Reviewer's report

Title: Analysis of patients with developmental disorder and normal array CGH results - the added value of high-resolution SNP array

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Reviewer: gaetan lesca

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Siggberg and coll. report on the analysis of 35 patients with developmental disorder using a high-resolution SNP array. These patients have been previously studied with 44K and 244K array CGH and these results have been published in a previous paper (Siggberg et al., 2010). The aim of the study presented here was to evaluate the added value of the high-resolution SNP array. They studied CNVs and segmental UPDs. Due to the high amount of data, the authors used different filters for selection of candidate regions/genes. They considered 23 CNVs and 23 regions of homozygosity that could be putatively correlated with the clinical phenotype. However, after further evaluation of the phenotype by clinicians and comparison of the frequency of the observed CNVs with a Finnish cohort, they concluded is that this higher resolution array does not contribute significantly to the etiological diagnosis of developmental disorders of unknown cause.

I globally agree with the conclusion of the authors but I have several comments:

- The main limitation of the study is the size of the cohort, which is rather small for a common and imprecise phenotype such as developmental disorders. A short clinical description of the patients may be useful (for example in a table).
- The overall design of the study is a little bit confusing. The use of a SNP array with such a high resolution generates a large amount of data but the restriction of genes already associated with a given phenotype (the last “filter” used by the authors was the clinical evaluation) is very stringent and may leave behind some potentially causative genes. The notion of phenotypically relevant genes is not obvious.
- The authors used different in-house reference sets of normal individuals. The use of some of these individuals as normal reference can introduce biases in the filtering process. For example, the healthy relatives of a patient may carry a predisposition CNV with reduced penetrance that may be excluded by excess. On the other hand, the fact that a CNV is found in the study group as well as in the 35 patients with an unexplained developmental disorder does not mean that this CNV has no deleterious consequences.
- The figure is not easy to understand. It may be more useful to have a table including, for example, the CNV < 9 kb (which is the resolution of the 244 k array) or the most interesting candidate genes.
- More changes were detected in samples with lesser quality. Can the authors mention how many of these changes were due to poor hybridization?
- The authors may cite a previous study of a large cohort of individuals studied with a very high resolution array (Conrad et al., Nature 2010;704-712).

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

**Quality of written English:** Acceptable

**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