Novel clinical and genetic insights into dysfunction of the ASC-1 complex

ASC-1 complex mutations in severe neuromuscular disorders

The transcriptional coactivator ASC-1 complex is composed of four subunits ASC-1 (TRIP4), ASCC1 (ASCC1), ASCC2 (ASCC2) and ASCC3 (ASCC3). Homozygous variants in TRIP4 (n=4 families) and in ASCC1 (n=4 families) were recently associated with Spinal muscular atrophy with congenital bone fractures 1 and 2. We present new findings in support of ASC-1 complex-related disease:

- Identification of novel TRIP4 and ASCC1 variants
- Description of four new families with ASC-1 neuromuscular disease
- Disease severity in correlation with mutated subunits and transcriptional consequences

Protein effects of known and novel mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Origin</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIP4 c.1679+1_1689=insC p.(Phe526Glyfs*13)</td>
<td>Hydramniosis, FTT, joint hyperlaxity, Pes varus, kyphoscoliosis, osteopenia, hypotonia, dysmorphic</td>
<td>Greece</td>
<td>13 years</td>
</tr>
<tr>
<td>TRIP4 c.512+1A p.(Cys171Tyr)</td>
<td>Joint contractures, FTT, hypotonia, neonatal respiratory distress, dysmorphic</td>
<td>Saudi Arabia</td>
<td>7 months</td>
</tr>
<tr>
<td>ASCC1 c.626+1G&gt;A p.(Arg216)*</td>
<td>Reduced fetal movement, edema, flexion contractures, thin bones, fractures, dysmorphic</td>
<td>Turkey</td>
<td>TOP at GW32</td>
</tr>
<tr>
<td>ASCC1 c.813+1A p.(Trp271)*</td>
<td>Reduced fetal movement, pleural effusion, fractures, scoliosis, thin ribs, osteopenia, hypotonia</td>
<td>Bahrain</td>
<td>Deceased at 27 days</td>
</tr>
</tbody>
</table>

Pedigrees and clinical findings

Figure 1: Association of disease severity and non-sense mediated mRNA decay

Figure 2: Pedigrees and photographs of novel patients homozygous for TRIP4 or ASCC1 variants Displayed features A) severe scoliosis, lipodystrophy, B) rigid knees, extended feet, clenched hands, arm fractures, C) scoliosis, thin ribs, fractures of femora and humerus

Table 1: Patient phenotype and origin

References