Reviewer's report

Title: Monozygotic Twins with Neurofibromatosis Type 1, Concordant Phenotype and Synchronous Development of MPNST and Metastasis

Version: 1  Date: 14 April 2010

Reviewer: Rebecca Johnson

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Minor Compulsory Revisions

1. Confirm that this in fact the first report of MZ twins with concordant tumors

See Am J Med Genet A. 2006 Oct 1;140(19):2080-4. Non-random associations and vascular fields in neurofibromatosis 1: a pathogenetic hypothesis. Lubinsky MS: This article references a previous report of concordance for tumors in NF1 “We have seen a MZ twin pair concordant for renal vascular hypertension, and another for unilateral ptosis. Other concordances have been reported, including both malformations and tumors, and combinations as well.” I do not see that it directly references these reports, however, and it’s possible that the authors are not referring to MZ twins with tumors.

Minor Discretionary Revisions

2. Overall this is a reasonable case report, although it would be greatly strengthened by more discussion the potential modifier genes for NF1, as well as the current thinking on progression of genetic changes from neurofibroma to MPNST. There are several recent reports on this, which the authors could review. For example,

a) There is a new article Neurogenetics. 2010 Apr 1. [Epub ahead of print] Analysis of NF1 somatic mutations in cutaneous neurofibromas from patients with high tumor burden. Thomas L, Kluwe L, Chuzhanova N, Mautner V, Upadhyaya M. that discusses modifier genes in NF1. These modifying loci may include deficiencies in mismatch repair genes and elements involved in cell cycle regulation (TP53, RB1). Somatic NF1 mutations were identified in (64%) of benign cutaneous neurofibromas sampled. Each mutation was distinct demonstrating the independent origin of each tumor. Somatic LOH of the TP53 and RB1 genes were identified in several cases, possibly demonstrating an alternative underlying molecular mechanism associated with the development of these benign tumors from this cohort of patients.

b) Another very recent article is relevant: J Cancer Res Clin Oncol. 2010 Mar 15. [Epub ahead of print] Molecular evolution of a neurofibroma to malignant peripheral nerve sheath tumor (MPNST) in an NF1 patient: correlation between histopathological, clinical and molecular findings. Spurlock G, Knight SJ, Thomas N, Kiehl TR, Guha A, Upadhyaya M. In samples from a single patient’s complex tumor, LOH for the NF1 locus increased progressively between areas of a single
tumor showing benign plexiform neurofibroma (PNF), atypical PNF, and MPNST tumor areas. Additional genetic changes, including losses of TP53, RB1, CDKN2A, and of several oncogenes and cell-cycle genes, were found only in the malignant MPNST.


d) Integrative genomic analyses of neurofibromatosis tumours identify SOX9 as a biomarker and survival gene. Miller SJ, et al showed upregulation of SOX9 in MPNSTS compared to benign tumors in NF1 patients.

3. In this case report, it would be ideal for the authors to show a a comparison of the molecular changes of the tumors from the two brothers (primary MPNSTs or metastatic lung lesions), which would begin to address the question of whether the development of tumors at similar ages was due to separate, stochastic genetic events or to similar molecular mechanisms. If the authors do not have access to tumor tissue, or means to analyze the genetic changes in the tumors, the case report can be published without this information, but its inclusion would strengthen the paper.

4. The following article presents an interesting theory that concordant vascular development in MZ twins could be a reason for the development of tumors in similar areas of the body. This could be considered in the authors’ discussion. Am J Med Genet A. 2006 Oct 1;140(19):2080-4. Non-random associations and vascular fields in neurofibromatosis 1: a pathogenetic hypothesis. Lubinsky MS

5. I have included some minor suggestions for the authors in a word document, which is attached.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'