Review Article

Update in genetic susceptibility in melanoma

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Abstract: Melanoma is the most deadly of the common skin cancers and its incidence is rapidly increasing. Approximately 10% of cases occur in a familial context. To date, cyclin-dependent kinase inhibitor 2A (*CDKN2A*), which was identified as the first melanoma susceptibility gene more than 20 years ago, is the main high-risk gene for melanoma. A few years later cyclin-dependent kinase 4 (*CDK4*) was also identified as a melanoma susceptibility gene. The technologic advances have allowed the identification of new genes involved in melanoma susceptibility: Breast cancer 1 (BRCA1) associated protein 1 (*BAP1*), *CXC* genes, telomerase reverse transcriptase (*TERT*), protection of telomeres 1 (*POT1*), *ACD* and *TERF2IP*, the latter four being involved in telomere maintenance. Furthermore variants in melanocortin 1 receptor (*MC1R*) and microphthalmia-associated transcription factor (*MITF*) give a moderately increased risk to develop melanoma. Melanoma genetic counseling is offered to families in order to better understand the disease and the genetic susceptibility of developing it. Genetic counseling often implies genetic testing, although patients can benefit from genetic counseling even when they do not fulfill the criteria for these tests. Genetic testing for melanoma predisposition mutations can be used in clinical practice under adequate selection criteria and giving a valid test interpretation and genetic counseling to the individual.

Keywords: Melanoma; melanoma susceptibility; familial melanoma; genetic counseling; cyclin-dependent kinase inhibitor 2A (CDKN2A); cyclin-dependent kinase 4 (CDK4); breast cancer 1 associated protein 1 (BAP1); protection of telomeres 1 (POT1); telomere

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Introduction

Melanoma is the most aggressive of the common skin cancers, being responsible for 75% of deaths from skin cancer (1). Melanoma incidence is rapidly increasing especially in Caucasian populations (1,2). Although development of melanoma during childhood is rare, it can appear at any age and is the second most diagnosed cancer among patients under 30 years old (3). For this reason, melanoma is one of the cancers with more years of productive life lost (4). If melanoma is diagnosed in its early stages, it can be cured by surgical removal. However, when the diagnosis is delayed, melanoma is the tumor with the highest metastatic capacity, since it increases by 10% per millimeter of thickness. Despite the improvement in survival of metastatic patients thanks to new targeted therapies, diagnosis and treatment of the initial tumor remains the best strategy for dealing with melanoma (5). Thus, the identification of individuals at high risk of developing melanoma is essential to reduce melanoma mortality, as prevention and early detection programs can be implemented.

Melanoma etiology is complex and heterogeneous as it involves environmental, phenotypic and genetic risk factors. The main environmental risk factor for melanoma is the exposure to ultraviolet radiation

(UVR) (6). UVR causes DNA damage through the formation of pyrimidine dimers, photoproducts, gene mutations, oxidative stress, inflammation and immunosuppression, favoring the carcinogenic process (7). UVR has been widely demonstrated to be implicated in nevo-genesis and melanoma-genesis. UVR can induce clinical changes (increased pigmentation, scale formation and erythema) as well as dermoscopic changes in pigmentation (changes in size and number of globules and dots, regression features such as bluish gray granules, blurred pigmented network and increased vascularity) (8-10). The use of sunscreen can prevent part of the UVR effects on nevi (11). Furthermore, a 10-year follow-up study showed that the daily use of sunscreen reduces the melanoma detection rate, suggesting that regular sunscreen use may prevent melanoma development (12). However, there are intrinsic risk factors that can predispose to melanoma. Phenotypic characteristics such as red or blond hair, blue or green eyes, fair skin with low tanning ability, freckles, multiple melanocytic nevi (100 or more) or 5 or more atypical nevi are associated with an increased risk to develop melanoma (13,14). Personal history of melanoma increases 5-8% the risk of developing a second melanoma (15,16). Finally, family history of melanoma has been widely associated with an increased melanoma risk (14).

Familial cancer syndromes are recognized for gathering high-risk features, including a cluster of relatives within the family who have the same or similar cancers as the patient, the development of cancer at a young age, the presentation of more than one synchronous or metachronous primary tumor or more than one tumor within a specific group of tumors that are features of a syndrome (17). Approximately 5-10% of melanoma cases occur in a familial context (18). In these families, melanoma susceptibility is inherited following an autosomal dominant inheritance pattern with incomplete penetrance (19). However, multiple primary melanoma patients also have inherited melanoma susceptibility (20).

This review aims to give an overview of the melanoma susceptibility genes known to date and genetic counseling in melanoma.

Melanoma susceptibility genes

High risk genes

Melanoma high risk genes are defined as genes that when mutated in an individual confer a high risk of developing melanoma and are usually associated with multiple melanoma cases within the family. Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) was the first gene associated with melanoma susceptibility. The *CDKN2A* gene is located in the 9p21 locus and encodes two tumor suppressor proteins p16INK4A and p14ARF via differential splicing and alternative reading frames. The protein p16INK4A, encoded by the α-transcript (composed by exon 1α, 2 and 3), promotes the arrest of the cell cycle in the G1 phase by inhibiting RB (retinoblastoma protein) phosphorylation through cyclin-dependent kinase 4 (CDK4). The β-transcript (composed by exon 1β, 2 and 3) encodes p14ARF and acts through the p53 pathway inducing the cell cycle arrest or favoring apoptosis (21). Furthermore, both p53 and p16INK4A play an important role on cell damage response and senescence (22). In 1992, Cannon-Albright and colleagues described for the first time 9p21 as a familial melanoma locus thanks to linkage analyses (23). Two years later the first germline mutations in *CDKN2A* were reported in familial melanoma (24). Many studies have been performed since then trying to investigate the role of *CDKN2A* in melanoma susceptibility. To date, *CDKN2A* is the main high risk gene involved in melanoma susceptibility (25). Mutations in that gene are found in around 20% of melanoma-prone families [*Figure 1*, references (25-39)], but the *CDKN2A* mutation frequency can range from 5% to 72% depending on the selection criteria used and the geographical areas (26,40). The *CDKN2A* mutation detection rate increases with the number of cases in the family. Mutations in *CDKN2A* are also detected in sporadic multiple primary melanoma patients (SMP). The *CDKN2A* mutation frequency in SMP with at least two primary melanoma is around 9% (20,27,41). As in familial studies, the probability to detect mutations in SMP increases with the number of total primaries. On the other hand, the probability to have *CDKN2A* mutations in sporadic melanoma patients without personal or familial history of melanoma is about 1% (42). The penetrance for melanoma in *CDKN2A* carriers varies between geographical areas and increases with age. Bishop and colleagues reported that at the age of 50, the melanoma penetrance for carriers was 13% in Europe, 50% in the US and 32% in Australia, whilst at the age of 80 the penetrance was 58% in Europe, 76% in the US and 91% in Australia (43). Furthermore, individuals

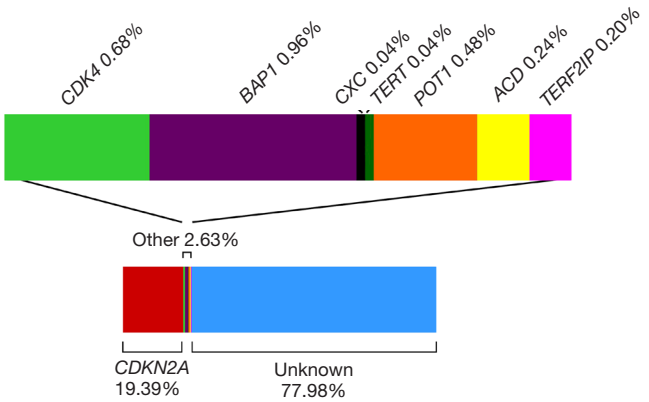

Figure 1 The figure represents the prevalence of mutations in high-risk melanoma susceptibility genes identified to date in melanoma-prone families. This figure includes the genetic information of 2,511 pedigrees: 487 *CDKN2A*, 17 *CDK4*, 24 *BAP1*, 1 *CXC*, 1 *TERT*, 12 *POT1*, 6 *ACD* and 5 *TERF2IP* mutated pedigrees respectively, and 1,958 families with unknown mutation. The data used to prepare this figure was that reported in previous research articles (25-39). We have excluded information from the Goldstein *et al.*'s study (26), from the groups belonging to GenoMEL consortium that have published updated reports of *CDKN2A* mutations alone, to avoid duplicates. For all those groups that have reported different updates of their families over time, we have selected the most recent article or the one that included a greater number of families. CDKN2A, cyclin-dependent kinase inhibitor 2A; CDK4, cyclin-dependent kinase 4; BAP1, Breast cancer 1 (BRCA1) associated protein 1; TERT, telomerase reverse transcriptase; POT1, protection of telomeres 1.

carrying *CDKN2A* germline mutations have an inherited risk to develop other cancer types beyond melanoma. A strong association between *CDKN2A* germline mutations and pancreatic cancer has been reported (27,40,44-48). Families with *CDKN2A* mutations also have an increased risk to develop breast, lung and other tobacco-related cancers (27,47,48).

CDK4 was the second high risk melanoma susceptibility gene identified (49). *CDK4* is an oncogene located within the 12q14 chromosomal region and encodes a protein that controls cell cycle progression through the G1 phase. To date mutations in this gene have been described in 17 melanoma-prone families and in all of them the mutation affects the same amino acid (Arginine 42) (50). This amino acid is located in the p16INK4A binding domain of the CDK4 protein. Thus, when *CDK4* is mutated, p16INK4A cannot inhibit the CDK4 kinase activity resulting in the progression of the cell cycle. *CDK4* mutation carriers phenotypically behave similarly to p16INK4A mutation carriers (50). This is consistent with the functional impact that mutations in both genes have at the cellular level, which results in the activation of the same pathway.

Breast cancer 1 (BRCA1) associated protein 1 (*BAP1*) germline mutations have been associated with a cancer syndrome characterized by the presence of broad tumor types: cutaneous melanoma, uveal melanoma, mesothelioma, renal cell carcinoma (RCC), atypical Spitz tumors, atypical intradermal tumors (MBAITs) and multiple basal cell carcinomas (51-65). However, the whole tumor spectrum associated with germline *BAP1* mutations is still unknown. *BAP1* is located in the chromosomal region 3p21 and encodes a protein that plays a tumor suppressor role through transcription regulation by chromatin remodeling and the ubiquitin-proteasome system. BAP1 is a deubiquitylase that participates in multi-protein complexes that regulate key pathways including the cell cycle, cell differentiation, cell death, gluconeogenesis and the DNA damage response (54). The frequency of *CDKN2A* wild-type melanoma-prone families with mutations in *BAP1* is not well established, but beyond cutaneous melanoma, families bearing *BAP1* mutations seem to be enriched by uveal melanoma, mesothelioma, RCC, other cutaneous tumors and other cancers.

Copy number variants (CNV) assessed genome wide, allowed the identification of a duplicated region on 4q13 segregating with melanoma in one melanoma-prone family (66), suggesting that some melanoma-prone families seem to carry mutations in private genes. The whole duplicated region contains 10 genes, most of them belonging to a family of CXC chemokines, such as melanoma growth-stimulating activity α (*CXCL1*) and interleukin 8 *(IL-8*). Both genes have been shown to stimulate melanoma growth *in vitro* and *in vivo* (66).

The most recent findings in melanoma susceptibility involve genes that play a role in telomere maintenance. Telomeres consist of tandem nucleotide repeats (TTAGGG) and are located at the ends of chromosomes. The telomerase enzyme, the shelterin protein complex and many other accessory proteins are also comprised in the telomeres. They maintain genomic stability and chromosomal integrity by protecting chromosome ends from degradation, end-to-end fusion, and atypical recombination (67). Telomeres shorten both with age and following exposures associated with cancer risk, such as

smoking and ultraviolet (UV) irradiation (68,69). Thus, telomere maintenance processes are natural candidates for explaining carcinogenesis (70). Horn and colleagues identified a germline mutation in the promoter of telomerase reverse transcriptase (*TERT*) in a melanoma-prone family using multipoint linkage analyses and target-enriched high-throughput sequencing. *TERT* is located in 5p15 and encodes the catalytic subunit of the telomerase, which is the ribonucleoprotein complex that maintains telomere length (71). Recently, two independent groups identified rare germline variants in protection of telomeres 1 (*POT1*) in 12 *CDKN2A* wild-type melanoma-prone families using next generation sequencing (72,73). *POT1* is located within the 7q31 chromosomal region and encodes a protein of the telomeric shelterin complex. POT1 plays an important role in telomere maintenance by preventing the inappropriate processing of the exposed chromosome ends, caused by pathways related to DNA damage response, and regulating telomerase function (74). Furthermore, Aoude and colleagues described germline mutations in melanoma-prone families located in two more genes involved in the shelterin complex, *ACD* and *TERF2IP*. This study included 510 melanoma-prone families without mutations in the known melanoma susceptibility genes to date. They identified six families with mutations in *ACD* and four families with *TERF2IP* mutations. The mutations were segregating with melanoma in the families (75). Overall, the germline mutations in genes that play a role in telomere maintenance (*TERT*, *POT1*, *ACD* and *TERF2IP*) may explain around 1% of familial melanoma cases, showing the relevance of telomere maintenance in melanoma susceptibility (*Figure 1*).

Figure 2 shows the interaction and pathways implicated until now in familial melanoma susceptibility.

Low to moderate risk genes

Melanocortin 1 Receptor *(MC1R)* is considered a moderate risk gene and its role in melanoma susceptibility has been widely studied. *MC1R*, located in 16q24, is one of the master regulator genes in human pigmentation and encodes the α melanocyte-stimulating hormone (α-MSH) receptor 1. *MC1R* is a highly polymorphic gene in the Caucasian population. Variants in *MC1R* have different functional effects, either at the level of α-MSH binding or cAMP signaling, resulting in changes in the ratio between eumelanin (brown pigment) and pheomelanin (red-yellow pigment, potentially mutagenic) ratio (76). *MC1R* variants are associated with skin and hair pigmentation and, independently of their phenotypic effect, *MC1R* variants are associated with an increased risk of developing melanoma (77). When the MC1R function is highly compromised, this usually results in the red hair color phenotype (RHC). The most common *MC1R* variants have been classified as r variants, when there is a low association with RHC (p.V60L, p.V92M, p.R163Q) and R variants, when they are highly associated with RHC (p.D84E, p.R142H, p.R151C, p.I155T, p.R160W, p.D294H) (78,79). The R variants are those most implicated in melanoma susceptibility. The melanoma risk conferred by R variants varies from two times risk per R allele in the general population to three times risk, in the familial melanoma context. The risk is additive, thus carriers of two R alleles have a 4 to 6 times increased risk than individuals without these variants. Studies assessing the modulator effect of *MC1R* variants in *CDKN2A* carriers demonstrate that the presence of *MC1R* variants increase the melanoma penetrance in *CDKN2A* carriers (80). The r variant p.R163Q is associated with increased risk of melanoma in high sun exposed geographic areas (81) and with a subtype of melanoma associated with chronic sun damage, lentigo maligna melanoma (82).

Microphthalmia-associated transcription factor *(MITF)* is also considered a moderate risk gene. Two independent groups identified the rare functional variant in *MITF* p.E318K (rs149617956) that increases melanoma risk and also predisposes to RCC (83,84). *MITF* is located in the chromosomal region 3p14 and is a master regulator gene of melanocyte development and differentiation, and it is also associated with melanoma development and progression (85). *MITF* p.E318K occurs at a conserved SUMOylation position and this variant decreases the number of SUMO-modified MITF forms. As SUMOylation of MITF represses its transcriptional activity, p.E318K increases the MITF transcriptional activity and may result in the up-regulation of distinct sets of genes. Furthermore, this variant promotes invasive and tumorigenic behaviors in melanoma and RCC cells and might favor a phenotypic switch of melanoma cells towards a tumor-initiating cell phenotype (84). The prevalence of p.E318K in melanoma patients ranges from 1.6% to 2.8%, whilst in a control population prevalence of this variant is 0.6% in French and Italian populations and 0.8% in UK and Australian populations (83,84,86). Furthermore, this variant has been associated with phenotypic features such as high nevi count, fair skin and non-blue eye color (83,87,88).

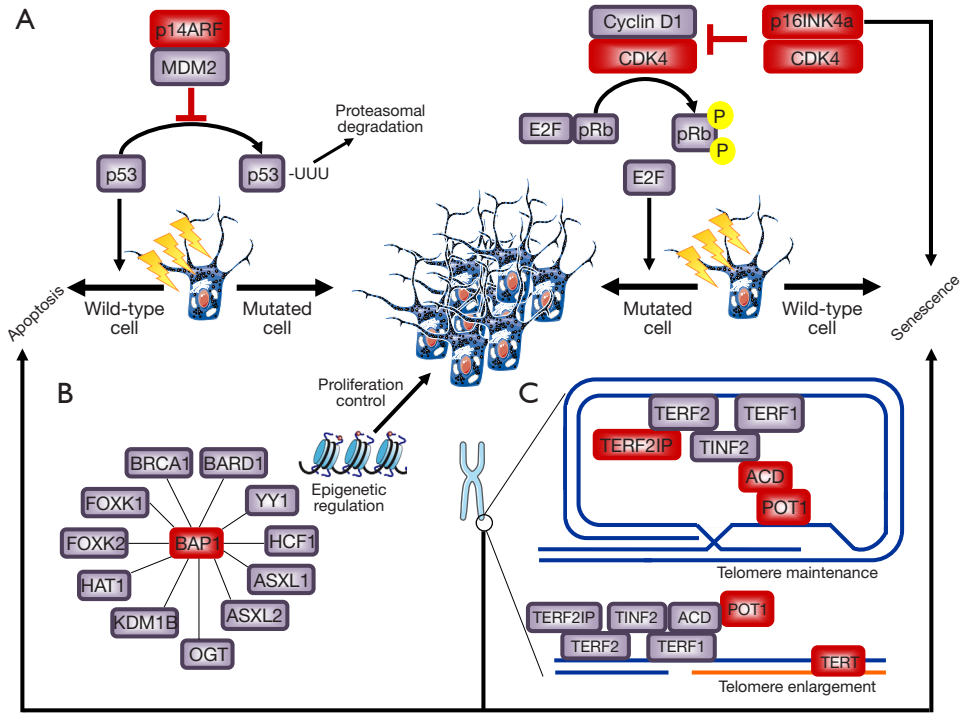

Figure 2 Cell biology functions and pathways of the genes involved in melanoma susceptibility. In red all proteins encoded by known high risk melanoma susceptibility genes. (A) *CDKN2A* encodes two different proteins p16INK4a and p14ARF. p16INK4a is an inhibitor of the cyclinD1/CDK4 complex and induces the arrest of the cell cycle. When p16INK4a can perform its function correctly, if a cell is damaged it can induce senescence. However when *CDKN2A* is mutated, the cyclinD1/CDK4 complex is not inhibited and phosphorylated pRb, releasing E2F transcription factor that can induce a cell cycle progression. If a cell is damaged the release of E2F can favor an aberrant proliferation that can lead to tumor development. In the same way, when CDK4 is mutated, p16INK4a cannot interact with it and cannot inhibit the release of E2F. p14ARF in front of a damaged cell induces apoptosis through the p53 pathway. If p14ARF is mutated, MDM2 can promote p53 ubiquitination and p53 is degraded in the proteasome. Thus when a cell is damaged, the lack of activation of p53 can allow that cell to avoid apoptosis (21). (B) BAP1 is involved mainly in epigenetic and gene transcription regulation interacting with multiple partners (54). When *BAP1* is mutated it cannot properly do its activity and this can lead to a dysregulation of gene transcription that can alter the proliferation controls. BAP1 has a tumor suppressor role, thus when a cell is damaged, mutant BAP1 cells can start proliferating in an aberrant way that can lead to the development of a tumor. (C) Telomeres form a protective structure at the ends of the chromosome (T-loop) that is covered by the shelterin complex (TERF2IP, TERF1, TERF2, TINF2, ACD and POT1). This complex also mediates the interaction between telomeres and the telomerase (TERT). Shelterin binds to the telomere through TERF1 and TERF2. POT1 binding to the single-stranded DNA overhang prevents access of telomerase to telomeres. When POT1 is unbound, the telomerase is able to extend telomeres. Furthermore when the telomeres are unprotected by the shelterin complex senescence and apoptosis can be induced. Mutations in genes lead to telomere dysregulation and can be involved in the development of a tumor when the cells are damaged (67-69,72-75). CDKN2A, cyclin-dependent kinase inhibitor 2A; CDK4, cyclin-dependent kinase 4; BAP1, Breast cancer 1 (BRCA1) associated protein 1; POT1, protection of telomeres 1.

Other genes containing common variants in the population show association with melanoma, but the risk conferred by these common variants is low. Each variant alone does not reach a two-fold increase melanoma risk (89). These genes are involved in different biological processes. There is a group of genes involved in the nevi count and pigmentation including: agouti signaling protein (*ASIP*) encoding an antagonist of α-MSH, Tyrosinase (*TYR*) encoding a protein implicated in eye color determination and tanning ability, Tyrosinase-related protein 1 (*TYRP1*) encoding a protein that stabilizes TYR, Oculocutaneous albinism II (*OCA2*) playing a role in eye color and pigmentation (90), Methylthioadenosine phosphorylase (*MTAP*) also implicated in human pigmentation and

paired box 3 (*PAX3*) involved in face and eye development and also associated with nevi count (91). There are also genes involved in the immunologic system such as some interleukins (IL-10, IL-1β), tumor necrosis factor alpha (*TNF-α*), human leukocyte antigen (*HLA*) class II genes (92) or interferon regulatory factor 4 (*IRF4*) (93). Another gene group is related with metabolism: cytochrome P450 family 2 (*CYP2D6*) that plays a role in the lipid metabolism, genes encoding glutathione transferases (*GSTM1*, *GSTT1* and *GSTP1*) (94), fat mass and obesity associated (*FTO*) encoding a protein related with the non-heme iron enzymes (95) and Vitamin D receptor (*VDR*) involved in mineral metabolism. Poly ADP-ribose polymerase 1 (*PARP1*), which encodes a chromatin-associated enzyme that modifies nuclear proteins, is also associated with melanoma (93).

Low to moderate risk genes have a weak impact on melanoma susceptibility and families with these variants usually have one or occasionally two melanoma cases. But if a combination of low to moderate variants is inherited, more melanoma cases could be present in the family. However, as UV radiation is the main environmental risk factor for melanoma, families with low to moderate risk variants living in areas with an increased UV radiation could have more melanoma cases (96).

Melanoma genetic counseling and management

Genetic counseling and risk assessment is the process of identifying and counseling individuals at increased risk of developing cancer, and distinguishing between those at high risk (high penetrance genes/families), those at a moderate increased risk (multifactorial etiology or low to moderate penetrance alleles), and those at average risk (97). This information can also be used to assess other at risk individuals within the family. Genetic counseling is offered to melanoma-prone families to better understand the meaning of the disease and genetic susceptibility, the inheritance pattern, the option of genetic testing, the understanding of all the possible results and the primary and secondary prevention of melanoma as well (96). The process includes melanoma risk assessment, the possibility of genetic testing, informed consent, disclosure of test results and psychosocial assessment as in other cancer genetic counseling or assessment (96,97). Doctors should refer patients with a personal and/or family history of melanoma, with features suggestive of having an increased melanoma risk, to a melanoma genetic assessment unit. Genetic counseling often implies genetic testing, but all patients can benefit from genetic counseling, even if they are not candidates for genetic testing. A broad number of reports highlight that genetic counseling in cancer is useful for the screening and management of patients (97). Genetic counseling aims to help patients and families. Genetic counselors should inform patients about the genetic risk factors for melanoma and other cancers, the indications for genetic testing, the chance of detecting a mutation, the possible reports (positive, negative or inconclusive), the possible implications for other family members, provide psychological assessment, and also offer recommendations for cancer screening and UV protection and how these might change with testing (96). Although mutations can be detected in these patients, families and patients negative for a familial mutation still have up to a two-fold greater risk of developing melanoma than that of the general population, due to other melanoma susceptibility genes and environmental factors shared between families (43,98).

To date, in melanoma genetic counseling, genetic testing is mainly focused on *CDKN2A* and *CDK4*. However, its use in clinical practice has been controversial due to the variation in the estimates of *CDKN2A* mutation penetrance (28-91%) depending on the study design, the ethnic background, UV exposure and co-inheritance of low to moderate predisposing variants (such as *MC1R* variants) (99). It is also difficult to assess patients because individuals negative for the mutation segregating in the family are still at increased risk of melanoma, compared with the general population. Genetic testing for melanoma predisposition mutations can be used in clinical practice under adequate selection criteria and giving a valid test interpretation and genetic counseling to the individual. People should understand that the interpretation of test results is difficult and the potential impact on clinical management is limited. Candidates for genetic testing should only be individuals with at least a 10% chance of carrying a mutation before the test is performed. These individuals should belong to melanoma-prone families or families with melanoma-related cancers (sarcoma, early onset breast cancer, brain tumors or pancreatic cancer) and/or have multiple primary melanomas. Patients with an early age at onset or with multiple or atypical nevi do not fulfill criteria for genetic testing, unless they also have a family history of melanoma (96,100,101). Leachman and colleagues described a very useful rule to select patients for genetic testing in melanoma according to the melanoma incidence in the general population and the prevalence of mutations in each region. In countries with a low melanoma incidence, such

as Southern European countries, the selection criteria for genetic counseling should follow the rule of two: individuals with two (synchronous or metachronous) primary melanomas and/or families with at least one invasive melanoma and one or more other diagnoses of melanoma and/or pancreatic cancers among first- or second-degree relatives on the same side of the family. Whilst countries with a moderate to high melanoma incidence, such as the USA and Northern European countries, should follow the rule of three: individuals with three or more primary invasive melanomas and families with at least one invasive melanoma and two more cases of melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family. For very high melanoma incidence countries, such as Australia, the rule of four may be suggested (102).

When genetic testing detects a melanoma predisposing mutation in a family, a screening cascade of individuals at risk is recommended. Individuals carrying *CDKN2A* mutations are included in prevention and early-detection programs that include the use of sun protection, dermatologic screening and self-skin examination, as an increased skin-cancer screening and surveillance by physicians and self-skin examination results in earlier detection of thinner melanomas (103-105). It has been demonstrated that melanoma genetic counseling has a positive impact on the improvement on total body skin examination and self-skin examination in unaffected individuals carrying germline mutations, after test reporting, while affected carriers maintain high levels of screening adherence (106). Furthermore, after melanoma genetic counseling unaffected members of high risk melanoma families report improvements in daily routine sun protection, showing that genetic counseling may motivate sustained improvements in prevention behaviors (107). Thus it is very important for both melanoma patients and unaffected individuals to be included in genetic counseling programs. Since an increased presence of smoking-related cancers has been detected in *CDKN2A* mutated families, advice to avoid smoking should also be included in the prevention programs (27,48). To date, individuals carrying *CDKN2A* mutations should be aware of the current lack of effective screening guidelines for pancreatic cancer (108), although magnetic resonance imaging surveillance can detect early-stage resectable pancreatic tumors (109).

In families where no *CDKN2A* mutation is identified, it should be stressed that the family is still at increased risk of melanoma on the basis of the family history. No further information on cancer risk is obtained, so these families should be managed according to family history (96). More studies should be necessary to understand the role of the other high-risk genes described to date (*BAP1*, *POT1*, *ACD*, *TERF2IP*, *TERT*, *CXCL1*), which methodology is better to asses them, or the role of the combination of the presence of different low to moderate risk variants, in *CDKN2A* wild-type families. The inclusion criteria for genetic testing of some of these genes also may differ. For example, *BAP1* genetic testing should be offered to families with a broader tumor spectrum including cutaneous and uveal melanoma, mesothelioma, RCC, and also with other skin tumors such as atypical intradermal tumors or basal cell carcinomas. The prevention and early detection programs for patients with mutations in *BAP1* should be modified based on the information provided of this cancer syndrome. *BAP1* mutation carriers should be closely monitored with, as an example, bi-annual dermatological and annual ophthalmological examinations and pulmonary/renal evaluations by imaging techniques (110). Moreover, many wild-type families for the known genes should carry private mutations that should be assessed by new approaches such as next generation sequencing, in order to detect the mutation responsible for the inherited susceptibility in the family and then improve the genetic counseling specifically in that family.

Conclusions

The new improvements in technology have led to the identification of new genes involved in melanoma susceptibility. However, the knowledge on melanoma susceptibility to date allows us to explain less than 30% of the genetic susceptibility in melanoma-prone families. In some cases the genetic susceptibility may be explained by the accumulation of the presence of low to moderate risk variants in the affected individuals. It is also possible that family aggregation can be explained by shared environmental exposures or also by chance. However next generation techniques can allow the identification of new genes involved in melanoma susceptibility.

Melanoma genetic counseling is important for patients and relatives to better understand the meaning of the disease and the genetic susceptibility. New studies are needed to assess the inclusion in genetic testing of the new genes related to melanoma susceptibility. However, knowing the genetic test results can also be important to refine the genetic counseling in the family as some of the

genes involved in melanoma susceptibility also predispose to other tumors. For this reason it is also important to analyze the role that the new genes identified in melanoma may play in the risk to develop other cancers.

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Footnote

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