Reviewer’s report

Title: Genetic variants in RET and risk of Hirschsprung's disease in Southeastern Chinese: a haplotype-based analysis

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Reviewer: Sam Moore

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Reported associations between specific RET promoter and intron 1 variations have been shown to interfere with RET function and increasing the risk to Hirschsprung Disease (HSCR) pathogenesis. Despite the fact that ethnic differences are thought to occur, previous studies in both Caucasian and Chinese patients have previously confirmed the susceptibility link of these RET variations to HSCR.

This is an interesting study of the RET genotypes at the -5G>A (rs10900296), -1A>C (rs10900297), c135G>A (rs1800858), c1296A>G (rs1800860) and c2307T>G (rs1800861) positions in 123 Hirschsprungs disease (HSCR) patients and 168 controls in a south-Eastern Chinese population.

Results show a significantly increased risk of HSCR associated with the RET variations at -5AA, -1CC, 135AA, 1296GG or 2307GG, which were observed to be in strong linkage disequilibrium, when compared to the counterpart wild genotype.

Furthermore, the increased risk of HSCR was also associated with the haplotype A-C-A-G-G and diplotype A-C-A-G-G/A-C-A-G-G, which further indicated a cumulative effect in the association between these SNPs and susceptibility of HSCR.

The conclusion that these are significant in HSCR seem justifiable and add to the developing body of knowledge of this condition.

These are important studies and well conducted which should be published. The statistics are adequate.

I feel that a few fairly minor modifications would improve the overall impact of the manuscript however but recommend that it be published subject to these alterations.

1. The introduction can be simplified
2. There is no mention of aganglionic length in these patients being studied in the methodology. As previous studies have shown differences with Long segment Hirschsprungs disease, this may influence the results
3. The sentence “To our best knowledge, this is the first study to investigate the contribution of the genotypes and haplotypes of these five SNPs in the pathogenesis of sporadic HSCR in Chinese population” is fair enough but the
authors may want to modify in the light of some recent publications.

4. The methodology refers to the subjects as being “Hans”. One assumes that this means Han Chinese. To avoid confusion (Hans is a boys name in certain languages) this should be clarified

5. I note that there was informed consent and that the study was approved by an ethical board. What should be made very clear is that this was also true of the controls.