Reviewer’s report

Title: Association between CYP19 gene SNP rs2414096 Polymorphism and polycystic ovary syndrome in Chinese women

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Reviewer: DJ Marioli

Reviewer’s report:

In the manuscript entitled “Association between CYP19 gene SNP rs2414096 polymorphism and polycystic ovary syndrome in Chinese women” by Jia-Li Jin et al., the authors address the question whether a single nucleotide polymorphism (rs2414096) located at exon 3 of the CYP19 gene is associated with PCOS and clinical characteristics of the syndrome. The authors conclude that rs2414096 SNP in CYP19 is one of the key factor of the etiopathogenesis of PCOS especially in adolescence.

The findings of the present study seem to be important to those with closely related research interests however the authors do not support them adequately, having in mind that they are opposing to previously reported data. Moreover, the authors do not provide enough evidence about their final conclusion that is rather a speculation than an outgrowth of their study. Based on the above comments the reviewer is unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions.

Therefore, the authors have to address the following major concerns and edit closely the language before the particular manuscript could be considered for publication in BMC medical genetics.

Declaration of interest: I declare that I have no competing interests

Major Compulsory Revisions

1. The phenotypic characteristics of the study cohort are not clear enough. One major concern regarding PCOS genetic studies is phenotypic heterogeneity within patients’ group. In the particular study, PCOS patients were diagnosed according to the Rotterdam ESHRE/ASRM 2003 consensus diagnostic criteria. Thus the patients’ cohort encompasses a broad spectrum of phenotypes which obscures the identification of genomic variants that exert modest or minor effect on specific quantitative phenotypic traits such as hyperandrogenemia that is closely related with CYP19. Therefore, please provide a separate table with the general characteristics of PCOS patients (anthropometric and hormonal measurements) expressed as mean value± SD in order to better define the phenotypic characteristics of PCOS patients, as a whole. Moreover, inclusion of non-hyperandrogenemic patients in the study might bias the sample and thus any minor effects of the particular SNP on circulating androgens might not be detectable. Therefore, the authors should further divide the patients’ group on the basis of biochemical hyperandrogenemia in order to assess any differences in
androgens between genotypic groups.

2. In materials and methods section you mention that blood samples were obtained at any time for subjects that had amenorrhea. In Table II standard deviation values for LH are too high showing that blood samples were collected in different phases of the menstrual cycle in PCOS subjects (the authors have included in the study cohort PCOS women in pre-ovulatory phase and women in the ovulatory phase). However, blood samples should have been collected after a spontaneous bleeding episode in PCOS women with oligo-/a-menorrhea, a policy that is crucial for hormonal values and especially gonadotropins and estradiol. Thus, any association with hormonal values could be attributed to differences in the menstrual cycle.

3. The authors should provide a solid explanation about the discrepancy observed with previously published studies. So far, all previous findings indicate that the particular polymorphism is associated with elevated androgen levels and thus reduces aromatase activity. Further proof of your allegation would be the association of the AA genotypic subgroup with higher Estrone/Androstenedione ratio. Did you measure these two steroids?

4. Based on your allegation, one would expect that testosterone (T) would be reduced in AA women. The authors should provide an explanation why they did not detect any differences in T levels between genotypic subgroups of PCOS patients.

5. The results of the present study (if adequately supported) provide evidence that CYP19 contributes to the etiopathogenesis of PCOS hyperandrogenism in Chinese women. Please rephrase your final conclusion in order to comply with your findings. Moreover, in the last paragraph of the discussion section you mention that “…this effect is more visible when the concentration of androgen in high…”. This conclusion is not adequately supported by your data unless you have compared hyperandrogenemic women and non-hyperandrogenemic women.

6. According to BMC medical genetics guidelines all references must be numbered consecutively, in square brackets, in the order in which they are cited in the text. Moreover, there are also inconsistencies in the reference style. Please correct it according to the instruction to authors.

Minor Essential Revisions

1. Abstract, background section, line 2: please correct as follows “….the clinical manifestations of polycystic….”

2. Abstract, background section, lines 5 & 6: please correct as follows “polymorphism is associated……. including 684 individuals”

3. Abstract, methods section, line 1: please correct as follows “….. including 684 individuals…”

4. Abstract, methods section, lines 2 & 3: please correct as follows “…..to assess the association of SNP rs2414096 with PCOS. Genotyping of SNP rs2414096 was conducted…….”
5. Abstract, results section, line 3: please correct as follows “E2/T was different …”
6. Abstract, results section, line 7: please correct as follows “genotypes both in PCOS patients…”
7. Abstract, conclusions section, line 1: please correct as follows “in the CYP19 gene is associated…”
8. Introduction, paragraph 1, line 3: replace the term :ovarian hyperandrogenism” by “clinical and/or biochemical hyperandrogenism”.
9. Introduction, paragraph 4, line 1: please correct as follows “…in androgens’ …”
10. Introduction, paragraph 4, line 2: Avoid the term “functional impact” as it suggests functional studies however your study is a genetic one. Please correct as follows : “…we investigated the impact of the particular gene polymorphism…”
11. Introduction, paragraph 4, line 3: The term “ovarian hyperandrogenemism” declares the source of androgen excess but how is it manifested in your cohort? Clarify if your patients have biochemical hyperandrogenemia or clinical hyperandrogenism or both. If you insist on using the specific term then you should give a definition in the materials and methods section.
12. Material and methods, paragraph 2, line 2: please correct as follows “Peripheral blood…..”.
13. Material and methods, Polymorphism Genotype analysis: The genotyping section may be shortened. If applicable, refer to the methods of genetic analysis as "according to a previously described protocol" (with reference).
14. Discussion, paragraph 4, line 3: please correct as follows “….. with another causal SNP, needs further investigation. “
15. Discussion, paragraph 4, line 4: please correct as follows “….. site still needs to be…. “
16. Discussion, page 3, paragraph 1, line 3: please correct as follows “…..with the etiopathogenesis of PCOS….. “
17. Discussion, page 3, paragraph 2, line 1: please correct as follows “We failed to find a difference…. “
18. Discussion, page 3, paragraph 2, line 4: please correct as follows “The etiopathogenesis of PCOS….. “
19. Discussion, page 3, paragraph 2, last line : please clarify what do you mean by the phrase “signal factor”. May be it is better of if you say “causal factor” or “causal genetic variant”.
20. Clarify if values in Table II are expressed as mean value±SD.