Author's response to reviews

Title: Complex Aetiology of an Apparently Mendelian Form of Mental Retardation

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Author's response to reviews: see over
To the editors of the *BMC Medical Genetics*

We hereby reply to the comments of the referees, concerning the manuscript MS: 1398211038165878 Complex Aetiology of an Apparently Mendelian Form of Mental Retardation, by Ana Beleza-Meireles, Ingrid Kockum, Qiu-Ping Yuan, Simone Picelli, Lennart Wetterberg Martin Schalling and Karl-Henrik Gustavson

We hope our answers will be satisfactory.

Yours Sincerely

The authors

Answers to reviewer 1:

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Major Compulsory Revisions

1. Phenotypic and laboratory examination

Since the success of linkage analysis often depends on the precise clinical description and exclusion of patients with mental retardation caused by different etiology, it is important to know how many mentally retarded individuals examined in this study underwent physical examination, karyotyping and subtelomeric rearrangement analysis. Have any of the patients been evaluated by a clinical geneticist?

All the mentally retarded individuals were physically examined by one of the authors-K H Gustavson, who is professor of pediatrics and clinical genetics and has worked in these fields for 45 years. Five of the patients underwent karyotyping and subtelomeric rearrangement analysis at the Clinical Genetic Department at the Karolinska Hospital.

Short stature and obesity have been observed in some of the individuals – what was the parental height in these patients?

The great majority of the parents were dead at the time for the clinical investigation in 1982, but they were were reported to be of normal height. The observed parents had normal height.

How many of the patients in this study had short stature and obesity? May be these patients represent a homogeneous subgroup of patients with MR caused by a mutation in a single gene? Were linkage analysis results examined on a subgroup of patients with short stature and obesity only?

Eight of the physically examined patients were shorter than their relatives and had a pycnic body type. Otherwise the physical examinations were normal and, in general, the patients looked very alike to their relatives. They had a normal body mass index and were thus not obese. None of the patients seem to belong to a particular subgroup.

Some of the patients in the original study had abnormal vision or abnormal hearing – were these patients excluded from this study?

Only one patient (VII:1 in Clinical genetics1986) had a mild hearing impairment. Three patients (VII:13, VIII:9, VII:15) had a vision decrease, which was caused by a common refraction error. These patients were not regarded as a specific subgroup.
Some of the patients in the original description of the extended family were reported to have chromosomal abnormalities (e.g. 13q+ mosaic) – were these patients excluded from the current study?

These chromosomal aberrations were not regarded as pathogenic and the patients were thus not excluded.

2. It is stated that “The present study included 24 individuals … including 9 mild mentally retarded individuals and 14 non affected individuals” 9 + 14 = 23, not 24. While in the methods section it was mentioned that genome-wide screening with microsatellite markers was performed on 24 individuals, 25 individuals are numbered in the pedigree – which individual was not included and why?

We have made a mistake in the first version of the manuscript. We included in our study 9 mild mentally retarded individuals (301, 304, 322, u1, u2, 319, u3, 829 and 830), one individual affected with schizophrenia and mild mental retardation (329), 13 non affected individuals (302, 303, 307, 323, 324, 309, 321, 330, 310, 311, 320, 326, 328) and one individual with schizophrenia (327). Individual 325 was not included due to insufficient phenotypic and biological data (Information added to the manuscript).

3. It is not clear from the description in the Methods section how many individuals were examined for copy number variations. If not all were examined, how was the selection of these particular samples performed?

Copy number analysis was performed in the individuals 301, 304, 322, u1, u2, 319, u3, 829, 830, 302, 303, 307, 323, 324, 309, 321, 330, 310 and 311. The individuals 320, 326, 327 and 328 were not included as they were not considered to be very informative. In this small sub-pedigree there is no MR affected individual (Information added to the manuscript).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. An additional gene causing autosomal recessive mental retardation has been recently identified (GRIK2) – this should be added in the Introduction and the reference list.
2. There is a mistake in numbering the references starting from reference 10
3. English spelling mistakes (e.g. dysmorphic and not dismorphic) should be corrected
4. Please provide a reference for the statement “genetic or inherited etiologies are implicated in two-third of cases” (Background section)

Corrected accordingly

Answers to reviewer 2:

The authors report a comprehensive linkage-wide genome analysis with 500 microsatellite markers in a 24 members of a family in which segregates mental retardation. The segregation of the disease does not conform to a simple mode of transmission. They have also performed a copy number analysis using an Affimetryx 250K SNP chip.

The study is extensive and well conducted. The conclusion seems adequate. There are few errors to correct: for example in the patient and method section, hydroxyhippuric should be corrected to hydroxyhippuric. In Supplement 2, I wonder what are the Mru individuals (needs a legend)?

Corrected accordingly