Reviewer's report

Title: Mucopolysaccharidosis III B and Mild Skeletal Anomalies: coexistence of NAGLU and CYP26B1 missense variations in the same patient in a Chinese family

Version: 0 Date: 18 Jan 2018

Reviewer: Shunji Tomatsu

Reviewer's report:
The authors describe "Mucopolysaccharidosis III B and Mild Skeletal Anomalies: Coexistence of NAGLU and CYP26B1 missence variations in the same patient in a Chinese family."

MPS III B is an autosomal recessive lysosomal storage disorder. It is caused by a critically reduced activity of NAGLU. Recently, an autosomal recessive disorder of skeletal dysplasia associated with CYP26B1 was reported in 3 families in which the patients were all homozygous variations. However, the co-occurrence of two rare diseases in a person is very rare. They found two novel pathogenic missence variations in NAGLU and CYP26B1 respectively. They reported an infant with biallelic variation both in NAGLU compound heterozygous c.1843C>T (p.R615C) and c.1224C>A (p.H408Q) and in CYP26B1-compound heterozygous c.529G>A (p.E177K) and c.525C>A (p.H175Q). All variations were novel, but predicted pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines. His main phenotypes were quite different from those reported, and were some combination of the two rare diseases, including epilepsy, early onset epileptic encephalopathy, hypermyotonia, skull deformity, dilatation of the lateral ventricles and premature closure of fontanel. This report will contribute to a better understanding of MPS III B due to NAGLU variation and skeletal dysplasia associated with CYP26B1. This study expands the mutational spectrum of NAGLU and CYP26B1. Besides, we should be aware of the importance of whole exome sequencing (WES) in diagnosing of rare diseases and the possibility of two rare diseases in one patient.

The article is written concisely on HSC for MPS II but there are some concerns and comments in this manuscript.

1. Specify how many cases were reported with concurrent mutant in two genes?
2. Specify which sign and symptom in this case is from MPS IIIB and CYP26B1 mutation.

3. Patients with MPS IIIB have clinical presentation at around 3 years old. Do the authors think all neurological signs and symptoms come from MPS IIIB in such an early stage?

Overall, the reviewer agrees that this is an interesting case report.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.
Unable to assess

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:
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