Reviewer's report

Title: c.1810 C>T Polymorphism of NTRK1 Gene is associated with reduced Survival in Neuroblastoma Patients

Version: 1 Date: 4 July 2009

Reviewer: Kate Matthay

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General Comments.

This is a report comparing the SNP polymorphisms of the NTRK1 gene using DHPLC and SSCP in 169 primary neuroblastoma tumors vs. 158 adult peripheral leukocyte DNA controls, and then assessing the prognostic value for EFS, OS and multivariate analysis with other known clinical and biologic risk factors. Twelve SNPs were identified with MAF>5% (including 3 known and 9 new ones), of which 5 were non-synonymous. Three seemed important by structure-function analysis, among which residue 604 (coded by c.1810C>T) was the only one evolutionarily conserved. In Cox multivariable regression analysis, this SNP was the only one that portended a worse outcome, and was independent of several other variables.

Major Comments

1. It is of concern that the controls were germline DNA from peripheral blood, while all the cases were from primary tumors. The investigators should at least verify in some of the cases that the SNP variant was germline, particularly since no link found to incidence of neuroblastoma. There are many cooperative tumor banks in the US and Europe with both germline and tumor DNA.

2. The patient population differs widely from the two sites, Poland and Italy; the Italian group consists mainly of low stage, younger patients, but, oddly, has a higher proportion of unfavorable histology (Table 1). The reasons for the discrepancy in the patient population and the reason for the high proportion of UH in the otherwise more favorable Italian group should be clarified.

3. The possible effect of the skewed population on the overall analysis should be addressed in the Discussion.

4. Results for aberrations of 11q are not provided, and these would be very interesting in understanding whether the SNPs in TRK in the younger patients are independently prognostic in the MYCN non-amplified group.

5. It is unusual that the stage 4 vs not-4 is not significant in multivariate analysis, and one wonders if this relates to the skewed population in the Italian group. On the other hand, stage 4 was significant for recurrence; please address this in discussion.

6. Despite the clinical and biological differences in the two groups of patients,
there was no significant difference in the MAF frequency; this should be explained.

7. With the very small number of patients in the group with the 1810CT, TT (n=12) it is difficult to state with confidence that this minor allele is not associated with other risk factors and also to do a multivariable analysis!

8. This work should be verified with a GWAS or larger number of patients.

Minor Comments

1. The number of patients in each group in the Kaplan Meier curves must be indicated in the legend, hard to read on the figure.

Discretionary Revisions
None

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'