Author's response to reviews

Title: Search for Copy Number Variants in Chromosomes 15q11-q13 and 22q11.2 in Obsessive Compulsive Disorder

Authors:

Richard Delorme (richard.delorme@rdb.aphp.fr)
Daniel Moreno-De-Luca (daniel.morenoDELuca@emory.edu)
Aurélie Gennetier (aurelie.gennetier@hotmail.fr)
Wolfgang Maier (wolfgang.maier@ukb.uni-bonn.de)
Pauline Chaste (pauline.chaste@rdb.aphp.fr)
Rainald Mössner (rainald.moessner@ukb.uni-bonn.de)
Hans Jorgen Grabe (grabeh@uni-greifswald.de)
Stephan Ruhrmann (stephan.ruhrmann@uk-koeln.de)
Peter Falkai (pfalkai@uni-goettingen.de)
Marie-Christine Mouren (marie-christine.mouren-simeoni@rdb.ap-hop-paris.fr)
Marion Leboyer (marion.leboyer@inserm.fr)
Michael Wagner (michael.wagner@ukb.uni-bonn.de)
Catalina Betancur (catalina.betancur@inserm.fr)

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Author's response to reviews: see over
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Dear Dr. Norton,

Thank you for your e-mail of February 22, 2010 and the comments of the referees concerning our manuscript entitled "Search for Copy Number Variants in Chromosomes 15q11-q13 and 22q11.2 in Obsessive Compulsive Disorder" by Delorme et al. (MS: 1351326200323622).

We have taken into account the comments of the referees to prepare the revised version. Please find enclosed our answers to the referees in the following pages.

We hope that after the modifications we have made to our manuscript, you will now find it acceptable for publication in BMC Medical Genetics.

Sincerely,

Catalina Betancur, M.D., Ph.D.
**Referee #1: Fiorella Gurrieri**

*This is the first study searching for specific CNVs in OCD. However, the search is conducted with commercial MLPA kits which analyze genes that, in a contiguous, are involved in clinically recognizable syndromes. I am not sure this is the ideal tool to find possible intragenic or single gene quantitative anomalies in a disorder which is usually non syndromic. In other words, I would expect for instance Prader Willi syndrome in an OCD case with a microdeletion in 15q11-q13 or a velocardiofacial syndrome in an OCD case with a microdeletion in 22q11 when this kind of commercial kits are used.*

The main purpose of our study was to screen for the typical deletions involved in Prader-Willi and DiGeorge syndromes, as none of the smaller deletions or duplications identified thus far at either locus has yet been shown to be pathogenic, despite extensive studies.

We agree with the referee that deletions of chromosomes 15q11-q13 and 22q11.2 are commonly associated with a syndromic appearance, but they may also exhibit highly variable phenotypic features and have sometimes been identified in subjects with subtle phenotypes. For instance, through systematic MLPA screening of patients with nonsyndromic autism spectrum disorders, we were able to identify several instances of Angelman, Prader-Willi and DiGeorge syndromes in subjects with atypical presentations, that had not been recognized by the psychiatrists or clinical geneticists that had evaluated them. As we mentioned in the Discussion (page 7), our OCD sample didn't include patients with overt syndromic presentations, but we hypothesized that it could have included individuals carrying 15q11-q13 and 22q11 microdeletions with atypical/subtle presentations.

**Referee #2: Humberto Nicolini**

*Major Compulsory Revisions: The lack of detection of cases needs to be better demonstrated. Even thought, it is mentioned that positive controls were used there is no figures showing these results. Also, the lack of a control group needs to be commented.*

Despite our negative results, MLPA is a highly sensitive method to screen for known microdeletion syndromes, and MLPA kits have been widely used in recent years to detect microrearrangements in the 15q11-q13 and 22q11 regions, with very positive results. We recently published a study (Depienne et al., Biol Psychiatry, 2009) using a similar MLPA approach to detect microrearrangements involving the 15q11-q13 region in a large cohort of patients with autism spectrum disorders. Four patients carrying 15q11-q13 abnormalities were detected: a supernumerary chromosome 15, a paternal interstitial duplication, and two subjects with Angelman syndrome, one with a maternal deletion and the other with a paternal uniparental disomy. We have also identified several other instances of 15q11-q13 and 22q11 deletions in patients with autism spectrum disorders (unpublished results). We used these patients with autism spectrum disorders carrying 15q11-q13 or 22q11 microrearrangements as positive controls in our study. We are thus confident, based on our previous experience as well as the extensive literature published in recent years, that MLPA is a very reliable method to screen for microdeletion syndromes, and that if we didn't identify any genomic imbalances at either locus it was because there were none in our sample of OCD subjects. We have added a sentence in the Discussion to mention this (page 7, 1st paragraph).
MLPA has become a widely used technique in the past years, with numerous papers published in the literature, so we don't think it is necessary to show results of deletions or duplications in controls (especially given that we don't have any positive results to show in OCD subjects).

Concerning the lack of a control group in our study, it is a standard practice in the field to study only patient samples when screening for known microdeletion syndromes or for rare mutations in disease genes. In the present study we wanted to know whether 15q11-13 and 22q11.2 deletions involved in Prader-Willi and DiGeorge syndromes could play a role in the development of OCD. There is no need to study a control group to answer this question.

Minor revisions: There is no mentioned if there is family history of mental retardation or OCD or tics. There is no mention of tic comorbidity. There is no mention of cognitive assessment or neuropsychological testing to determine IQ.

The first degree relatives of the French patients were directly screened for axis I psychiatric disorders. Thus, we added in the revised manuscript the information concerning the family history of tics and OCD (page 6). We also added information about tic comorbidity in the French subjects. Unfortunately, equivalent data were not available for the German sample.

As mentioned in the original manuscript, we excluded patients with clear dysmorphic features or severe mental retardation. However, we did not perform any neuropsychological tests to determine the IQ of the participants. We added this information in the revised manuscript (page 5, last line).