Research Letter

Germline Duplication of Chromosomes 10p15.3 and Yp11.32 in a Man With Learning Disability and Early Onset Cutaneous Malignant Melanoma

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To the Editor:

Newer molecular cytogenetic analysis methods such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) have facilitated identification of cytogenetic abnormalities in solid tumors. In parallel, CGH has been rapidly adopted in the clinical evaluation of individuals with developmental delays. We recently evaluated an 18-year-old male with a history of learning disabilities who developed a cutaneous malignant melanoma (CMM) in a non-sun-exposed area. He was the only child born to a non-consanguineous couple. His father was a healthy 40-year-old of mixed European ancestry. His mother was of Italian ancestry and had died at age 30 of an insulin reaction from type 1 diabetes. There was no family history of melanoma or any cancers at unusual ages. He developed a rapidly enlarging lesion in his posterior scalp that was initially thought to be inflammatory but subsequently became black. A diagnostic biopsy showed a Clark level IV nodular melanoma, 3.3 mm in thickness with ulceration and with one occipital node positive for a micrometastatic melanoma. On his physical examination he was a well nourished young man of normal stature with dark brown hair, brown eyes and relatively fair skin with no evidence of excessive solar damage or tanning (Fig. 1). There were no unusual pigmented lesions anywhere else on examination. He had been healthy prior to this diagnosis, but was noted to have had significant learning disabilities. Clinical mutation analysis showed no mutations within the CDKN2A gene and sequence analysis of CDK4 gene showed no mutations [GeneDX, Gaithersburg, MD] but microarray analysis showed two areas of duplication including chromosomes 10p15.3 and X/Yp11.32 (pseudoautosomal region). Microarray analysis of the patient’s father showed that he was a carrier of the X/Yp11.32 duplication and therefore confirmed its origin as the Y chromosome. We cannot determine if the chromosome 10p15.3 duplication was of maternal origin or was de novo. The final report from Signature Genomic Laboratory was reported as arr cgh Xp22.33 Yp11.32 (RP13-76L22, RP11-946P8, RP11-309M23)x3 pat, 10p15.3 (RP11-105A22, RP11-58N22, RP11-89K18)x3.

Several CMM susceptibility loci have been reported, including the tumor suppressor gene, CDKN2A on chromosome 9p21; the CDK4 oncogene on chromosome 12q14; and linkage to both 1p36 and 1p22 in melanoma family studies [Kamb et al., 1994; Zuo et al., 1996; Gillanders et al., 2003; Molven et al., 2005]. In addition, Petty et al. [1993a,b] reported an unbalanced reciprocal translocation of chromosome 5 and 9, an important factor of melanoma tumorigenesis. Other genes reported to be low-risk susceptibility variants include MCIR on chromosome 16q24.3, ARLTS1 on chromosome 1q42, NBS1 on chromosome 8q21, and others [Box et al., 2001; Frank et al., 2006; Meyer et al., 2007]. None of these seem directly relevant to the current case report.

A recent study of 76 melanoma cell lines using a genome-wide high-density single nucleotide microarray showed frequent chromosomal losses of 9p, 10p, 10q, 9q, 6q, 11q, 17p, and 5q, which are consistent with prior reports [Poetsch et al., 2003;
Stark and Hayward, 2007]. In the same study, copy number increases were found most commonly (>20%) involving chromosomes 2p, 6p, 7p, 7q, 9q, 20q, and 22q. Only one cell line was reported to have amplification of 10p, and this was the MAP3K8 gene at 10p11.2. The sex chromosomes were not studied. In a second study of 47 melanoma cell lines using tiling-resolution array comparative genomic hybridization, copy number gains were found most frequently on chromosomes 1q, 7p, 7q, 8q, 17q, and 20q [Jönsson et al., 2007]. We could not find reports of duplication or amplification of either chromosome 10p15.3 or Yp11 to be associated with CMM or any other phenotype.

We speculate on how either of these duplications may have predisposed to this man’s phenotype. The subtelomeric region, 10p15.3, contains DIP2C, which encodes Disco-interacting Protein 2 and is expressed in nearly all tissues, including adult brain. Alterations in expression of its close homologue, DIP2B, by a trinucleotide expansion, analogous to that seen in Fragile X Syndrome, is a cause of mental retardation [Winneppeninckx et al., 2007]. Conceivably, a duplication involving DIP2C may be of relevance to the learning disabilities in this patient, but we could find no associations with melanoma. The platelet-type phosphofructokinase, PFKP, also maps to 10p15.3 but has not been implicated in neoplasia. The Kruppel-like factor-6 (KLF6 gene), a protooncogene transcription factor that up-regulates p21 in a p53-independent manner is mapped to 10p15 [Cho et al., 2005]. Somatic mutations in prostate and gastric cancer have been reported, but this gene has not been associated with melanoma [Narla et al., 2001]. Several genes of interest map to 10p15-10p15.1 including RTE1, a repressor of telomerase expression, DNMT2, which methylates small RNAs, RBM17, an RNA binding motif protein that is part of the spliceosome, and PRKCQ, a serine threonine kinase involved with cellular differentiation and proliferation. It is unknown if the duplicated area might perturb function of any of these genes. Examination of the genes in the pseudoautosomal area of the Y chromosome does not yield strong candidates for melanoma predisposition. A gene in the pseudoautosomal area of Xp22.3 was reported to be among 361 sequences that discriminated between melanomas associated with distant metastasis-free survival [Winneppeninckx et al., 2006], but no site on the Y chromosome was reported in that study.

In summary, we report on a patient with CMM at early age in the context of germline duplications of chromosomes 10p15.3 and Yp11.32, neither of which is known to be associated with predisposition to melanoma. It is not clear if these observations are coincidental or etiologic.

REFERENCES


