Assessment of melanoma candidate genes in a meta-analysis of 16,534 melanoma cases

Editor

Cutaneous melanoma (CM) accounts for the majority of deaths from skin cancer and its development is an interplay between phenotypic characteristics[1], environmental exposures[2] and genetic risk factors[3]. Several genetic variants have been found to be strongly associated with risk of melanoma using a candidate gene approach.

The aim of our study was to identify, novel CM genetic factors, using all candidate genes encompassed in the MelGene database (www.melgene.org), a comprehensive online database[3-5], by assessing their association in the largest GWAS published up to date[6]. Promising signals were selected for replication in UK-Biobank (https://www.ukbiobank.ac.uk/), a prospective cohort study of 500,000 participants and two independent samples of CM patients and healthy controls from Greece and Cyprus. The results of the initial GWAS and the three replication studies were finally combined using a meta-analysis framework.

760 variants were retrieved from the MelGene database and tested for association in a meta-analysis of 11 GWAS consisting of 12,874 CM cases and 23,303 controls of European ancestry[6]. We calculated a false discovery rate and variants that surpassed this p-value threshold were genotyped in three independent replication samples from UK, Greece and Cyprus. We excluded variants robustly associated with CM or in linkage disequilibrium with already known loci. The results from the GWASs and replication stages were synthesized in a meta-analysis.

The UK-Biobank data release contains genotypes of 488,377 participants. We included unrelated individuals of European ancestry only and we identified CM cases via record linkage to the UK National Health Service (NHS) Central Registers. We therefore, ended up with 2,871 cases whose first cancer diagnosis was CM and 349,984 cancer-free participants. The sample from Greece/Cyprus involved 771/32 unrelated cases and 744/201 healthy controls[7,8].

From the 760 variants, that were selected as candidate genetic markers for association with CM, after removing those that failed to surpass the pre-defined cutoff of p-value<9.1×10^{-5}, duplicates, SNPs that have been previously robustly associated with CM[3, 6] or other CM related phenotypes[9, 10] and those that were in LD with the already known loci (i.e., r^2>0.3) we ended up with SNP rs909253 (+252 G/A) in the *Lymphotoxin Alpha* (*LT-alpha* or *TNF-beta*) gene.

A total of 2,871 cases and 349,984 controls from UK-Biobank, 758 cases and 738 controls from Greece and 31 cases and 193 controls from Cyprus were analysed, after removing individuals that were not successfully genotyped during the quality control process, consisting a total sample size of 3,660 total melanoma cases and 350,915 controls.

Overall, the meta-analysis of the 11 GWAS indicated a protective effect for the G allele with the risk of CM (OR: 0.921, 95% CI: 0.887, 0.957; p-value=$2.7x10^{-5}$; I^2=0%) (Fig.1). However, the estimates from the three replication samples were not statistically significant (summary OR: 0.961, 95% CI: 0.913, 1.012, p-value=0.13). The combined meta-analysis OR from the GWAS and the replication dataset was 0.935 (95% CI: 0.907, 0.965; p-value=$1.95x10^{-5}$; I^2=39.8%).

Overall, in this work we aimed to establish novel genetic markers associated with CM by integrating already existing information derived from GWAS. After evaluating the candidate genes reported in the MelGene database, our elimination procedure identified one SNP for further follow-up in the available replication resources. However, whilst replication samples from UK-Biobank, Greece and Cyprus yielded a similar OR, the SNP did not reach genome wide significance and currently cannot be considered a genuine CM locus – given the small ORs a very large genetic association study will be required to determine if this SNP is a false positive or if it has a real, but small, effect on CM. Future candidate studies on these variants should be avoided and interest should be shifted to larger GWAS.

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Legends

Figure 1. Summary of the GWAS meta-analysis and three replication studies for the association of one SNP in Lymphotoxin Alpha gene with cutaneous melanoma.