Reviewer's report

Title: Terminal chromosome 4q deletion syndrome: a case report and mapping of critical intervals for associated phenotypes

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Reviewer: Marcella Zollino

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Vona et al report on a case of terminal chromosome 4q deletion syndrome, which is discussed along with several additional cases reported in DECIPHER, in the attempt of mapping critical intervals for associated phenotypes.

This is a single case report, in which a relatively large 4q35.1q35.2 deletion is associated to subtle phenotypic features, namely CHD, hearing impairment, cryptorchidism and sub-mucous cleft palate. Of note, normal intellectual development was described.

Authors made a great effort in dissecting the nonspecific and highly variable phenotypes associated with partial 4q deletions, and in discussing about candidate genes for some key features. Genetic test are appropriated.

However several criticisms are in order:
- Large chromosome deletions, as the present one, make the pathogenic link between haploinsufficiency of specific genes and distinctive clinical signs questionable (positional effect?, complex model of pathogenesis?)
- DECIPHER data, although helpful, are incomplete in some cases, as considered by the authors
- The present genotype-phenotype correlation analysis further confirms that several features characterizing the 4q deletion syndrome phenotype show significant incomplete penetrance; in addition, other signs (see cryptorchidism) are nonspecific
- The final message of the MS cannot be easily inferred.

Level of interest: An article of limited interest

Quality of written English: Acceptable

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

Declaration of competing interests:

No competing interests