Background Information

- Epileptic encephalopathies are a genetically heterogeneous group of disorders associated with frequent seizures and developmental delay or regression, and exome sequencing (ES) has led to the identification of novel genes associated with these disorders (McTague et al., 2016).
- Guanine-binding proteins (G proteins) are a family of signal transducing molecules which function as heterotrimers consisting of alpha, beta and gamma subunits. The alpha subunit binds the guanine nucleotide, is capable of hydrolyzing GTP, and interacts with specific receptor and effector molecules (Sullivan et al., 1986).
- The GNA11 gene encodes the alpha subunit of subtype 1 inhibitory G protein, a member of the G protein family and the inhibitory GTP-binding regulator of adenylate cyclase (Sullivan et al., 1986; Bray et al., 1987).

Methods

- Exome sequencing was performed on 9,659 patients with developmental delay or intellectual disability and their parents (when available).
- The sequencing methodology and variant interpretation protocol has been previously described (Tanaka et al., 2015).

Results

- Four de novo heterozygous missense variants in GNA11 affecting two residues were identified in five individuals from unrelated proband-parent trios.
- The five probands were male, between 3-11 years of age, with developmental delay and intellectual disability.
- Four probands were reported with seizures of varying types, including infantile spasms, generalized tonic-clonic, focal onset, and complex partial seizures.
- All variants were absent from the ExAC database as well as from our internal ES database of unaffected individuals.
- All of our variants occurred at highly conserved residues 40 or 48 (p.Gly40Cys, p.Gly40Arg, p.Thr48Lys, and p.Thr48Ile) variants. These are located within or in the proximity of the conserved GDP/GTP binding motif in the GNA11 protein (Gia1). The Thr48 residue has been shown to be the guanine nucleotide binding site based on Gia1 crystal structure. Alteration of amino acid at 40 or 48 may disrupt GTP/GDP binding and impact catalytic function of Gia1.
- Two Gly40 variants (p.Gly40Cys/c.118G>T and p.Gly40Arg/c.118G>C) variants affected a highly conserved nucleotide position located in the end of exon 1 and are predicted to damage the splice donor site of intron 1, which may alter gene splicing.

Table 1. Clinical Presentation of Patients with heterozygous de novo GNA11 variants

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical presentation</th>
<th>GNA11 Variant</th>
<th>Developmental Delay</th>
<th>Seizures</th>
<th>Autism</th>
<th>Hypotonia</th>
<th>Brain abnormalities</th>
<th>Head Circumference</th>
<th>Short Stature</th>
<th>Dysmorphic Features</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>p.Thr48Lys</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>unknown</td>
<td>microcephaly</td>
<td>-</td>
<td>+</td>
<td>bilateral inguinal hernia and cryptorchidism</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>p.Thr48Lys</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>cerebral atrophy with bitemporal malformation of cortical development</td>
<td>microcephaly</td>
<td>-</td>
<td>none reported</td>
<td>mild hip dysplasia</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>p.Gly40Ile</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>normal MRI</td>
<td>macrocephaly</td>
<td>-</td>
<td>none reported</td>
<td>bilateral clubfeet, limb reductions due to amniotic band syndrome</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>p.Gly40Arg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>unknown</td>
<td>within normal limits</td>
<td>+</td>
<td>+</td>
<td>hyperphagia, overweight</td>
</tr>
</tbody>
</table>

Conclusions

- All identified variants in the GNA11 gene occurred at highly conserved codons 40 or 48.
- Similar to the previously described GNA13 gene, all GNA11 variants lie in or in close proximity to the GDP/GDP binding site, and might interfere with GDP/GTP binding of Gia1, presumably leading to a dominant negative effect in Gia1.
- Disruption of GNA11 was reported to cause long term memory defects in mice (Pineda et al., 2004). One de novo heterozygous variant in GNA11 affecting a residue of the GDP/GTP binding site (p.Gln204Arg) has been previously identified as a variant of interest in an individual with autism (Turner et al., 2016).
- Multiple missense variants clustering in a region involved in GDP/GTP binding in the GNA13 gene, which encodes the alpha subunit of subtype 3 inhibitory G protein, have been previously reported to cause auriculocondylar syndrome, likely through a dominant negative effect (Rieder et al., 2012; Romenelli et al., 2015).

Identified sequence changes of interest were confirmed in all members of the family on whom biospecimens were available by di-deoxy DNA sequence analysis.

References