

Reviewer's report

Title: Genetic Etiology of CHARGE Syndrome: High Density SNP Genotyping to Detect a Common Deletion

Version: 2 **Date:** 7 October 2004

Reviewer: Brian Schutte

Reviewer's report:

General

The paper by Lalani et al., "Genetic etiology of CHARGE syndrome..." suffers from the fact that a recently published study showed that deletions of and mutations in the gene CHD7 on 8q12 were found to cause most (12/19) cases of CHARGE syndrome (Vissers et al., Nat Genet 2004). Consequently, although the technical aspects of this paper remain valid and interesting, the original medical genetic context for this study has been superceded.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. For this paper to be acceptable for publication, I recommend that additional studies be performed to increase the relevance for this technique to CHARGE syndrome. Toward this end, I recommend that additional SNP genotyping be performed to saturate the region on 8p12 that contains CHD7. In this case, saturation means a >95% chance of detecting a deletion in this region by SNP genotyping. Also, I recommend that FISH be performed across this region in the samples from the cases as independent confirmation of their genotyping results.
2. The methods are new and exciting. However, sufficient detail is not provided. I recommend that the authors provide, as supplemental material, a list of SNPs used in the analysis, and their allele frequency in their population.
3. An important technical point of this paper is the power of the SNP genotyping method to detect deletions. I recommend that an expert statistician review these calculations.
4. The title is misleading. From my first read of the title, I construed that the genetic etiology for CHARGE syndrome was determined in this paper. This is not the case. Upon completion of the suggested additional experiments, this title will likely be justified.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The authors need to provide the accurate name for BAC clones used for FISH.

Discretionary Revisions (which the author can choose to ignore)

1. It is likely that CHARGE is genetically heterogeneous, and their SNP genotyping method can be used to detect deletions in other CHARGE loci. The other members of the CHD family are excellent

candidates. However, 7/8 CHD family members, interestingly, are located near centromeres. As the authors state, such regions are challenging to study. Thus, the authors may be inclined to use the lessons learned by the saturation genotyping around CHD7 and apply them to the other candidate genes.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes

Declaration of competing interests:

none