Author’s response to reviews

Title: Xp11.22 Duplications in Four Unrelated Chinese Families: Delineating the Genotype-phenotype Relationship for HSD17B10 and FGD1

Authors:

Qingming Wang (wqm0404@sina.com)
Pengliang Chen (goodcpl@163.com)
Jianxin Liu (dgfyrsk@163.com)
Jiwu Lou (598337047@qq.com)
Yanhui Liu (yh523120@sina.com)
Haiming Yuan (haimingyuan@sina.cn)

Version: 2 Date: 18 Dec 2019

Author’s response to reviews:

Dear Editor:
We are delighted to resubmit the manuscript entitled “Xp11.22 Duplications in Four Unrelated Chinese Families: Delineating the Genotype-phenotype Relationship for HSD17B10 and FGD1” after revising it following reviewers’ comments and suggestions. Please see our point by point response to your reviewers’ comments.

Reviewer reports:
Orsetta Zuffardi (Reviewer 1): BMC Medical Genomics
Xp11.22 Duplications in Four Unrelated Chinese Families: Delineate the Genotype-phenotype Relationship for HSD17B10 and FGD1
The manuscript reports on four unrelated male probands, who were ascertained for intellectual disability and/or other disorders, all carrying a CNV gain at Xp11.22. In each case, the authors define the genomic rearrangement through a deep molecular sequencing approach in order to delineate precise genotype-phenotype relationship. To this aim, they compare the duplication of each of their cases with those reported in the literature and in DECIPHER.
The main problem of the manuscript relies in the writing style that does not fit with the scientific English. It is therefore necessary for the manuscript to be reviewed by a native English speaker.
Response: The manuscript has been reviewed by a native English speaker according to reviewer’s suggestion.

The following points are also problematic:
The Xp11.22 region contains a few inversion polymorphisms (see Database of Genomic Variants). The authors should discuss whether some of the CNVs could be mediated by these polymorphisms.
Response: It was well known that recurrent copy number variants (CNVs) was mediated by non-allelic homologous recombination-prone low copy repeats (LCRs). Currently, no studies show that sporadic CNVs such as Xp11.22 microduplication could be mediated by these polymorphisms.
The authors propose that FGD1 "may be a potential dosage-sensitive gene responsible for hypogonadism observed in our patients." Indeed, "given that FGD1 gene is duplicated exclusively in the three unrelated patients who all displayed strikingly similar hypogonadism phenotype and other Xp11.22 duplication patients did not show this feature, it was reasonable to speculate that FGD1 was likely to be a dosage-sensitive gene and FGD1 duplication may be responsible for hypogonadism observed in our patients."

Based on the literature regarding the Rho family of small GTP-binding proteins similar to the FGD1 protein, the authors should speculate how the duplication of FGD1 may lead to a phenotype overlapping its LoF.

Response: We noticed that our probands (Families 3 and 4) and DECIPHER patient 249490 all presented with strikingly similar hypogonadism phenotypes, which have not been reported in all previously described Xp11.22 duplication patients, and FGD1 gene was duplicated exclusively in the three patients. Therefore, it was speculated that FGD1 duplication may be responsible for hypogonadism observed in our patients and that FGD1 was likely to be a dosage-sensitive gene. Currently, there is no evidence for triplosensitivity for FGD1 (the triplosensitivity score for the FGD1 gene is zero based on the ClinGen gene dosage sensitivity scoring protocol). It remained largely unknown about how the duplication of FGD1 may lead to a phenotype overlapping its LoF. Here, we just provide the first evidence that FGD1 duplication seems to be associated with hypogonadism including cryptorchidism, small testes, and micropenis. Certainly, additional clinical cases and functional studies are needed to prove this hypothesis.

To strengthen their hypothesis that partial HUWE1 copy number gain does not contribute to ID and language delay that was observed in the proband of Family 1 and DECIPHER patient 263219, the authors state that a partial HUWE1 duplication was also reported in Database of Genomic Variants (esv3576879, chrX:53529972-53593214).

However, looking at gnomAD SVs v2.1, this variant is present in 2 out 21694 alleles, corresponding to a frequency of 0.00009219 and is only present in females. A recurrent rearrangement with these characteristics, is very likely pathogenetic in males.

Response: Froyen et al. (2012) reported three unrelated pedigrees (Family HF, ON2, CC1) with partial HUWE1 duplication. In families HF and CC1, the healthy grandfather and father, respectively, also harbor the partial HUWE1 duplication. In family ON2, the equally affected brother of the proband did not carry the aberration. Therefore, it was concluded that this partial HUWE1 duplication does not correlate with the ID phenotype since segregation analysis provided contradictory evidence. Here, we reported the proband (in our Family 1) with Xp11.22 duplication involving the partial HUWE1 gene. WGS test revealed that Xp11.22 region contained an entire HUWE1 gene and a partial HUWE1 gene and they were arranged in tandem orientation. It could be predicated that mRNA product transcribed by the partial HUWE1 gene would be decayed. Based on these evidences, it could be concluded that the partial HUWE1 copy number gain would probably not contribute to ID and may be an extremely rare polymorphic variant, as described by Froyen et al. (2012).

Aleksander Jamsheer, Ph.D., M.D. (Reviewer 2): Wang et al. present a report of four patients carrying Xp11.22 duplications of different sizes. All affected male individuals manifested intellectual disability (ID), including delayed speech and also some additional features depending on size of the duplication and its gene content. The authors suggest two dosage-sensitive genes, HSD17B10 and FGD1, which - once duplicated - are responsible for ID/psychomotor retardation and hypogonadism, respectively. Hypogonadism, including cryptorchidism, small testes, and micropenis was not linked to FGD1
duplications, and indeed FGD1 seems to be a perfect candidate gene for this phenotype. With their study, the authors expand the phenotypic spectrum of Xp11.22 duplications and provide useful genotype-phenotype correlations helpful in the prognosis and genetic counseling of patients carrying duplications spanning the different portions of Xp11.22 region.

However, several minor remarks should be addressed prior to publication.
1) Page 3, lines 4-5, sentence starting with "He presented with mild ID…"
If the patient was examined at the age of 4 years, why was mild intellectual disability recognized? Was the patient psychologically assessed? What was the IQ and which test was used?
2) Page 4, line 21, please correct "electroencephalographic" to "electroencephalography".
3) Page 4, lines 35-36, please correct "7 moths" to "7 months".
4) Page 5, line 50 and page 7 lines 6-7, "duplication was direct". What does this mean? Do you mean that the duplication was in tandem orientation? Please be precise.
5) Page 7, line 2-4, "…duplication at Xp11.22 was a disease-causing effect". Please correct the sentence.
6) Page 8, lines 4-5, abstract, list of abbreviations "Aarskoh-Scott syndrome" should be corrected to "Aarskog-Scott syndrome" throughout the manuscript.
Response: We have polished the manuscript according to reviewer’s suggestion.

We hope you find this revised version is of much better quality and meet journal’s standard. We appreciate your reviewers’ input and your help. We look forward to hearing from you.

Best regards!

Haiming Yuan