Common and rare variants in the genetic susceptibility to melanoma

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155 College Street, Toronto, ON

Abstract: Incidence of melanoma, a skin cancer affecting melanocytes, has been rising steadily over the past 50 years. When diagnosed at a late stage, melanoma has poor survival rates and it is the most fatal of all skin cancers. Melanoma results from multiple genetic and environmental factors. The only established environmental factor is sun exposure, but its relationship with melanoma is complex. Genetic susceptibility to melanoma shows a broad spectrum of genetic variation from rare mutations conferring a high risk to common genetic variants conferring a low to moderate risk. Genome-wide association studies (GWAS) have been successful in identifying 16 loci harbouring common genetic variants associated with melanoma and melanoma-related phenotypes (pigmentation, nevi). However, the functional role of the genetic variants within these loci is mostly unknown. By taking MC1R (melanocortin 1 receptor) gene as a paradigm, we have shown that genotypic imputations and multi-marker analysis can pinpoint the gene with a potentially functional role in disease among all genes belonging to a disease-associated region. However, re-sequencing is needed to provide a full picture of disease-related variation. The genetic variants identified by GWAS only account for a part of melanoma risk and many other genes remain to be discovered. Integration of biological knowledge with genome-wide SNP data is one route to facilitate gene discovery. We have undertaken pathway-based analysis, using various methods, to characterize new melanoma genes. The outcomes from this approach will be discussed. On the other hand, integration of clinical and genetic research can be a powerful and cost-effective strategy to identify rare variants. The collection of a series of patients showing both melanoma and renal cell carcinoma (RCC) has enabled the identification of a germline missense substitution in MITF (microphthalmia-associated transcription factor), a candidate gene for melanoma and RCC. By sequencing MITF, we identified the Mi-E318K substitution (frequency of 0.3% in controls) that increased the risk of developing melanoma, RCC or both cancers. Functional studies showed that Mi-E318K severely impairs sumoylation into the link between sumoylation, transcription and cancer. Therefore, the use of various strategies can decipher the genetic architecture of a complex disease such as melanoma and can improve our understanding of the mechanisms underlying tumor development.

Profile: Florence Demenais is INSERM Director of Research and Head of the Genetic Variation and Human Diseases Unit, sponsored by both INSERM and University Paris Diderot, Paris, France. She received her medical and quantitative genetics degrees from the University of Paris. Dr. Demenais trained as a postdoctoral fellow in the Department of Biostatistics, University of North Carolina at Chapel Hill (USA), with Prof. Robert Elston. She conducted most of her scientific career in statistical genetics and genetic epidemiology at INSERM. From 1987 to 1991, she was Associate Professor in the Division of Biostatistics, Howard University Cancer Center, Washington, DC, where she worked with Dr. George Bonney on the regressive models for familial analysis of complex diseases. In 1991, Dr. Demenais joined Prof. Mark Lathrop’s group at INSERM in Paris and was promoted to INSERM Director of Research. Since 1995, she has been the Head of several INSERM research laboratories. She has made important contributions to the development and assessment of statistical methodology for combined segmentation-linkage analysis and association studies and to the identification of genes and gene-environment interactions in common multifactorial diseases including infectious diseases, cancers, and asthma. She has coordinated large-scale studies of various multifactorial diseases nationally and internationally. She is the co-author of more than 150 publications with a number of them in leading journals. Dr. Demenais has served on many advisory boards and scientific committees. She has trained many doctoral and postdoctoral fellows. Amongst other honours, she was the recipient of the INSERM award in Genetic Epidemiology in 2003 and of the French Academy of Sciences award in Epidemiology in 2010. In 2008, Dr. Demenais was President of the International Genetic Epidemiology Society.

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