Gene Variants in Multiple Melanomas

Patients with multiple primary cutaneous malignant melanomas in Norway have a significantly higher likelihood of carrying a *MC1R* variant and an *ASIP* haplotype than blood donors, according to a recently published case-control study by Helsing et al. No association with *TYR* and *TYRP1* variants was found.

This is a summary of a paper recently published by *Helsing P, Nymoen DA, Rootwelt H, Vårdal M, Akslen LA, Molven A, Andresen PA.* MC1R, ASIP, TYR *and* TYRP1 *gene variants in a population-based series of multiple primary melanomas. Genes Chromosomes Cancer 2012; 51: 654–661. E-published on 23.3.2012.*

Patients with multiple primary melanomas often have a positive family history of melanoma, indicating an hereditary component of the disease mechanism. Known genetic risk factors are rare, high-penetrant germline mutations in 2 genes encoding key regulators of the cell cycle, *CDKN2A* and *CDK4*, and common, low-penetrant alleles of the pigmentation gene *MC1R*. More recently, single nucleotide polymorphisms (SNPs) of 3 other genes affecting melanogenesis, *ASIP, TYR* and *TYRP1*, have been linked to increased risk of melanoma in genome-wide association studies.

The effect of common variants of the susceptibility genes *MC1R*, *ASIP*, *TYR* and *TYRP1* on the risk of multiple primary melanoma, with or without *CDKN2A/CDK4* mutations, has been investigated recently in a case-control study published in the journal Genes, Chromosomes & Cancer (1).

Patients with multiple primary melanomas (*n*=388) were identified through the Norwegian Cancer Registry, having a history of at least 2 primary melanomas, of which maximally one could be an *in situ* melanoma. Randomly selected, anonymous Norwegian blood donors (*n*=420) were used as controls, almost all of the donors were ethnic Norwegians and other Caucasians. *MC1R* allele frequencies were determined for 9 non-synonymous coding variants and one promoter variant.

At least one of the genotyped *MC1R* variants was detected in 334 patients with multiple primary melanomas (87.8%) vs 314 in the control population (78.3%; OR=1.73, 95% CI 1.18–2.52). The maximum number of variants carried by 1 individual was 2, both among patients and controls. Arg151Cys and Arg160Trp, the main red-hair colour (RHC) variants for attributable risk, were the most frequent *MC1R* polymorphisms, being found in 12.5% and 11.6% of the controls, respectively.

Significant frequency differences between patients and controls were observed for Asp84Glu (OR=5.77, CI 1.97–16.89) and Arg151Cys (OR=1.80, CI 1.36–2.37), both being more prevalent among patients with multiple primary melanomas. Arg160Trp was significantly associated with melanoma only in the group of mutation-positive cases, where 20 out of 30 patients were heterozygous for this variant (OR=3.50, CI 1.97–6.22). An even higher OR was found for mutation positives carrying the Asp84Glu allele (OR=10.92, CI 2.39–49.97). Furthermore, a significant association was found for the MC1R promoter variant c.226A>T (OR=1.87, CI 1.10–3.18) in the group of mutation-positive patients.

The OR for developing multiple primary melanomas was higher with 2 RHC variant alleles compared with 1 or no RHC alleles. In patients with no *CDKN2A*/*CDK4* mutations, there was a trend of developing more than 2 melanomas when carrying at least 1 RHC variant (OR=1.44, CI 0.77–2.70).

Eight of 9 possible ASIP genotypes, based on the SNPs rs1015362A>G and rs4911414G>T, were observed. Four of these genotypes had the rs1015362-G and rs4911414-T alleles represented. The frequency of the *ASIP* haplotype AH was estimated to be 11.3% in patients and 6.9% in control persons, giving a significantly increased risk of melanoma (OR=1.72, CI 1.12–2.49). No increased risk was observed for *TYR* or *TYRP1*.

The study confirms that *MC1R* polymorphisms are relatively frequent in the Norwegian population, and even more frequent in patients with multiple primary melanomas. The variants with the highest effect appeared to be Asp84Glu and Arg151Cys, whereas Asp84Glu and Arg160Pro increased the risk of multiple primary melanomas in *CDKN2A*/*CDK4* mutation-positive patients. Carriers of 2 RHC variants of *MC1R* showed the highest risk of developing melanoma. However, *MC1R* is a low-penetrance melanoma gene, and a clinical implication of determining the *MC1R* status remains to be shown.

Per Helsing, the paper's first author, is a senior consultant at the Department of Dermatology, Oslo University Hospital, Oslo, Norway. The co-authors are molecular biologists, pathologists, and a statistician at Oslo University Hospital in Oslo and Haukeland University Hospital in Bergen.

Petter Gjersvik, Country Editor, Norway
Department of Dermatology, Oslo University Hospital, Oslo, Norway. E-mail: petter.gjersvik@rikshospitalet.no