Published in final edited form as:
Pigment Cell Melanoma Res. 2009 October ; 22(5): 527–528. doi:10.1111/j.1755-148X.2009.00622.x.

Genome-Wide Associations Studies for Melanoma and Nevi

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Two new genome wide association studies (GWAS) add to our understanding of genetic risk factors for development of melanoma and melanocytic nevi.

Familial melanoma accounts for ~10% of cases. Thus far, causative genetic mutations have been identified through linkage studies, which typically find high penetrance, low frequency genetic variants. Approximately 40% of affected families have CDKN2A mutations and a small number of families carry CDK4 mutations. The genetic basis of the remainder of familial cases is unknown. Linkage studies suggest a susceptibility locus on the short arm of chromosome 1, and there may be many alleles that increase risk by a small amount.

High frequency alleles with small effects on melanoma risk in European populations have been identified in MC1R (melanocortin 1 receptor), ASIP (agouti signaling protein), TYR (tyrosinase), and TYRP (tyrosinase related protein). These associations were identified via directed investigation of polymorphisms in genes known to be involved in pigmentation. MC1R variants have been shown to contribute to melanoma risk, even beyond their marked effect on pigmentation phenotype. In contrast, other variants associated with freckling and sun sensitivity have not found to be associated with melanoma thus far in association studies (SLC24A4, KITLG, OCA2).

The GenoMEL consortium performed a genome wide association study (GWAS) to look broadly for associations of common, low-penetrance genetic variations with melanoma (Bishop et al. 2009). rs258322, the single nucleotide polymorphism (SNP) with the highest association at 16q24 (which contains MC1R), was found to have a per-allele odds ratio (OR) of 1.67 for melanoma. This SNP was also found to be associated with hair color and pigmentation in a previous GWAS. That study showed that the SNP's correlation with the two phenotypes was due to functional variants in MC1R that are in linkage disequilibrium (LD) with rs258322. Bishop et al. note the magnitude of the association for rs258322 with melanoma is similar to that recently described for MC1R variants and it is likely that the association at rs258322 is due to functional MC1R variants. In contrast, rs8059973 which is ~90Kb from MC1R was found to have an independent association with melanoma; replication and fine mapping of this SNP must be completed before the significance of this association is understood. Bishop et al. also replicated previously suggested associations–one with a coding variant in TYR (tyrosinase) (OR=1.27) and another in 20q11.22, near ASIP.

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Coverage of:

Falchi M, Bataille V, Hayward NK, Duffy DL, Bishop JAN, Pastinen T, Cervino A, Zhao ZZ, Deloukas P, Soranzo N, Elder DE, Barrett JH, Martin NG, Bishop DT, Montgomery GW, Spector TD. Genome-wide association study identifies variants at 9p21 and 22q13 associated with development of cutaneous nevi. Nat. Genet. 2009 Aug ;41(8):915-919.

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In addition to hits near MC1R, TYR and ASIP, Bishop et al. found a novel association for two SNPs in 9p21. The two SNPs were independently associated with melanoma, spanning the region that contains CDKN2A. rs[b–z] 329 (OR=1.18) is ~150kB downstream from CDKN2A, within an intron of MTAP (methylthioadenosine phosphorylase). MTAP is often co-deleted with CDKN2A, and plays a role in adenine and methionine salvage. Reduced expression of MTAP has been previously demonstrated in malignant melanoma, but the functional consequences are unclear. A second SNP in 9p21, rs1011970, is 87kB upstream of CDKN2A and is within ANRIL, an antisense non-coding RNA that overlaps with the promoter of CDKN2A and the transcribed sequence of CDKN2B. As the study population was enriched for family history of melanoma, early age of onset, and multiple primaries, it is possible that a higher number of high penetrance CDKN2A mutations in the study population couldcontribute to this effect. As the CDKN2 mutation status of the patients carrying the associated nearby SNPs is not known, associations could be due to CDKN2A mutations arising on different genetic backgrounds. While rare, mutations in CDKN2A have very high penetrance, and the selection of patients could have pushed the expected frequency of CDKN2A mutations well above the 2% expected in an unselected cohort of melanoma patients. Alternatively, these signals could be due to high frequency low risk alleles affecting CDKN2A function in a novel way (supported by a study showing melanoma risk associated with common variants in CDKN2A (Debniak et al. 2006)) or by variants in nearby genes.

The number of melanocytic nevi is positively correlated with melanomarisk, more so than pigmentation and tanning response differences. Individuals at particularly increased risk are those with large or “dysplastic nevi”. Increased nevus counts are also associated with increased UV exposure. Nevi frequently harbor mutations in BRAF and NRAS, the same as those found in melanoma, and a subset of melanomas arises within nevi. Previously, linkage studies in twins identified an association with nevus counts near the CDK2A locus in addition to linkage with other loci.

A recent GWAS by Falchi et al. 2009 for nevus count using cohorts from the UK and Australia also found a strong association with SNPs at 9q21. The SNP with the highest association, rs4636294, is located in the 5′UTR of MTAP. Overall, the signals within 9p21 overlapped with those found to be associated with melanoma in the study discussed previously. As the cohort for the nevus association study was not enriched for individuals with an increased melanoma risk, this finding supports the existence of low penetrance variants affecting melanocytic proliferation, i.e. nevi and melanoma, in this region. An additional association with nevus count was identified within 22q13, with rs2284063 showing the lowest p-value. This SNP lies within an intron of PLA2G6, a member of the phospholipase A2 gene family. The associations identified accounted for less than 3% of the variance in nevus counts across all populations studied, therefore many additional genetic factors likely remain to be discovered. After identifying associations with nevus count using one cohort, the authors tested for and found associations between these SNPs and melanoma in a separatecase control sample. Factoring nevus count into their model reduced the risk attributed to each SNP. Thus the risk of melanoma associated with the 9p21 and 22q13 loci is at least partially mediated via nevus count. Bishop et al. replicated the association with the SNPs at 22q13 with melanoma.

Given the relationship between nevus count and melanoma and the associations of the SNPs identified in the nevus study with melanoma, the causative variants at 9p21 are quite possibly the same for both phenotypes. PLA2G6 is interesting due to known associations with lung cancer susceptibility and roles in cell growth and proliferation, but the association with nevus count was stronger for nearby imputed SNPs, some of which are not located within the transcript of PLA2G6 but closer to other genes. Thus the causative variant may not act through PLA2G6.

In contrast to the melanoma GWAS, the GWAS for nevus count did not identify a signal in the MC1R region, consistent with prior reports indicating that MC1R variants are associated with pigmentation phenotypes, freckling and melanoma, but not with nevus counts. Given the current model where nevi are composed of melanocytes with UV induced genetic alterations that are held in check by senescence mechanisms (Mooi and Peeper, 2006), these findings raise the question: how does MC1R increases melanoma risk without having an apparent effect on nevus counts? As the melanoma risk conveyed through MC1R variation varies with the type of melanoma (Landi, 2006), future GWAS association studies stratified by histologic subtype or somatic mutations of the tumor may shed light on this interesting question.

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