Author's response to reviews

Title: Two novel connexin32 mutations cause early onset X-linked Charcot-Marie-Tooth

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Author's response to reviews: see over
Reviewer 1

Major Compulsory Revision
1. The entire manuscript was edited by a person proficient in the English language.
2. The abstract was added information about the two families (severity, type of neuropathy and electrophysiology). The text on molecular effects of the mutations was abbreviated, to the essence of the mutations, i.e. stop codon leads to translation of a shorter protein, and amino acid change from cysteine to tyrosine thus disrupting at least one of the three disulfide bridges. Hence, we think our conclusion is reasonable given the position of mutations.

Minor essential revisions
1. This is not correct. The gap junction is made up of six subunits, each of the subunits are polypeptides.
2. Text changed accordingly
3. Corrected “variabilis”
4. Corrected the inconsistency.
5. Added pedigree number in parenthesis when appropriate.
6. Text adjusted according to reviewers comment.
7. Text edited and ref. added according to reviewers suggestions.
8. We already wrote “Thus, balance problems might represent a CNS symptom, since balance is based on vision, proprioception and equilibrium.”
9. The range of conduction velocities was 25-49 m/s which is intermediate type as >38 m/s is axonal, and <38 m/s is demyelinating.
10. This is a typo we added the amplitude.

Discretionary Revision
1. Added to text
2. Positive deleted.
3. Phrasing changed.
4. Added text BAEP and SSEP were not conducted.
5. Corrected according to suggestion.
6. Sentence deleted.
7. As this reviewer prefer that we reduced our speculation, we refrained from these hypothesis.
8. Corrected.

Reviewer 2

Major Compulsory Revision
Age 18 year was a typo, obligate gene carrier patient V-1 was 8 years old. We also expanded the discussion see text.

Discretionary Revision
1. We added neurophysiology results of the obligate carrier (family 2, V-1) and the method section on neurophysiology was expanded with the required information.
2. The patients were investigated once. Text added in method section and in the discussion.
3. Mutation in connexin genes can cause a variety of disorders and we think this is important to mention.

Reviewer 3

Minor Compulsory Revision
1. We have shortened the discussion about abortion. Although we can not prove any relation between CMT and abortion, we did not encounter any explanation for the high number of abortions in family 1. Thus, we find it important to mention and tried not to overemphasize this observation. We also added the sentence “increased rate of abortions has not been described in other CMTX families”.

**Reviewer 4**

“A few points that should be addressed”

1. Text changed accordingly. Two sentences added, one in Methods and one in Results section and ref. added according to suggestions.
2. Text added in figure legends accordingly.
3. Clinically affected and the obligate gene carrier V-1 in family 2 did have the mutation, while the clinically unaffected members investigated in these families did not have the mutation, other controls were not used in this study. However mutations in the same codons have been described in the literature, i.e.:

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Amino Acid Change</th>
<th>Disorder</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.223C&gt;T</td>
<td>Arg75Trp</td>
<td>CMT1X / CMT2 (+CNS involvement)</td>
<td>Bone et al., 1997</td>
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<td></td>
<td></td>
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<td>Latour et al., 1997</td>
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<td>Silander et al., 1997</td>
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<td></td>
<td></td>
<td></td>
<td>Numakura et al., 2002</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Taylor et al., 2003</td>
</tr>
<tr>
<td>c.224G&gt;A</td>
<td>Arg75Gln</td>
<td>CMT1X</td>
<td>Tan et al., 1996</td>
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<td>Silander et al., 1997</td>
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<td>Haites et al., 1998</td>
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<td>Numakura et al., 2002</td>
</tr>
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<td>Bone et al., 1997</td>
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<tr>
<td>c.535T&gt;C</td>
<td>Cys179Arg</td>
<td>CMT1X</td>
<td>Bone et al., 1997</td>
</tr>
</tbody>
</table>

4. Figure legends are expanded.