Reviewer's report

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

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Reviewer: Kleopas A Kleopa

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General
This is an interesting report of two families with early onset X-linked Charcot-Marie-Tooth disease (CMT1X) caused by two novel connexin32 mutations. The clinical study is interesting, detailed and well done but the manuscript needs a thorough revision and some improvements in the presentation and discussion of the results.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. The entire manuscript needs vigorous editing for correct spelling and grammar by someone proficient in the English language.
2. The abstract does not adequately summarize the essence of the study which is the clinical phenotype in the two families (severity, type of neuropathy, electrophysiology). All speculations about the molecular effects of the mutations should be removed from the abstract (and especially from the results section) as they are not supported by any data presented. The conclusion in the abstract also needs rewriting. I suggest something like: “We describe two families with X-linked CMT carrying novel mutations in the gene encoding connexin32, characterized by unusually severe phenotypes of early onset”.

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. Connexin32 is a gap junction protein and not a “polypeptide”. Six gap junction proteins form hexamers (hemichannels), and two apposing hexamers form gap junctions. All other terms used by the authors in this regard are confusing and should be corrected.
2. “Affected” should be “affected individuals” or “affected family members”
3. In page 3, correct “variabilis”
5. When referring to individual patients (such as the “seven years old girl”) please indicate their pedigree number in parenthesis to help the reader.
6. From the data presented it is not really justified to say that the seven year old girl had normal findings, since her sural SNAP is not given, her peroneal CMAP amplitudes are asymmetric and in low-normal range, and no upper extremity recordings are presented.
7. Page 8: The discussion of the Cx32 role in the placenta should be separated in a different paragraph and not overemphasized. Please minimize speculations, as increased rate of abortions has not been described in any other CMTX families with over 300 other Cx32 mutations, not even in families with mutations of similar nature and in similar domains of the protein, comparable age at onset and disease severity. It should also be noted that other gap junction proteins (Cx26, Cx43) are expressed in the placenta (Pfarrer et al., Placenta. 2006 Jan;27(1):79-86) and may compensate for the possible loss of Cx32 function.
8. In page 9, the authors state that proprioception was normal in nearly all patients, yet how they explain the fact that most of them had a positive Romberg’s sign?
9. In page 10, second paragraph: it is not correct to conclude that these families have intermediate type of CMT. This is a different form of CMT altogether. Furthermore, the nerve conduction velocities presented are
clearly in the demyelinating range, especially in male patients and especially in the upper limbs.

10. Table 4: Sural amplitude for patient V-2 (Fa,.2) is missing, while the velocity is given.

Discretionary Revisions (which the author can choose to ignore)

1. In page 3, last sentence, note that not only subclinical CNS symptoms or MRI abnormalities, but also acute or chronic CNS clinical manifestations have been described in CMTX patients.

2. In Page 6, last section, what are “positive clinical characteristics”? In the same section, the authors should mention whether their patients had or not any other illnesses that may accelerate neuropathy, such as diabetes or other medical history.

3. In page 8, first paragraph: correct “distal delays” to “distal motor latencies” if this is what is meant.

4. Did the patient with abnormal VEP have any visual disturbance clinically? Did he have other evoked potential studies (BAEP, SSEP) done?

5. In page 10, line 8: not the mutations but the disease has an earlier onset.

6. In page 10, the sentence “This could be nerve conduction velocity measurement error” is confusing and should be deleted, since asymmetry is also evident in the amplitudes of the responses and is generally common in CMTX.

7. In the discussion the authors should also address the following issues:
   7.1. Compare the phenotypes associated with the new mutations reported with phenotypes of previously reported mutations in same domains/ positions of the protein.
   7.2. Could modifier genes or particularly severe molecular effects, for example gain-of-function mechanisms (such as leaky hemichannels: see Liang et al., Ann Neurol 2005;57:749-754) account for these severe phenotypes?
   7.3. Expression and functional studies of these mutations?

8. Table 2: correct “metatarsal”

9. Table 4: What does under EMG “peripheral neurogenic lesion” mean? I think a more precise term would be “distal acute/chronic denervation”.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests