PubMed

Display Settings: Abstract

Nature. 2011 Oct 19;480(7375):94-8. doi: 10.1038/nature10539.

A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma.

Bertolotto C, Lesueur F, Giuliano S, Strub T, de Lichy M, Bille K, Dessen P, d'Hayer B, Mohamdi H, Remenieras A, Maubec E, de la Fouchardière A, Molinié V, Vabres P, Dalle S, Poulalhon N, Martin-Denavit T, Thomas L, Andry-Benzaquen P, Dupin N, Boitier F, Rossi A, Perrot JL, Labeille B, Robert C, Escudier B, Caron O, Brugières L, Saule S, Gardie B, Gad S, Richard S, Couturier J, Teh BT, Ghiorzo P, Pastorino L, Puig S, Badenas C, Olsson H, Ingvar C, Rouleau E, Lidereau R, Bahadoran P, Vielh P, Corda E, Blanché H, Zelenika D, Galan P; French Familial Melanoma Study Group, Aubin F, Bachollet B, Becuwe C, Berthet P, Bignon YJ, Bonadona V, Bonafe JL, Bonnet-Dupeyron MN, Cambazard F, Chevrant-Breton J, Coupier I, Dalac S, Demange L, d'Incan M, Dugast C, Faivre L, Vincent-Fétita L, Gauthier-Villars M, Gilbert B, Grange F, Grob JJ, Humbert P, Janin N, Joly P, Kerob D, Lasset C, Leroux D, Levang J, Limacher JM, Livideanu C, Longy M, Lortholary A, Stoppa-Lyonnet D, Mansard S, Mansuy L, Marrou K, Matéus C, Maugard C, Meyer N, Nogues C, Souteyrand P, Venat-Bouvet L, Zattara H, Chaudru V, Lenoir GM, Lathrop M, Davidson I, Avril MF, Demenais F, Ballotti R, Bressac-de Paillerets B.

1] INSERM, U895 (équipe 1), Equipe labélisée Ligue Contre le Cancer, C3M, 06204 Nice, France [2] Université of Nice Sophia-Antipolis, UFR Médecine, 06204 Nice, France [3] Centre Hospitalier Universitaire de Nice, Service de Dermatologie, 06204 Nice, France [4].

Abstract

So far, no common environmental and/or phenotypic factor has been associated with melanoma and renal cell carcinoma (RCC). The known risk factors for melanoma include sun exposure, pigmentation and nevus phenotypes; risk factors associated with RCC include smoking, obesity and hypertension. A recent study of coexisting melanoma and RCC in the same patients supports a genetic predisposition underlying the association between these two cancers. The microphthalmia-associated transcription factor (MITF) has been proposed to act as a melanoma oncogene; it also stimulates the transcription of hypoxia inducible factor (HIF1A), the pathway of which is targeted by kidney cancer susceptibility genes. We therefore proposed that MITF might have a role in conferring a genetic predisposition to co-occurring melanoma and RCC. Here we identify a germline missense substitution in MITF (Mi-E318K) that occurred at a significantly higher frequency in genetically enriched patients affected with melanoma, RCC or both cancers, when compared with controls. Overall, Mi-E318K carriers had a higher than fivefold increased risk of developing melanoma, RCC or both cancers. Codon 318 is located in a small-ubiquitin-like modifier (SUMO) consensus site (ΨKXE) and Mi-E318K severely impaired SUMOylation of MITF. Mi-E318K enhanced MITF protein binding to the HIF1A promoter and increased its transcriptional activity compared to wild-type MITF. Further, we observed a global increase in Mi-E318K-occupied loci. In an RCC cell line, gene expression profiling identified a Mi-E318K signature related to cell growth, proliferation and inflammation. Lastly, the mutant protein enhanced melanocytic and renal cell clonogenicity, migration and invasion, consistent with a gain-of-function role in tumorigenesis. Our data provide insights into the link between SUMOylation, transcription and cancer.

Comment in

Cancer genomics: Finding a rare variant. [Nat Rev Cancer. 2011]
Microphthalmia-associated transcription factor, melanoma, and renal carcinoma: the small ubiquitin-like modifier connection. [Pigment Cell Melanoma Res. 2011]

PMID: 22012259 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources