**Supplementary file S1.** Functions of genes in the ± 250 kbp region upstream and downstream the locus Hapmap49624-BTA-47893 on BTA2, detected as significant in 100% of the pair-wise contrasts performed using Limousin as reference breed.

***PMS1*** (PMS1 Homolog 1, Mismatch Repair System Component) encodes a protein belonging to the mutL/hexB family. It is thought to be involved in the repair of DNA mismatches, being considered to be a component of the **DNA mismatch repair** (MMR) complex composed at least of MSH2, MSH3, MSH6, PMS1 and MLH1. An increasing body of evidence indicates that MMR is involved in **UV-induced tumorigenesis of melanoma** and nonmelanoma skin cancer [1,2]. A *PMS1* truncation mutation has been recently described in a patient with **uveal melanoma**, **ocular surface melanosis**, and nevus of Ota [3], a blue **hyperpigmentation** that occurs on the face, most often appearing on the white of the eye. Loss of PMS1 has been identified also in **dermal melanomas** [4-6]. Microsatellite instability and/or mutations in other mismatch repair genes have been also found in uveal melanomas [7-9], in dermal melanoma [10-18] and in benign as well as melanocytic dysplastic nevi [19-21, 14]. A general upregulation of genes involved in the MMR system was observed in **dysplastic nevi** and in the transition from radial growth phase melanomas to vertical growth phase melanomas, confirming that consistent DNA damage occurs during **melanoma** progression [22-24]. Mutations at MMR genes were also observed in hamartoma polyp tissue of patients with the **Peutz-Jeghers syndrome**, a rare disease with clinical manifestations of **pigmented spots on the lips, mucous membranes and extremities**, scattered gastrointestinal polyps, and susceptibility to tumors [25]. In a patient with the Peutz-Jeghers syndrome, Vageli et al. [26] reported a reduction of mRNA expression of *MLH1* in the biopsy from the **oral pigmented area**, and of all the four considered MMR genes in hamartomatous polyps, compared to levels found in peripheral blood. Mutations at MMR genes have been also reported in a syndrome termed constitutional mismatch repair deficiency (CMMR-D), characterized by association between the presence of multiple **cafe´-au-lait spots** and skin-fold freckling, adenomatous colonic polyps with early-onset colorectal carcinoma, and a predisposition to a variety of pediatric malignancies [27]. Also, somatic inactivation of the *NF1* gene through mismatch repair defects has been proposed to explain the occurrence of cafe´-au-lait spots and other features of neurofibromatosis type 1 in affected patients, consistently with the evidence that the *NF1* gene is a mutational target in mismatch repair–deficient cells [28]. MMR genes have been also implicated in **vitiligo**. Indeed, in humans, the 3′-end of the *VIT* cDNA sequence has been shown to be complementary to the 3′-end of hMSH6, a G/T mismatch repair [29]. Preliminary results indicated that decreased levels of VIT1 are associated with increased levels of hMSH6. Complementary stretches of mRNA can hybridize within the cell, and as double-stranded RNA can mediate post-transcriptional gene silencing, the VIT1 transcript potentially modifies the level of G/T mismatch repair protein in the cell [30]. In fact, high levels of hMSH6 may reflect increased DNA damage in vitiligo melanocytes [31].

**ORMDL1** (ORMDL Sphingolipid Biosynthesis Regulator 1) encodes a transmembrane protein anchored in the endoplasmic reticulum that act as a **negative regulator of sphingolipid synthesis** [32]. The sphingolipid metabolic pathway is a fundamental feature of all eukaryotic cells, required to produce complex sphingolipids, such as sphingomyelin and the glycosphingolipid family, that are plasma-membrane building blocks. It also generates bioactive metabolites (such as ceramide, sphingosine, and sphingosine-1-phosphate) that alter cell activities, including growth regulation and apoptosis, through interactions with receptors and enzymes [33]. *ORMDL1* belongs to the evolutionarily conserved ORMDL family [34]. Notably, ORMDL proteins have been shown to directly regulate activity of serine palmitoyl transferase (SPT), the rate-limiting step in **ceramide** biosynthesis [35,36]. Several lines of evidence demonstrated that free-cholesterol induced an autophagic-mediated increase in the turnover of ORMDL1. ORMDL proteins have been recognized as responders to cholesterol excess, exiting the ER to activate SPT and increase sphingomyelin biosynthesis, possibly buffering cellular cholesterol excess [37]. *ORMDL1* was isolated by Araki et al. [38] who showed that it is specifically down‐regulated in association with *PS1* (presenilin 1) mutations. They also showed that *ORMDL1* suppression affects **presenilin-γ‐secretase activity**, with γ‐secretase being responsible for the production of amyloidogenic β‐amyloid protein, whose accumulation in senile plaques appears to play a key role in the pathogenesis of Alzheimer's disease, thus highlighting *ORMDL1* relevance in presenilin‐γ‐secretase function and possibly Alzheimer [38]. Experiments using yeast knockout strains also suggest that ORMDL functions in correct **protein folding** and/or **trafficking in the endoplasmic reticulum** [34]. Miller et al. [39] refers that ORMDL3, a member of the ORMDL family, has been shown to induce expression of genes with potential importance to the pathogenesis of asthma including **metalloproteases** (MMP-9 and ADAM-8), CC chemokines (CCL-20 also known as MIP-3α), and CXC chemokines (IL-8 and CXCL-10) in normal human lung bronchial epithelial cells, and that it activates the ATF6 pathway, one of three branches of the ER localized **unfolded protein response** (UPR). Other studies have suggested that ORMDL3 may impact the PERK/eIF2α pathway, interacts with SERCA-2 and inhibits its function. ORMDL3 mRNA abundance was shown to depend on STAT6. The latter would not be directly regulating ORMDL3 expression, rather through a STAT6-dependent mediator.

Interestingly, zebrafish larvae presenting genome-edited mutations at the **presenilin** gene (i) initially show grossly normal melanotic **skin pigmentation** but subsequently loose this as they grow while retaining pigmentation in the retinal pigmented epithelium, or (ii) retain faint skin melanotic pigmentation once adults [40]. Mammalian presenilins have also been found necessary for **tyrosinase trafficking and melanin formation** by a γ-secretase-dependent mechanism [41,42]. The two tyrosinase-related proteins, tyrosinase-related protein 1 (Tyrp1) and dopachrome tautomerase (DCT) (also known as tyrosinase-related protein 2 (Tyrp2)), are implicated in the activity of the intramembrane protease, γ-secretase. A partial loss-of-function in melanotic pigment formation has been observed in a mouse model of the PSEN1 fAD mutation M146V. In mammals, the protein *silver* (coded by the *SILV* gene, also known as premelanosomal protein, ***PMEL***) can also be cleaved by proteases including γ-secretase to form a natural functional amyloid that facilitates melanin formation. *Silver* is expressed in pigment cells of the eye and skin, which synthesize melanin pigments within melanosomes. After a juxta-membrane cleavage, the C-terminal fragment of SILV is then processed by the γ-secretase complex to release an intracellular domain fragment into endosomal precursors to form amyloid fibrils. These ultimately become melanosomes [40].

As what concerns a possible role of presenilin-activated **unfolded protein response** (UPR), we recall here that tyrosinase, the first and rate-limiting enzyme in melanin biosynthesis, undergoes an extended period of post-translational modification, including N-linked glycosylation and disulfide bond formation-dependent folding in the endoplasmic reticulum (ER) in order to attain a functional tertiary structure. This process requires classical ER chaperones as well as melanocyte-specific factors. Mutations at four loci, encoding melanocyte-specific genes have been shown to result in **tyrosinase misfolding**, namely tyrosinase itself (TYR), the oculocutaneous albinism type 2 gene (OCA2), tyrosinase-related protein 1 (TYRP1) and OCA4. Misfolding results in **peptide retention** in the ER, the primary cellular site for protein synthesis and folding. A complex quality control system ensures that only correctly folded proteins are transported to the Golgi for further modification or to their site of activity. Misfolded proteins are either refolded or targeted for **proteasomal degradation**. Accumulation of unfolded proteins in the ER exerts a stress on the organelle which if unchecked activates the signal cascade known as the unfolded protein response (UPR). In the event that the stress is not resolved, the UPR can induce **apoptosis**. To this regard, **a role for UPR in vitiligo**, a disease that results from localized death of skin melanocytes, has been suggested [43].

Also, in zebrafish, presenilins were shown to influence **Notch signaling** resulting in perturbed neurogenesis and trunk and tail **neural crest development** [44].

Mutations in *PSENEN*, which encodes presenilin enhancer protein 2 (PEN-2), a subunit of the **γ-secretase complex**, was shown to underline a type of Dowling-Degos disease, which is characterized by progressive reticulate **hyperpigmentation** and small, dark-brown hyperkeratotic papules on the trunk, face, flexures, large skin folds, and extremities [45].

***OSGEPL1*** (O-Sialoglycoprotein Endopeptidase Like 1) encodes a protein that is a subunit of the multiprotein KEOPS complex, whose molecular mechanisms of actions remain elusive. *OSGEPL1* is involved in mitochondrial genome maintenance [46] and, hence, proper mitochondrial function. For a discussion on the **close connection between melanosomes and mitochondria function**, please, see Supplementary file S4. Together with YRDC, another subunit of the KEOPS complex, OSGEPL1 is responsible for a key step in the maturation of mitochondrial tRNAs, a N 6-Threonylcarbamoyladenosine (t6A) modification (t6A37). *OSGEPL1* knockout cells exhibited respiratory defects and reduced mitochondrial translation, suggesting that t6A37 plays a critical role in this process [47]. *In vivo* impairment of KEOPS proteins has been associated with various pathological conditions, generally characterized by **neurological and neurodegenerative symptoms** [48]. Another diseases associated with *OSGEPL1* is **hemochromatosis** (Type 4). This condition is characterized, among other classical features, by **hyperpigmentation of the skin**, usually most evident on sun-exposed skin, particularly on the face. Hyperpigmentation of external genitalia, flexion folds, scars, nipple areola, buccal mucosa and conjunctiva can also be observed in some patients. The color of skin is generally **slate grey or brownish bronze**. It in not yet clear whether the hyperpigmentation is due to (i) hemosiderin deposition resulting in diffuse, slate-gray darkening or (ii) increased production of melanin in the epidermis [49], or both. Some studies suggested that **hemosiderin**, as well as iron, other bivalent cations, and heavy metals **may stimulate melanogenesis** [50-52] and that melanosomes of dysplastic naevi and melanoma cells contained higher amounts of iron [53]. The *OSGEPL1* paralog, *OSGEP*, has been identified as the glycoprotease responsible for regulating the response of primary acute promyelocytic leukemia (APL) cells to UPR-induced apoptosis through **processing of misfolded** N-CoR (nuclear hormone receptor corepressor) **proteins**. Down-regulation of *OSGEP* was shown to favor **apoptosis** in APL cells [54]. For a discussion of the connection between unfolded protein response (UPR) and pigmentation, please, see the above gene *ORMDL1*. Specific interactions with *OSGEP* and *LAGE3*, which are human orthologues of the KEOPS complex were identified for the PRAME (**preferentially expressed antigen in melanoma**) oncoprotein, a BC-box subunit of a Cullin2-based **E3 ubiquitin ligase** [55], first identified and cloned as the antigen responsible for an anti-tumor immune response in a melanoma patient [56] and reported to repress **retinoic acid signaling** **in melanoma cell lines** [57]. PRAME specifically interacted with the KEOPS complex and recruited Cullin2-based E3 ubiquitin ligases to KEOPS, although it was not possible in this study to define whether KEOPS could be the ubiquitination targets of Cullin2-PRAME [55]. In yeast, inactivation of a KEOPS subunit specifically inhibited telomere recombination, a phenomenon known to elicit genome instability and to accelerate **cellular aging**, thus significantly extending **cell longevity** in both telomerase-positive and pre-senescing telomerase-negative cells [58]. In *Saccharomyces cerevisiae*, the KEOPS complex was shown to play a role in **cell polarity** by contributing to proper localization of a bud-site landmark protein [59]. The KEOPS complex was also identified as a transcription factor [60]. Components of KEOPS are nuclear proteins that associate with chromatin *in vivo* and are important for **inducible gene transcription** [60]. A KEOPS subunit has been shown to functionally interact with **glutaredoxin** [61], which is known to act as a cytosolic iron-sulfur (Fe-S) cluster assembly factor that facilitates (2Fe-2S) cluster insertion into a subset of cytosolic proteins [62,63]. In addition, in *Pyroccocus abyssi*, OSGEP was shown to contain an **iron** (Fe3+) atom, that was reduced into Fe2+ by treatment with ascorbic acid [64]. Another KEOPS subunit was shown to possess kinase activity toward **p53** and to be activated by the **Akt/PKB** signaling pathway [65]. As p53 is a major protein in the control of genome integrity, a role for the KEOPS complex in **checking DNA damage** has also been proposed [64]. Literature evidences of the roles of **p53 in melanocyte biology and pathology** have been provided [66-70]. Inactivation of **Akt/PKB** has been associated with **reduced cell proliferation** in a melanocyte cell line, as well as **reduced cell pigmentation** by inhibition of the tyrosinase activity [71]. Akt/PKB has been widely shown to be involved in the regulation of melanogenesis [72-76].

***ANKAR*** (Ankyrin and Armadillo Repeat Containing) encodes a protein containing ankyrin and armadillo repeats. Tandem-repeat domains are one of the most abundant classes of protein–protein interaction domains. Some of the most common repeat domains include the ankyrin (ANK) and armadillo (ARM) domains. Tandem-repeat containing proteins are present in all domains of life and function in nearly every cellular process, including cell–cell signaling, cytoskeleton integrity, transcription and cell–cycle regulation, inflammatory response, development, and various transport phenomena [77,78]. The multiple specificities of ankyrin repeats are potentially physiologically significant, through which distinct pathways can be cross-linked or coordinated [79]. Also, ankyrin repeats may play a role as chaperones in the phenomenon of protein folding induced by binding. The *ANKAR* paralog, *ARMC4*, encodes a protein that is thought to be involved in **ciliary organization and function**. This protein has been shown to localize to the ciliary axonemes and at the ciliary base of respiratory cells. Studies indicate that mutations in this gene cause partial **outer dynein arm defects** in respiratory cilia. The cilia of cells with mutations in this gene displayed either reduced ciliary beat frequency and amplitude, or, complete immotility. Some individuals with **primary ciliary dyskensia** (PCD) have been shown to have mutations in this gene. A possible role of primary cilia in pigment disorders has been highlighted in the **Bardet-Biedl Syndrome**, a pleiotropic genetically heterogeneous disorder, characterized, among other features, by **pigmentary retinopathy**. It is caused by impairment of the BBSome complex function. Indeed, the hetero-octameric BBSome complex plays a central role in primary cilia homeostasis. The complex acts as a cargo adapter that recognizes signaling proteins and links them to the intra-flagellar transport machinery. In zebrafish, knockdown of the BBS genes resulted in **delayed retrograde melanosome transport** (i.e. melanosome retraction to the perinuclear region) [80]. The BBSome gene *BBS9* was highlighted as under selection in the semi-feral Sasi-Ardi sheep breed from Western Pyrenees [81]. While the authors emphasize the involvement of the gene in energy metabolism and, as such, they argument it may have been under environmental selection pressure in relation with climate changes, the diluted red phenotype (“cream wool and a fawn face”; “uniform blonde or reddish color”, observed in this breed may, in our opinion be worthwhile of consideration for possible **pigmentation dilution** effects. In addition, primary cilia have been shown to negatively regulate melanogenesis in melanocytes and pigmentation in a human skin model [82]. Moreover, primary cilia have been demonstrated to have a crucial role in **neural crest cell development** [83] and, in zebrafish, cilia dysfunction has been associated with **mis-localization of melanocytes** in the head as well as absence of melanophores in the midline of the trunk [84]. Also, in the **Joubert Syndrome** ciliopathy [85], **retinal pigmentary alterations** are observed features. Impaired **melanosome recruitment** as well as **ciliogenesis defects** were observed in zebrafish mutants for the MCRS1 gene [86]. Ciliobrevins, the first specific small-molecule **antagonists of cytoplasmic dynein** were shown to **perturb protein trafficking within the primary cilium**, leading to their malformation as well as **preventing melanosome aggregation** [87]. Also, please, see Supplementary file 1, notably in what concerns the *PRICKLE2*, *GBF1* and *SUFU* genes.

***ASNSD1*** (Asparagine Synthetase Domain Containing 1) encodes a protein whose Gene Ontology annotations include **asparagine synthase** (glutamine-hydrolyzing) **activity**. Its paralog is indeed *ASNS*, which encodes the enzyme asparagine synthetase, responsible for conversion of aspartate and glutamine to asparagine and glutamate in an ATP-dependent reaction [88]. Studies on *ASNSD1* are very few. An inactivating mutation in the *ASNSD1* gene was shown to be associated with **progressive degenerative myopathy** in mice [89]. Several studies have, instead, been performed on *ASNS* which will be briefly and not exhaustively presented in what follows. *ASNS* has been found to be **up-regulated in various cancer types**, including gastric cancer tissues [90], lung cancer tissues [91], glioblastomas [92], and often associated with poor prognosis [93,94]. Li et al. [94] provided evidence for *ASNS* **involvement in the regulation of melanoma cell growth and cell cycle control**. Indeed, in melanoma cells, inhibition of *ASNS* expression significantly suppressed cell growth and induced a G0/G1 cell cycle arrest. Knockdown of *ASNS* remarkably downregulated the expression levels of cyclins and cyclin-dependent kinases, two kinds of crucial cell cycle regulatory molecules, and upregulated the expression of p21, a potent inhibitor of cyclin-dependent kinases. A marked reduction in proliferation of patient fibroblasts when cultured in asparagine-limited growth medium [95] and arrest of cell cycle progression at G0/G1 phase in lung cancer cells [91] have been also described. The accumulated evidences highlight that maintenance of intracellular asparagine levels is critical for cancer cell growth. Indeed, asparagine regulates mTORC1 complex activity and protein synthesis and, through regulation of serine uptake, it influences serine metabolism and nucleotide synthesis, suggesting that asparagine is involved in coordinating protein and nucleotide synthesis and is an important regulator of cancer cell amino acid homeostasis, anabolic metabolism and proliferation [96]. In colorectal cancer, the expression of *ASNS* was upregulated by mutated *KRAS*, with mutations in the *KRAS* gene being found in various types of cancer, and it was induced by KRAS-activated signaling pathways, in particular the PI3K-AKT-mTOR pathway [97]. Inhibition of *ASNS* was shown to induce p53/p21-dependent **senescence** and cell cycle arrest through a mechanism involving modulation of LKB1 activity [98].

Moreover, asparagine synthethase has been shown to be induced by **unfolded protein response** (UPR) under ER stress [99,100] (please, also see the *ORMDL1* gene, presented above, for a **role of UPR in pigmentation**). Induction of asparagine synthetase by the endoplasmic reticulum stress was shown to associate with inhibition of **lysosome acidification** while knockdown of *ASNS* restored **autophagic flux** [101]. Inhibition of either autophagy or *ASNS* was shown to reduce tumor cell proliferation, migration, and invasion, linking *ASNS* overexpression with poor clinical outcome in multiple cancers [102]. Asparagine synthetase has also been shown to undergoe regulated recruitment to the **mitotic spindles** and that it may have acquired a second role in mitosis similar to other metabolic enzymes that contribute to **metabolic reprogramming in cancer cells** [103].

Asparagine residues plays a role in **N-linked glycosylation** of proteins, a process, in which carbohydrates are attached to asparagine residues (N) residing within a conserved sequence pattern. Mature human **tyrosinase** is a type 1 membrane-bound glycoprotein Genetic changes affecting the conserved patterns near asparagine residues are associated with OCA1 **albinism**. In the cell, N-glycosylation plays an essential role in the **transfer of tyrosinase from ER to the cytoplasm** and in maintaining its **folding, stability** (and hence degradation rate), and **enzymatic activity**. The glycosylation of tyrosinase might regulate the melanin production in different types of cultured melanoma cells. It has been proven in mouse melanoma cells, that inhibition of the early steps of the N-glycosylation process strongly affects tyrosinase activity, thereby changing melanin synthesis. Moreover, the abnormal N-glycosylation process is related to the **depigmented phenotype of human melanomas** [104].

It has been shown that the 5′ UTR of *ASNSD1* holds an **upstream open reading frame** (ORF) capable of producing a cytoplasmic small ORF-encoded peptide whose peptide sequence is conserved across vertebrates, that has been named *ASDURF*. *ASDURF* has been shown to encode a protein with significant sequence and computationally predicted structural homology to the **prefoldin** chaperone family. ASDURF can bind to other prefoldin subunits of the prefoldin-like module (PFDL) which is part of the **PAQosome** complex, essential for the assembly and stabilization of other macromolecular complexes involved in essential cellular functions such as protein synthesis, ribosome biogenesis, transcription, splicing, and others [105,106]. In pathophysiological **stress conditions**, such as ER stress, **UVB exposure**, and others, start codon recognition and translation initiation is generally hindered, resulting in overall translational repression that conversely favors expression of upstream ORF-regulated mRNAs by bypassing these regulatory elements. In other words, upstream ORFs are one of the examples of post-transcriptional strategies employed by the cell to reorganize its protein expression landscape in an effort to restore homeostasis [107]. Whole genome expression profiles of **melanocytes from dysplastic naevi** and adjacent normal skin subjected to Gene Ontology (GO)-based comparative statistical analysis yielded significantly differentially expressed GO classes including “prefoldin complex” and validation of genes from the top GO classes confirmed an heterogeneous **differential expression pattern** [108]. Prefoldins have been shown to play important roles in **cancer development and progression** [109], and in promoting **epithelial-mesenchymal transition** [110], stability of axonemal **dynein** heavy chains [111], biogenesis of cytoskeletal-related proteins and **cytoskeletal assembly** during the folding of actin and tubulin monomers, **disruption of neuroblast polarity** and overgrowth, **development of central nervous system** , androgen and estrogen receptors transcriptional activity [112] and male fertility [113]. The involvement of prefoldin subunits in the cytoplasmic assembly of some non-cytoskeletal complexes has also been established [114]. Prefoldins are also believed to detect proteins that have folded incorrectly and target them to other chaperones that allow for repeat attempts at **refolding** [115]. Prefoldins would play a role in quality control against protein aggregation, and dysfunction of prefoldin is one of the causes of neurodegenerative diseases [116]. A prefoldin-like protein has been shown to be an integral component of the **NF-kB** (see Supplementary file S4 for NF-kB) enhanceosome and to be essential for its nuclear function [117].

***SLC40A1*** (Solute Carrier Family 40 Member 1 alias Ferroportin-1) encodes a protein that may be involved in **iron** ion transmembrane transporter activity. Defects in this gene are a cause of hemochromatosis (see *OSGEPL1* gene above for a link between **hemochromatosis, iron and pigmentation**). *SLC40A1* has been shown to be a manganese-responsive protein that decreases manganese cytotoxicity and accumulation [118] and can also function as a **manganese exporter** [119,120] or also export other **divalent cations** [121]. Manganese is an essential divalent cation that functions as a **cofactor** for the activity of numerous enzymes in cellular processes. For example, the addition of manganese divalent cations resulted in a significant increase in basal adenylate cyclase activity stimulated by a-MSH in melanoma cells was and in enhanced inhibitory powers of adenosine, normally known to be an inhibitor of the hormone-stimulated melanoma adenylate cyclase activity [122]. As another example, the amount of SOD2, a mitochondrial manganese‐dependent superoxide dismutase was found to increase when **melanin synthesis** was inhibited in normal human melanocytes, suggesting that the manganese-dependent induction of *SOD* could be correlated with melanogenesis [123]. Laddha et al. implicated a polymorphism at *SOD2* with **vitiligo** and proposed this polymorphism may be a risk factor for the disease [124], although contrasting reports have been published on this topic [125]. In melanoma patients, activity of SOD2 showed a clear increment with melanoma progression [126] and serum manganese superoxide dismutase had been suggested as a tumour marker for malignant melanoma [127].

**Normal human** **melanocytes** were shown to bind with greater strength to extracellular matrix substrates in the presence of manganese than calcium, presumably through conformational changes in the integrin molecule induced by occupation of the metal-ion-binding site [128]. A similar result was obtained by Searles et al. [129] in normal non-metastatic and **malignant metastatic human melanocytes**. They indeed demonstrated that the **integrin-dependent adhesion** of the above cell types to ECM was modulated by divalent cations, with a stronger effect exerted by manganese, followed by magnesium and calcium. The cation-modulating mechanism of integrin adhesion involves a non-covalent association of the cation molecule with binding sites on the extracellular region of integrins. In addition, manganese was shown to constitutively activate integrins in the absence of ligand, initiating a "post-integrin" cell adhesion cascade through non-integrin mechanisms. In melanoma cells, manganese ions were observed to induce integrin- and Rho kinase-dependent **focal adhesion** and stress fibre formation, as well as reduced melanoma migration [130].

Treatment of **vitiligo** patients with a preparation of an UVB-activated pseudocatalase complex containing manganese stopped the progression of active vitiligo in 95% of cases, even in patients with long lasting disease, induced stable and complete repigmentation and allowed to observe the presence of functioning melanocytes in all patients, possibly derived from a reservoir of a small population of quiescent melanocytes or precursors that has been hypothesized to exist even after many years of disease, since the authors were able to establish melanocyte cell cultures from lesional and nonlesional epidermis from patients with vitiligo of different disease duration [131].

Erway et al. [132] highlighted that *pallid* mice had a dietary manganese requirement few hundred times higher than normal mice. Based on their results, they formulated the hypothesis of a **relationship between melanocytes and trace elements**. Mice homozygous for the *pallid* spontaneous mutation have a light, yellow-brown coat, in combination with slightly abnormal behaviour, abnormal postural responses and head tilting due to the absence of otoliths in many but not all mutant mice. The effect of *pallid* on behaviour and otolith morphology appears to be a result of manganese deficiency. In 1972, Cotzias et al. [133] highlighted that, in pallid mice, **transportation** through the tissues of **manganese**, **L-dopa** (a precursor of melanins) and L-tryptophan was **slower** than observed in black C57Bl/6J mice. Previously, they demonstrated that **melanin granules are very rich in manganese**, and differences in the concentration of manganese were observed in pigmented vs. non-pigmented tissues in adjacent areas of the scalp and skin in human, dog and cattle and in darker vs lighter unicoloured barbs of multicoloured feathers from chicken, turkey and pheasant. In cattle conjunctiva, the **pigmentation also clearly reflected the concentration of manganese** [134]. Pallid mice have prolonged bleeding time due to a platelet storage pool deficiency (SPD) characterized by a normal platelet number but a deficiency in the number of platelet dense granules and in the serotonin, ATP, and ADP content of the granules. Interestingly, two other mouse coat colour mutants, *muted* (Bloc1s5mu) and *mocha* (Ap3dmh), present a similar concatenation of pigment, otolith, and platelet SPD abnormalities, which also occur in human **Hermansky-Pudlak syndrome**, associated with mutations in several different genes implicated in **lysosome-related organelles biogenesis**. Interestingly, interactions of divalent cations other than calcium [135,136] with bilayer lipids have been shown to permit **Rab- and SNARE-dependent** **membrane fusion** [137-147]. **Rab proteins** have been shown to represent **a major component of the melanosome proteome** Chi et al [148]. Expression levels of Rab2A, as well as Rab29, were shown to be **down-regulated by α-MSH** in melanoma cell lines [149]. In addition, several studies demonstrated the role of Rab proteins in melanocyte function. Rab1A and Rab36 were shown to mediate **anterograde and retrograde melanosome transport in melanocytes**, respectively Ishida, Matsui, T. [150,151]. Knock-down of Rab4A was shown to result in defective **melanosome maturation** [152]. Rab7 was shown to regulates **maturation** **of** melanosomal matrix protein **Pmel17** [153]. **Tyrosinase and tyrosinase-related protein 1** were shown to require Rab7 for their **intracellular transport** [154] while, in another study, Rab40C was shown to be a regulator of **Tyrp1 trafficking** in melanocytes [155]. Rab9A was shown to be required for **delivery of cargo from recycling endosomes to melanosomes** [156]. Rab11b was proposed to mediate **melanin transfer between donor melanocytes and acceptor keratinocytes** via coupled exo/endocytosis [157]. Rab17 was shown to regulate **melanocytic filopodia formation and melanosome trafficking** [158]. Rab21 activation was shown to be required for **dendrite formation in melanocytes** [159]. Rab22A was shown to regulate **cargo transport to melanosomes in melanocytes** [160]. Melanocyte cell lines were also shown to employ a Rab27a-regulated exocytic system [161-162]. The Rab27a gene is also implicated in the **Griscelli syndrome**, a rare, autosomal recessive disorder, characterized by **pigmentary dilution of the skin and the hair**, the presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes [163]. Finally, activation of Rab32/38 by HPS4 (one of the genes whose mutations have been associated with **Hermansky-Pudlak syndrome**, accompanied by **premature hair greying**) has been shown to be essential for **melanogenesis** of cultured melanocytes [164].

Moreover, several metal ion binding proteins, including *SLC40A1*, together with genes involved in the **Wnt signalling pathway** and in the regulation of gene transcription, were found to be differentially expressed in ERα-positive breast tumours, mutated *vs*. wild-type at the *PIK3CA* gene encoding the catalytic subunit of the **phosphatidylinositol 3-kinase** (PI3K). Deregulation of the **PI3K signalling pathway** is frequent in human cancers. Activation of PI3K activates the serine/threonine kinase **AKT**, which in turn regulates several signalling pathways controlling cell survival, apoptosis, proliferation, motility, and adhesion [165].

Possibly worth of mention the fact that a **manganese-stimulated aminopeptidase** isolated from the bovine cerebrum was shown to inactivate L-prolyl-L-leucyl-glycinamide (PLG) [166], also known as **melanocyte-stimulating hormone release inhibiting factor** or MIF-1, a peptide originated by enzymically-controlled degradation of oxytocin in the hypothalamus [167,168], which has been shown to inhibit the release of the **melanocyte-stimulating hormone (-MSH)** from the pituitary [169-171]. as well as from the hypothalamus [172], where -MSH release has been shown to respond to different diurnal rhythms, suggesting independent release mechanisms in the pituitary and hypothalamus [173].

***LOC100848294*** Uncharacterized locus

***WDR75*** (WD Repeat Domain 75, alias UTP17, alias NET16) encodes a **ribosome biogenesis** factor which is part of the ribosomal **small subunit (SSU) processome** required for processing of RNA precursors of the small subunit rRNA (18S) and whose impairment is associated with **cell cycle arrest** [174]. Ribosome biogenesis has been shown to be one of the major gene networks **upregulated in melanoma after UVR exposure** [175] and to be part of the process of **melanocytes reprogramming during tumor transformation** [176,177]. Since nucleolar size is closely related to its function in ribosome biogenesis, enlarged nucleoli observed in melanoma suggests a potential **link between increased ribosome biogenesis** **and melanoma** [178]. Ribosome biogenesis is aberrantly regulated in cancer, with **MAPK** and **PI3K/AKT/mTOR pathways** being linked to these processes [181]. Since the rate of protein synthesis is proportional to the rate of cell proliferation and growth, cancer cells must rely heavily on protein synthesis. This reliance on protein synthesis can be attributed not only to disruption of translational control at the level of mRNA translation but also to accelerated ribosome biogenesis [179]. Recently, **a link between ribosome biogenesis and the tumor suppressor p53** was discovered, characterized by inhibition of p53 ubiquitination thus leading to **cell cycle arrest, apoptosis, or senescence**. Thus, disruption of ribosome biogenesis can impair rDNA transcription, ribosome generation, and mRNA translation, while activating the tumor suppressor p53 to cause cell cycle arrest and apoptosis [180,181].

WDR75 belongs to the WD repeat domain containing protein family. Another WD repeat domain containing protein, WIPI1, a regulator of **vesicle trafficking**, has been demonstrated to be involved in regulating the expression of **MITF** and of **pigmentation** [182]. WD repeats allow WIPI1 to bind to phosphatidylinositol 3-phosphate and phosphatidylinositol 3,5-bisphosphate. Studies suggest that although WIPI1 localizes to multiple different vesicular compartments under normal nutritional conditions, it localizes to the autophagosome under conditions of starvation or TORC1 inhibition [183]. In yeast, it functions to retrieve membrane from the amphisome after fusion of the autophagosome with the lysosome, and also acts as a phosphatidylinositol 3,5-bisphosphate effector to remodel the membrane of vacuoles. Yeast cells deficient in this protein fail to initiate **autophagy** correctly [183]. In COS-7 cells, WIPI1 was shown to regulate **trans-Golgi-endosomal protein trafficking** [184]. Although published studies suggest that WIPI1 controls endosome/autophagosome dynamics in other cell types [185,186], an RNAi screen determined that WIPI1 depletion also significantly **inhibited the accumulation of MITF and TYR mRNA** **in melanoma cells** [182] even though *WIPI1* has no DNA binding domain or nuclear localization signal [184]. A subsequent study revealed that WIPI1 **represses** **TORC1 signaling**, leading to the **increased transcription of MITF target genes and melanosome maturation**. Taken together, these studies define a role for *WIPI1* and MTOR signaling in melanogenesis that is distinct from their role in autophagy [183].

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