The incidence of cutaneous melanoma (CM) has steadily increased among populations of European descent during the past five decades. Metastatic melanoma is the leading cause of skin cancer–related mortality and is characterized by a poor prognosis and limited treatment options (1,2). As early detection of CM provides the best opportunity for cure, identification of high-risk individuals is an important preventative strategy for reducing mortality. Susceptibility to CM is likely determined by an interaction of environmental risk factors including excessive exposure to ultraviolet radiation (3) and genetically controlled phenotypic traits such as nevus propensity, red or blonde hair, light-colored eyes, fair skin, and limited tanning ability (4,5). The heritability, that is, the contribution of genetic factors to CM risk, has been estimated to be 18%–55% (6,7). Approximately, 5%–10% of patients exhibit low-penetrance genes, the most consistent association with CM is more complex, involving numerous genetic risk factors of relatively high frequencies but low penetrance (10,11). Among the low-penetrance genes, the most consistent association with CM has been reported for the gene encoding melanocortin-1 receptor (MC1R) on chromosome 16q24.3 (12,13). Other putative risk alleles involved in various cellular pathways such as pigmentation, DNA repair, oxidation stress, apoptosis, cell growth, and melanocyte differentiation and migration have also been implicated in melanoma susceptibility (14).

Within the last 15 years, approximately 150 genetic association studies including two GWAS (15,16) have been published that claim or refute associations between CM risk and putative genes.
CONTEXT AND CAVEATS

Prior knowledge
Previous studies, including genome-wide association studies, have identified genetic variants associated with cutaneous melanoma (CM).

Study design
Data were collected from all genetic association studies in the CM field. Meta-analyses were performed for all polymorphisms identified in four or more independent case-control datasets. Supplementary meta-analyses were done for polymorphisms for which three datasets from GWAS were available. The epidemiological credibility of statistically significant associations between loci and CM was measured using the Human Genome Epidemiology Network Venice criteria.

Contribution
This is the first field synopsis and meta-analysis of genetic variants associated with CM. The main meta-analyses identified eight loci statistically significantly associated with CM, five of which had genome-wide statistical significance and strong epidemiological credibility. Supplementary analyses identified one additional locus with genome-wide statistical significance and strong epidemiological credibility for an association with CM. The accumulated evidence was reported on the publicly accessible regularly updated MelGene website (www.MelGene.org).

Implications
This study comprehensively reports on the genome-wide statistical significance and epidemiological credibility of CM susceptibility genes. MelGene will provide a potential forum to report genes associated with CM as they are identified in future genetic studies.

Limitations
Some studies may have been excluded from the analyses and random errors may be found in some of the study entries. Because the meta-analyses were based on summary-level data, some potential confounders and other types of bias could not be accounted for, and both gene–gene and gene–environment interactions could not be assessed. Also, as is standard of systematic meta-analyses, publication bias could not be ruled out.

From the Editors

melanoma genes. Although highly valuable for the understanding of the underlying pathogenesis and for the assessment of risk prediction, the increasing amount of information has become difficult to evaluate and interpret. To assess the evidence and strength of genetic associations with CM, we have collected and comprehensively cataloged all genetic association studies published in the field and conducted systematic meta-analyses for all eligible polymorphisms. Systematic field synopses and meta-analyses have previously been performed for other diseases using similar study designs (17–22). Furthermore, we have graded the epidemiological validity of nominally statistically significant meta-analysis results by applying the Venice criteria proposed by the Human Genome Epidemiology Network. Detailed summaries of all association studies and meta-analysis results are available on a regularly updated publicly available online database, MelGene (23), which currently highlights the most promising genetic loci associated with CM risk.

Methods

Collection and Management of Eligible Studies

Search Strategy. We searched the PubMed database (24) by using the search terms “melanoma AND associate* AND gene*” for studies published on or before March 31, 2009, after which daily PubMed searches were performed (Figure 1). In addition, we searched the references of included publications and the table of contents in relevant journals on genetics, dermatology, and oncology. We also searched PubMed using the keywords “melanoma AND [name of every gene identified in included publications].” Furthermore, we screened the Human Genome and Epidemiology Network Navigator (25) for additional publications as well as the Melanoma Molecular Maps Project (26), a large online database, which reports published melanoma genetic association studies.

Inclusion and Exclusion Criteria. Studies included in MelGene had to assess the association between a polymorphism and CM. We included all relevant case–control studies that have been published in a peer-reviewed journal. We did not include those without healthy control subjects (ie, studies that examined genetic associations with phenotypic variables among individuals with CM alone or among different types of cancer). Studies with a family-based approach were listed in the qualitative gene summary overview on MelGene but were not subjected to meta-analysis. We excluded highly penetrant mutations only present in patients but not found in control subjects. We included studies on polymorphisms with three or more alleles (such as the HLA and MICA genes) in the qualitative gene summaries, but considered them for meta-analysis only if genotype frequencies of one allele compared with all other alleles were consistently reported. Abstracts from conference proceedings or scientific meetings were excluded. The criteria to establish a diagnosis had to be a histologically proven CM, either invasive or in situ. We excluded studies of patients with non-CM (including uveal melanoma) or with metastatic disease of an unknown primary cancer. Whenever an article studied more than one phenotype, only CM-specific data were included. Although publication in the English language was part of the criteria for this study, no articles published in a language other than English were identified.

Genotype and Allele Distributions. We used the National Center for Biotechnology Information Single Nucleotide Polymorphism Database identifiers when provided (rs numbers). If an rs number was not specified in the respective publications, we generally used the most common definition provided in the primary publications. Genotype distributions were extracted from eligible publications for each polymorphism and listed on MelGene. Whenever allele frequencies, but not genotype frequencies, were reported in the original articles, we calculated the genotype frequencies on the basis of the reported allele frequencies and sample sizes, assuming that no deviations from Hardy–Weinberg equilibrium occurred, unless reported otherwise. We contacted the authors of publications with missing genotype data by email and if no response was received, the respective studies were labeled as no data provided on MelGene, unless there was information on odds ratios (ORs) and/or corresponding 95% confidence intervals (CIs) calculated on the basis of allelic contrasts. Approximately, 3% of all genotypes
remained unavailable. For studies of overlapping populations, we included only one study in the respective meta-analyses, and whenever possible, the study with the largest sample size was included.

GWAS and GWAS-Replication Studies. Because of the absence of publicly available CM-GWAS datasets, we extracted the allele frequencies or per-allele odds ratios (15,16) from the original GWAS publications and included them in the main meta-analyses when applicable. We also included data from GWAS-replication studies, that is, studies assessing the association of melanoma with selected variants derived from GWAS on CM-related traits including hair, eye, and skin pigmentation; basal cell carcinoma; and melanocytic nevi (27–31). To capture all the important information from the limited number of GWAS and GWAS-replication studies, we also performed supplementary meta-analyses on polymorphisms for which only three datasets from CM-GWAS and/or GWAS-replication datasets were available (27–29).

Statistical Analyses

Meta-analyses. Random-effects summary odds ratios and 95% confidence intervals (32) were calculated on the basis of study-specific unadjusted odds ratios and 95% confidence intervals using allelic contrasts for all variants with case–control genotype data available before July 31, 2010 (the data freeze). C) The publication search continued after the date of the data freeze and yielded four additional articles until October 14, 2010. Data from articles of this period have not been included in the meta-analyses of the current article but are included in the online database. Asterisks indicate that the number of nominally statistically significant and non-statistically significant genes does not sum to the total number of genes because genes encoding cyclin-dependent kinase 2A, the melanocortin-1 receptor, and the vitamin D receptor contained polymorphisms showing both statistically significant ($P < .05$) and non-statistically significant genetic variants identified by meta-analysis.

Sensitivity Analyses and Between-Study Heterogeneity. The sensitivity analyses of the main meta-analyses results entailed calculating summary odds ratios and 95% confidence intervals for all studies excluding the initial report and after excluding studies violating Hardy–Weinberg equilibrium in control subjects according
to a χ² test implemented in the Hardy–Weinberg R package (P ≤ .05). When cell counts were below five, Fisher exact test was used. Between-study heterogeneity was assessed by calculating the F heterogeneity metric. F is estimated by the Q statistic (F = [(Q − df)/Q] × 100) and describes the percentage of variability in point estimates that is because of heterogeneity rather than sampling error (33,34). Contrary to the Q statistic, F does not depend on the number of studies and can be compared across meta-analysis results calculated from different sample sizes. Generally, values greater than 50% represent high heterogeneity (33,34). When there are few studies, both Q and F carry considerable uncertainty and should be interpreted cautiously (35).

Estimating the Credibility of Statistically Significant Associations. Each nominally statistically significant result of the main meta-analysis was graded on the basis of the Human Genome Epidemiology Network Venice criteria for the assessment of cumulative evidence of genetic associations (36,37). These criteria take into account the amount of evidence (sample size measured as the number of minor alleles), consistency of replication (heterogeneity across studies measured as F), and protection from bias (the bias reason, in particular including sensitivity analysis as outlined above, assessments of the strength of the association, small-study bias (38), and evidence for an excess of statistically significant results (39)). On the basis of the analysis, the overall epidemiological credibility was graded as strong (grade A), moderate (grade B), or weak (grade C). For more details on these criteria, see the Supplementary Methods (available online).

The MelGene Database

Demographic details of the studies included in our meta-analyses, genotype data, forest plots, and cumulative meta-analyses results can be found on the publicly available continuously updated MelGene website (http://www.melgene.org) (23).

Results

Literature Searches

After an initial screening of 3113 articles, 145 individual publications reporting on 745 genetic variants in 181 different genes were included in MelGene at the time of the data freeze on July 31, 2010 (Figure 1), including two CM-GWAS (15,16). Both the number of polymorphisms evaluated across all publications and the combined sample size per publication have steadily increased in the past 20 years, with a median of 12 polymorphisms (interquartile range [IQR] = 1–37) and 985 combined patients and control subjects (IQR = 330–1781) between 1992 and 2002, and a median of 82 polymorphisms (IQR = 56–195) and 12613 combined patients and control subjects (IQR = 10 272–20 501) between 2002 and 2010. The most extensively studied genes include MCIR, the vitamin D receptor (VDR), and the agouti signaling protein (ASIP) (18%, 7%, and 6% of the publications listed on MelGene, respectively) (Supplementary Figure 1, available online).

Results of the Main Meta-analyses

Of the 745 polymorphisms included on MelGene, 42 variants in 18 loci fulfilled our criteria for meta-analysis with data available from at least four independent case–control datasets. The meta-analyses were conducted on the basis of a median of six independent case–control datasets (IQR = 5–9). For the number of combined patients and control subjects in specific datasets, see Supplementary Table 1 (available online). Of the variants analyzed, 19 (45%) of 42 in eight loci had nominally statistically significant associations with CM (P < .05) after inclusion of all ethnicities (Table 1 and Supplementary Table 1, available online). These loci comprise the chromosomal region 5p15.33 containing the genes encoding telomerase reverse transcriptase (TERT) and cleft lip and palate-associated transmembrane protein 1-like protein (CLPTM1L); 5p13.2 containing the gene that encodes solute carrier family 45 member 2 (SLC45A2); 9p23 containing the gene for tyrosine-related protein 1 (TTRP1); 9p21.3 containing CDKN2A; 11q14.3 containing the gene encoding tyrosinase (TYR); 12q13.11 containing VDR; 16q24.3 containing MC1R; and 20q11.22 containing the gene ASIP, and genes encoding the myosin heavy chain 7B (MYH7B) and the phosphatidylinositol glycan anchor biosynthesis class U protein (PIGU). Stratification for European ancestry when applicable did not change the overall results (the ancestry-specific meta-analysis results are displayed on the respective forest plots in Supplementary Figure 2, available online). The MelGene website continues to be updated with newly published studies (23).

Genetic Variants Nominally Statistically Significantly Associated With CM in the Main Meta-analyses

The median allelic summary odds ratio was 1.37 (range = 1.05–3.04) for all statistically significant polymorphisms (P < .05) on the basis of a median of seven independent datasets (IQR = 4–19; Supplementary Table 1, available online). To account for the impact of loci with multiple associated single-nucleotide polymorphisms (SNPs), the summary odds ratio was also calculated for the best result per gene (defined according to the SNP with the best Venice score and then according to P), yielding a median summary odds ratio of 1.25 (range = 1.12–2.50). Four loci achieved genome-wide statistical significance (P < 1 × 10⁻⁶), namely MCIR (rs1805007, rs1805008, and rs1805009), MYH7B/PIGU (rs1885120 and rs910873), TYR (rs1126809 and rs1393350), and SLC45A2 (rs16891982; Supplementary Table 1, available online). Dominant and recessive meta-analysis models were also calculated, but neither provided evidence for the association of additional loci with CM nor did the statistical significance of the associations change substantially (data not shown). Twenty-three SNPs in 11 genes did not show statistical significance for association with CM (P ≥ .05) upon meta-analysis, neither on combination of all ancestries nor after stratification for European ancestry (Supplementary Table 1, available online). The sample size was statistically significantly different by Wilcoxon rank sum test when compared with previously reported statistically significant findings (P < .001). For the sample sizes of the individual non-statistically significant polymorphisms, see Supplementary Table 1 (available online). Of note, none of these non-statistically significant polymorphisms have been reported as associated with CM in a GWAS (15,16), although coverage of some loci with the current genotyping platforms may not be optimal.

Supplementary Meta-analyses on Data From GWAS and GWAS-Replication Studies

To assess the evidence for the association of prominent GWAS-identified loci with CM for which less than four independent datasets were available, we performed supplementary meta-analyses...
Table 1: Genetic variants associated with cutaneous melanoma after meta-analyses of at least four independent datasets (main meta-analyses

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Location (nearest gene)</th>
<th>Polymorphism</th>
<th>Allele contrast</th>
<th>Ethnicity</th>
<th>No. of datasets</th>
<th>No. of subjects</th>
<th>MAF</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYRP1</td>
<td>9p21.3</td>
<td>C</td>
<td>T vs C</td>
<td>All</td>
<td>7</td>
<td>41895</td>
<td>0.65</td>
<td>3.0 × 10^-3</td>
<td>1.15 (1.03 to 1.27)</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>12q13.11</td>
<td>C</td>
<td>C</td>
<td>All</td>
<td>9</td>
<td>1885182</td>
<td>0.99</td>
<td>5.6 × 10^-3</td>
<td>1.15 (1.08 to 1.22)</td>
</tr>
<tr>
<td>MYH7B</td>
<td>16q24.3</td>
<td>G</td>
<td>G</td>
<td>NA</td>
<td>21</td>
<td>7440</td>
<td>0.40</td>
<td>7.1 × 10^-3</td>
<td>1.15 (1.08 to 1.22)</td>
</tr>
<tr>
<td>TYR</td>
<td>11q23.3</td>
<td>C</td>
<td>C</td>
<td>NA</td>
<td>21</td>
<td>12662097</td>
<td>0.068</td>
<td>2.7 × 10^-4</td>
<td>1.15 (1.08 to 1.22)</td>
</tr>
<tr>
<td>VDR</td>
<td>20q11.2</td>
<td>C</td>
<td>C</td>
<td>NA</td>
<td>21</td>
<td>12662097</td>
<td>0.068</td>
<td>2.7 × 10^-4</td>
<td>1.15 (1.08 to 1.22)</td>
</tr>
</tbody>
</table>

Grading of Associations

Table 1 lists the variant with the best graded result per genetic locus when applying the Venice interim criteria (36,37) to all meta-analysis results with at least nominal statistical significance for association with CM. For a list of all Venice-graded meta-analysis results and variants, see Supplementary Table 1 (available online). Five genetic loci were found to have strong epidemiological credibility (grade A) for at least one SNP (SLC45A2, TYRP1, TYR, MCI1R, and MYH7B), whereas three loci (CDKN2A, VDR, and CLPTM1L) were found to have only weak credibility (grade C) because of criterion 3 (protection from bias). The main reasons for low grades in the last criterion (protection from bias) were the presence of a summary odds ratio less than 1.15 that can easily be dissipated even by relatively small biases in a meta-analysis of published data (eg, CLPTM1L and VDR), or loss of statistical significance after excluding the initial study and exclusion of Hardy–Weinberg equilibrium-violating datasets (eg, CDKN2A). In our supplementary meta-analyses of data from GWAS and GWAS-replication studies, four variants (rs10757257, rs2218220, rs1335510, and rs7023329) in the CDKN2A/MATP locus showed a genome-wide statistically significant association with CM and furthermore, were assigned an overall strong epidemiological credibility with a grade of A (Table 2); thus, assuming one single underlying association signal in this region, the CDKN2A/MATP locus has strong cumulative evidence for association with CM as well.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Location, bp†</th>
<th>Allele contrast</th>
<th>Ethnicity</th>
<th>N (all)</th>
<th>No. of datasets</th>
<th>MAF</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC647979</td>
<td>rs1335510</td>
<td>21756089</td>
<td>A vs T</td>
<td>All</td>
<td>28</td>
<td>13</td>
<td>5 × 10^{-6}</td>
<td>0.070</td>
<td>0.306</td>
<td>0.415</td>
</tr>
<tr>
<td>MTAP</td>
<td>rs1204552</td>
<td>21756089</td>
<td>A vs T</td>
<td>All</td>
<td>12</td>
<td>3</td>
<td>1.59 × 10^{-2}</td>
<td>0.095</td>
<td>1.66 (1.48 to 1.86)</td>
<td></td>
</tr>
<tr>
<td>MC1R</td>
<td>rs10757257</td>
<td>21756089</td>
<td>A vs G</td>
<td>All</td>
<td>10</td>
<td>3</td>
<td>3.0 × 10^{-2}</td>
<td>0.487</td>
<td>1.36 (1.27 to 1.45)</td>
<td></td>
</tr>
<tr>
<td>AFG3L1</td>
<td>rs10757257</td>
<td>21756089</td>
<td>A vs T</td>
<td>All</td>
<td>10</td>
<td>3</td>
<td>1.59 × 10^{-2}</td>
<td>0.487</td>
<td>1.36 (1.27 to 1.45)</td>
<td></td>
</tr>
<tr>
<td>MYH7B</td>
<td>rs258322</td>
<td>21756089</td>
<td>A vs G</td>
<td>All</td>
<td>12</td>
<td>3</td>
<td>0.070</td>
<td>0.306</td>
<td>0.415</td>
<td></td>
</tr>
<tr>
<td>CDKN2A</td>
<td>rs10757257</td>
<td>21756089</td>
<td>A vs T</td>
<td>All</td>
<td>10</td>
<td>3</td>
<td>1.59 × 10^{-2}</td>
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<tr>
<td>TYRP1</td>
<td>rs258322</td>
<td>21756089</td>
<td>A vs G</td>
<td>All</td>
<td>12</td>
<td>3</td>
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<td>0.487</td>
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<td></td>
</tr>
</tbody>
</table>

* CI = confidence interval, N = number of patients and control subjects combined across all included datasets, OR = odds ratio. Allelic ORs, CIs, and p-values (two-sided) were calculated using the DerSimonian–Laird random-effects model (32). 
† Location is on the basis of the Human Genome Build hg19 (40). 
‡ Alleles in patients and control subjects combined across all included datasets, OR = odds ratio. Allelic ORs, CIs, and p-values (two-sided) were calculated using the DerSimonian–Laird random-effects model (32). 
§ Each statistically significant meta-analysis result was graded according to the Human Genome Epidemiology Network Venice criteria. Venice grading: A = grade A (strong epidemiological credibility), B = grade B (modest epidemiological credibility), and C = grade C (weak epidemiological credibility). 
** Gene” denotes the gene in the respective locus into which the listed SNP maps, whereas “nearest gene” refers to the most proximal gene in the respective locus if the SNP itself does not map into a gene region. It should be noted that these genes are not necessarily the genes that are functionally affected by the genetic association finding in this locus. 
* p-value < 2 × 10^{-6} 
** p-value < 5 × 10^{-8} 
†† p-value < 1 × 10^{-10} 
§§ p-value < 5 × 10^{-15}

**Comparison With Previously Published Meta-analyses**

Six meta-analyses in the CM field had been published as of July 31, 2010, including analysis of a total of 35 SNPs across nine different genetic loci (43–48). In comparison, 83 SNPs across 18 genetic loci were meta-analyzed for our study when combining main and supplementary meta-analyses. The median overall sample size for all SNPs was approximately 8400 combined patients and control subjects in the previous meta-analyses, whereas our study had a median of approximately 11,500 combined patients and control subjects for the same SNPs. For a detailed comparison with previous meta-analyses, see Supplementary Table 3 (49–52) and Supplementary Figure 3 (available online).

**Discussion**

We have conducted, to the best of our knowledge, the first comprehensive and systematic field synopsis of genetic association studies in CM. We more than doubled the number of meta-analyses on genetic variants thus far published in the field of CM. Our synopsis provides an integrated perspective of the accumulated evidence of genetic associations in CM, the results of which are accessible online at the dedicated, regularly updated searchable MelGene website. We identified eight independent genetic loci nominally statistically significantly associated with CM, of which six (MC1R, TYR, TYRP1, SLC45A2, ASIP/PIGU/MYH7B, and CDKN2A/MTAP) were found to have strong epidemiological credibility.

Whereas most studies included in the synopsis used a candidate gene approach, the findings of two recent GWAS have also been included, to the extent of the available data (15,16). Of the six loci with strong credibility, four (MC1R, TYR, TYRP1, and SLC24A5) were previously proposed by candidate gene studies, and two (20q11.22, ASIP/PIGU/MYH7B and 9p21.3, MTAP) were first evaluated by GWAS, although adjacent candidate genes had previously been considered (ASIP and CDKN2A, respectively). Our findings suggest a complementary role for candidate studies and GWAS for CM (53). In studies of other cancer phenotypes, few candidate variants have been validated by GWAS, whereas none of the newly discovered variants in the respective cancer phenotypes had previously been considered in the candidate era (54). It is possible that with larger sample sizes and more comprehensive platforms, some additional previously proposed candidate genes for CM may reach genome-wide statistical significance. Despite the indisputable successes of recent GWAS (15,16) and GWAS-related studies (27–31), the available platforms currently do not cover all human genetic variation. Therefore, it is likely that there are some CM susceptibility genes that are missed by current approaches but may be captured by more comprehensive coverage through extensive imputation using the 1000 genomes resource (55,56) and next-generation resequencing projects. In this context, MelGene provides a dynamic resource to evaluate the constantly evolving evidence for those genetic associations by use of a comprehensive and up-to-date meta-analysis approach.

The loci showing the most compelling risk effect estimates in the MelGene meta-analyses contain genes that seemingly play an important role in modulating pigmented traits of the skin, hair, and/or eyes. However, these CM association findings have to be interpreted cautiously because many of these candidates were...
tested for association with melanoma because of their association to pigmented phenotypes. *MC1R* on chromosome 16q24.3 encodes a cell-surface G-protein-coupled receptor that binds to alpha-melanocyte-stimulating hormone, leading to the production of the photoprotective brown/black eumelanin (57). *MC1R* loss-of-function polymorphisms have been reported to cause a shift of melanogenesis from eumelanin to the red and yellow pheomelanin, resulting in lighter skin, freckles, and red hair color (58,59).

*TYR* on chromosome 11q14.3 encodes tyrosinase, which controls the rate-limiting step of melanin biosynthesis. Rs1126809 (R402Q), a common *TYR* SNP that shows the strongest association with CM in our meta-analyses, has been reported to reduce the catalytic activity of tyrosinase (60) and has been associated with blue vs green eyes, and skin sensitivity to the sun (61). The association signal of rs1393350, yielding the second strongest association in the MelGene analyses for this locus was reported as being independently associated with CM in a recent GWAS (15). Similar to *TYR*, *TYRP1* on chromosome 9p23 encodes an enzyme of the pigmentary system required for the eumelanization of melanosomes (62). Germine mutations of *TYRP1* are the cause of oculocutaneous albinism type 3, and coding variants associated with CM have been associated with eye and hair color (61). SLC45A2 on chromosome 5p13.2 encodes a melanocyte differentiation antigen that is overexpressed in melanoma cell lines (63). For the nonsynonymous SNP rs16891982 (F374L) that is associated with CM with genome-wide statistical significance in this study, the ancestral Leu allele has been found more frequently in Southern Europe and is associated with dark skin, eye, and hair color in people of European ancestry (64–66). Finally, the two statistically significant variants at chromosome 20q11.22 fall within the *PIGU* gene (also known as *CDC91L1*), which is involved in cell cycle control and within the *MYH7B* gene, respectively. These statistically significant variants at chromosome 20q11.22 may not be disease-modifying variants, but may be positional markers that highlight an unidentified melanoma risk locus adjacent to *ASIP* (16). Although the identification of associated SNPs in the vicinity of *CDKN2A* (*MTAP*, 9p21.3) (15) possibly reflect the effects of highly penetrant *CDKN2A* mutations via linkage disequilibrium not tagged by currently known common variants, the concurrence of low to moderate independent risk effects in the *MTAP* locus itself may directly influence melanocytic proliferation (42). This hypothesis is also supported by an association signal with nevi count in *MTAP* (29), suggesting a shared susceptibility of nevi and melanoma. Thus, there may be at least two genetically distinct effects influencing melanoma susceptibility, that is, those mainly influencing pigmentation and those associated with nevus development (67).

Our study does have some limitations. First, despite the use of different strategies to identify eligible studies for MelGene, some studies may have been erroneously excluded. Also, although manual data extraction from the included studies followed an established protocol, it is possible that some study entries contain random errors. In addition, our analyses focused on allelic contrasts. However, we also performed an analysis of genotypic models that yielded similar results. Another limitation of our study is that lack of access to individual data precludes more refined analyses and adjustment for potential confounders and other types of bias, for example, pigmentation status, age, and sex which may potentially lead to false-positive or false-negative meta-analysis results, or different magnitudes of effect. Furthermore, lack of individual data does not allow the assessment of potential gene–gene and gene–environment interactions. We assessed potential sources of bias by extensive sensitivity analyses on the data summary level, but our study is limited because potential undetectable bias can never be ruled out, particularly publication bias. Although we tested for small-study effects, publication bias cannot be entirely excluded in retrospective meta-analyses. Finally, several of the nominally statistically significant associations may still be false-positive results. However, this is unlikely for those associations that have strong credibility on the basis of the Venice criteria and those that have reached levels of genome-wide statistical significance.

In summary, we present a systematic and comprehensive assessment of the current evidence of genetic epidemiology research in CM. The putative risk factors that have emerged from the meta-analyses—accessible on MelGene—represent the most promising CM susceptibility genes described to date. The integration of results from future small- and large-scale genetic association studies in MelGene will further expand our knowledge of the underlying genetic mechanisms of CM.

**References**


Notes
F. Chatzinasiou and C. M. Lill contributed equally to this work.

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