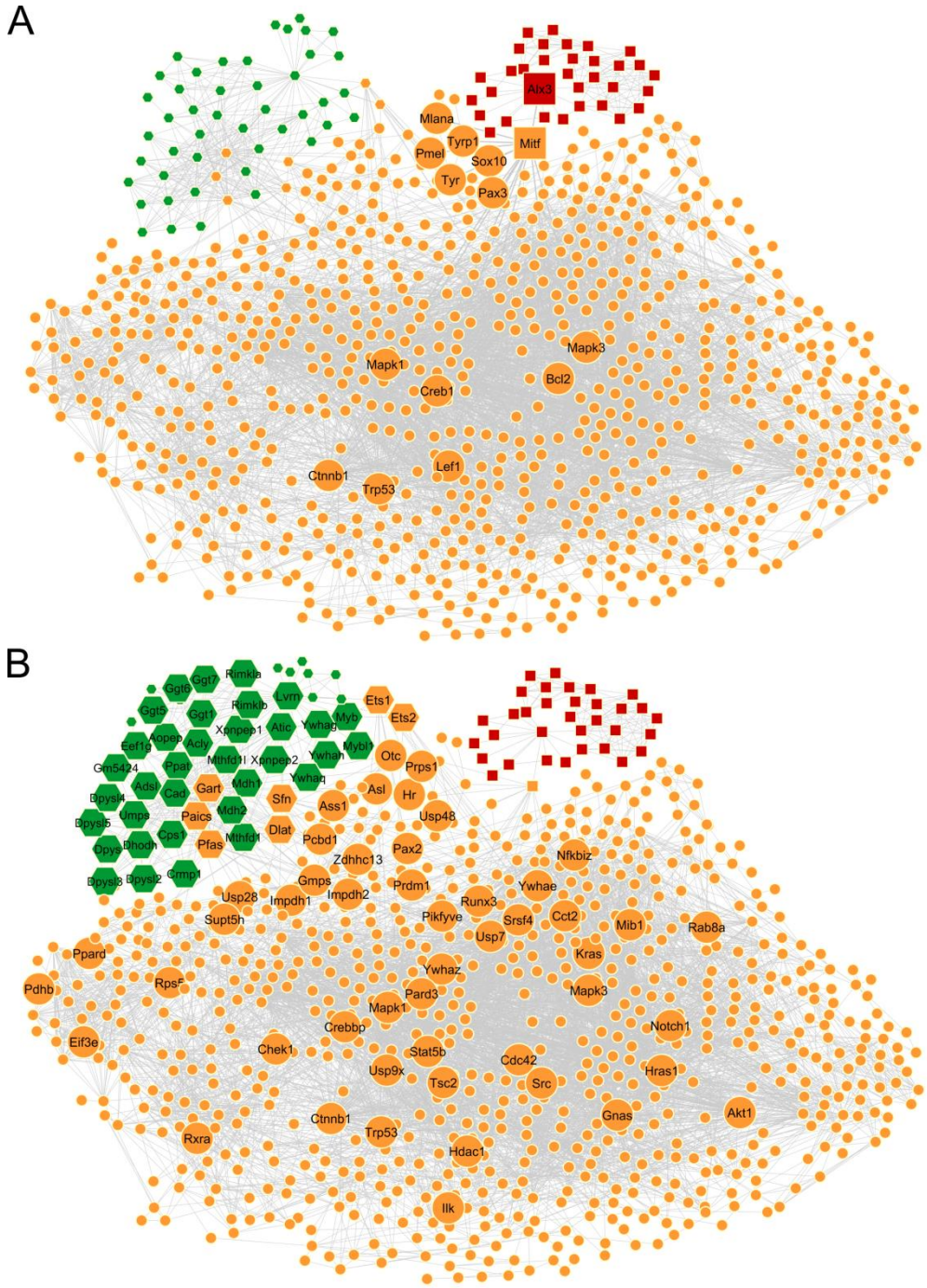

Figure 4. CGP network (comprising 842 nodes), resulting from the merging of the 'Main' network (orange nodes) with periodic coat patterning networks (green hexagons for the *Lvrn*-related network; red squares for the *Alx3*-related network). We highlight as larger-sized polygons the nodes that serve as connectors (along with their first-neighborhood nodes) between the 'Main' network and the *Alx3*-related network (panel A), and between the 'Main' network and the *Lvrn*-related network (panel B).

SUPLEMENTARY MATERIAL

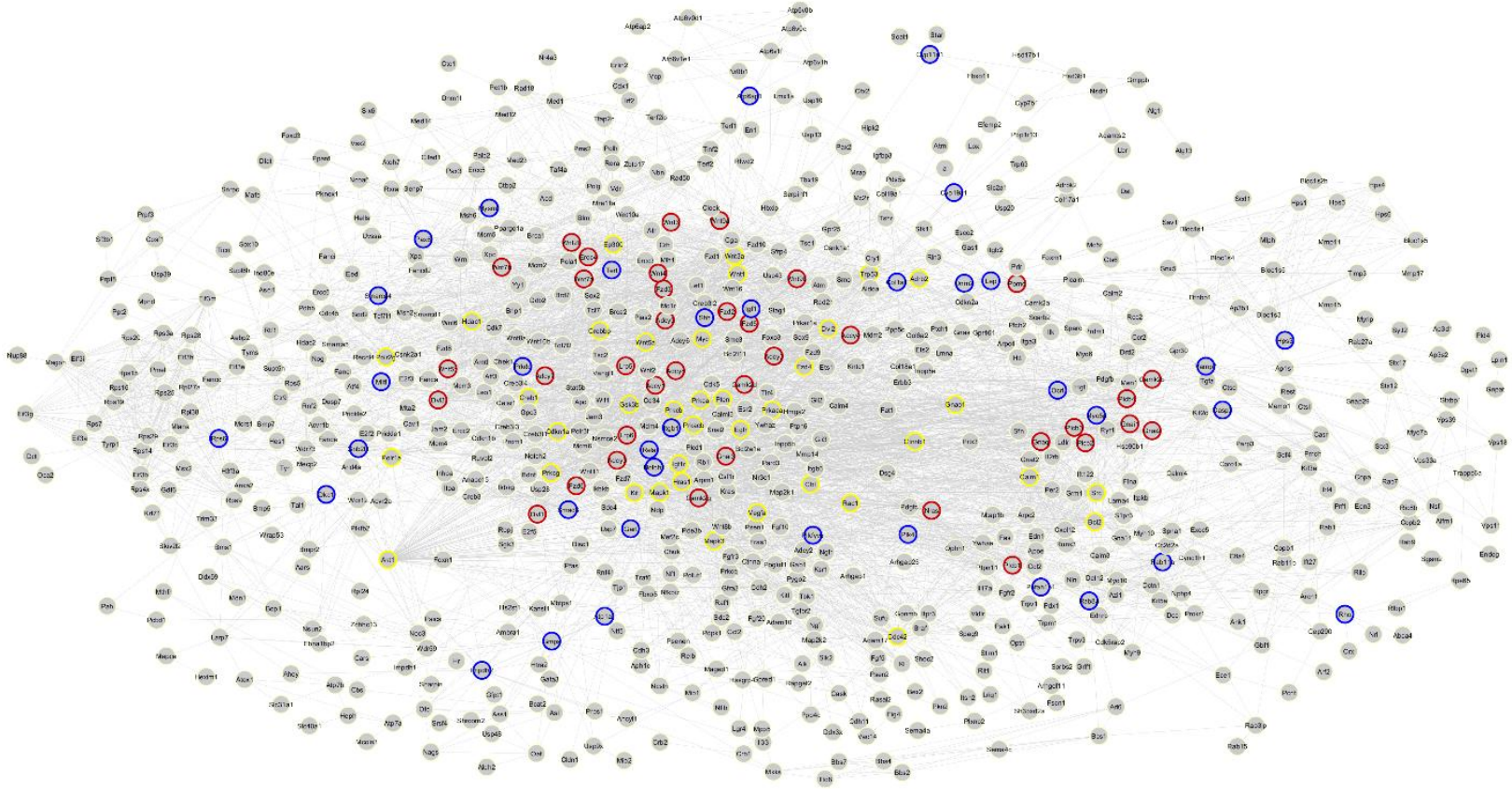

Figure S1. 'Main' network, resulting from a STRING search using the baseline list of genes from BioMart, KEGG and Baxter et al. (2018). The blue borders indicate bottlenecks, the red ones are hubs, and the yellow ones are the hub-bottlenecks.

Table S1. Genes from BioMart that compose our baseline dataset.

Approach	Mouse gene symbol	Phenotype description
BioMart	1700003F12Rik	abnormal skin coloration
BioMart	1700007G11Rik	abnormal retinal pigmentation
BioMart	1700008O03Rik	abnormal hair growth
BioMart	1700008O03Rik	sparse hair
BioMart	1700027J19Rik	abnormal coat/hair pigmentation
BioMart	4930453N24Rik	abnormal coat/hair pigmentation
BioMart	4930453N24Rik	irregular coat pigmentation
BioMart	4933402N03Rik	abnormal hair growth
BioMart	4933402N03Rik	sparse hair
BioMart	a	abnormal coat/hair pigmentation
BioMart	a	abnormal hair follicle melanogenesis
BioMart	a	abnormal pinna hair pigmentation
BioMart	a	abnormal skin pigmentation
BioMart	a	abnormal tail hair pigmentation
BioMart	a	abnormal ventral coat pigmentation
BioMart	a	absent coat pigmentation
BioMart	a	darkened coat color
BioMart	a	irregular coat pigmentation
BioMart	a	yellow coat color
BioMart	Aars	abnormal hair shaft morphology
BioMart	Aars	focal hair loss
BioMart	Aars	hair follicle degeneration
BioMart	Aars	hair follicle outer rooth sheath hyperplasia
BioMart	Abca4	abnormal retinal pigment epithelium morphology
BioMart	Abi2	abnormal iris pigmentation
BioMart	Acd	abnormal hair texture
BioMart	Acd	hyperpigmentation
BioMart	Acd	increased ear pigmentation
BioMart	Acd	increased tail pigmentation
BioMart	Acd	retarded hair growth
BioMart	Acd	sparse hair
BioMart	Ace2	yellow coat color
BioMart	Acer1	abnormal awl hair morphology
BioMart	Acer1	abnormal coat/ hair morphology
BioMart	Acer1	abnormal hair cuticle
BioMart	Acer1	abnormal hair follicle bulge morphology
BioMart	Acer1	abnormal hair follicle development
BioMart	Acer1	abnormal hair follicle infundibulum morphology
BioMart	Acer1	abnormal hair follicle morphology
BioMart	Acer1	abnormal hair growth
BioMart	Acer1	abnormal hair shaft morphology
BioMart	Acer1	abnormal retinal pigmentation
BioMart	Acer1	abnormal zigzag hair morphology
BioMart	Acer1	dilated hair follicle infundibulum
BioMart	Acer1	sparse hair
BioMart	Acp2	abnormal hair follicle morphology
BioMart	Acp2	delayed hair appearance
BioMart	Acp2	thin hair shaft
BioMart	Actrt3	abnormal coat/ hair morphology
BioMart	Acvr1b	abnormal coat/ hair morphology
BioMart	Adam17	abnormal coat/hair pigmentation
BioMart	Adam17	abnormal hair follicle development
BioMart	Adam17	abnormal hair follicle morphology
BioMart	Adam17	abnormal hair follicle orientation
BioMart	Adam17	distorted hair follicle pattern
BioMart	Adam17	waved hair
BioMart	Adam9	abnormal retinal pigment epithelium morphology

BioMart	Adamts13	abnormal retinal pigmentation
BioMart	Adamts2	abnormal hair follicle morphology
BioMart	Adamts20	abnormal coat/hair pigmentation
BioMart	Adamts20	abnormal hair follicle melanin granule distribution
BioMart	Adamts20	abnormal hair follicle melanocyte morphology
BioMart	Adamts20	abnormal skin pigmentation
BioMart	Adamtsl4	abnormal retinal pigment epithelium morphology
BioMart	Adamtsl4	abnormal retinal pigmentation
BioMart	Afap1l2	abnormal coat/ hair morphology
BioMart	Ahcyl1	abnormal retinal pigmentation
BioMart	Ahr	abnormal auchene hair morphology
BioMart	Ahr	abnormal coat/ hair morphology
BioMart	Ahr	abnormal hair follicle morphology
BioMart	Ahr	abnormal hair shaft morphology
BioMart	Ahrr	abnormal retinal pigmentation
BioMart	Aifm1	focal hair loss
BioMart	Aifm1	sparse hair
BioMart	Akt1	underdeveloped hair follicles
BioMart	Aldh16a1	abnormal retinal pigmentation
BioMart	Aldh2	hyperpigmentation
BioMart	Alg1	abnormal coat/hair pigmentation
BioMart	Alk	delayed hair appearance
BioMart	Alk	delayed skin pigmentation appearance
BioMart	Alx4	delayed hair appearance
BioMart	Alx4	focal dorsal hair loss
BioMart	Anapc15	abnormal skin coloration
BioMart	Ank1	abnormal skin pigmentation
BioMart	Ankle1	abnormal coat/hair pigmentation
BioMart	Ap3b1	abnormal coat/hair pigmentation
BioMart	Ap3b1	abnormal eye pigmentation
BioMart	Ap3b1	abnormal foot pigmentation
BioMart	Ap3b1	abnormal skin pigmentation
BioMart	Ap3b1	decreased ear pigmentation
BioMart	Ap3b1	decreased eye pigmentation
BioMart	Ap3b1	decreased tail pigmentation
BioMart	Ap3b1	diluted coat color
BioMart	Ap3b1	hypopigmentation
BioMart	Ap3d1	abnormal retinal pigment epithelium morphology
BioMart	Ap3d1	decreased eye pigmentation
BioMart	Ap3d1	diluted coat color
BioMart	Aph1c	abnormal coat/hair pigmentation
BioMart	Apoe	abnormal retinal pigment epithelium morphology
BioMart	Apoe	retinal pigment epithelium atrophy
BioMart	Apof	abnormal coat/ hair morphology
BioMart	Arcn1	abnormal hair shaft melanin granule distribution
BioMart	Arcn1	diluted coat color
BioMart	Arf2	abnormal coat/hair pigmentation
BioMart	Arhgap1	abnormal hair growth
BioMart	Arhgap25	abnormal retinal pigmentation
BioMart	Arhgap35	retinal pigment epithelium hyperplasia
BioMart	Arhgef11	abnormal retinal pigmentation
BioMart	Arid4a	ruffled hair
BioMart	Arntl	abnormal hair cycle
BioMart	Arntl	abnormal hair cycle anagen phase
BioMart	Arntl	abnormal hair follicle matrix region morphology
BioMart	Arntl	retarded hair growth
BioMart	Arpc2	abnormal coat/hair pigmentation
BioMart	Arpc4	abnormal hair texture
BioMart	Arsk	abnormal retinal pigmentation
BioMart	Ascl1	abnormal skin pigmentation
BioMart	Asl	abnormal coat/ hair morphology

BioMart	Asl	abnormal hair follicle morphology
BioMart	Asl	small hair follicles
BioMart	Ass1	abnormal hair follicle development
BioMart	Ass1	abnormal hair follicle morphology
BioMart	Ass1	delayed hair appearance
BioMart	Ass1	sparse hair
BioMart	Atf3	abnormal retinal pigmentation
BioMart	Atf4	delayed hair appearance
BioMart	Atf4	ruffled hair
BioMart	Atox1	hypopigmentation
BioMart	Atp7a	abnormal awl hair morphology
BioMart	Atp7a	abnormal coat/hair pigmentation
BioMart	Atp7a	abnormal zigzag hair morphology
BioMart	Atp7a	absent coat pigmentation
BioMart	Atp7a	coarse hair
BioMart	Atp7a	diluted coat color
BioMart	Atp7b	diluted coat color
BioMart	Atp7b	hypopigmentation
BioMart	Atp8a2	abnormal retinal pigment epithelium morphology
BioMart	Atr	abnormal coat/hair pigmentation
BioMart	Atr	decreased hair follicle number
BioMart	Atrn	abnormal coat/hair pigmentation
BioMart	Atrn	darkened coat color
BioMart	B4galt1	decreased hair follicle number
BioMart	B4galt1	sparse hair
BioMart	Barx2	abnormal coat/hair pigmentation
BioMart	Barx2	abnormal hair cycle
BioMart	Barx2	abnormal skin pigmentation
BioMart	Barx2	short hair
BioMart	Bbs4	abnormal retinal pigment epithelium morphology
BioMart	BC027072	abnormal retinal pigment epithelium morphology
BioMart	BC027072	abnormal retinal pigmentation
BioMart	Bcat2	sparse hair
BioMart	Bcat2	thin hair shaft
BioMart	Bcl2	abnormal coat/hair pigmentation
BioMart	Bcl2	absent hair follicle melanin granules
BioMart	Bcl2	diluted coat color
BioMart	Bcl2	hypopigmentation
BioMart	Bcl2	irregular coat pigmentation
BioMart	Bcl2a1a	focal hair loss
BioMart	Bcl7a	abnormal skin coloration
BioMart	Bdnf	abnormal hair cycle
BioMart	Bend3	abnormal coat/hair pigmentation
BioMart	Best1	abnormal retinal pigment epithelium morphology
BioMart	Bex2	abnormal coat/hair pigmentation
BioMart	Bloc1s1	absent eye pigmentation
BioMart	Bloc1s2	absent eye pigmentation
BioMart	Bloc1s3	abnormal eye pigmentation
BioMart	Bloc1s3	abnormal hair follicle melanin granule morphology
BioMart	Bloc1s3	decreased ear pigmentation
BioMart	Bloc1s3	decreased tail pigmentation
BioMart	Bloc1s3	diluted coat color
BioMart	Bloc1s4	abnormal choroid pigmentation
BioMart	Bloc1s4	abnormal melanogenesis
BioMart	Bloc1s4	abnormal retinal pigmentation
BioMart	Bloc1s4	decreased eye pigmentation
BioMart	Bloc1s4	diluted coat color
BioMart	Bloc1s4	hypopigmentation
BioMart	Bloc1s5	abnormal eye pigmentation
BioMart	Bloc1s5	abnormal retinal pigment epithelium morphology
BioMart	Bloc1s5	decreased eye pigmentation

BioMart	Bloc1s5	diluted coat color
BioMart	Bloc1s5	hypopigmentation
BioMart	Bloc1s6	decreased eye pigmentation
BioMart	Bloc1s6	diluted coat color
BioMart	Bmp7	abnormal hair follicle morphology
BioMart	Bmp7	abnormal retinal pigment epithelium morphology
BioMart	Bmp7	abnormal retinal pigmentation
BioMart	Bmp7	hair follicle outer rooth sheath hyperplasia
BioMart	Bmp7	retinal pigment epithelium atrophy
BioMart	Bms1	abnormal coat/hair pigmentation
BioMart	Brca1	abnormal awl hair morphology
BioMart	Brca1	abnormal coat/hair pigmentation
BioMart	Brca1	abnormal hair follicle morphology
BioMart	Brca1	abnormal hair growth
BioMart	Brca1	abnormal skin pigmentation
BioMart	Brca1	decreased hair follicle number
BioMart	Brd7	abnormal coat/ hair morphology
BioMart	Btbd16	abnormal skin coloration
BioMart	Btd	abnormal coat/hair pigmentation
BioMart	C1qtnf5	abnormal retinal pigmentation
BioMart	Carmil2	abnormal coat/hair pigmentation
BioMart	Cask	absent hair follicles
BioMart	Cask	focal hair loss
BioMart	Caskin1	abnormal coat/hair pigmentation
BioMart	Casp3	abnormal retinal pigment epithelium morphology
BioMart	Casr	abnormal coat/hair pigmentation
BioMart	Cbl	abnormal foot pigmentation
BioMart	Cbl	darkened coat color
BioMart	Cbl	increased ear pigmentation
BioMart	Cbl	increased tail pigmentation
BioMart	Cbs	abnormal hair follicle morphology
BioMart	Cbs	abnormal hair growth
BioMart	Cc2d2a	focal dorsal hair loss
BioMart	Ccdc77	sparse hair
BioMart	Ccl2	abnormal retinal pigment epithelium morphology
BioMart	Ccr2	abnormal retinal pigment epithelium morphology
BioMart	Cd109	abnormal hair follicle infundibulum morphology
BioMart	Cd109	abnormal hair growth
BioMart	Cd109	abnormal hair shaft morphology
BioMart	Cd109	dilated hair follicles
BioMart	Cd109	sparse hair
BioMart	Cd34	abnormal hair follicle morphology
BioMart	Cd46	abnormal retinal pigment epithelium morphology
BioMart	Cdc123	abnormal coat/hair pigmentation
BioMart	Cdk5rap2	premature hair loss
BioMart	Cdkn1a	abnormal auchene hair morphology
BioMart	Cdkn1a	abnormal awl hair morphology
BioMart	Cdkn1a	decreased zigzag hair amount
BioMart	Cdkn1b	abnormal retinal pigment epithelium morphology
BioMart	Cdsn	abnormal hair follicle morphology
BioMart	Cdsn	abnormal hair shaft morphology
BioMart	Celsr1	abnormal hair follicle orientation
BioMart	Celsr1	ruffled hair
BioMart	Celsr1	whorled hair
BioMart	Cep290	abnormal retinal pigment epithelium morphology
BioMart	Cers4	abnormal hair follicle morphology
BioMart	Cers4	abnormal hair texture
BioMart	Cers4	hair follicle degeneration
BioMart	Cers4	progressive hair loss
BioMart	Ces1f	abnormal skin coloration
BioMart	Cfh	abnormal retinal pigment epithelium morphology

BioMart	Chic2	abnormal coat/hair pigmentation
BioMart	Chrng	abnormal skin pigmentation
BioMart	Chuk	abnormal hair follicle development
BioMart	Chuk	abnormal hair follicle morphology
BioMart	Cidea	diluted coat color
BioMart	Cidea	dry hair
BioMart	Cidea	focal hair loss
BioMart	Cidea	focal hair loss in head/neck region
BioMart	Cisd2	abnormal coat/hair pigmentation
BioMart	Cisd2	decreased hair follicle number
BioMart	Cisd2	ruffled hair
BioMart	Clcn1	sparse hair
BioMart	Clcn2	abnormal retinal pigment epithelium morphology
BioMart	Clcn7	abnormal retinal pigment epithelium morphology
BioMart	Cldn1	abnormal hair growth
BioMart	Cln8	abnormal retinal pigment epithelium morphology
BioMart	Clock	abnormal hair cycle
BioMart	Clock	abnormal hair cycle anagen phase
BioMart	Clps	sparse hair
BioMart	Cmbl	abnormal hair growth
BioMart	Col17a1	abnormal coat/hair pigmentation
BioMart	Col17a1	abnormal hair growth
BioMart	Col17a1	focal hair loss
BioMart	Col17a1	sparse hair
BioMart	Col18a1	abnormal iris pigment epithelium
BioMart	Col18a1	abnormal iris stromal pigmentation
BioMart	Col19a1	focal hair loss
BioMart	Col1a1	focal hair loss
BioMart	Coq9	premature hair loss
BioMart	Corin	abnormal awl hair morphology
BioMart	Corin	abnormal zigzag hair morphology
BioMart	Corin	diluted coat color
BioMart	Cotl1	abnormal coat/hair pigmentation
BioMart	Cox5b	abnormal skin coloration
BioMart	Cox7c	abnormal skin coloration
BioMart	Crb1	abnormal retinal pigment epithelium morphology
BioMart	Crx	abnormal retinal pigmentation
BioMart	Csnk2a1	abnormal retinal pigmentation
BioMart	Cst6	abnormal coat/ hair morphology
BioMart	Cst6	abnormal hair follicle morphology
BioMart	Cst6	sparse hair
BioMart	Ctc1	sparse hair
BioMart	Ctdspl2	abnormal skin coloration
BioMart	Ctla4	variable depigmentation
BioMart	Ctnna1	abnormal retinal pigment epithelium morphology
BioMart	Ctnna1	abnormal retinal pigmentation
BioMart	Ctns	abnormal retinal pigmentation
BioMart	Cts6	abnormal retinal pigmentation
BioMart	Ctsd	abnormal hair cycle
BioMart	Ctsl	abnormal coat/ hair morphology
BioMart	Ctsl	abnormal hair cycle
BioMart	Ctsl	abnormal hair cycle catagen phase
BioMart	Ctsl	abnormal hair follicle development
BioMart	Ctsl	abnormal hair follicle morphology
BioMart	Ctsl	abnormal hair follicle orientation
BioMart	Ctsl	abnormal hair growth
BioMart	Ctsl	abnormal hair shaft morphology
BioMart	Ctsl	delayed hair appearance
BioMart	Ctsl	hair follicle degeneration
BioMart	Ctsl	hair follicle outer rooth sheath hyperplasia
BioMart	Ctsl	short hair

BioMart	Ctsl	sparse hair
BioMart	Ctsl	underdeveloped hair follicles
BioMart	Cux1	abnormal coat/ hair morphology
BioMart	Cux1	abnormal hair follicle morphology
BioMart	Cux1	abnormal hair follicle orientation
BioMart	Cux1	abnormal hair shaft morphology
BioMart	Cux1	absent auchene hairs
BioMart	Cux1	absent awl hair
BioMart	Cux1	absent guard hair
BioMart	Cux1	absent zigzag hairs
BioMart	Cux1	darkened coat color
BioMart	Cux1	enlarged hair follicles
BioMart	Cux1	sparse hair
BioMart	Cxcl17	abnormal coat/hair pigmentation
BioMart	Cyb561	abnormal coat/hair pigmentation
BioMart	Cyp19a1	abnormal coat/hair pigmentation
BioMart	Cyp26b1	abnormal hair follicle development
BioMart	Cyp7b1	abnormal coat/ hair morphology
BioMart	D430041D05Rik	abnormal coat/hair pigmentation
BioMart	D630023F18Rik	abnormal retinal pigmentation
BioMart	Dact2	abnormal coat/ hair morphology
BioMart	Dact2	abnormal skin coloration
BioMart	Dbi	abnormal coat/ hair morphology
BioMart	Dcc	abnormal retinal pigmentation
BioMart	Dcp2	abnormal coat/hair pigmentation
BioMart	Dct	abnormal coat/hair pigmentation
BioMart	Dct	abnormal iris pigmentation
BioMart	Dct	diluted coat color
BioMart	Ddx59	abnormal coat/hair pigmentation
BioMart	Def6	abnormal hair growth
BioMart	Degs1	sparse hair
BioMart	Dgat1	abnormal coat/ hair morphology
BioMart	Dgat1	abnormal hair cycle
BioMart	Dgat1	abnormal hair cycle anagen phase
BioMart	Dgat1	abnormal hair shedding
BioMart	Dgat1	sparse hair
BioMart	Dixdc1	abnormal retinal pigmentation
BioMart	Dnase1l2	abnormal hair shaft morphology
BioMart	Dnm1l	abnormal coat/ hair morphology
BioMart	Dock7	abnormal digit pigmentation
BioMart	Dock7	abnormal skin pigmentation
BioMart	Dock7	diluted coat color
BioMart	Dock7	non-pigmented tail tip
BioMart	Dph1	abnormal eye pigmentation
BioMart	Dph6	abnormal coat/hair pigmentation
BioMart	Dram2	abnormal coat/hair pigmentation
BioMart	Drd2	darkened coat color
BioMart	Drd2	hyperpigmentation
BioMart	Dsc1	hair follicle comedo
BioMart	Dsc1	hair follicle degeneration
BioMart	Dsg3	abnormal hair cycle
BioMart	Dsg3	abnormal hair follicle morphology
BioMart	Dsg3	abnormal hair growth
BioMart	Dsg3	abnormal hair shaft morphology
BioMart	Dsg3	focal hair loss
BioMart	Dsg3	premature hair loss
BioMart	Dsg3	sparse hair
BioMart	Dsg4	abnormal hair cortex morphology
BioMart	Dsg4	abnormal hair cycle anagen phase
BioMart	Dsg4	abnormal hair cycle catagen phase
BioMart	Dsg4	abnormal hair follicle inner root sheath morphology

BioMart	Dsg4	abnormal hair follicle morphology
BioMart	Dsg4	abnormal hair growth
BioMart	Dsg4	abnormal hair shaft morphology
BioMart	Dsg4	abnormal hair texture
BioMart	Dsg4	abnormal skin pigmentation
BioMart	Dsg4	absent guard hair
BioMart	Dsg4	brittle hair
BioMart	Dsg4	distorted hair follicle pattern
BioMart	Dsg4	enlarged hair follicles
BioMart	Dsg4	hair follicle degeneration
BioMart	Dsg4	hair follicle outer rooth sheath hyperplasia
BioMart	Dsg4	short hair
BioMart	Dsg4	sparse hair
BioMart	Dsp	abnormal hair medulla
BioMart	Dsp	abnormal hair medullary septa cells
BioMart	Dsp	abnormal hair shaft morphology
BioMart	Dsp	abnormal hair texture
BioMart	Dsp	ruffled hair
BioMart	Dsp	sparse hair
BioMart	Dst	abnormal skin pigmentation
BioMart	Dtnbp1	abnormal choroid melanin granule morphology
BioMart	Dtnbp1	abnormal coat/hair pigmentation
BioMart	Dtnbp1	abnormal eye pigmentation
BioMart	Dtnbp1	abnormal iris pigmentation
BioMart	Dtnbp1	abnormal retinal pigment epithelium morphology
BioMart	Dtnbp1	abnormal retinal pigmentation
BioMart	Dtnbp1	decreased eye pigmentation
BioMart	Dtnbp1	diluted coat color
BioMart	Duoxa2	abnormal hair growth
BioMart	Dusp7	abnormal coat/hair pigmentation
BioMart	E2f2	progressive hair loss
BioMart	E2f3	ruffled hair
BioMart	E2f5	ruffled hair
BioMart	Ece1	abnormal Harderian gland pigmentation
BioMart	Eda	abnormal coat/ hair morphology
BioMart	Eda	abnormal coat/hair pigmentation
BioMart	Eda	abnormal guard hair morphology
BioMart	Eda	abnormal hair follicle development
BioMart	Eda	abnormal hair follicle pheomelanosome pheomelanin content
BioMart	Eda	abnormal hair growth
BioMart	Eda	abnormal hair texture
BioMart	Eda	abnormal skin pigmentation
BioMart	Eda	absent guard hair
BioMart	Eda	absent hair follicle pheomelanosome pheomelanin
BioMart	Eda	absent zigzag hairs
BioMart	Eda	coarse hair
BioMart	Eda	focal hair loss
BioMart	Eda	hairless
BioMart	Eda	hairless tail
BioMart	Eda	increased curvature of hairs
BioMart	Eda	short hair
BioMart	Eda	sparse hair
BioMart	Eda	yellow coat color
BioMart	Edar	abnormal auchene hair morphology
BioMart	Edar	abnormal awl hair morphology
BioMart	Edar	abnormal coat/ hair morphology
BioMart	Edar	abnormal coat/hair pigmentation
BioMart	Edar	abnormal hair cycle
BioMart	Edar	abnormal hair follicle development
BioMart	Edar	abnormal hair follicle morphology
BioMart	Edar	abnormal hair growth

BioMart	Edar	abnormal hair texture
BioMart	Edar	absent auchene hairs
BioMart	Edar	absent duvet hair
BioMart	Edar	absent guard hair
BioMart	Edar	absent hair follicles
BioMart	Edar	absent zigzag hairs
BioMart	Edar	darkened coat color
BioMart	Edar	focal hair loss
BioMart	Edar	hairless tail
BioMart	Edar	sparse hair
BioMart	Edaradd	abnormal coat/ hair morphology
BioMart	Edaradd	abnormal coat/hair pigmentation
BioMart	Edaradd	abnormal hair follicle development
BioMart	Edaradd	abnormal hair growth
BioMart	Edaradd	abnormal hair texture
BioMart	Edaradd	abnormal skin pigmentation
BioMart	Edaradd	absent guard hair
BioMart	Edaradd	absent zigzag hairs
BioMart	Edaradd	decreased hair follicle number
BioMart	Edaradd	delayed hair appearance
BioMart	Edaradd	focal hair loss
BioMart	Edaradd	short hair
BioMart	Edaradd	sparse hair
BioMart	Edaradd	underdeveloped hair follicles
BioMart	Eddm3b	abnormal iris pigmentation
BioMart	Ednrb	abnormal choroid pigmentation
BioMart	Ednrb	abnormal coat/hair pigmentation
BioMart	Ednrb	abnormal foot pigmentation
BioMart	Ednrb	abnormal hair follicle melanocyte morphology
BioMart	Ednrb	abnormal pigmentation pattern
BioMart	Ednrb	abnormal tail pigmentation
BioMart	Ednrb	absent coat pigmentation
BioMart	Ednrb	variable depigmentation
BioMart	Eed	diluted coat color
BioMart	Efemp1	abnormal hair growth
BioMart	Efemp1	abnormal retinal pigment epithelium morphology
BioMart	Efemp1	coarse hair
BioMart	Efemp1	premature hair loss
BioMart	Efemp1	retinal pigment epithelium atrophy
BioMart	Efemp2	focal dorsal hair loss
BioMart	Egfr	abnormal hair cortex keratinization
BioMart	Egfr	abnormal hair cycle
BioMart	Egfr	abnormal hair follicle development
BioMart	Egfr	abnormal hair follicle inner root sheath morphology
BioMart	Egfr	abnormal hair follicle morphology
BioMart	Egfr	abnormal hair follicle orientation
BioMart	Egfr	abnormal hair growth
BioMart	Egfr	abnormal hair medulla
BioMart	Egfr	abnormal hair shaft morphology
BioMart	Egfr	abnormal hair texture
BioMart	Egfr	abnormal skin pigmentation
BioMart	Egfr	decreased hair follicle number
BioMart	Egfr	delayed hair appearance
BioMart	Egfr	distorted hair follicle pattern
BioMart	Egfr	increased curvature of guard hairs
BioMart	Egfr	increased curvature of hairs
BioMart	Egfr	increased foot pad pigmentation
BioMart	Egfr	short hair
BioMart	Egfr	sparse hair
BioMart	Egfr	waved hair
BioMart	Eif4enif1	abnormal skin coloration

BioMart	Elovl3	abnormal coat/ hair morphology
BioMart	Elovl3	abnormal coat/hair pigmentation
BioMart	Elovl3	abnormal hair follicle melanin granule morphology
BioMart	Elovl3	abnormal hair follicle morphology
BioMart	Elovl3	irregular coat pigmentation
BioMart	Elovl3	ruffled hair
BioMart	Elovl3	sparse hair
BioMart	Elovl3	yellow coat color
BioMart	Emc4	abnormal coat/hair pigmentation
BioMart	Eml1	delayed hair appearance
BioMart	En1	abnormal digit pigmentation
BioMart	En1	abnormal hair follicle dermal papilla morphology
BioMart	En1	abnormal hair follicle development
BioMart	Endog	abnormal coat/hair pigmentation
BioMart	Ercc2	abnormal coat/ hair morphology
BioMart	Ercc2	abnormal hair follicle morphology
BioMart	Ercc2	brittle hair
BioMart	Ercc2	enlarged hair follicles
BioMart	Ercc2	sparse hair
BioMart	Erlin2	abnormal hair growth
BioMart	Erp44	abnormal coat/hair pigmentation
BioMart	Esr2	abnormal hair cycle catagen phase
BioMart	Esr2	accelerated hair follicle regression
BioMart	Ets2	abnormal hair follicle orientation
BioMart	Ets2	increased curvature of auchene hairs
BioMart	Ets2	increased curvature of awl hairs
BioMart	Ets2	increased curvature of guard hairs
BioMart	Ets2	increased curvature of zigzag hairs
BioMart	Ets2	waved hair
BioMart	Fa2h	abnormal hair follicle morphology
BioMart	Fa2h	abnormal hair shaft morphology
BioMart	Fa2h	delayed hair appearance
BioMart	Fa2h	delayed hair regrowth
BioMart	Fa2h	focal hair loss
BioMart	Fa2h	sparse hair
BioMart	Fam107b	abnormal coat/ hair morphology
BioMart	Fam151b	abnormal retinal pigmentation
BioMart	Fam83g	waved hair
BioMart	Fancl	abnormal coat/hair pigmentation
BioMart	Fas	ruffled hair
BioMart	Fat1	retinal pigment epithelium atrophy
BioMart	Fbxo11	decreased hair follicle number
BioMart	Fcrla	abnormal coat/hair pigmentation
BioMart	Fgf10	abnormal hair follicle bulb morphology
BioMart	Fgf10	abnormal hair follicle morphology
BioMart	Fgf10	abnormal hair shaft morphology
BioMart	Fgf10	decreased hair follicle number
BioMart	Fgf10	increased hair follicle apoptosis
BioMart	Fgf20	abnormal auchene hair morphology
BioMart	Fgf20	abnormal awl hair morphology
BioMart	Fgf20	abnormal hair follicle development
BioMart	Fgf20	abnormal zigzag hair morphology
BioMart	Fgf20	absent guard hair
BioMart	Fgf5	abnormal auchene hair morphology
BioMart	Fgf5	abnormal coat/ hair morphology
BioMart	Fgf5	abnormal guard hair morphology
BioMart	Fgf5	abnormal hair cycle
BioMart	Fgf5	abnormal hair cycle anagen phase
BioMart	Fgf5	abnormal hair growth
BioMart	Fgf5	abnormal zigzag hair morphology
BioMart	Fgf5	increased guard hair length

BioMart	Fgf5	long hair
BioMart	Fgfr2	abnormal hair follicle development
BioMart	Fgfr2	abnormal hair follicle morphology
BioMart	Fgfr2	abnormal skin pigmentation
BioMart	Fgfr2	decreased hair follicle number
BioMart	Fig4	abnormal hair follicle morphology
BioMart	Fig4	decreased hair follicle number
BioMart	Fig4	diluted coat color
BioMart	Fig4	hypopigmentation
BioMart	Flg	abnormal hair cuticle
BioMart	Fmnl3	abnormal skin coloration
BioMart	Fndc3b	abnormal coat/hair pigmentation
BioMart	Foxe1	abnormal hair follicle orientation
BioMart	Foxe1	abnormal hair shaft morphology
BioMart	Foxe1	increased curvature of hairs
BioMart	Foxe1	sparse hair
BioMart	Foxe1	waved hair
BioMart	Foxj3	abnormal coat/ hair morphology
BioMart	Foxj3	abnormal skin coloration
BioMart	Foxn1	abnormal coat/ hair morphology
BioMart	Foxn1	abnormal hair cortex keratinization
BioMart	Foxn1	abnormal hair cortex morphology
BioMart	Foxn1	abnormal hair cuticle
BioMart	Foxn1	abnormal hair follicle bulb morphology
BioMart	Foxn1	abnormal hair follicle development
BioMart	Foxn1	abnormal hair follicle inner root sheath morphology
BioMart	Foxn1	abnormal hair follicle morphology
BioMart	Foxn1	abnormal hair growth
BioMart	Foxn1	abnormal hair shaft morphology
BioMart	Foxn1	abnormal skin pigmentation
BioMart	Foxn1	brittle hair
BioMart	Foxn1	hairless
BioMart	Foxn1	reduced hair shaft melanin granule number
BioMart	Foxn1	underdeveloped hair follicles
BioMart	Foxo3	abnormal retinal pigmentation
BioMart	Foxq1	abnormal hair cortex morphology
BioMart	Foxq1	abnormal hair growth
BioMart	Foxq1	abnormal hair medulla
BioMart	Foxq1	abnormal hair shaft morphology
BioMart	Foxq1	abnormal hair texture
BioMart	Fras1	abnormal hair growth
BioMart	Frem2	abnormal coat/hair pigmentation
BioMart	Frem2	irregular coat pigmentation
BioMart	Frem2	sparse hair
BioMart	Frmd4b	abnormal skin coloration
BioMart	Fryl	abnormal skin pigmentation
BioMart	Fuz	absent eye pigmentation
BioMart	Fzd4	diluted coat color
BioMart	Fzd6	abnormal hair follicle orientation
BioMart	Gab1	abnormal hair follicle development
BioMart	Gas1	abnormal retinal pigment epithelium morphology
BioMart	Gas1	decreased eye pigmentation
BioMart	Gata3	abnormal hair cuticle
BioMart	Gata3	abnormal hair cycle
BioMart	Gata3	abnormal hair follicle morphology
BioMart	Gata3	abnormal hair shaft melanin granule distribution
BioMart	Gata3	abnormal hair shaft morphology
BioMart	Gata3	abnormal hair texture
BioMart	Gata3	focal dorsal hair loss
BioMart	Gata3	waved hair
BioMart	Gdpd5	abnormal skin coloration

BioMart	Gfra2	accelerated hair follicle regression
BioMart	Ggps1	abnormal coat/ hair morphology
BioMart	Ggt1	abnormal coat/hair pigmentation
BioMart	Ggt1	diluted coat color
BioMart	Gli2	progressive hair loss
BioMart	Glycam1	abnormal retinal pigmentation
BioMart	Gna11	darkened coat color
BioMart	Gna11	hyperpigmentation
BioMart	Gna11	increased ear pigmentation
BioMart	Gna11	increased foot pad pigmentation
BioMart	Gna11	increased tail pigmentation
BioMart	Gnaq	darkened coat color
BioMart	Gnaq	hyperpigmentation
BioMart	Gnaq	increased ear pigmentation
BioMart	Gnaq	increased foot pad pigmentation
BioMart	Gnaq	increased tail pigmentation
BioMart	Gnpat	abnormal retinal pigment epithelium morphology
BioMart	Gorab	decreased hair follicle number
BioMart	Gorab	underdeveloped hair follicles
BioMart	Gpnmb	abnormal iris pigmentation
BioMart	Gpr143	abnormal ciliary body pigmentation
BioMart	Gpr143	abnormal iris pigment epithelium
BioMart	Gpr143	abnormal retinal pigment epithelium morphology
BioMart	Gpr143	abnormal retinal pigmentation
BioMart	Gpr173	abnormal skin coloration
BioMart	Gpr25	abnormal skin coloration
BioMart	Grhl1	abnormal hair follicle morphology
BioMart	Grhl1	delayed hair appearance
BioMart	Grhl1	focal hair loss
BioMart	Grhl1	sparse hair
BioMart	Grm1	hyperpigmentation
BioMart	Gsdma3	coarse hair
BioMart	Gsdma3	decreased hair follicle number
BioMart	Gsdma3	long hair
BioMart	Gsdma3	progressive hair loss
BioMart	Gsdma3	sparse hair
BioMart	Gsta4	abnormal coat/hair pigmentation
BioMart	Gt(ROSA)26Sor	abnormal retinal pigment epithelium morphology
BioMart	Hbs1l	abnormal retinal pigmentation
BioMart	Hectd1	abnormal coat/hair pigmentation
BioMart	Hells	abnormal coat/hair pigmentation
BioMart	Heph	abnormal coat/ hair morphology
BioMart	Herc3	abnormal hair follicle bulge morphology
BioMart	Hmga2	long hair
BioMart	Hoxb8	focal hair loss
BioMart	Hoxc13	abnormal hair growth
BioMart	Hoxc13	brittle hair
BioMart	Hoxc13	hairless tail
BioMart	Hps1	abnormal choroid pigmentation
BioMart	Hps1	abnormal ciliary body pigmentation
BioMart	Hps1	abnormal iris pigmentation
BioMart	Hps1	decreased ear pigmentation
BioMart	Hps1	decreased eye pigmentation
BioMart	Hps1	decreased tail pigmentation
BioMart	Hps1	diluted coat color
BioMart	Hps3	abnormal choroid pigmentation
BioMart	Hps3	abnormal eye pigmentation
BioMart	Hps3	abnormal iris pigmentation
BioMart	Hps3	abnormal retinal pigmentation
BioMart	Hps3	absent eye pigmentation
BioMart	Hps3	diluted coat color

BioMart	Hps4	abnormal choroid pigmentation
BioMart	Hps4	abnormal ear pigmentation
BioMart	Hps4	abnormal eye pigmentation
BioMart	Hps4	abnormal retinal pigment epithelium morphology
BioMart	Hps4	abnormal skin pigmentation
BioMart	Hps4	diluted coat color
BioMart	Hps5	abnormal choroid pigmentation
BioMart	Hps5	abnormal coat/hair pigmentation
BioMart	Hps5	abnormal eye pigmentation
BioMart	Hps5	abnormal foot pigmentation
BioMart	Hps5	abnormal retinal pigment epithelium morphology
BioMart	Hps5	decreased ear pigmentation
BioMart	Hps5	decreased eye pigmentation
BioMart	Hps5	decreased foot pigmentation
BioMart	Hps5	decreased tail pigmentation
BioMart	Hps5	diluted coat color
BioMart	Hps6	abnormal coat/hair pigmentation
BioMart	Hps6	abnormal eye pigmentation
BioMart	Hps6	decreased ear pigmentation
BioMart	Hps6	decreased eye pigmentation
BioMart	Hps6	diluted coat color
BioMart	Hr	abnormal hair cycle
BioMart	Hr	abnormal hair follicle dermal papilla morphology
BioMart	Hr	abnormal hair follicle infundibulum morphology
BioMart	Hr	abnormal hair follicle inner root sheath morphology
BioMart	Hr	abnormal hair follicle morphology
BioMart	Hr	abnormal hair growth
BioMart	Hr	abnormal hair shaft morphology
BioMart	Hr	absent hair follicle dermal papilla
BioMart	Hr	dilated hair follicle infundibulum
BioMart	Hr	dilated hair follicles
BioMart	Hr	distended hair follicles
BioMart	Hr	hair follicle degeneration
BioMart	Hr	hairless
BioMart	Hr	progressive hair loss
BioMart	Hr	sparse hair
BioMart	Hs2st1	abnormal retinal pigment epithelium morphology
BioMart	Hsd17b1	abnormal retinal pigmentation
BioMart	Htra2	sparse hair
BioMart	Ide	abnormal hair texture
BioMart	Ids	abnormal coat/ hair morphology
BioMart	Idua	sparse hair
BioMart	Ift27	abnormal hair follicle development
BioMart	Ift27	absent hair follicles
BioMart	Ift27	small hair follicles
BioMart	Ift27	underdeveloped hair follicles
BioMart	Igf1	abnormal hair follicle development
BioMart	Igf1r	abnormal hair follicle morphology
BioMart	Igf1r	decreased hair follicle number
BioMart	Igf1r	small hair follicles
BioMart	Igfbp3	abnormal coat/hair pigmentation
BioMart	Il2rb	abnormal hair texture
BioMart	Il33	abnormal coat/ hair morphology
BioMart	Inhba	retarded hair growth
BioMart	Inhba	short hair
BioMart	Inhba	sparse hair
BioMart	Irf2	premature hair loss
BioMart	Irf6	decreased hair follicle number
BioMart	Itgb2	abnormal hair follicle dermal papilla morphology
BioMart	Itgb6	abnormal hair follicle morphology
BioMart	Itgb6	decreased hair follicle number

BioMart	Itpa	underdeveloped hair follicles
BioMart	Itpkb	sparse hair
BioMart	Itpr3	abnormal coat/ hair morphology
BioMart	Itpr3	abnormal hair cycle
BioMart	Itpr3	abnormal hair growth
BioMart	Itpr3	sparse hair
BioMart	Itsn2	abnormal coat/ hair morphology
BioMart	Jam2	abnormal retinal pigmentation
BioMart	Kansl1	abnormal coat/hair pigmentation
BioMart	Kat14	abnormal eye pigmentation
BioMart	Kcnh3	abnormal retinal pigmentation
BioMart	Kdm7a	abnormal hair follicle bulge morphology
BioMart	Kdm7a	abnormal hair follicle morphology
BioMart	Kdm8	abnormal iris pigmentation
BioMart	Kif2c	abnormal skin coloration
BioMart	Kit	abnormal coat/hair pigmentation
BioMart	Kit	abnormal ear pigmentation
BioMart	Kit	abnormal eye pigmentation
BioMart	Kit	abnormal skin pigmentation
BioMart	Kit	abnormal ventral coat pigmentation
BioMart	Kit	absent coat pigmentation
BioMart	Kit	absent skin pigmentation
BioMart	Kit	diluted coat color
BioMart	Kit	irregular coat pigmentation
BioMart	Kit	variable depigmentation
BioMart	Kitl	abnormal coat/hair pigmentation
BioMart	Kitl	abnormal skin pigmentation
BioMart	Kitl	absent coat pigmentation
BioMart	Kitl	absent skin pigmentation
BioMart	Kitl	decreased foot pigmentation
BioMart	Kitl	decreased tail pigmentation
BioMart	Kitl	diluted coat color
BioMart	Kitl	hyperpigmentation
BioMart	Kitl	increased ear pigmentation
BioMart	Kitl	irregular coat pigmentation
BioMart	Kl	decreased hair follicle number
BioMart	Kl	sparse hair
BioMart	Kntc1	abnormal coat/hair pigmentation
BioMart	Krt10	ruffled hair
BioMart	Krt10	waved hair
BioMart	Krt17	abnormal hair cycle
BioMart	Krt17	abnormal hair follicle matrix region morphology
BioMart	Krt17	abnormal hair follicle melanin granule morphology
BioMart	Krt17	abnormal hair follicle morphology
BioMart	Krt17	abnormal hair medulla
BioMart	Krt17	abnormal hair shaft morphology
BioMart	Krt17	brittle hair
BioMart	Krt17	hair follicle degeneration
BioMart	Krt17	increased hair follicle apoptosis
BioMart	Krt2	abnormal skin pigmentation
BioMart	Krt2	increased ear pigmentation
BioMart	Krt2	increased foot pad pigmentation
BioMart	Krt2	increased tail pigmentation
BioMart	Krt25	abnormal hair follicle inner root sheath morphology
BioMart	Krt25	abnormal hair follicle morphology
BioMart	Krt25	abnormal hair shaft morphology
BioMart	Krt25	abnormal hair texture
BioMart	Krt25	increased curvature of guard hairs
BioMart	Krt25	waved hair
BioMart	Krt27	abnormal guard hair morphology
BioMart	Krt27	abnormal hair growth

BioMart	Krt27	abnormal hair shaft morphology
BioMart	Krt27	abnormal zigzag hair morphology
BioMart	Krt27	waved hair
BioMart	Krt4	abnormal skin pigmentation
BioMart	Krt71	abnormal hair cortex morphology
BioMart	Krt71	abnormal hair follicle inner root sheath morphology
BioMart	Krt71	abnormal hair follicle morphology
BioMart	Krt71	abnormal hair shaft morphology
BioMart	Krt71	focal dorsal hair loss
BioMart	Krt71	focal hair loss
BioMart	Krt71	waved hair
BioMart	Krt71	whorled hair
BioMart	Krt75	abnormal hair cuticle
BioMart	Krt75	abnormal hair follicle morphology
BioMart	Krt75	abnormal hair medulla
BioMart	Krt75	abnormal hair shaft morphology
BioMart	Krt76	abnormal hair cycle
BioMart	Krt76	increased foot pad pigmentation
BioMart	Krt76	increased tail pigmentation
BioMart	Krt9	hyperpigmentation
BioMart	Krtap17-1	abnormal coat/ hair morphology
BioMart	Ksr1	abnormal hair cycle
BioMart	Ksr1	abnormal hair follicle development
BioMart	Ksr1	abnormal hair follicle inner root sheath morphology
BioMart	Ksr1	abnormal hair follicle morphology
BioMart	Ksr1	abnormal hair follicle orientation
BioMart	Ksr1	abnormal hair shaft morphology
BioMart	Ksr1	decreased hair follicle number
BioMart	Ksr1	sparse hair
BioMart	Kxd1	abnormal choroid melanin granule morphology
BioMart	Kxd1	abnormal retinal melanin granule morphology
BioMart	L1cam	abnormal coat/hair pigmentation
BioMart	Lama4	abnormal coat/hair pigmentation
BioMart	Lamtor5	abnormal skin coloration
BioMart	Lbr	abnormal coat/ hair morphology
BioMart	Lbr	abnormal hair growth
BioMart	Lbr	delayed hair appearance
BioMart	Lbr	sparse hair
BioMart	Lca5	abnormal retinal pigmentation
BioMart	Ldlr	abnormal retinal pigment epithelium morphology
BioMart	Lef1	abnormal hair follicle development
BioMart	Lef1	abnormal hair follicle morphology
BioMart	Lef1	absent hair follicle melanin granules
BioMart	Lef1	decreased hair follicle number
BioMart	Lef1	underdeveloped hair follicles
BioMart	Lgr4	decreased hair follicle number
BioMart	Lhx2	decreased hair follicle number
BioMart	Lhx2	underdeveloped hair follicles
BioMart	Liph	abnormal coat/ hair morphology
BioMart	Liph	abnormal hair cuticle
BioMart	Liph	abnormal hair follicle inner root sheath morphology
BioMart	Liph	abnormal hair medulla
BioMart	Liph	abnormal hair shaft melanin granule morphology
BioMart	Liph	waved hair
BioMart	Lipi	retarded hair growth
BioMart	Lmna	abnormal hair cycle anagen phase
BioMart	Lmna	abnormal hair follicle morphology
BioMart	Lmo7	abnormal retinal pigmentation
BioMart	Lncpint	abnormal hair follicle development
BioMart	Lonrf3	abnormal hair growth
BioMart	Lpin1	abnormal hair growth

BioMart	Lpin1	retarded hair growth
BioMart	Lpin1	ruffled hair
BioMart	Lrig1	abnormal hair shedding
BioMart	Lrig1	distorted hair follicle pattern
BioMart	Lrp4	abnormal hair follicle development
BioMart	Lrp5	abnormal retinal pigment epithelium morphology
BioMart	Lrp6	sparse hair
BioMart	Lrrc8a	waved hair
BioMart	Lrrfip1	abnormal skin coloration
BioMart	Lyst	abnormal choroid pigmentation
BioMart	Lyst	abnormal ciliary body pigmentation
BioMart	Lyst	abnormal coat/hair pigmentation
BioMart	Lyst	abnormal eye pigmentation
BioMart	Lyst	abnormal foot pigmentation
BioMart	Lyst	abnormal hair follicle melanocyte morphology
BioMart	Lyst	abnormal hair shaft melanin granule shape
BioMart	Lyst	abnormal iris pigment epithelium
BioMart	Lyst	abnormal iris pigmentation
BioMart	Lyst	abnormal retinal pigment epithelium morphology
BioMart	Lyst	abnormal retinal pigmentation
BioMart	Lyst	abnormal skin pigmentation
BioMart	Lyst	absent hair follicle melanin granules
BioMart	Lyst	decreased ear pigmentation
BioMart	Lyst	decreased eye pigmentation
BioMart	Lyst	decreased tail pigmentation
BioMart	Lyst	delayed hair regrowth
BioMart	Lyst	diluted coat color
BioMart	Lyst	enlarged hair follicle melanin granules
BioMart	Lyst	hypopigmentation
BioMart	Lyst	premature hair loss
BioMart	Mab21l1	abnormal retinal pigment epithelium morphology
BioMart	Mab21l2	abnormal retinal pigment epithelium morphology
BioMart	Maged1	abnormal hair cycle catagen phase
BioMart	Map1b	delayed hair appearance
BioMart	Mbtps1	abnormal coat/hair pigmentation
BioMart	Mbtps1	hypopigmentation
BioMart	Mc1r	abnormal coat/hair pigmentation
BioMart	Mc1r	abnormal hair follicle melanogenesis
BioMart	Mc1r	abnormal hair follicle pheomelanosome pheomelanin content
BioMart	Mc1r	abnormal melanogenesis
BioMart	Mc1r	abnormal skin pigmentation
BioMart	Mc1r	darkened coat color
BioMart	Mc1r	decreased ear pigmentation
BioMart	Mc1r	decreased tail pigmentation
BioMart	Mc1r	hyperpigmentation
BioMart	Mc1r	yellow coat color
BioMart	Mc5r	abnormal coat/ hair morphology
BioMart	Mcm2	abnormal coat/hair pigmentation
BioMart	Mcm2	sparse hair
BioMart	Mcoln3	diluted coat color
BioMart	Mcoln3	variegated coat color
BioMart	Mcph1	abnormal eye pigmentation
BioMart	Mdm1	abnormal retinal pigment epithelium morphology
BioMart	Mdm1	abnormal retinal pigmentation
BioMart	Mdm1	retinal pigment epithelium hyperplasia
BioMart	Mecp2	focal hair loss
BioMart	Mecp2	ruffled hair
BioMart	Med1	abnormal retinal pigmentation
BioMart	Memo1	abnormal skin coloration
BioMart	Mertk	abnormal retinal pigment epithelium morphology
BioMart	Mertk	abnormal retinal pigmentation

BioMart	Mertk	retinal pigment epithelium atrophy
BioMart	Mettl16	abnormal coat/hair pigmentation
BioMart	Mettl7b	abnormal coat/hair pigmentation
BioMart	Mfrp	abnormal retinal pigment epithelium morphology
BioMart	Mfsd12	absent coat pigmentation
BioMart	Mfsd12	diluted coat color
BioMart	Mfsd12	grizzled coat color
BioMart	Mfsd2a	abnormal retinal pigment epithelium morphology
BioMart	Mfsd8	abnormal coat/hair pigmentation
BioMart	Mgrn1	abnormal coat/hair pigmentation
BioMart	Mgrn1	darkened coat color
BioMart	Mir205	abnormal coat/ hair morphology
BioMart	Mir205	abnormal hair follicle development
BioMart	Mir205	abnormal hair follicle morphology
BioMart	Mitf	abnormal choroid pigmentation
BioMart	Mitf	abnormal coat/hair pigmentation
BioMart	Mitf	abnormal eye pigmentation
BioMart	Mitf	abnormal foot pigmentation
BioMart	Mitf	abnormal hair follicle melanocyte morphology
BioMart	Mitf	abnormal hair follicle morphology
BioMart	Mitf	abnormal Harderian gland pigmentation
BioMart	Mitf	abnormal iris pigmentation
BioMart	Mitf	abnormal retinal pigment epithelium morphology
BioMart	Mitf	abnormal retinal pigmentation
BioMart	Mitf	abnormal skin pigmentation
BioMart	Mitf	absent coat pigmentation
BioMart	Mitf	absent eye pigmentation
BioMart	Mitf	decreased eye pigmentation
BioMart	Mitf	decreased tail pigmentation
BioMart	Mitf	diluted coat color
BioMart	Mitf	hypopigmentation
BioMart	Mitf	irregular coat pigmentation
BioMart	Mitf	variable depigmentation
BioMart	Mitf	variegated coat color
BioMart	Mkln1	diluted coat color
BioMart	Mlana	abnormal coat/ hair morphology
BioMart	Mlana	abnormal hair follicle melanocyte morphology
BioMart	Mlana	diluted coat color
BioMart	Mlph	diluted coat color
BioMart	Mmgt2	abnormal coat/hair pigmentation
BioMart	Mmp11	abnormal skin coloration
BioMart	Mmp14	focal hair loss
BioMart	Mmp15	abnormal skin coloration
BioMart	Mocs2	abnormal hair growth
BioMart	Mogs	abnormal skin coloration
BioMart	Mpv17	abnormal coat/hair pigmentation
BioMart	Mpv17	decreased hair follicle number
BioMart	Mpv17l2	abnormal coat/hair pigmentation
BioMart	Mpzl2	abnormal coat/hair pigmentation
BioMart	Mpzl3	abnormal coat/ hair morphology
BioMart	Mpzl3	abnormal coat/hair pigmentation
BioMart	Mpzl3	abnormal hair follicle melanocyte morphology
BioMart	Mpzl3	abnormal hair follicle morphology
BioMart	Mpzl3	abnormal hair follicle regression
BioMart	Mpzl3	abnormal hair shaft morphology
BioMart	Mpzl3	abnormal hair texture
BioMart	Mpzl3	brittle hair
BioMart	Mpzl3	decreased hair follicle number
BioMart	Mpzl3	dilated hair follicles
BioMart	Mpzl3	hair follicle degeneration
BioMart	Mpzl3	underdeveloped hair follicles

BioMart	Msx2	abnormal hair shedding
BioMart	Msx2	abnormal retinal pigment epithelium morphology
BioMart	Msx2	delayed hair regrowth
BioMart	Msx2	premature hair loss
BioMart	Mta2	decreased hair follicle number
BioMart	Mthfr	sparse hair
BioMart	mt-Rnr2	delayed hair appearance
BioMart	Mturn	abnormal coat/ hair morphology
BioMart	Myh10	abnormal skin coloration
BioMart	Myo10	abnormal coat/hair pigmentation
BioMart	Myo10	abnormal tail pigmentation
BioMart	Myo10	decreased tail pigmentation
BioMart	Myo5a	abnormal coat/hair pigmentation
BioMart	Myo5a	abnormal ear pigmentation
BioMart	Myo5a	abnormal epidermal pigmentation
BioMart	Myo5a	abnormal foot pigmentation
BioMart	Myo5a	abnormal hair follicle melanin granule morphology
BioMart	Myo5a	abnormal hair follicle melanocyte morphology
BioMart	Myo5a	abnormal tail pigmentation
BioMart	Myo5a	diluted coat color
BioMart	Myo5a	hypopigmentation
BioMart	Myo7a	abnormal retinal pigment epithelium morphology
BioMart	Mysm1	abnormal coat/ hair morphology
BioMart	Mysm1	abnormal coat/hair pigmentation
BioMart	Mysm1	abnormal hair cycle
BioMart	Mysm1	abnormal hair follicle morphology
BioMart	Mysm1	decreased tail pigmentation
BioMart	Mysm1	distorted hair follicle pattern
BioMart	Nadk2	abnormal coat/hair pigmentation
BioMart	Naglu	abnormal retinal pigment epithelium morphology
BioMart	Nags	sparse hair
BioMart	Ncoa6	abnormal eye pigmentation
BioMart	Ndp	abnormal retinal pigmentation
BioMart	Ndufs4	focal hair loss
BioMart	Ndufs4	premature hair loss
BioMart	Ndufs4	sparse hair
BioMart	Nek1	sparse hair
BioMart	Nfkbiz	abnormal hair growth
BioMart	Ngf	abnormal hair growth
BioMart	Ngfr	absent hair follicles
BioMart	Nmnat1	retinal pigment epithelium atrophy
BioMart	Nog	abnormal hair follicle development
BioMart	Nphp4	abnormal retinal pigmentation
BioMart	Nrl	abnormal retinal pigment epithelium morphology
BioMart	Nsun2	abnormal hair cycle
BioMart	Nsun2	abnormal hair cycle anagen phase
BioMart	Nsun2	abnormal hair shedding
BioMart	Ntf5	abnormal hair cycle
BioMart	Ntmt1	premature hair loss
BioMart	Oat	abnormal coat/hair pigmentation
BioMart	Oat	abnormal hair follicle morphology
BioMart	Oat	abnormal retinal pigment epithelium morphology
BioMart	Oat	retarded hair growth
BioMart	Oat	ruffled hair
BioMart	Obp2a	abnormal coat/hair pigmentation
BioMart	Oca2	abnormal coat/hair pigmentation
BioMart	Oca2	abnormal eye pigmentation
BioMart	Oca2	absent eye pigmentation
BioMart	Oca2	darkened coat color
BioMart	Oca2	decreased ear pigmentation
BioMart	Oca2	decreased eye pigmentation

BioMart	Oca2	diluted coat color
BioMart	Oca2	mosaic coat color
BioMart	Oca2	variegated coat color
BioMart	Oca2	yellow coat color
BioMart	Ostm1	abnormal coat/hair pigmentation
BioMart	Otc	abnormal coat/hair pigmentation
BioMart	Otc	sparse hair
BioMart	Otx2	abnormal retinal pigment epithelium morphology
BioMart	Ovol1	abnormal auchene hair morphology
BioMart	Ovol1	abnormal awl hair morphology
BioMart	Ovol1	abnormal hair shaft morphology
BioMart	Ovol1	ruffled hair
BioMart	Ovol1	splitting of guard hairs
BioMart	Pacsin3	abnormal hair growth
BioMart	Padi3	abnormal coat/ hair morphology
BioMart	Padi3	abnormal hair shaft morphology
BioMart	Padi3	coarse hair
BioMart	Pah	diluted coat color
BioMart	Pah	hypopigmentation
BioMart	Pax2	abnormal retinal pigmentation
BioMart	Pax3	absent coat pigmentation
BioMart	Pax3	absent skin pigmentation
BioMart	Pax6	decreased eye pigmentation
BioMart	Pcbd1	hypopigmentation
BioMart	Pde3b	abnormal coat/hair pigmentation
BioMart	Pdgfb	abnormal retinal pigment epithelium morphology
BioMart	Pdgfc	abnormal retinal pigmentation
BioMart	Pdpk1	abnormal eye pigmentation
BioMart	Pds5a	decreased hair follicle number
BioMart	Pdx1	sparse hair
BioMart	Pepd	abnormal agouti pigmentation
BioMart	Pepd	darkened coat color
BioMart	Pepd	irregular coat pigmentation
BioMart	Per2	abnormal coat/hair pigmentation
BioMart	Pex3	abnormal hair follicle bulge morphology
BioMart	Pfkfb2	abnormal retinal pigmentation
BioMart	Phactr4	abnormal retinal pigment epithelium morphology
BioMart	Pias2	abnormal retinal pigmentation
BioMart	Pitx3	abnormal iris pigmentation
BioMart	Pknox1	abnormal retinal pigment epithelium morphology
BioMart	Pkp3	abnormal auchene hair morphology
BioMart	Pkp3	abnormal awl hair morphology
BioMart	Pkp3	abnormal hair cuticle
BioMart	Pkp3	abnormal hair follicle inner root sheath morphology
BioMart	Pkp3	abnormal hair follicle orientation
BioMart	Pkp3	abnormal hair medulla
BioMart	Pkp3	abnormal hair medulla air spaces
BioMart	Pkp3	abnormal zigzag hair morphology
BioMart	Pkp3	brittle hair
BioMart	Pkp3	retarded hair growth
BioMart	Pkp3	ruffled hair
BioMart	Pkp3	sparse hair
BioMart	Pkp3	underdeveloped hair follicles
BioMart	Plcd1	abnormal hair follicle morphology
BioMart	Pld4	sparse hair
BioMart	Plxnb2	abnormal coat/hair pigmentation
BioMart	Pmel	abnormal choroid melanin granule morphology
BioMart	Pmel	abnormal retinal melanin granule morphology
BioMart	Pmel	abnormal tail hair pigmentation
BioMart	Pmel	diluted coat color
BioMart	Pmel	irregular coat pigmentation

BioMart	Pmel	reduced hair shaft melanin granule number
BioMart	Pnn	decreased hair follicle number
BioMart	Polg	abnormal coat/hair pigmentation
BioMart	Polg	premature hair loss
BioMart	Polh	abnormal ear pigmentation
BioMart	Polr3f	abnormal hair growth
BioMart	Pomc	diluted coat color
BioMart	Pomc	yellow coat color
BioMart	Pot1b	hyperpigmentation
BioMart	Ppard	abnormal hair follicle development
BioMart	Ppard	underdeveloped hair follicles
BioMart	Ppp1r13l	sparse hair
BioMart	Ppp1r13l	thin hair shaft
BioMart	Ppp1r13l	waved hair
BioMart	Ppp1r32	abnormal coat/hair pigmentation
BioMart	Ppp5c	abnormal coat/hair pigmentation
BioMart	Ppt2	abnormal retinal pigment epithelium morphology
BioMart	Prf1	ruffled hair
BioMart	Prickle1	abnormal hair follicle morphology
BioMart	Prickle1	abnormal hair follicle orientation
BioMart	Primpol	abnormal retinal pigmentation
BioMart	Prkcq	abnormal retinal pigmentation
BioMart	Prkcq	decreased eye pigmentation
BioMart	Prkcq	retinal pigment epithelium atrophy
BioMart	Prkdc	hyperpigmentation
BioMart	Prlr	abnormal coat/ hair morphology
BioMart	Prlr	abnormal hair cycle
BioMart	Prlr	coarse hair
BioMart	Prodh	abnormal coat/hair pigmentation
BioMart	Prokr1	abnormal retinal pigmentation
BioMart	Prom1	abnormal eye pigmentation
BioMart	Prom1	abnormal retinal pigment epithelium morphology
BioMart	Prom1	abnormal retinal pigmentation
BioMart	Prom2	abnormal retinal pigmentation
BioMart	Prpf3	abnormal retinal pigment epithelium morphology
BioMart	Prpf8	abnormal retinal pigment epithelium morphology
BioMart	Prph2	abnormal retinal pigment epithelium morphology
BioMart	Prss8	abnormal hair growth
BioMart	Prss8	abnormal hair medulla
BioMart	Prss8	abnormal hair shaft morphology
BioMart	Prss8	short hair
BioMart	Prss8	sparse hair
BioMart	Ptpn6	abnormal skin pigmentation
BioMart	Ptpn6	absent skin pigmentation
BioMart	Ptpn6	focal hair loss
BioMart	Pts	diluted coat color
BioMart	Pygo2	abnormal hair follicle development
BioMart	Rab15	abnormal retinal pigmentation
BioMart	Rab27a	abnormal coat/hair pigmentation
BioMart	Rab27a	abnormal Harderian gland pigmentation
BioMart	Rab27a	abnormal skin pigmentation
BioMart	Rab27a	diluted coat color
BioMart	Rab27a	hypopigmentation
BioMart	Rab38	abnormal coat/hair pigmentation
BioMart	Rab38	abnormal eye pigmentation
BioMart	Rab38	abnormal hair follicle melanogenesis
BioMart	Rab38	abnormal iris pigmentation
BioMart	Rab38	abnormal skin pigmentation
BioMart	Rab38	decreased eye pigmentation
BioMart	Rab38	diluted coat color
BioMart	Rabggta	diluted coat color

BioMart	Rad18	abnormal coat/ hair morphology
BioMart	Rad18	abnormal hair texture
BioMart	Raf1	ruffled hair
BioMart	Raf1	small hair follicles
BioMart	Raf1	underdeveloped hair follicles
BioMart	Rag1	abnormal coat/hair pigmentation
BioMart	Rag1	abnormal skin pigmentation
BioMart	Rasal2	abnormal hair growth
BioMart	Rasal2	sparse hair
BioMart	Rasgrp4	abnormal retinal pigmentation
BioMart	Rassf8	abnormal coat/ hair morphology
BioMart	Rassf9	abnormal hair cycle
BioMart	Rassf9	abnormal hair cycle anagen phase
BioMart	Rassf9	abnormal hair shaft morphology
BioMart	Rbms1	abnormal coat/ hair morphology
BioMart	Rbp1	abnormal retinal pigment epithelium morphology
BioMart	Rcc2	abnormal coat/hair pigmentation
BioMart	Recql4	abnormal coat/ hair morphology
BioMart	Recql4	abnormal tail pigmentation
BioMart	Recql4	absent coat pigmentation
BioMart	Rela	distorted hair follicle pattern
BioMart	Rela	small hair follicles
BioMart	Relb	ruffled hair
BioMart	Rgn	abnormal hair cycle
BioMart	Rhbdf2	abnormal hair follicle inner root sheath morphology
BioMart	Rhbdf2	abnormal hair shaft melanin granule shape
BioMart	Rhbdf2	abnormal hair shaft morphology
BioMart	Rho	abnormal retinal pigmentation
BioMart	Rlbp1	abnormal coat/hair pigmentation
BioMart	Rln3	abnormal coat/hair pigmentation
BioMart	Rora	absent duvet hair
BioMart	Rora	retarded hair growth
BioMart	Rora	sparse hair
BioMart	Rpe65	abnormal retinal pigment epithelium morphology
BioMart	Rpe65	abnormal retinal pigmentation
BioMart	Rpgr	abnormal retinal pigmentation
BioMart	Rps19bp1	abnormal skin coloration
BioMart	Rs1	abnormal retinal pigment epithelium morphology
BioMart	Rtbdn	abnormal retinal pigmentation
BioMart	Runx3	abnormal auchene hair morphology
BioMart	Runx3	abnormal zigzag hair morphology
BioMart	Runx3	sparse hair
BioMart	Rxra	diluted coat color
BioMart	Ryr1	underdeveloped hair follicles
BioMart	S1pr3	abnormal skin coloration
BioMart	Sav1	underdeveloped hair follicles
BioMart	Scd1	abnormal hair cycle
BioMart	Scd1	abnormal hair follicle bulb morphology
BioMart	Scd1	abnormal hair follicle development
BioMart	Scd1	abnormal hair follicle inner root sheath morphology
BioMart	Scd1	abnormal hair follicle morphology
BioMart	Scd1	abnormal hair follicle outer root sheath morphology
BioMart	Scd1	abnormal hair growth
BioMart	Scd1	abnormal hair shaft morphology
BioMart	Scd1	decreased hair follicle number
BioMart	Scd1	distorted hair follicle pattern
BioMart	Scd1	enlarged hair follicles
BioMart	Scd1	progressive hair loss
BioMart	Scd1	short hair
BioMart	Scd1	sparse hair
BioMart	Scd2	sparse hair

BioMart	Scg5	abnormal hair growth
BioMart	Scg5	sparse hair
BioMart	Sdc2	abnormal coat/hair pigmentation
BioMart	Secisbp2	abnormal retinal pigmentation
BioMart	Sema3c	abnormal extracutaneous pigmentation
BioMart	Sema3c	hypopigmentation
BioMart	Sema4a	abnormal retinal pigment epithelium morphology
BioMart	Sema4a	decreased eye pigmentation
BioMart	Senp7	abnormal coat/hair pigmentation
BioMart	Serpinc1	abnormal retinal pigment epithelium morphology
BioMart	Serpinf1	abnormal retinal pigmentation
BioMart	Setd4	abnormal retinal pigmentation
BioMart	Setd5	abnormal coat/hair pigmentation
BioMart	Sfn	decreased hair follicle number
BioMart	Sfn	distorted hair follicle pattern
BioMart	Sgk3	abnormal coat/ hair morphology
BioMart	Sgk3	abnormal hair cuticle
BioMart	Sgk3	abnormal hair cycle
BioMart	Sgk3	abnormal hair cycle anagen phase
BioMart	Sgk3	abnormal hair follicle bulb morphology
BioMart	Sgk3	abnormal hair follicle dermal papilla morphology
BioMart	Sgk3	abnormal hair follicle development
BioMart	Sgk3	abnormal hair follicle inner root sheath morphology
BioMart	Sgk3	abnormal hair follicle morphology
BioMart	Sgk3	abnormal hair follicle orientation
BioMart	Sgk3	abnormal hair growth
BioMart	Sgk3	abnormal hair medulla
BioMart	Sgk3	abnormal hair shaft morphology
BioMart	Sgk3	abnormal hair texture
BioMart	Sgk3	accelerated hair follicle regression
BioMart	Sgk3	distorted hair follicle pattern
BioMart	Sgk3	short hair
BioMart	Sgk3	sparse hair
BioMart	Sgk3	thick hair follicle outer rooth sheath
BioMart	Sgk3	thin hair follicle inner root sheath
BioMart	Sgk3	thin hair shaft
BioMart	Sgk3	waved hair
BioMart	Sgsh	abnormal hair texture
BioMart	Sharpin	abnormal hair follicle morphology
BioMart	Sharpin	abnormal hair shaft morphology
BioMart	Sharpin	premature hair loss
BioMart	Shh	abnormal hair follicle development
BioMart	Shh	abnormal hair follicle morphology
BioMart	Shh	abnormal hair follicle orientation
BioMart	Shh	abnormal hair shaft morphology
BioMart	Shh	absent hair follicles
BioMart	Sik2	darkened coat color
BioMart	Slc24a5	abnormal ciliary body pigmentation
BioMart	Slc24a5	abnormal coat/hair pigmentation
BioMart	Slc24a5	abnormal dermal pigmentation
BioMart	Slc24a5	abnormal ear pigmentation
BioMart	Slc24a5	abnormal epidermal pigmentation
BioMart	Slc24a5	abnormal hair shaft melanin granule morphology
BioMart	Slc24a5	abnormal hair shaft melanin granule shape
BioMart	Slc24a5	abnormal iris pigmentation
BioMart	Slc24a5	abnormal retinal pigment epithelium morphology
BioMart	Slc24a5	abnormal retinal pigmentation
BioMart	Slc24a5	hypopigmentation
BioMart	Slc27a4	decreased hair follicle number
BioMart	Slc27a4	sparse hair
BioMart	Slc30a4	abnormal coat/hair pigmentation

BioMart	Slc30a4	abnormal hair shaft morphology
BioMart	Slc30a4	hair follicle degeneration
BioMart	Slc35c1	ruffled hair
BioMart	Slc35c2	abnormal coat/ hair morphology
BioMart	Slc39a2	ruffled hair
BioMart	Slc45a2	abnormal coat/hair pigmentation
BioMart	Slc45a2	abnormal eye pigmentation
BioMart	Slc45a2	abnormal skin pigmentation
BioMart	Slc45a2	absent eye pigmentation
BioMart	Slc45a2	decreased eye pigmentation
BioMart	Slc45a2	decreased skin pigmentation
BioMart	Slc45a2	diluted coat color
BioMart	Slc45a2	hypopigmentation
BioMart	Slc45a2	irregular coat pigmentation
BioMart	Slc5a7	abnormal hair growth
BioMart	Slc6a19	abnormal coat/hair pigmentation
BioMart	Slc7a11	diluted coat color
BioMart	Slc9a8	abnormal retinal pigmentation
BioMart	Smad3	ruffled hair
BioMart	Smc3	abnormal coat/hair pigmentation
BioMart	Smoc1	abnormal coat/hair pigmentation
BioMart	Smoc1	abnormal retinal pigment epithelium morphology
BioMart	Snai2	abnormal coat/hair pigmentation
BioMart	Snai2	abnormal skin pigmentation
BioMart	Snai2	decreased forehead pigmentation
BioMart	Snai2	diluted coat color
BioMart	Snx5	abnormal coat/hair pigmentation
BioMart	Soat1	abnormal hair growth
BioMart	Soat1	abnormal hair medulla
BioMart	Soat1	abnormal hair shaft morphology
BioMart	Sod2	abnormal retinal pigment epithelium morphology
BioMart	Sorbs2	abnormal retinal pigmentation
BioMart	Sox10	absent coat pigmentation
BioMart	Sox10	absent hair follicle melanin granules
BioMart	Sox10	absent skin pigmentation
BioMart	Sox10	darkened coat color
BioMart	Sox10	decreased foot pigmentation
BioMart	Sox10	diluted coat color
BioMart	Sox10	non-pigmented tail tip
BioMart	Sox18	abnormal hair growth
BioMart	Sox18	darkened coat color
BioMart	Sox18	hairless
BioMart	Sox18	sparse hair
BioMart	Sox2	abnormal auchene hair morphology
BioMart	Sox2	abnormal awl hair morphology
BioMart	Sox2	abnormal guard hair morphology
BioMart	Sox2	abnormal zigzag hair morphology
BioMart	Sox2	yellow coat color
BioMart	Sox21	abnormal hair cuticle
BioMart	Sox21	abnormal hair shaft morphology
BioMart	Sp6	abnormal hair cuticle
BioMart	Sp6	abnormal hair follicle inner root sheath morphology
BioMart	Sp6	abnormal hair shaft morphology
BioMart	Sp6	hairless
BioMart	Spag9	absent skin pigmentation
BioMart	Spag9	diluted coat color
BioMart	Sparc	abnormal coat/hair pigmentation
BioMart	Spink1	sparse hair
BioMart	Spink10	sparse hair
BioMart	Spink5	abnormal hair follicle morphology
BioMart	Spink5	abnormal hair shaft morphology

BioMart	Spns2	abnormal eye pigmentation
BioMart	Spta1	abnormal skin pigmentation
BioMart	Spta1	delayed hair appearance
BioMart	Src	diluted coat color
BioMart	Srsf4	abnormal coat/hair pigmentation
BioMart	St14	abnormal hair follicle development
BioMart	St14	abnormal hair shaft morphology
BioMart	St14	decreased hair follicle number
BioMart	Stag1	decreased hair follicle number
BioMart	Stat5b	abnormal hair growth
BioMart	Stat5b	sparse hair
BioMart	Stra6	abnormal retinal melanin granule morphology
BioMart	Stra6	abnormal retinal pigment epithelium morphology
BioMart	Supt20	abnormal retinal pigment epithelium morphology
BioMart	Supt7l	abnormal hair texture
BioMart	Szt2	diluted coat color
BioMart	Taco1	grizzled coat color
BioMart	Taco1	ruffled hair
BioMart	Tal1	abnormal hair follicle development
BioMart	Tal1	abnormal skin pigmentation
BioMart	Tal1	focal hair loss
BioMart	Tal1	sparse hair
BioMart	Tarbp1	abnormal skin coloration
BioMart	Tbc1d32	abnormal retinal pigment epithelium morphology
BioMart	Tbccd1	abnormal skin coloration
BioMart	Tbk1	abnormal hair cycle anagen phase
BioMart	Tbk1	sparse hair
BioMart	Tbx15	abnormal coat/hair pigmentation
BioMart	Tbx15	irregular coat pigmentation
BioMart	Tbx19	abnormal ventral coat pigmentation
BioMart	Tbx19	hypopigmentation
BioMart	Tceal9	abnormal hair growth
BioMart	Tet1	irregular coat pigmentation
BioMart	Tfap2a	abnormal retinal pigment epithelium morphology
BioMart	Tfec	abnormal coat/hair pigmentation
BioMart	Tgfa	abnormal coat/ hair morphology
BioMart	Tgfa	abnormal hair follicle development
BioMart	Tgfa	abnormal hair follicle morphology
BioMart	Tgfa	abnormal hair follicle orientation
BioMart	Tgfa	abnormal hair medulla
BioMart	Tgfa	abnormal hair shaft morphology
BioMart	Tgfa	abnormal hair texture
BioMart	Tgfa	abnormal zigzag hair morphology
BioMart	Tgfa	decreased guard hair length
BioMart	Tgfa	increased curvature of hairs
BioMart	Tgfa	waved hair
BioMart	Tgm3	abnormal hair cortex keratinization
BioMart	Tgm3	abnormal hair cuticle
BioMart	Tgm3	abnormal hair shaft morphology
BioMart	Tgm3	abnormal hair texture
BioMart	Tgm3	abnormal zigzag hair morphology
BioMart	Tgm3	brittle hair
BioMart	Tgm3	decreased zigzag hair amount
BioMart	Tgm3	increased curvature of hairs
BioMart	Tgm3	thin hair shaft
BioMart	Tgm3	waved hair
BioMart	Ticrr	hairless
BioMart	Timp3	abnormal retinal pigment epithelium morphology
BioMart	Timp3	ruffled hair
BioMart	Tlr4	abnormal retinal pigment epithelium morphology
BioMart	Tm9sf4	abnormal hair follicle morphology

BioMart	Tmem30b	abnormal coat/hair pigmentation
BioMart	Tmem79	abnormal coat/hair pigmentation
BioMart	Tmem79	abnormal hair cortex keratinization
BioMart	Tmem79	abnormal hair cuticle
BioMart	Tmem79	abnormal hair cycle
BioMart	Tmem79	abnormal hair follicle development
BioMart	Tmem79	abnormal hair growth
BioMart	Tmem79	abnormal hair shaft morphology
BioMart	Tmem79	abnormal retinal pigmentation
BioMart	Tmem79	abnormal zigzag hair morphology
BioMart	Tmem79	brittle hair
BioMart	Tmem79	darkened coat color
BioMart	Tmem79	increased curvature of zigzag hairs
BioMart	Tmem79	sparse hair
BioMart	Tmprss6	abnormal hair follicle infundibulum morphology
BioMart	Tmprss6	abnormal hair follicle morphology
BioMart	Tmprss6	focal hair loss
BioMart	Tmprss6	progressive hair loss
BioMart	Tmprss6	sparse hair
BioMart	Tmprss6	thin hair follicle outer rooth sheath
BioMart	Tom1l2	focal hair loss
BioMart	Tpp2	focal hair loss
BioMart	Traf6	abnormal coat/ hair morphology
BioMart	Traf6	abnormal hair follicle development
BioMart	Traf6	abnormal skin pigmentation
BioMart	Traf6	absent guard hair
BioMart	Trappc6a	abnormal retinal pigmentation
BioMart	Trappc6a	irregular coat pigmentation
BioMart	Trp53	abnormal coat/ hair morphology
BioMart	Trp53	abnormal digit pigmentation
BioMart	Trp53	darkened coat color
BioMart	Trp53	increased foot pad pigmentation
BioMart	Trp53	increased tail pigmentation
BioMart	Trp63	abnormal hair follicle development
BioMart	Trp63	abnormal hair shaft morphology
BioMart	Trp63	absent hair follicles
BioMart	Trp63	decreased hair follicle number
BioMart	Trps1	abnormal hair follicle development
BioMart	Trps1	abnormal hair follicle morphology
BioMart	Trps1	decreased hair follicle number
BioMart	Trpv1	abnormal hair cycle
BioMart	Trpv1	abnormal hair cycle catagen phase
BioMart	Trpv1	abnormal hair cycle telogen phase
BioMart	Trpv3	abnormal coat/ hair morphology
BioMart	Trpv3	abnormal hair follicle orientation
BioMart	Trpv3	waved hair
BioMart	Ttc7	abnormal hair cuticle
BioMart	Ttc7	abnormal hair shaft morphology
BioMart	Ttc7	abnormal skin pigmentation
BioMart	Ttc7	abnormal tail pigmentation
BioMart	Ttc7	sparse hair
BioMart	Tub	abnormal retinal pigment epithelium morphology
BioMart	Tulp1	abnormal retinal pigment epithelium morphology
BioMart	Twist2	abnormal hair follicle morphology
BioMart	Twist2	abnormal hair growth
BioMart	Twist2	decreased hair follicle number
BioMart	Twist2	sparse hair
BioMart	Tyr	abnormal coat/hair pigmentation
BioMart	Tyr	abnormal eye pigmentation
BioMart	Tyr	abnormal hair follicle melanogenesis
BioMart	Tyr	abnormal iris pigmentation

BioMart	Tyr	abnormal skin pigmentation
BioMart	Tyr	absent coat pigmentation
BioMart	Tyr	absent eye pigmentation
BioMart	Tyr	absent hair follicle melanin granules
BioMart	Tyr	absent skin pigmentation
BioMart	Tyr	decreased ear pigmentation
BioMart	Tyr	decreased eye pigmentation
BioMart	Tyr	diluted coat color
BioMart	Tyr	hypopigmentation
BioMart	Tyr	irregular coat pigmentation
BioMart	Tyr	variegated coat color
BioMart	Tyr	variegated eye pigmentation pattern
BioMart	Tyrp1	abnormal coat/hair pigmentation
BioMart	Tyrp1	abnormal iris pigmentation
BioMart	Tyrp1	decreased eye pigmentation
BioMart	Tyrp1	diluted coat color
BioMart	Unc119	abnormal retinal pigment epithelium morphology
BioMart	Usf2	abnormal ventral coat pigmentation
BioMart	Usp39	abnormal coat/hair pigmentation
BioMart	Vac14	diluted coat color
BioMart	Vcp	focal hair loss
BioMart	Vdr	abnormal coat/ hair morphology
BioMart	Vdr	abnormal hair follicle development
BioMart	Vdr	abnormal hair follicle morphology
BioMart	Vegfa	coarse hair
BioMart	Vldlr	abnormal retinal pigment epithelium morphology
BioMart	Vldlr	abnormal retinal pigmentation
BioMart	Vps33a	abnormal choroid pigmentation
BioMart	Vps33a	abnormal eye pigmentation
BioMart	Vps33a	abnormal iris pigmentation
BioMart	Vps33a	abnormal retinal pigment epithelium morphology
BioMart	Vps33a	diluted coat color
BioMart	Vps33a	hypopigmentation
BioMart	Vsx2	abnormal retinal pigment epithelium morphology
BioMart	Vsx2	abnormal retinal pigmentation
BioMart	Vsx2	decreased eye pigmentation
BioMart	Wdr12	abnormal coat/hair pigmentation
BioMart	Wdr59	abnormal skin coloration
BioMart	Xpc	abnormal hair follicle morphology
BioMart	Xxylt1	abnormal retinal pigmentation
BioMart	Ydjc	abnormal retinal pigmentation
BioMart	Zdhhc13	abnormal hair cycle
BioMart	Zdhhc13	abnormal hair follicle morphology
BioMart	Zdhhc13	abnormal hair growth
BioMart	Zdhhc13	abnormal hair shaft morphology
BioMart	Zdhhc13	decreased hair follicle number
BioMart	Zdhhc13	sparse hair
BioMart	Zdhhc21	abnormal hair cycle
BioMart	Zdhhc21	abnormal hair follicle morphology
BioMart	Zdhhc21	abnormal hair follicle orientation
BioMart	Zdhhc21	abnormal hair follicle physiology
BioMart	Zdhhc21	abnormal hair growth
BioMart	Zdhhc21	abnormal hair medullary septa cells
BioMart	Zdhhc21	abnormal hair shaft melanin granule morphology
BioMart	Zdhhc21	dilated hair follicle infundibulum
BioMart	Zdhhc21	premature hair loss
BioMart	Zdhhc21	short hair
BioMart	Zdhhc21	sparse hair
BioMart	Zdhhc21	underdeveloped hair follicles
BioMart	Zfp141	abnormal skin pigmentation
BioMart	Zmpste24	abnormal hair follicle morphology

BioMart	Zmpste24	premature hair loss
BioMart	Zswim5	abnormal coat/hair pigmentation
BioMart	Zzef1	abnormal coat/hair pigmentation

Table S1. Genes from melanogenesis KEGG (mmu04916) that compose our baseline dataset.

Approach	Mouse gene symbol	Gene description
KEGG mmu04916	a	agouti signaling protein
KEGG mmu04916	Adcy1	adenylate cyclase 1
KEGG mmu04916	Adcy2	adenylate cyclase 2
KEGG mmu04916	Adcy3	adenylate cyclase 3
KEGG mmu04916	Adcy4	adenylate cyclase 4
KEGG mmu04916	Adcy5	adenylate cyclase 5
KEGG mmu04916	Adcy6	adenylate cyclase 6
KEGG mmu04916	Adcy7	adenylate cyclase 7
KEGG mmu04916	Adcy8	adenylate cyclase 8
KEGG mmu04916	Adcy9	adenylate cyclase 9
KEGG mmu04916	Calm1	calmodulin
KEGG mmu04916	Calm2	calmodulin
KEGG mmu04916	Calm3	calmodulin
KEGG mmu04916	Calm4	calmodulin
KEGG mmu04916	Calm5	calmodulin
KEGG mmu04916	Calml3	calmodulin
KEGG mmu04916	Calml4	calmodulin
KEGG mmu04916	Camk2a	calcium/calmodulin-dependent protein kinase (CaM kinase) II
KEGG mmu04916	Camk2b	calcium/calmodulin-dependent protein kinase (CaM kinase) II
KEGG mmu04916	Camk2d	calcium/calmodulin-dependent protein kinase (CaM kinase) II
KEGG mmu04916	Camk2g	calcium/calmodulin-dependent protein kinase (CaM kinase) II
KEGG mmu04916	Creb1	cyclic AMP-responsive element-binding protein 1
KEGG mmu04916	Creb3	cyclic AMP-responsive element-binding protein 3
KEGG mmu04916	Creb3l1	cyclic AMP-responsive element-binding protein 3
KEGG mmu04916	Creb3l2	cyclic AMP-responsive element-binding protein 3
KEGG mmu04916	Creb3l3	cyclic AMP-responsive element-binding protein 3
KEGG mmu04916	Creb3l4	cyclic AMP-responsive element-binding protein 3
KEGG mmu04916	Crebbp	E1A/CREB-binding protein
KEGG mmu04916	Ctnnb1	catenin beta 1
KEGG mmu04916	Dct	dopachrome tautomerase
KEGG mmu04916	Dvl1	segment polarity protein dishevelled
KEGG mmu04916	Dvl2	segment polarity protein dishevelled
KEGG mmu04916	Dvl3	segment polarity protein dishevelled
KEGG mmu04916	Edn1	endothelin-1
KEGG mmu04916	Ednrb	endothelin receptor type B
KEGG mmu04916	Ep300	E1A/CREB-binding protein
KEGG mmu04916	Fzd1	frizzled 1/7
KEGG mmu04916	Fzd10	frizzled 9/10
KEGG mmu04916	Fzd2	frizzled 2
KEGG mmu04916	Fzd3	frizzled 3
KEGG mmu04916	Fzd4	frizzled 4
KEGG mmu04916	Fzd5	frizzled 5/8
KEGG mmu04916	Fzd6	frizzled 6
KEGG mmu04916	Fzd7	frizzled 1/7
KEGG mmu04916	Fzd8	frizzled 5/8
KEGG mmu04916	Fzd9	frizzled 9/10
KEGG mmu04916	Gnai1	guanine nucleotide-binding protein G(i) subunit alpha
KEGG mmu04916	Gnai2	guanine nucleotide-binding protein G(i) subunit alpha
KEGG mmu04916	Gnai3	guanine nucleotide-binding protein G(i) subunit alpha
KEGG mmu04916	Gnao1	guanine nucleotide-binding protein G(o) subunit alpha
KEGG mmu04916	Gnaq	guanine nucleotide-binding protein G(q) subunit alpha
KEGG mmu04916	Gnas	guanine nucleotide-binding protein G(s) subunit alpha
KEGG mmu04916	Gsk3b	glycogen synthase kinase 3 beta
KEGG mmu04916	Hras	GTPase HRas
KEGG mmu04916	Kit	proto-oncogene tyrosine-protein kinase Kit
KEGG mmu04916	Kitl	KIT ligand
KEGG mmu04916	Kras	GTPase KRas

KEGG mmu04916	Lef1	lymphoid enhancer-binding factor 1
KEGG mmu04916	Map2k1	mitogen-activated protein kinase kinase 1
KEGG mmu04916	Map2k2	mitogen-activated protein kinase kinase 2
KEGG mmu04916	Mapk1	mitogen-activated protein kinase 1/3
KEGG mmu04916	Mapk3	mitogen-activated protein kinase 1/3
KEGG mmu04916	Mc1r	melanocortin 1 receptor
KEGG mmu04916	Mitf	microphthalmia-associated transcription factor
KEGG mmu04916	Nras	GTPase NRas
KEGG mmu04916	Plcb1	phosphatidylinositol phospholipase C, beta
KEGG mmu04916	Plcb2	phosphatidylinositol phospholipase C, beta
KEGG mmu04916	Plcb3	phosphatidylinositol phospholipase C, beta
KEGG mmu04916	Plcb4	phosphatidylinositol phospholipase C, beta
KEGG mmu04916	Pomc	proopiomelanocortin
KEGG mmu04916	Prkaca	protein kinase A
KEGG mmu04916	Prkacb	protein kinase A
KEGG mmu04916	Prkca	classical protein kinase C alpha type
KEGG mmu04916	Prkcb	classical protein kinase C beta type
KEGG mmu04916	Prkcg	classical protein kinase C gamma type
KEGG mmu04916	Raf1	RAF proto-oncogene serine/threonine-protein kinase
KEGG mmu04916	Tcf7	transcription factor 7
KEGG mmu04916	Tcf7l1	transcription factor 7-like 1
KEGG mmu04916	Tcf7l2	transcription factor 7-like 2
KEGG mmu04916	Tyr	tyrosinase
KEGG mmu04916	Tyrp1	tyrosinase-related protein 1
KEGG mmu04916	Wnt1	wingless-type MMTV integration site family, member 1
KEGG mmu04916	Wnt10a	wingless-type MMTV integration site family, member 10
KEGG mmu04916	Wnt10b	wingless-type MMTV integration site family, member 10
KEGG mmu04916	Wnt11	wingless-type MMTV integration site family, member 11
KEGG mmu04916	Wnt16	wingless-type MMTV integration site family, member 16
KEGG mmu04916	Wnt2	wingless-type MMTV integration site family, member 2
KEGG mmu04916	Wnt2b	wingless-type MMTV integration site family, member 2
KEGG mmu04916	Wnt3	wingless-type MMTV integration site family, member 3
KEGG mmu04916	Wnt3a	wingless-type MMTV integration site family, member 3
KEGG mmu04916	Wnt4	wingless-type MMTV integration site family, member 4
KEGG mmu04916	Wnt5a	wingless-type MMTV integration site family, member 5
KEGG mmu04916	Wnt5b	wingless-type MMTV integration site family, member 5
KEGG mmu04916	Wnt6	wingless-type MMTV integration site family, member 6
KEGG mmu04916	Wnt7a	wingless-type MMTV integration site family, member 7
KEGG mmu04916	Wnt7b	wingless-type MMTV integration site family, member 7
KEGG mmu04916	Wnt8a	wingless-type MMTV integration site family, member 8
KEGG mmu04916	Wnt8b	wingless-type MMTV integration site family, member 8
KEGG mmu04916	Wnt9a	wingless-type MMTV integration site family, member 9
KEGG mmu04916	Wnt9b	wingless-type MMTV integration site family, member 9

Table S1. Genes from Baxter *et al.* (2018) that compose our baseline dataset.

Approach	Mouse gene symbol	Species with phenotype	Source
Baxter 2018	2610301B20Rik	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	4930453N24Rik	Mouse	MGI
Baxter 2018	a	Mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Abca12	Zebrafish	ZFIN
Baxter 2018	Abcb6	Human, zebrafish	GO, OMIM, ZFIN
Baxter 2018	Abhd11	Zebrafish	ZFIN
Baxter 2018	Acd	Mouse	MGI
Baxter 2018	Acvr2a	Mouse	Pubmed
Baxter 2018	Adam10	Human, mouse	OMIM
Baxter 2018	Adam17	Mouse	MGI
Baxter 2018	Adamts20	Mouse	GO, MGI
Baxter 2018	Adamts9	Mouse	GO, MGI
Baxter 2018	Adar	Human	OMIM
Baxter 2018	Adcy5	Zebrafish	ZFIN
Baxter 2018	Adgra2	Zebrafish	ZFIN
Baxter 2018	Adrb2	Zebrafish	GO, ZFIN
Baxter 2018	Aebp2	Mouse	MGI
Baxter 2018	Afg3l1	Mouse	MGI
Baxter 2018	Afg3l2	Mouse	MGI
Baxter 2018	Ahcy	Zebrafish	ZFIN
Baxter 2018	Alcam	Zebrafish	ZFIN
Baxter 2018	Aldh2	Mouse	MGI
Baxter 2018	Aldoa	Zebrafish	GO, ZFIN
Baxter 2018	Alg13	Zebrafish	ZFIN
Baxter 2018	Alx3	Other animal model	OMIM
Baxter 2018	Ambra1	Zebrafish	ZFIN
Baxter 2018	Anxa2	Cell-based	Pubmed
Baxter 2018	Ap1s1	Zebrafish	OMIM, ZFIN
Baxter 2018	Ap3b1	Human, mouse	GO, OMIM, MGI
Baxter 2018	Ap3d1	Mouse	GO, OMIM, MGI
Baxter 2018	Ap3s2	Zebrafish	ZFIN
Baxter 2018	Apc	Mouse	OMIM, MGI
Baxter 2018	Arcn1	Mouse	GO, OMIM, MGI
Baxter 2018	Arl6	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Arl6ip1	Zebrafish	ZFIN
Baxter 2018	Ate1	Mouse	MGI
Baxter 2018	Atg7	Mouse	Pubmed
Baxter 2018	Atm	Human	OMIM
Baxter 2018	Atoh7	Zebrafish	GO, ZFIN
Baxter 2018	Atox1	Mouse	OMIM, MGI
Baxter 2018	Atp1a1	Zebrafish	GO, ZFIN
Baxter 2018	Atp6ap1	Zebrafish	GO, ZFIN
Baxter 2018	Atp6ap2	Zebrafish	GO, ZFIN
Baxter 2018	Atp6v0b	Zebrafish	GO, ZFIN
Baxter 2018	Atp6v0c	Zebrafish	ZFIN
Baxter 2018	Atp6v0d1	Zebrafish	GO, ZFIN
Baxter 2018	Atp6v1e1	Zebrafish	ZFIN
Baxter 2018	Atp6v1f	Zebrafish	ZFIN
Baxter 2018	Atp6v1h	Zebrafish	GO, ZFIN
Baxter 2018	Atp7a	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Atp7b	Mouse	MGI
Baxter 2018	Atr	Mouse	MGI
Baxter 2018	Atrn	Mouse	GO, OMIM, MGI
Baxter 2018	Bace2	Mouse, zebrafish	GO, ZFIN, PubMed
Baxter 2018	Barx2	Mouse	MGI
Baxter 2018	Bbip1	Zebrafish	GO, ZFIN
Baxter 2018	Bbs1	Zebrafish	GO, ZFIN

Baxter 2018	Bbs2	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Bbs4	Zebrafish	GO, MGI, ZFIN
Baxter 2018	Bbs7	Zebrafish	GO, ZFIN
Baxter 2018	Bcl2	Mouse	GO, OMIM, MGI
Baxter 2018	Bcl2l11	Mouse	GO
Baxter 2018	Blm	Human	OMIM
Baxter 2018	Bloc1s3	Human, mouse	GO, OMIM, MGI
Baxter 2018	Bloc1s4	Mouse	GO, OMIM, MGI
Baxter 2018	Bloc1s5	Mouse	GO, OMIM, MGI
Baxter 2018	Bloc1s6	Human, Mouse	GO, OMIM, MGI, PubMed
Baxter 2018	Bmp5	Zebrafish	ZFIN
Baxter 2018	Bmpr2	Mouse	Pubmed
Baxter 2018	Bnc2	Zebrafish	GO, ZFIN
Baxter 2018	Braf	Human, mouse	OMIM, MGI
Baxter 2018	Brca1	Mouse	MGI
Baxter 2018	Brca2	Human	OMIM
Baxter 2018	Brip1	Human	OMIM
Baxter 2018	Btd	Mouse	MGI
Baxter 2018	Cars	Zebrafish	ZFIN
Baxter 2018	Cav1	Zebrafish	ZFIN
Baxter 2018	Cbl	Mouse	MGI
Baxter 2018	Cbs	Human	OMIM
Baxter 2018	Ccdc28b	Zebrafish	ZFIN
Baxter 2018	Cct2	Zebrafish	GO, ZFIN
Baxter 2018	Cdc25a / Cdc25b	Zebrafish	ZFIN
Baxter 2018	Cdc42	Mouse, zebrafish	GO, ZFIN, PubMed
Baxter 2018	Cdc73	Zebrafish	ZFIN
Baxter 2018	Cdh11	Zebrafish	ZFIN
Baxter 2018	Cdh2	Zebrafish	GO, ZFIN
Baxter 2018	Cdh3	Human, cell-based	GO, OMIM
Baxter 2018	Cdk5	Mouse	Pubmed
Baxter 2018	Cdk7	Mouse	MGI
Baxter 2018	Cdkn2a	Human	OMIM
Baxter 2018	Cdx1	Mouse	MGI
Baxter 2018	Cep131	Zebrafish	GO
Baxter 2018	Cep290	Zebrafish	GO, MGI, ZFIN
Baxter 2018	Cga	Zebrafish	ZFIN
Baxter 2018	Chd7	zebrafish, Cell- based	GO, OMIM, ZFIN
Baxter 2018	Chek1	Mouse	Pubmed
Baxter 2018	Cib2	Zebrafish	OMIM, ZFIN
Baxter 2018	Cisd2	Mouse	MGI
Baxter 2018	Cited1	Cell-based	Pubmed
Baxter 2018	Clcn7	Mouse	Pubmed
Baxter 2018	Col17a1	Mouse	MGI
Baxter 2018	Col6a2	Zebrafish	ZFIN
Baxter 2018	Colec11	Zebrafish	ZFIN
Baxter 2018	Cop1	Mouse	MGI
Baxter 2018	Copa	Zebrafish	ZFIN
Baxter 2018	Copb1	Zebrafish	ZFIN
Baxter 2018	Copb2	Zebrafish	ZFIN
Baxter 2018	Corin	Mouse	MGI
Baxter 2018	Coro1a	Zebrafish	ZFIN
Baxter 2018	Cplx4	Zebrafish	ZFIN
Baxter 2018	Cpsf1	Zebrafish	ZFIN
Baxter 2018	Crb2	Zebrafish	MGI, ZFIN
Baxter 2018	Creb3l2	Zebrafish	ZFIN
Baxter 2018	Crh	Zebrafish	GO, ZFIN
Baxter 2018	Csf1r	Zebrafish	GO, ZFIN
Baxter 2018	Csnk1a1	Mouse	Pubmed
Baxter 2018	Ctbp2	Zebrafish	GO, ZFIN
Baxter 2018	Ctc1	Human	OMIM

Baxter 2018	Ctla4	Mouse	MGI
Baxter 2018	Ctnnb1	Mouse	MGI
Baxter 2018	Ctns	Human	GO, OMIM
Baxter 2018	Ctr9	Zebrafish	GO, ZFIN
Baxter 2018	Ctsd	Zebrafish	GO, ZFIN
Baxter 2018	Cxcl12	Zebrafish	ZFIN
Baxter 2018	Cyp11a1	Human	OMIM
Baxter 2018	Dct	Mouse	OMIM, MGI
Baxter 2018	Dctn1	Cell-based	GO
Baxter 2018	Dctn2	Cell-based	GO
Baxter 2018	Ddb2	Human	OMIM
Baxter 2018	Ddx3x	Human	OMIM
Baxter 2018	Dhrsx	Zebrafish	ZFIN
Baxter 2018	Dio2	Zebrafish	GO, ZFIN
Baxter 2018	Disc1	Zebrafish	ZFIN
Baxter 2018	Dkc1	Human	OMIM
Baxter 2018	Dlat	Zebrafish	ZFIN
Baxter 2018	Dmxl2	Zebrafish	ZFIN
Baxter 2018	Dnm2	Zebrafish	ZFIN
Baxter 2018	Dock7	Mouse	GO, OMIM, MGI
Baxter 2018	Drd2	Mouse	GO, MGI
Baxter 2018	Dsg4	Mouse	MGI
Baxter 2018	Dstyk	Human	OMIM
Baxter 2018	Dtnbp1	Human, mouse, zebrafish	GO, OMIM, MGI
Baxter 2018	Dync1h1	Zebrafish	ZFIN
Baxter 2018	Dzank1	Zebrafish	ZFIN
Baxter 2018	Ebna1bp2	Zebrafish	ZFIN
Baxter 2018	Ece1	Mouse	OMIM, MGI
Baxter 2018	Ece2	Zebrafish	GO, ZFIN
Baxter 2018	Eda	Mouse	GO, MGI
Baxter 2018	Edar	Mouse	GO, MGI
Baxter 2018	Edaradd	Mouse	MGI
Baxter 2018	Edn1	Mouse	Pubmed
Baxter 2018	Edn3	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Ednrb	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Eed	Mouse	MGI
Baxter 2018	Egfr	Mouse	MGI
Baxter 2018	Eif3b	Zebrafish	ZFIN
Baxter 2018	Eif3c	Mouse	MGI
Baxter 2018	Eif3e	Zebrafish	GO, ZFIN
Baxter 2018	Eif3g	Zebrafish	ZFIN
Baxter 2018	Eif3h	Zebrafish	ZFIN
Baxter 2018	Eif3i	Zebrafish	ZFIN
Baxter 2018	En1	Mouse	GO, MGI
Baxter 2018	Enpp1	Human	OMIM
Baxter 2018	Epg5	Human	OMIM
Baxter 2018	Erbb3	Zebrafish	GO, ZFIN
Baxter 2018	Ercc2	Human, mouse	OMIM, MGI
Baxter 2018	Ercc3	Human	OMIM
Baxter 2018	Ercc4	Human	OMIM
Baxter 2018	Ercc5	Human	OMIM
Baxter 2018	Ercc6	Human	OMIM
Baxter 2018	Esco2	Human, zebrafish	OMIM, ZFIN
Baxter 2018	Ets1	Mouse	MGI
Baxter 2018	Exoc5	Zebrafish	GO, ZFIN
Baxter 2018	Fam57b	Zebrafish	ZFIN
Baxter 2018	Fanca	Human	OMIM
Baxter 2018	Fancc	Human	OMIM
Baxter 2018	Fancd2	Human	OMIM
Baxter 2018	Fance	Human	OMIM
Baxter 2018	Fanci	Human	OMIM

Baxter 2018	Fbxo5	Zebrafish	ZFIN
Baxter 2018	Fbxw4	Zebrafish	ZFIN
Baxter 2018	Fgfr3	Human	OMIM
Baxter 2018	Fhl1/Fhl4	Zebrafish	ZFIN
Baxter 2018	Fig4	Mouse	GO, OMIM, MGI
Baxter 2018	Flna	Human	OMIM
Baxter 2018	Fmr1	Human	OMIM
Baxter 2018	Foxd3	Zebrafish	GO, ZFIN
Baxter 2018	Foxm1	Zebrafish	ZFIN
Baxter 2018	Foxn1	Mouse	MGI
Baxter 2018	Frem2	Mouse, zebrafish	MGI, ZFIN
Baxter 2018	Fscn1	Mouse	Pubmed
Baxter 2018	Fto	Zebrafish	ZFIN
Baxter 2018	Fzd4	Mouse	MGI
Baxter 2018	Gart	Zebrafish	GO, ZFIN
Baxter 2018	Gas7	Zebrafish	ZFIN
Baxter 2018	Gata3	Mouse	MGI
Baxter 2018	Gbf1	Zebrafish	ZFIN
Baxter 2018	Gdf6	Zebrafish	ZFIN
Baxter 2018	Gdpd3	Zebrafish	ZFIN
Baxter 2018	Gfpt1	Zebrafish	GO, ZFIN
Baxter 2018	Ggt1	Mouse	MGI
Baxter 2018	Gja4	Zebrafish	GO, ZFIN
Baxter 2018	Gja5	Zebrafish	GO, ZFIN
Baxter 2018	Gli3	Mouse	GO, OMIM, MGI
Baxter 2018	Gmppb	Zebrafish	OMIM, ZFIN
Baxter 2018	Gmps	Zebrafish	GO, ZFIN
Baxter 2018	Gna11	Mouse	GO, OMIM, MGI
Baxter 2018	Gnai3	Human	Pubmed
Baxter 2018	Gnaq	Mouse	GO, OMIM, MGI
Baxter 2018	Gnas	Human	OMIM
Baxter 2018	Gnat2	Zebrafish	ZFIN
Baxter 2018	Gpatch3	Zebrafish	ZFIN
Baxter 2018	Gpc3	Mouse	MGI
Baxter 2018	Gper1	Cell-based	Pubmed
Baxter 2018	Gpnmb	Human, cell-based	GO, OMIM, MGI
Baxter 2018	Gpr143	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Gpr161	Mouse	MGI
Baxter 2018	Gpr89	Mouse	MGI
Baxter 2018	Grk3	Zebrafish	GO, ZFIN
Baxter 2018	Grm1	Mouse	OMIM, MGI
Baxter 2018	Gtf2ird1	Mouse	MGI
Baxter 2018	Gtpbp3	Zebrafish	ZFIN
Baxter 2018	H3F3a	Zebrafish	ZFIN
Baxter 2018	Hdac1	Mouse, zebrafish	GO, MGI, ZFIN
Baxter 2018	Hdac2	Mouse	Pubmed
Baxter 2018	Hells	Mouse	MGI
Baxter 2018	Hes1	Mouse	Pubmed
Baxter 2018	Hexim1	Zebrafish	ZFIN
Baxter 2018	Hgf	Mouse	OMIM, MGI
Baxter 2018	Hipk2	Zebrafish	GO, ZFIN
Baxter 2018	Hirip3	Zebrafish	ZFIN
Baxter 2018	Hoxa13	Zebrafish	ZFIN
Baxter 2018	Hoxb7	Zebrafish	ZFIN
Baxter 2018	Hps1	Human, mouse	GO, OMIM, MGI
Baxter 2018	Hps3	Human, mouse	GO, OMIM, MGI
Baxter 2018	Hps4	Human, mouse	GO, OMIM, MGI
Baxter 2018	Hps5	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Hps6	Human, mouse	GO, OMIM, MGI
Baxter 2018	Hras	Human, mouse	OMIM
Baxter 2018	Hsd3b1	Zebrafish	GO, ZFIN

Baxter 2018	Hsp90b1	Mouse	Pubmed
Baxter 2018	Htra1	Zebrafish	MGI, ZFIN
Baxter 2018	Htt	Zebrafish	GO, ZFIN
Baxter 2018	Ids	Human	OMIM
Baxter 2018	Idua	Human	OMIM
Baxter 2018	Ier3ip1	Zebrafish	ZFIN
Baxter 2018	Ift122	Zebrafish	ZFIN
Baxter 2018	Ift27	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Igfbp7	Zebrafish	ZFIN
Baxter 2018	Igsf11	Zebrafish	GO, ZFIN
Baxter 2018	Ikbkb	Mouse	MGI
Baxter 2018	Ikbkg	Human, mouse	OMIM, MGI
Baxter 2018	Il17a	Cell-based	Pubmed
Baxter 2018	Ilk	Mouse, zebrafish	MGI, ZFIN
Baxter 2018	Impdh1	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Ino80e	Zebrafish	ZFIN
Baxter 2018	Inpp5b	Zebrafish	GO, ZFIN
Baxter 2018	Inpp5e	Zebrafish	GO, ZFIN
Baxter 2018	Ippk	Zebrafish	GO
Baxter 2018	Irf4	Human	OMIM
Baxter 2018	Irx1	Zebrafish	ZFIN
Baxter 2018	Irx2	Zebrafish	ZFIN
Baxter 2018	Itga3	Zebrafish	ZFIN
Baxter 2018	Itgb1	Mouse	MGI
Baxter 2018	Jam3	Zebrafish	GO, ZFIN
Baxter 2018	Kbtbd8	Cell-based	OMIM
Baxter 2018	Kcnj13	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Kctd15	Zebrafish	ZFIN
Baxter 2018	Kif13a	Cell-based	GO
Baxter 2018	Kif3a	Zebrafish	ZFIN
Baxter 2018	Kif5a	Zebrafish	ZFIN
Baxter 2018	Kit	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Kitl	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Kras	Mouse	MGI
Baxter 2018	Krt1	Mouse	MGI
Baxter 2018	Krt14	Human	OMIM
Baxter 2018	Krt17	Mouse	MGI
Baxter 2018	Krt2	Mouse	MGI
Baxter 2018	Krt27	Mouse	MGI
Baxter 2018	Krt4	Mouse	MGI
Baxter 2018	Krt5	Human	OMIM
Baxter 2018	Krt75	Mouse	MGI
Baxter 2018	Krt76	Mouse	GO, MGI
Baxter 2018	Krt9	Mouse	MGI
Baxter 2018	Larp7	Zebrafish	ZFIN
Baxter 2018	Lef1	Mouse, zebrafish	GO, MGI, ZFIN
Baxter 2018	Leo1	Zebrafish	GO, ZFIN
Baxter 2018	Lep	Zebrafish	ZFIN
Baxter 2018	Lhx2	Zebrafish	ZFIN
Baxter 2018	Liph	Mouse	MGI
Baxter 2018	Lmln	Zebrafish	GO, ZFIN
Baxter 2018	Lmna	Mouse	MGI
Baxter 2018	Lmx1a	Mouse	MGI
Baxter 2018	Lox	Zebrafish	ZFIN
Baxter 2018	Lrmda	Human, Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Lrsam1	Zebrafish	ZFIN
Baxter 2018	Ltk	Zebrafish	GO, ZFIN
Baxter 2018	Lvrn	Other animal model	OMIM
Baxter 2018	Lyst	Human, mouse	GO, OMIM, MGI
Baxter 2018	Mafb	Zebrafish	ZFIN
Baxter 2018	Magoh	Mouse	MGI

Baxter 2018	Map1lc3a	Cell-based	Pubmed
Baxter 2018	Map2k1	Cell-based	GO
Baxter 2018	Map2k2	Cell-based	Pubmed
Baxter 2018	Mapk3	Zebrafish	ZFIN
Baxter 2018	Masp1	Zebrafish	ZFIN
Baxter 2018	Matn1	Zebrafish	ZFIN
Baxter 2018	Mbtps1	Mouse	MGI
Baxter 2018	Mc1r	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Mc2r	Human	OMIM
Baxter 2018	Mcm2	Mouse	MGI
Baxter 2018	Mcm4	Human	OMIM
Baxter 2018	Mcoln3	Mouse	OMIM, MGI
Baxter 2018	Mcrs1	Zebrafish	ZFIN
Baxter 2018	Mdm2	Mouse	MGI
Baxter 2018	Mdm4	Mouse	MGI
Baxter 2018	Mdn1	Zebrafish	ZFIN
Baxter 2018	Med12	Zebrafish	GO, ZFIN
Baxter 2018	Med14	Zebrafish	ZFIN
Baxter 2018	Med23	Zebrafish	GO, ZFIN
Baxter 2018	Mef2c	Mouse	GO
Baxter 2018	Memo1	Mouse	MGI
Baxter 2018	Men1	Human	OMIM
Baxter 2018	Meox1	Zebrafish	GO, ZFIN
Baxter 2018	Mepce	Zebrafish	ZFIN
Baxter 2018	Mesp1	Zebrafish	ZFIN
Baxter 2018	Mfsd12	Mouse	GO, OMIM, MGI
Baxter 2018	Mgrn1	Mouse	OMIM, MGI
Baxter 2018	Mib1	Zebrafish	GO, ZFIN
Baxter 2018	Mib2	Zebrafish	GO, ZFIN
Baxter 2018	Mitf	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Mkks	Zebrafish	GO, ZFIN
Baxter 2018	Mkln1	Mouse	MGI
Baxter 2018	Mlana	Mouse, cell-based	GO, OMIM, MGI
Baxter 2018	Mlh1	Human	OMIM
Baxter 2018	Mlph	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Mmp17	Zebrafish	ZFIN
Baxter 2018	Mpnd	Zebrafish	ZFIN
Baxter 2018	Mpp5	Zebrafish	ZFIN
Baxter 2018	Mpv17	Mouse, zebrafish	GO, MGI, ZFIN
Baxter 2018	Mpzl3	Mouse	MGI
Baxter 2018	Mrap	Human	OMIM
Baxter 2018	Mreg	Mouse	GO, OMIM
Baxter 2018	Msh2	Human	OMIM
Baxter 2018	Msh6	Human	OMIM
Baxter 2018	Myc	Mouse	GO, MGI
Baxter 2018	Mycbp2	Zebrafish	GO, ZFIN
Baxter 2018	Myh9	Zebrafish	ZFIN
Baxter 2018	Myo10	Mouse	MGI
Baxter 2018	Myo5a	Human, mouse	GO, OMIM, MGI
Baxter 2018	Myo6	Cell-based	Pubmed
Baxter 2018	Myrip	Cell-based	Pubmed
Baxter 2018	Mysm1	Mouse	GO, MGI
Baxter 2018	Naa10	Zebrafish	ZFIN
Baxter 2018	Nbn	Human	OMIM
Baxter 2018	Ncstn	Zebrafish	ZFIN
Baxter 2018	Nf1	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Nfib	Cell-based	OMIM
Baxter 2018	Ninl	Zebrafish	ZFIN
Baxter 2018	Nnt	Human	OMIM
Baxter 2018	Noc3l	Zebrafish	ZFIN
Baxter 2018	Notch1	Mouse	MGI

Baxter 2018	Notch2	Mouse	MGI
Baxter 2018	Noto	Zebrafish	GO, ZFIN
Baxter 2018	Nr0b1	Human	OMIM
Baxter 2018	Nr3c1	Zebrafish	ZFIN
Baxter 2018	Nr4a3	Other animal model	OMIM
Baxter 2018	Nrarp	Zebrafish	GO, ZFIN
Baxter 2018	Nras	Human, mouse	OMIM, MGI
Baxter 2018	Nsdhl	Mouse	MGI
Baxter 2018	Nsf	Zebrafish	GO, ZFIN
Baxter 2018	Nsmce2	Mouse	MGI
Baxter 2018	Nup88	Zebrafish	ZFIN
Baxter 2018	Oat	Mouse	MGI
Baxter 2018	Oca2	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Ocrl	Zebrafish	GO, ZFIN
Baxter 2018	Ophn1	Mouse	MGI
Baxter 2018	Optn	Zebrafish	ZFIN
Baxter 2018	Ostm1	Mouse	OMIM, MGI
Baxter 2018	Otud5	Zebrafish	ZFIN
Baxter 2018	Ovol1	Zebrafish	GO, ZFIN
Baxter 2018	pafah1b1	Zebrafish	ZFIN
Baxter 2018	Pah	Human, mouse	OMIM, MGI
Baxter 2018	Paics	Zebrafish	GO, ZFIN
Baxter 2018	Pak1	Zebrafish	ZFIN
Baxter 2018	Palb2	Human	OMIM
Baxter 2018	Paqr7	Cell-based	Pubmed
Baxter 2018	Pard3	Mouse	OMIM, ZFIN,
Baxter 2018	Parn	Human	OMIM
Baxter 2018	Parp3	Zebrafish	ZFIN
Baxter 2018	Pax3	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Pax7	Zebrafish	GO, ZFIN
Baxter 2018	Pcbd1	Mouse	MGI
Baxter 2018	Pcdh10	Zebrafish	Pubmed
Baxter 2018	Pcnt	Human	OMIM
Baxter 2018	Pdhb	Zebrafish	GO, ZFIN
Baxter 2018	Pepd	Mouse	MGI
Baxter 2018	Pfas	Mouse	MGI
Baxter 2018	Picalm	Mouse	MGI
Baxter 2018	Pigk	Zebrafish	ZFIN
Baxter 2018	Pikfyve	Mouse	Pubmed
Baxter 2018	Pkn2	Zebrafish	ZFIN
Baxter 2018	Pknox1	Zebrafish	MGI, ZFIN
Baxter 2018	Plk4	Zebrafish	ZFIN
Baxter 2018	Plxnb2	Mouse	MGI
Baxter 2018	Pmch	Zebrafish, cell- based	GO
Baxter 2018	Pmel	Mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Pms2	Human	OMIM
Baxter 2018	Pnn	Zebrafish	ZFIN
Baxter 2018	Poc1b	Zebrafish	OMIM, ZFIN
Baxter 2018	Pofut1	Human, zebrafish	OMIM, ZFIN
Baxter 2018	Poglut1	Human	OMIM
Baxter 2018	Pogz	Zebrafish	ZFIN
Baxter 2018	Pola1	Human	OMIM
Baxter 2018	Polg	Mouse	MGI
Baxter 2018	Polh	Human, mouse	OMIM, MGI
Baxter 2018	Polr1a	Zebrafish	OMIM, ZFIN
Baxter 2018	Polr2g	Zebrafish	ZFIN
Baxter 2018	Pomc	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Pot1b	Mouse	OMIM, MGI
Baxter 2018	Ppargc1a	Mouse	GO
Baxter 2018	Ppp4c	Zebrafish	ZFIN
Baxter 2018	Prdm1	Zebrafish	GO, ZFIN

Baxter 2018	Prickle2	Zebrafish	ZFIN
Baxter 2018	Prkar1a	Human	OMIM
Baxter 2018	Prkdc	Mouse	MGI
Baxter 2018	Prps1	Zebrafish	GO, ZFIN
Baxter 2018	Psen1	Zebrafish	GO, ZFIN
Baxter 2018	Psen2	Zebrafish	GO, ZFIN
Baxter 2018	Psenen	Human, zebrafish	GO, OMIM, ZFIN
Baxter 2018	Ptch1	Mouse, zebrafish	MGI, ZFIN
Baxter 2018	Ptch2	Zebrafish	ZFIN
Baxter 2018	Pten	Human, mouse	OMIM, MGI
Baxter 2018	Ptpn11	Human, mouse, zebrafish	OMIM, MGI, ZFIN
Baxter 2018	Ptpn21	Zebrafish	ZFIN
Baxter 2018	Ptpn6	Mouse	MGI
Baxter 2018	Pts	Mouse	MGI
Baxter 2018	Pxdn	Mouse	MGI
Baxter 2018	Rab11a	Zebrafish	GO, ZFIN
Baxter 2018	Rab11b	Cell-based	GO
Baxter 2018	Rab17	Cell-based	Pubmed
Baxter 2018	Rab1a	Cell-based	Pubmed
Baxter 2018	Rab27a	Human, mouse	GO, OMIM, MGI
Baxter 2018	Rab32	Cell-based	GO
Baxter 2018	Rab36	Cell-based	Pubmed
Baxter 2018	Rab38	Mouse	GO, OMIM, MGI
Baxter 2018	Rab3ip	Zebrafish	GO, ZFIN
Baxter 2018	Rab7	Cell-based	GO
Baxter 2018	Rab8a	Zebrafish	GO
Baxter 2018	Rab9	Cell-based	GO
Baxter 2018	Rabggta	Mouse	OMIM, MGI
Baxter 2018	Rac1	Mouse	GO, MGI
Baxter 2018	Rack1	Mouse	GO, MGI
Baxter 2018	Rad21	Zebrafish	ZFIN
Baxter 2018	Rad50	Mouse	MGI
Baxter 2018	Radil	Zebrafish	ZFIN
Baxter 2018	Raf1	Human, mouse	OMIM
Baxter 2018	Rag1	Mouse	MGI
Baxter 2018	Rapgef2	Cell-based	GO
Baxter 2018	Raph1	Mouse	MGI
Baxter 2018	Rax	Zebrafish	ZFIN
Baxter 2018	Rb1	Zebrafish, cell-based	MGI, ZFIN
Baxter 2018	Rbpj	Mouse	GO, MGI
Baxter 2018	Recql4	Human, mouse	OMIM, MGI
Baxter 2018	Rest	Mouse	MGI
Baxter 2018	Rhbdf2	Mouse	MGI
Baxter 2018	Ric8b	Zebrafish	GO, ZFIN
Baxter 2018	Rilp	Cell-based	Pubmed
Baxter 2018	Rit1	Human	OMIM
Baxter 2018	Rnf2	Zebrafish	ZFIN
Baxter 2018	Rnf41	Zebrafish	GO, ZFIN
Baxter 2018	Rpgr	Zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Rpl24	Mouse	OMIM, MGI
Baxter 2018	Rpl27a	Mouse	MGI
Baxter 2018	Rpl38	Mouse	MGI
Baxter 2018	Rps14	Zebrafish	ZFIN
Baxter 2018	Rps19	Mouse	MGI
Baxter 2018	Rps20	Mouse	MGI
Baxter 2018	Rps6	Mouse	Pubmed
Baxter 2018	Rps7	Mouse	OMIM, MGI
Baxter 2018	Rtf1	Zebrafish	GO, ZFIN
Baxter 2018	Ruvbl2	Mouse	MGI
Baxter 2018	Rxra	Mouse	MGI
Baxter 2018	Sash1	Human	Pubmed

Baxter 2018	Scarb2	Zebrafish	ZFIN
Baxter 2018	Scube2	Zebrafish	ZFIN
Baxter 2018	Sdc2	Zebrafish	ZFIN
Baxter 2018	Sdc4	Zebrafish	ZFIN
Baxter 2018	Sdf4	Zebrafish	ZFIN
Baxter 2018	Sema4c	Mouse	MGI
Baxter 2018	Sf3b1	Zebrafish	GO, ZFIN
Baxter 2018	Sfpq	Zebrafish	ZFIN
Baxter 2018	Sfrp4	Mouse	Pubmed
Baxter 2018	Sgpl1	Human	OMIM
Baxter 2018	Sgsm2	Cell-based	GO
Baxter 2018	Sh3bp4	Cell-based	Pubmed
Baxter 2018	Sh3pxd2a	Zebrafish	ZFIN
Baxter 2018	Shh	Zebrafish	MGI, ZFIN
Baxter 2018	Shoc2	Human	OMIM
Baxter 2018	Shroom2	Other animal model	OMIM
Baxter 2018	Sik2	Mouse	MGI
Baxter 2018	Six6	Zebrafish	OMIM, ZFIN
Baxter 2018	Skiv2l2	Zebrafish	ZFIN
Baxter 2018	Slc12a2	Zebrafish	ZFIN
Baxter 2018	Slc16a2	Zebrafish	ZFIN
Baxter 2018	Slc17a5	Human	OMIM
Baxter 2018	Slc17a6	Zebrafish	ZFIN
Baxter 2018	Slc22A7	Zebrafish	ZFIN
Baxter 2018	Slc24a5	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Slc29a3	Human	OMIM
Baxter 2018	Slc2a1	Zebrafish	ZFIN
Baxter 2018	Slc30a4	Mouse	MGI
Baxter 2018	Slc31a1	Mouse	MGI
Baxter 2018	Slc36a1	Other animal model	Pubmed
Baxter 2018	Slc40a1	Zebrafish	ZFIN
Baxter 2018	Slc45a2	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Slc7a11	Mouse	MGI
Baxter 2018	Smarca4	Mouse, zebrafish	GO, ZFIN, PubMed
Baxter 2018	Smarca5	Mouse	Pubmed
Baxter 2018	Smarcal1	Human	OMIM
Baxter 2018	Smarcd1	Zebrafish	ZFIN
Baxter 2018	Smchd1	Mouse	Pubmed
Baxter 2018	Smo	Human, zebrafish	OMIM, ZFIN
Baxter 2018	Snai2	Human, mouse	GO, OMIM, MGI
Baxter 2018	Snap29	Zebrafish	ZFIN
Baxter 2018	Snrpc	Zebrafish	ZFIN
Baxter 2018	Sox10	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Sox18	Mouse	OMIM, MGI
Baxter 2018	Sox2	Mouse	GO, MGI
Baxter 2018	Sox5	Other animal model	Pubmed
Baxter 2018	Sox9	Mouse, zebrafish	GO, MGI, ZFIN
Baxter 2018	Spag9	Mouse	MGI
Baxter 2018	Spred1	Human	OMIM
Baxter 2018	Src	Mouse	MGI
Baxter 2018	Srm	Zebrafish	ZFIN
Baxter 2018	St3gal5	Human	OMIM
Baxter 2018	Star	Human	OMIM
Baxter 2018	Stim1	Zebrafish, Cell-based	Pubmed
Baxter 2018	Stk11	Human	OMIM
Baxter 2018	Stx12	Cell-based	Pubmed
Baxter 2018	Stx17	Other animal model	Pubmed
Baxter 2018	Stx3	Cell-based	GO
Baxter 2018	Stxbp1	Zebrafish	ZFIN
Baxter 2018	Sufu	Mouse	MGI
Baxter 2018	Sulf1	Zebrafish	GO, ZFIN

Baxter 2018	Supt5	Zebrafish	ZFIN
Baxter 2018	Supt6	Zebrafish	ZFIN
Baxter 2018	Sytl2	Cell-based	GO, OMIM
Baxter 2018	Szt2	Mouse	GO, MGI
Baxter 2018	Taco1	Mouse	MGI
Baxter 2018	Taf4	Mouse	MGI
Baxter 2018	Tbc1d10a	Cell-based	OMIM
Baxter 2018	Tbc1d10b	Cell-based	OMIM
Baxter 2018	Tbcd	Zebrafish	ZFIN
Baxter 2018	Tbx10	Mouse	MGI
Baxter 2018	Tbx15	Mouse	MGI
Baxter 2018	Tbx19	Mouse	MGI
Baxter 2018	Tenm3	Zebrafish	ZFIN
Baxter 2018	Terf1	Mouse	OMIM, MGI
Baxter 2018	Terf2	Mouse	OMIM, ZFIN
Baxter 2018	Terf2ip	Mouse	MGI
Baxter 2018	Tert	Human	OMIM, ZFIN
Baxter 2018	Tet2	Zebrafish	ZFIN
Baxter 2018	Tet3	Zebrafish	ZFIN
Baxter 2018	Tfap2a	Mouse, zebrafish	GO, MGI, ZFIN
Baxter 2018	Tfap2c	Zebrafish	ZFIN
Baxter 2018	Tfap2e	Zebrafish	GO, ZFIN
Baxter 2018	Tfpi2	Zebrafish	ZFIN
Baxter 2018	Tgfbr2	Mouse	Pubmed
Baxter 2018	Thra	Zebrafish	ZFIN
Baxter 2018	Tinf2	Human	OMIM
Baxter 2018	Tjp1	Zebrafish	GO, ZFIN
Baxter 2018	Tmprss6	Zebrafish	ZFIN
Baxter 2018	Tpcn2	Human, Zebrafish	OMIM, ZFIN
Baxter 2018	Traf6	Mouse	MGI
Baxter 2018	Trappc6a	Mouse	GO, OMIM, MGI
Baxter 2018	Trim32	Zebrafish	GO, ZFIN
Baxter 2018	Trim33	Zebrafish	GO, ZFIN
Baxter 2018	Trp53	Mouse, zebrafish	MGI, ZFIN
Baxter 2018	Trp63	Human	OMIM
Baxter 2018	Trpm1	Other animal model	OMIM
Baxter 2018	Trpm7	Mouse, zebrafish	GO, ZFIN, PubMed
Baxter 2018	Tsc1	Human	OMIM
Baxter 2018	Tsc2	Human	OMIM
Baxter 2018	Tshr	Zebrafish	ZFIN
Baxter 2018	Ttc8	Zebrafish	GO, OMIM, ZFIN
Baxter 2018	Tyms	Zebrafish	ZFIN
Baxter 2018	Tyr	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Tyrp1	Human, mouse, zebrafish	GO, OMIM, MGI, ZFIN
Baxter 2018	Ubxn4	Zebrafish	ZFIN
Baxter 2018	Uchl3	Zebrafish	ZFIN
Baxter 2018	Uqcrfs1	Mouse	MGI
Baxter 2018	Usb1	Zebrafish	ZFIN
Baxter 2018	Usf2	Mouse	MGI
Baxter 2018	Usp10	Zebrafish	ZFIN
Baxter 2018	Usp13	Zebrafish	GO, ZFIN
Baxter 2018	Usp20	Zebrafish	ZFIN
Baxter 2018	Usp28	Zebrafish	ZFIN
Baxter 2018	Usp3	Zebrafish	ZFIN
Baxter 2018	Usp36	Zebrafish	ZFIN
Baxter 2018	Usp43	Zebrafish	ZFIN
Baxter 2018	Usp45	Zebrafish	ZFIN
Baxter 2018	Usp48	Zebrafish	ZFIN
Baxter 2018	Usp53	Zebrafish	ZFIN
Baxter 2018	Usp7	Zebrafish	ZFIN
Baxter 2018	Usp9x	Human	OMIM

Baxter 2018	Uvssa	Human	OMIM
Baxter 2018	Uxt	Zebrafish	ZFIN
Baxter 2018	Vac14	Mouse	OMIM, MGI
Baxter 2018	Vamp7	Cell-based	Pubmed
Baxter 2018	Vangl1	Mouse	GO
Baxter 2018	Vdr	Zebrafish	ZFIN
Baxter 2018	Vps11	Zebrafish	GO, ZFIN
Baxter 2018	Vps18	Zebrafish	GO, ZFIN
Baxter 2018	Vps33a	Mouse	GO, MGI
Baxter 2018	Vps39	Zebrafish	GO, ZFIN
Baxter 2018	Wdpcp	Zebrafish	ZFIN
Baxter 2018	Wdr73	Zebrafish	OMIM, ZFIN
Baxter 2018	Wif1	Cell-based	Pubmed
Baxter 2018	Wipi1	Cell-based	Pubmed
Baxter 2018	Wnt1	Mouse	Pubmed
Baxter 2018	Wnt3a	Mouse	Pubmed
Baxter 2018	Wnt7a	Mouse	MGI
Baxter 2018	Wrap53	Human	OMIM
Baxter 2018	Wrn	Human	Pubmed
Baxter 2018	Xpa	Human, mouse	GO, OMIM
Baxter 2018	Xpc	Human	GO, OMIM
Baxter 2018	Ywhae	Mouse	Pubmed
Baxter 2018	Ywhaz	Mouse	GO
Baxter 2018	Yy1	Mouse	Pubmed
Baxter 2018	Zbtb17	Mouse	MGI
Baxter 2018	Zdhhc21	Mouse	MGI
Baxter 2018	Zeb2	Mouse	GO
Baxter 2018	Zic2	Mouse, zebrafish	GO, MGI, ZFIN
Baxter 2018	Zmpste24	Human	OMIM

Table S2. 'Main' network centrality results.

Hub		Bottleneck		Hub-bottleneck		
Gene	**Degree**	**Gene**	**Betweenness**	**Gene**	**Degree**	**Betweenness**
Dvl1	45	*Gart*	21493.29878	*Trp53*	97	65007.21022
Gnai1	45	*Gmps*	16259.4143	*Akt1*	96	59290.81899
Gnai3	44	*Vamp7*	14821.29278	*Ctnnb1*	86	41680.9798
Dvl3	42	*Gnb2l1*	13872.53286	*Hras1*	79	14119.82059
Gnai2	41	*Rab8a*	13818.60555	*Kras*	77	13647.57208
Wnt3	41	*Rps6*	13258.513	*Gsk3b*	72	25321.50658
Wnt4	41	*Ocrl*	11815.54443	*Prkaca*	69	29653.08069
Wnt7a	41	*Pikfyve*	11808.34407	*Src*	68	21884.89362
Lrp6	40	*Igf1*	11220.80098	*Mapk3*	65	11409.86713
Wnt9a	40	*Lep*	10854.45003	*Egfr*	64	28944.16894
Adcy3	39	*Smad3*	10254.7688	*Mapk1*	62	10991.25247
Adcy4	39	*Mitf*	9897.42113	*Ep300*	61	27782.17408
Adcy5	39	*Atp1a1*	9724.85102	*Prkacb*	61	13858.74629
Adcy8	39	*Notch1*	9410.4651	*Wnt5a*	58	9418.48524
Adcy9	39	*Tert*	9075.28057	*Dvl2*	55	9498.1368
Camk2g	39	*Hps3*	8372.70818	*Crebbp*	52	16578.34751
Wnt7b	39	*Myo5a*	8294.58881	*Prkcb*	52	12556.96889
Adcy1	38	*Rab11a*	8110.70758	*Calm1*	51	16874.73799
Adcy7	38	*Rho*	8077.14977	*Cdc42*	51	23680.78259
Wnt5b	38	*Smarca4*	7644.60228	*Gnao1*	50	5894.87329
Camk2b	37	*Plk4*	7601.08152	*Prkca*	49	6808.70802
Camk2d	37	*Atp6ap1*	7051.80194	*Wnt3a*	49	5141.26935
Fzd3	37	*Cyp19a1*	6909.80418	*Fzd4*	48	6849.64223
Fzd6	36	*Dnm2*	6800.11559	*Wnt1*	48	6707.96723
Gnaq	36	*Col1a1*	6757.75645	*Myc*	46	9782.06142
Fzd2	35	*Itgb1*	6755.2353	*Prkcg*	46	7314.49668
Fzd5	35	*Mysm1*	6721.13391	*Creb1*	44	6362.97857
Lrp5	35	*Impdh2*	6525.57917	*Rac1*	43	14457.52929
Ercc4	34	*Dkc1*	6482.55167	*Igf1r*	42	6448.48482
Plcb1	34	*Casp3*	6432.09077	*Pten*	40	5339.20746
Plcb2	34	*Pax6*	6049.6823	*Polr2g*	39	17494.40224
Plcb3	34	*Prkdc*	5945.71551	*Kit*	37	5475.77265
Plcb4	34	*Edn1*	5909.21028	*Cbl*	36	6976.13603
Wnt2b	33	*Pafah1b1*	5699.53814	*Adrb2*	35	7904.75348
Wnt9b	33	*Cyp11a1*	5656.57978	*Cdkn1a*	35	5654.50382
Nras	32	*Rela*	5613.37875	*Hdac1*	35	6021.47012
Pomc	32	*Shh*	5254.40828	*Bcl2*	34	5797.34759

Table S3. CGP network centrality results.

Hub		Bottleneck		Hub-bottleneck		
Gene	**Degree**	**Gene**	**Betweenness**	**Gene**	**Degree**	**Betweenness**
Wnt3a	49	*Mitf*	63898.15201	*Trp53*	97	82753.50118
Dvl1	45	*Alx3*	52253.42857	*Akt1*	96	70995.7221
Gnai1	45	*Mrto4*	18866.45079	*Ctnnb1*	86	65206.93099
Gnai3	44	*Gmps*	18865.3929	*Hras1*	79	15534.36994
Dvl3	42	*Rab8a*	16265.2758	*Kras*	77	15044.79491
Gnai2	41	*Lvrn*	16229.6651	*Gsk3b*	72	26196.14001
Wnt3	41	*Vamp7*	16007.93059	*Prkaca*	69	31598.59234
Wnt4	41	*Gnb2l1*	14651.72111	*Src*	68	28546.39164
Wnt7a	41	*Pikfyve*	14133.98806	*Mapk3*	65	18917.56621
Lrp6	40	*Rps6*	13971.31315	*Egfr*	64	31257.98417
Wnt9a	40	*Igf1*	12696.33573	*Mapk1*	62	18166.86197
Adcy3	39	*Notch1*	12618.92935	*Ep300*	61	29321.8393
Adcy4	39	*Lep*	12245.46504	*Prkacb*	61	14610.39166
Adcy5	39	*Smad3*	11297.46341	*Wnt5a*	58	10013.87151
Adcy8	39	*Atp1a1*	10721.41059	*Dvl2*	55	9909.62181
Adcy9	39	*Sfn*	10599.32554	*Gart*	53	69374.54664
Camk2g	39	*Efnb1*	9832	*Crebbp*	52	18072.30324
Wnt7b	39	*Tert*	9797.00946	*Prkcb*	52	13352.98256
Adcy1	38	*Hps3*	9155.5265	*Calm1*	51	18982.23419
Adcy7	38	*Myo5a*	9060.02083	*Cdc42*	51	31736.58876
Wnt5b	38	*Rho*	8883.45569	*Gnao1*	50	6152.63846
Camk2b	37	*Rab11a*	8827.30964	*Prkca*	49	7476.04267
Camk2d	37	*Plk4*	8302.77846	*Fzd4*	48	7315.0059
Fzd3	37	*Smarca4*	8255.41537	*Wnt1*	48	7466.19872
Fzd6	36	*Adrb2*	8176.25844	*Myc*	46	10238.59237
Gnaq	36	*Impdh2*	7851.00387	*Prkcg*	46	7571.61649
Adrb2	35	*Atp6ap1*	7651.59284	*Creb1*	44	11897.39576
Fzd2	35	*Cyp19a1*	7537.40365	*Rac1*	43	15500.42968
Fzd5	35	*Dnm2*	7294.45625	*Igf1r*	42	6960.29099
Lrp5	35	*Col1a1*	7277.69943	*Pten*	40	5837.32405
Ercc4	34	*Itgb1*	7174.51558	*Pfas*	39	12690.56494
Plcb1	34	*Dkc1*	7130.13814	*Polr2g*	39	18348.24232
Plcb2	34	*Mysm1*	7040.86098	*Kit*	37	5708.89923
Plcb3	34	*Casp3*	6980.25386	*Cbl*	36	7336.56098
Plcb4	34	*Edn1*	6800.29016	*Cdkn1a*	35	5965.3258
Wnt2b	33	*Ets1*	6487.052	*Hdac1*	35	6902.75652
Wnt9b	33	*Pax6*	6485.79748	*Bcl2*	34	9408.29326
Atm	32	*Chek1*	6445.18002	*Polr1a*	33	18111.64658
Nras	32	*Cyp11a1*	6298.55215	*Gnas*	32	6812.82542
Pomc	32	*Prkdc*	6213.85975	*Ocrl*	32	13369.84937
Tcf7l2	32	*Pafah1b1*	6106.7972	*Vegfa*	32	5716.51769
Wnt2	32	*Rela*	5872.21702			
Wnt6	32	*Col18a1*	5705.35232			

CAPÍTULO III. CONSIDERAÇÕES FINAIS

Neste trabalho aplicamos uma abordagem de redes de interações, a partir de genes de desenvolvimento de pelo, pigmentação de padronização periódica, para caracterizar como sistema o mecanismo molecular que dirige do fenótipo de pelagem em mamíferos. Além de construir a rede mais completa até o momento com foco neste fenótipo, também apresentamos pela primeira vez as redes de interações dos genes *Lvrn* e *Alx3*, que possuem outras funções conhecidas além de pigmentação, podendo ser futuramente também utilizadas para questões relacionadas com outros fenótipos afetados por esses genes.

Aqui, verificamos a essencialidade de interessantes rotas metabólicas, como Wnt e endotelina, para a topologia da rede do fenótipo. Estas, mesmo já com papel conhecido em pigmentação e desenvolvimento da pelagem, até agora não tinham sua importância completamente reconhecida observando-se um envolvimento amplo de diversos participantes em diferentes etapas da formação do fenótipo. Além disso, o fator de transcrição Mitf, principal regulador do melanócito e da melanogênese, foi identificado como um dos principais conectores dentro da rede. Tais resultados apontam para genes que, na topologia da rede, são essenciais para correto funcionamento da mesma. Estes podem ser alvos de outros tipos de estudos, como verificação do seu papel em determinadas doenças que não tenham sido diretamente relacionadas a eles, mas que por associação podem ter um papel importante.

As observações do presente estudo permitiram ampliar nosso conhecimento sobre o mecanismo molecular que dirige o fenótipo da pelagem, abrangendo tanto o desenvolvimento de pelos quanto o processo de pigmentação, e particularmente o mecanismo de desenvolvimento de padrões periódicos de pelagem. Verificamos que os processos relacionados aos genes *Alx3* e *Lvrn* parecem de fato ser independentes. Entretanto, não se exclui a possibilidade de ambos serem ativos em diferentes etapas do desenvolvimento do fenótipo. Além disso, identificamos interessantes genes candidatos a preencherem a falta de informações sobre o mecanismo de estabelecimento via Lvrn e implementação de padrão via Edn3, como o *Sfn* e *Ets1*.

Nossos resultados demonstram a aplicabilidade da abordagem de biologia de sistemas na caracterização de mecanismos complexos, além de se mostrar um importante meio exploratório para investigar mecanismos não completamente caracterizados, permitindo o desenvolvimento de hipóteses sobre os mesmos. Ao fornecer novos conhecimentos e discussões sobre o mecanismo responsável pela padronização periódica da pelagem via *Lvrn* e

Alx3, é possível sugerir novos genes participantes no fenótipo, os quais devem ser explorados mais profundamente por meio de abordagens experimentais.

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ANEXO A – Comprovante de submissão de artigo científico

PIGMENT CELL & MELANOMA Research

Systems biology of mammalian pigmentation and hair development genes reveals essentiality of Wnt signaling and insights into periodic coat patterning

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