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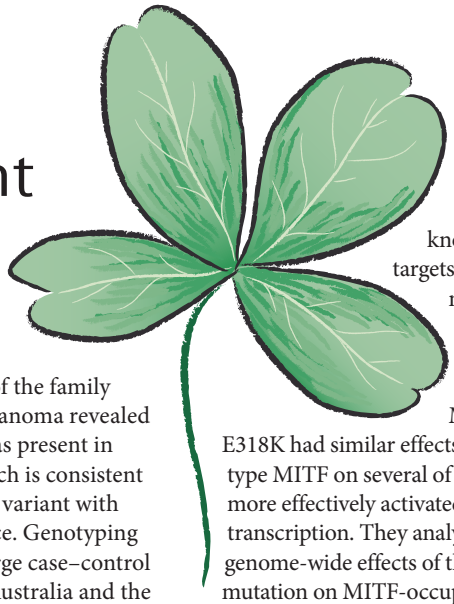
CANCER GENOMICS

Finding a rare variant



Familial melanoma has been linked to mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and *CDK4*, but these two genes account for only a minority of genetic risk. Two studies reported in *Nature* have now identified a germline mutation in microphthalmia-associated transcription factor (*MITF*) that predisposes to familial melanoma, as well as to sporadic melanoma and renal cell carcinoma (RCC).

Melanoma and RCC coexist in some patients, an association that has been suggested to involve genetic predisposition. Bertolotto *et al.* proposed that MITF might have a role owing to its oncogenic role in melanomas and its ability to induce the transcription of hypoxia-inducible factor 1α (*HIF1A*), the pathway of which is disrupted in RCC. They sequenced *MITF* in 62 patients with both cancers and discovered a heterozygous germline mutation resulting in substitution of glutamic acid 318 with lysine (E318K) that was significantly more frequent than in controls. MITF E318K also significantly increased susceptibility to melanoma and RCC alone; carriers of this mutation had a more than fivefold increased risk of developing either or both of these cancers.

Working independently, Yokoyama *et al.* sequenced the genome of a patient with melanoma who came from a family with eight melanoma cases that were negative for *CDKN2A* and *CDK4* mutations. They found 410 novel variants that were predicted to affect the structure of a protein, and prioritized a single nucleotide polymorphism in *MITF* — which also leads to the E318K substitution — for follow-up. Sequencing of *MITF* in seven of the family members with melanoma revealed that this variant was present in three patients, which is consistent with it being a risk variant with medium penetrance. Genotyping of *MITF* in four large case–control sample sets from Australia and the United Kingdom indicated that MITF E318K occurs significantly more frequently in cases than in controls and thus correlates with an increased risk of melanoma in the general population. Furthermore, the E318K variant was associated with the melanoma-associated phenotypes of increased naevus count and non-blue eye colour, but not with other pigmentation traits.

> “MITF E318K … correlates with an increased risk of melanoma in the general population.”

The E318K mutation in MITF occurs within a small-ubiquitin-like modifier (SUMO) consensus site. Both groups confirmed that this mutation disrupts sumoylation, and that this loss of sumoylation enhances transcription of some, but not of all, MITF-responsive genes. Yokoyama *et al.* analysed whole-genome expression profiles following inducible expression of either wild-type MITF or MITF E318K in two melanoma cell lines with low expression of endogenous MITF, and identified several genes that were differentially regulated, including some genes involved in pigmentation, but others were regulated similarly by both wild-type and mutant MITF. Bertolotto *et al.* first looked at several known MITF targets in a melanoma cell line and noted that MITF E318K had similar effects to wild-type MITF on several of these, but more effectively activated *HIF1A* transcription. They analysed genome-wide effects of the E318K mutation on MITF-occupied loci using chromatin immunoprecipitation, which indicated a higher overall promoter occupancy by MITF E318K compared with wild-type (22,157 versus 9,107 occupied sites), but not all MITF-responsive genes showed preferential occupation by MITF E318K. This method also confirmed the increase in MITF E318K occupancy at the *HIF1A* promoter. Finally, they showed that expression of MITF E318K could enhance *in vitro* migration, invasion and colony formation of both melanoma and RCC cell lines.

Both papers have demonstrated different ways of finding new rare susceptibility mutations that might not be detected by approaches such as linkage analysis or genome-wide association studies. They have also shown a new link between deregulated sumoylation and cancer.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPERS Bertolotto, C. *et al.* A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma. *Nature* 19 Oct 2011 (doi:10.1038/nature10539) | Yokoyama, S. *et al.* A novel recurrent mutation in *MITF* predisposes to familial and sporadic melanoma. *Nature* 13 Nov 2011 (doi:10.1038/nature10630)