Identification of the rare compound heterozygous variants in the NEB gene in a Korean family with intellectual disability, epilepsy and early-childhood-onset generalized muscle weakness

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BACKGROUND

- We examined a Korean family with complex phenotypes characterized by intellectual disability, epilepsy and early-childhood-onset generalized muscle weakness.
- Since we did not find any abnormality using several conventional genetic tests for detection of chromosomal aberrations, gene copy number variations and mitochondrial gene mutations, we aimed to identify disease-causing genetic alteration(s) in this family.
- We conducted whole-exome sequencing (WES) in this family. After filtering the WES data, we compared five exome sequences of two affected siblings, one unaffected sibling and the unaffected parents, and we determined the allele frequency of the identified variants in an Asian population.
- Finally, we selected one candidate variant pair which is unique in the patients and corresponds to an autosomal recessive genetic model.

RESULTS

The two affected siblings had the same compound heterozygous variation in the NEB gene encoding nebulin, which was composed of two different missense variants: c.2603T>C (p.L868P) in exon 27 and c.21340C>T (p.R7114W) in exon 143.

CLINICAL DESCRIPTION

F1 15 year-old
- CC: epilepsy, intellectual disability and quadriplegia
- PE: Quadriaparesis with contracture of multiple joints, wheelchair-bound
- FHx: Her older brother also has similar clinical presentation.
- PHx: Apparently normal until the age of 12 months, she showed normal developmental milestones such as head control, roll over, crawling, and walking.
- At the age of 13 months, she developed neonatal seizure episodes which were not controlled by anti-seizure medicines. Along with intractable seizure episodes, her development eventually showed regression, getting to wheelchair-bound at the age of 13 years with no meaningful words and totally dependent activities of daily living.
- Brain MRI: NL
- 46, XX
- aCGH (Roche NimbleGen CGX-3 135K whole-Genome Array): NL
- Southern blotting for CGG repeats of FMR1: < 40 repeats
- Sequencing for MC21: NL
- Sequencing analysis for the detection of mutations in mitochondrial DNA

Table 1 Clinical features of the two patients

<table>
<thead>
<tr>
<th>Functional evaluation</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual muscle test (extremity grade right/ left)</td>
<td>Upper: 2/2</td>
<td>Upper: 3/3</td>
</tr>
<tr>
<td>Full-scale intellectual quotient</td>
<td>&lt; 25</td>
<td>&lt; 25</td>
</tr>
<tr>
<td>Verbal intellectual quotient</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Performance intellectual quotient</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Social quotient</td>
<td>0.6</td>
<td>16.1</td>
</tr>
<tr>
<td>Needle electromyography</td>
<td>Not available</td>
<td>Myopathic findings</td>
</tr>
</tbody>
</table>

*Measured by the Korean Wechsler Adult Intelligence Scale.
*Measured by the Korean Vineland Social Maturity Scale.

Mutations in NEB

- Although the function of nebulin in brain is unknown, nebulin is one of actin regulators.
- Cytoskeletons such as actin and microtubule have critical roles in synaptic functions of the brain. Formation of synapses and synaptic plasticity requires cytoskeletons.
- Abnormalities of actin-binding proteins could cause dysfunction of the actin cytoskeleton. Since nebulin is an actin regulator like dystrophin, it seems that synaptic excitability and synaptic plasticity could be altered by a dysfunction of actin cytoskeleton caused by NEB mutations.

CONCLUSION

- Based on extremely low allele frequency, in silico prediction and literature review as well as the myopathic findings on the needle electromyography study, we concluded that this compound heterozygous NEB variation may be a sound candidate for the disease-causing mutation in this family.
- Exon 143 is involved in developmental stage-specific alternative splicing and might harbor a regulatory function utilized during muscle maturation.