Author's response to reviews

Title: Analysis of EIF4G1 gene with Parkinson's disease in ethnic Chinese population

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Version: 2 Date: 24 November 2012

Author's response to reviews: see over
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Title: EIF4G1 gene variants are not associated with Parkinson's disease in the ethnic Chinese population

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The Biomed Central Editorial Team

Object: MS: 4918415488045198 - EIF4G1 gene variants are not associated with Parkinson's disease in the ethnic Chinese population. Kai Li et al.

Thank you for consideration of our manuscript for publication in your journal. We have reviewed the above manuscript according to your reviewer’s comments.

Editor's comment:

Authors should carefully change their introduction by adding a complete list of known genes associated with autosomal dominant Parkinson's disease (SNCA, LRRK2, UCHL1, GIGYF2, VSP35), recessive parkinsonism (PRKN, PINK1, and DJ-1), and more complex forms of recessive parkinsonism (ATP13A2, PLA2G6, and FBXO7). Please check carefully the available literature regarding the genetics of Parkinson's disease.

- Thank you for your comment, we added the genes you mentioned above, we also added Omi/Htr2 as known genes associated with autosomal dominant Parkinson's disease after carefully reading Suzanne Lesage[1] and Shinsuke Fujioka [2] reviews.

Reviewer # 1 (Carles Vilarino-Guell)

Reviewer's report:

Li et al present a study characterizing eIF4G1 in 29 familial probands of Chinese ethnicity followed by genotyping of three missense variants in ~500 cases and ~500 controls. Overall the study design is appropriate, but there are several errors in the manuscript.

-Major Compulsory Revisions-

1. The conclusion drawn in the abstract is inaccurate, the authors can conclude that pathogenic mutations in eIF4G1 are not common in Han Chinese as the previously reported mutations were not identified and they did not identify any Chinese specific ones. However they cannot conclude that there are no associated variants as they only genotyped three and two were monomorphic.

   - The conclusion drawn in the abstract has been changed as follows: Our data indicates that in ethnic Chinese population, pathogenic mutation p.R1205H in EIF4G1 is not common and rs2178403, rs13319149 in exons of EIF4G1 are not associated with PD. EIF4G1 is not a frequent cause of PD in ethnic Chinese population. And we also changed our manuscript’s title “EIF4G1 gene variants are not associated with Parkinson's disease in the ethnic Chinese population” to “Analysis of
EIF4G1 gene with Parkinson's disease in ethnic Chinese population”.

2. The description of the variants identified in EIF4G1 is not accurate. The authors reported variants according to NM_198241.2, as with the original study by Chartier Harlin et al (I think); as there are many transcripts from this gene it is important to describe the transcript used for describing the variants. Regardless, the authors have started counting the exons from the first coding exon, not the real first exon; as a result, their promoter variant is not in the promoter but in intron 2, rs13319149 is in exon 7 not 5, and so on… all the positions need to be changed and the reference transcript used stated.

   • Thanks for your comments. In our study, we do use NM_198241.2 to describe the variants identified in EIF4G1; we have added NM_198241.2 to describe the transcript in our revised manuscript, and we have recounted the exons and changed all the positions of the variants with stating the reference transcript NM_198241.2. Thanks a lot.

3. Statistical analyses of genotypes are performed with two degrees of freedom. This is not accurate as there are only two independent variables and as such the degrees of freedom should be one.

   • Thanks for your comments and suggestions. But with this comment, we have some questions with statistical analyses, and would like to present them now for a discussion. In your opinion, statistical analyses of genotypes should not been performed with two degrees of freedom. It is
not accurate as there are only two independent variables and as such the
degrees of freedom should be one. However, we think that statistical
analyses of genotypes should been performed with two degrees of
freedom. Whether the SNP rs2178403 is a dominant mode of inheritance
or a recessive mode is not clear, it is not accurate to definite the genotype
of rs2178403 as two independent variables. It should be A/A, A/G and
G/G three independent variables, while the alleles of the SNP are A and G
two independent variables. As a result, we don’t change this part in our
revised manuscript. However if you do like us to change the statistical
analyses, do let us know. Thanks for your comments and suggestions.

- Minor Essential Revisions –

1. The introduction states that “to date, the (should not be there)
mutations in SNCA, LRRK2, PINK1, ATP13A (is missing a 2), PLA2G6,
and VPS35 are known to cause familial PD” This statement is missing
PRKN, DJ1 and probably FOBX7 if they include PLA2G6.

   • Thank you for your comment, this question has been stated by the
     Editor above, too. And we have added the genes you mentioned in our
     revised paper.

2. The authors don’t state very clearly why they only genotyped two of the
variants they identified in their sequencing until the discussion. It would
be advantageous to state from the very beginning that two of the variants
are missense while the third is silent; and hence no further genotyped.
• Thank you for your comment, the statement why we only genotyped two of the variants we identified has been changed to be stated in the parts of the abstract and genetic analysis.

3. The authors use the sentence “no mutations” throughout the manuscript to describe previously reported mutations, this doesn’t come across very clearly and they should rewrite those statements. In addition, the variant of interest p.R1205H is consistently called c.3614G>A. I strongly advice the authors to use the protein position (or both) as mutations are most commonly reported from proteins.

• Thank you for your comment, in the paper, we used “no mutations” to address that we didn’t find any mutation in this gene in the twenty nine probands of autosomal-dominant, late-onset PD families, including mutations previously reported. We have rewritten “no mutations” as follows: We did not detect any mutation in the exon regions in the EIF4G1 gene in any of the twenty nine probands of autosomal-dominant, late-onset PD families. The variant of interest c.3614G>A has been changed by p.R1205H in our revised paper. Thanks for your comments and advice.

4. The description of the study by Chartier-Harlin et al in the introduction is excessive, it should be cut down significantly. Just stating how it was identified is sufficient, hence the description of the two potential loci, and the fine mapping is overkill. Similarly, the first three paragraphs of the
discussion are excessive and they should be combined with this one paragraph in the introduction to describe the function of eIF4G1.

- We have cut down and rewritten the introduction and discussion of the manuscript briefly and concisely. The discussion of the paper in our revised manuscript is as follows:

Discussion

*EIF4G1* gene was confirmed as a candidate gene causing PD by Chartier-Harlin et al [6, 7]. However, recently, three other groups screened *EIF4G1* mutations in their cohorts, and found *EIF4G1* gene mutations may not be a confirmed cause of PD in their populations with the result that they also found mutations in the healthy controls [13-15]. This raises questions about the causality of the gene with regard to PD. In our study, we also got negative results by conducting a comprehensive genetic analysis of *EIF4G1* gene. The specific mutation p.R1205H firstly identified by Chartier-Harlin is important in PD with regulating cell survival in response to stressors [6, 7]. However, in our population, none of the 503 sporadic PD and 508 healthy controls carried it. This may suggest that different populations may have different pathogenic mutations. Considering the result that Schulte et al [15] found the mutation p.R1205H presents in controls in Central European population, we suggest that the effect of the same mutation differs in different
populations. rs13319149 and rs2178403, with no significant difference in either genotype frequencies or allele frequencies, are probably benign polymorphisms. *EIF4G1* is considered as a pathogenic gene with late-onset PD. But, in our study, the twenty-nine probands of autosomal-dominant, late-onset PD families are not typical late-onset PD. As the average age-onset is 50.33±9.56 years; it may contribute to our negative results. Also, the sample size is not large enough, either. Further larger scale genetic studies should be performed.

5. *In the genetic analysis section of the methods the authors provide the results of the sequencing analysis. This is out of place and should be removed.*

   • Done

6. *Table 3 and 4 present age at onset and gender specific association, however there is no mention of these analyses in the manuscript. These two tables should be removed. Similarly Figure 1 is unnecessary.*

   • Done

- Discretionary Revisions –

I would recommend the authors cut down the manuscript to a shorter format if suitable to the journal. This is a simple report describing the sequencing of *eIF4G1* in 29 probands and genotyping of one previously reported pathogenic mutations, one polymorphic and one monomorphic SNP in 1,000 samples; with negative results.
• We have cut down and rewritten the introduction and discussion of the manuscript briefly and concisely.

Reviewer # 2 (Owen Ross)

Reviewer's report:

The article of Li et al. describes a study on the role of EIF4G1 variation in PD patients from China. The authors screen a small series of late-onset patients with apparent autosomal dominant pattern of inheritance. They then screen a larger case-control series for three variants, of which two are not observed. This is a relatively small study but adds data to the field.

-Major Compulsory Revisions-

1. The authors should highlight that their samples are not typical late-onset cases but most are early-onset with an average age—onset 50 years.

   • Thank you for your comment. We have highlighted that our samples are not typical late-onset cases in the discussion part of our paper in our revised manuscript. In our discussion, we suggest that it may contribute to our negative results, too.

2. The authors should run the other reported EIF4G1 variants in PD, and a set of tagging SNPs if they want to conclusively say there is no association with disease in their population. The authors should highlight that the 3614G>A is the original R1205H.
Thank you for your comment. The conclusion drawn in the paper has been changed as follows: Our data indicates that in ethnic Chinese population, pathogenic mutation p.R1205H in *EIF4G1* is not common and rs2178403, rs13319149 in exons of *EIF4G1* are not associated with PD. *EIF4G1* is not a frequent cause of PD in ethnic Chinese population. And we also changed our manuscript’s title “*EIF4G1* gene variants are not associated with Parkinson's disease in the ethnic Chinese population” to “Analysis of *EIF4G1* gene with Parkinson's disease in ethnic Chinese population”. c.3614G>A has been changed by p.R1205H in our revised paper. Thanks for your comments and advice.

3. In the Background the authors refer to PD genes and highlight *ATP13A(2)* and *PLA2G6* (which don’t cause PD) but don’t report *PINK1* or *DJ-1*.

Thank you for your comment, we added the genes you mentioned above, and we also added *ATP13A2* and *PLA2G6* as known genes associated with autosomal recessive Parkinson's disease after carefully reading Suzanne Lesage[1] and Shinsuke Fujioka [2] reviews.

1. Lesage S, Brice A: **Role of mendelian genes in "sporadic" Parkinson's disease.** Parkinsonism Relat Disord 2012, **18** Suppl 1:S66-S70.


4. The authors could shorten their manuscript, the first two paragraphs of the discussion is a repeat of the introduction, Tables 3 and 4 could be supplemental if needed and Figure 1 is unnecessary.
We have cut down and rewritten the introduction and discussion of the manuscript briefly and concisely. We have deleted Tables 3, 4 and Figure 1 in our revised paper.

5. The authors should provide the primers that were used as supplemental or reference the study they got them from if not original.

• Thank you for your comment. We have provided the primers used in our study as supplementary table1 in our revised manuscript.

6. The authors should have a native English speaker check the language and grammar.

• Done