Reviewer's report

Title: Single nucleotide polymorphism rs708567 in IL-17RC gene is associated with a susceptibility to and curve severity of adolescent idiopathic scoliosis in a Chinese Han population: a case-control study

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Reviewer: Patrick Edery

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The present paper, entitled « Single nucleotide polymorphism rs708567…case-control study » by Song Z et al is a case-control association study aiming at showing that polymorphism rs708567 is associated to adolescent idiopathic scoliosis (AIS) and AIS curve severity. This polymorphism locates within the IL-17RC gene, therefore considered by the authors as an AIS susceptibility gene.

Major compulsory revisions

1. The present study is presented as a replication study. However, the primary results do not appear to have been published elsewhere that in an abstract of the American Society of Human Genetics in 2010: “Dormans JP et al, quoted as ref 18”. Should these results be considered as sound results? In my opinion it remains debatable, especially since Dormans JP is a co-author of a subsequently published association study which does not mention IL-17RC as an AIS susceptibility gene: Sharma S et al, Hum Mol Genet 2011 (quoted as ref 1). This reference is provided by the authors only to illustrate the AIS prevalence. In my view, the present results should be discussed with respect to those of the previously published AIS association studies, in particular the articles by Sharma S et al, Hum Mol Genet 2011 and by Takahashi Y et al, Nat Genet 2011: 1237-1241.

2. Whether only polymorphism rs708567 has been studied or other polymorphisms have been also studied in the present cohort is unclear to me. If other polymorphisms have been studied, a Bonferoni correction should be applied to the statistical results. This information should be provided by the authors.

Minor essential revisions

1. More details must be provided on the Cobb's angle distributions in GG and AG patients.

2. Discordant results are provided in the results section of the abstract: “P = 0.004” and in the results section: “P = 0.007”. This should be clarified.

3. A statistically significant difference between the GG and AG distributions does
not mean that IL-17RC is a modifying gene, as stated at the end of the abstract. See for definition of a modifier gene, the paper by Emmanuelle Genin, Josué Feingold, Françoise Clerget-Darpoux entitled “Identifying modifier genes of monogenic diseases: strategies and difficulties. Human Genetics 124, 4 (2008) 357-68.”

4. Regarding parametric linkage studies two important references were not quoted, namely: Salehi LB et al, Hum Genet, 2002; 111: 401-4 and Edery P et al, Eur J Hum Genet, 2011: 19: 865-9. These missing references should be added to the paper.

5. The putative consequences of polymorphism rs708567 on the IL-17RC gene function should be indicated. Is it a synonymous change? Nonsense? Missense? Possibly affecting splicing? This information should be provided. Whether rs708567 is actually the S111L missense mutation of the IL-17RC gene discussed in the Abstract by Dormans JP et al should be clearly said.

6. In the Discussion section, the sentences regarding the hypothetical role of the IL-17RC gene, its nature and possible function are confusing. The fifth paragraph of the Discussion section should be re-written to improve clarity. In particular, it is not always obvious whether the authors refer to the gene or to the protein. Genes should be written in italics and uppercase, everywhere in the paper, according to the widely accepted nomenclature.

7. In the first paragraph of the Materials and Methods section, it is stated that patients with braces were excluded from the case-only study, because bracing can change the natural history of AIS patients. One can assume that physiotherapy or surgical treatments may also change the natural history of the disease. Were these patients detected? Were they also excluded from this case-only study or not, and why? This should be indicated in the paper.

8. Indicating in table 2 both a 1.550 OR for genotype GG and a 0.645 OR for genotype AG is a redundant information (OR of 1.55 for GG versus AG means that the AIS risk for GG is 1.55 that of AG; it is equivalent to say that the risk for AG is 0.645 fold that of GG). The same remark can be made for the ORs provided both for the G and A alleles. One OR only should be provided for the GG genotype on the one hand and one OR only should be given for the G allele on the other hand.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**
'I declare that I have no competing interests'