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

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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

Table 1: Patient phenotype and origin

GENE	PHENOTYPE	ORIGIN	AGE
TRIP4 c.1678+1_1678+2insC p.(Phe526Glyfs*13)	Hydramniosis, FTT, joint hyperlaxity, Pes varus, kyphoscoliosis, osteopenia, hypotonia, dysmorphic	Greece	13 years
TRIP4 c.512G>A p.(Cys171Tyr)	Joint contractures, FTT, hypotonia, neonatal respiratory distress, dysmorphic	Saudi Arabia	7 months
ASCC1 c.626+1G>A p.(Asp164*)	Reduced fetal movement, edema, flexion contractures, thin bones, fractures, dysmorphic	Turkey	TOP at GW32
ASCC1 c.813G>A p.(Trp271*)	Reduced fetal movement, pleural effusion, fractures, scoliosis, thin ribs, osteopenia, hypotonia	Bahrain	Deceased at 27 days

Protein effects of known and novel mutations

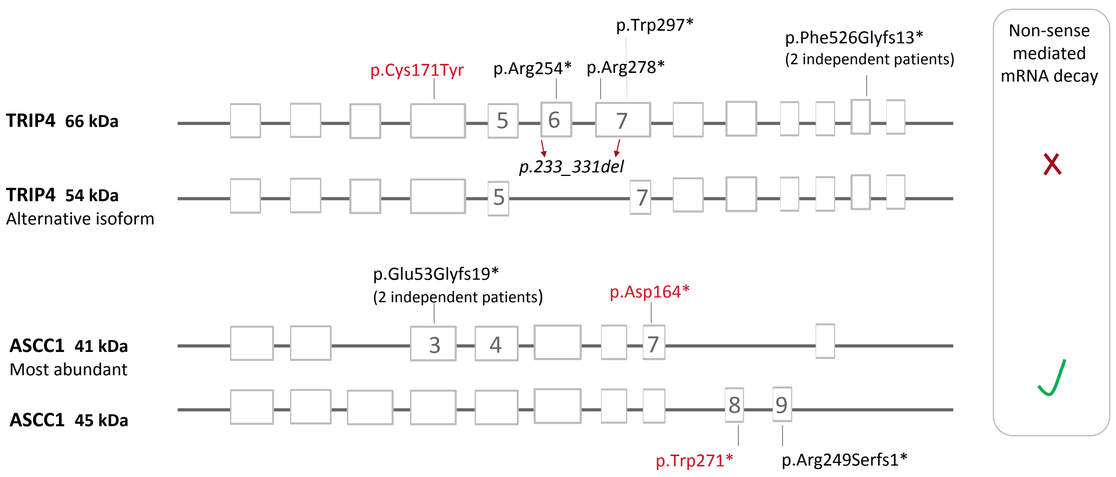

Figure 1: Association of disease severity and non-sense mediated mRNA decay

ASC-1 complex model

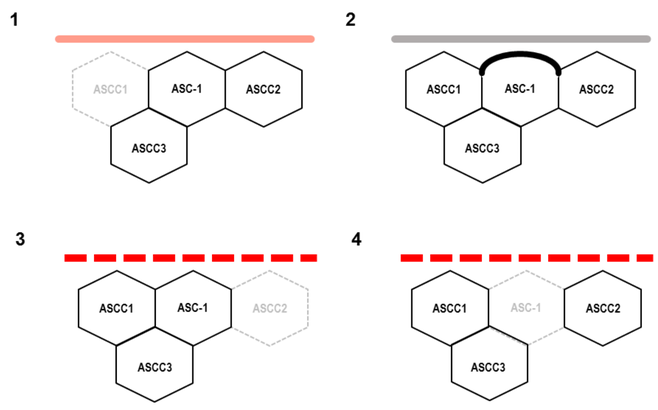

Figure 3: Model of critical components based on published and internal data. 1- Loss of ASCC1 and 2- structural alteration of ASC-1 (TRIP4) with less severe consequences than 3,4- Loss of ASCC2 and ASC-1, stippled line displays early lethality

Pedigrees and clinical findings

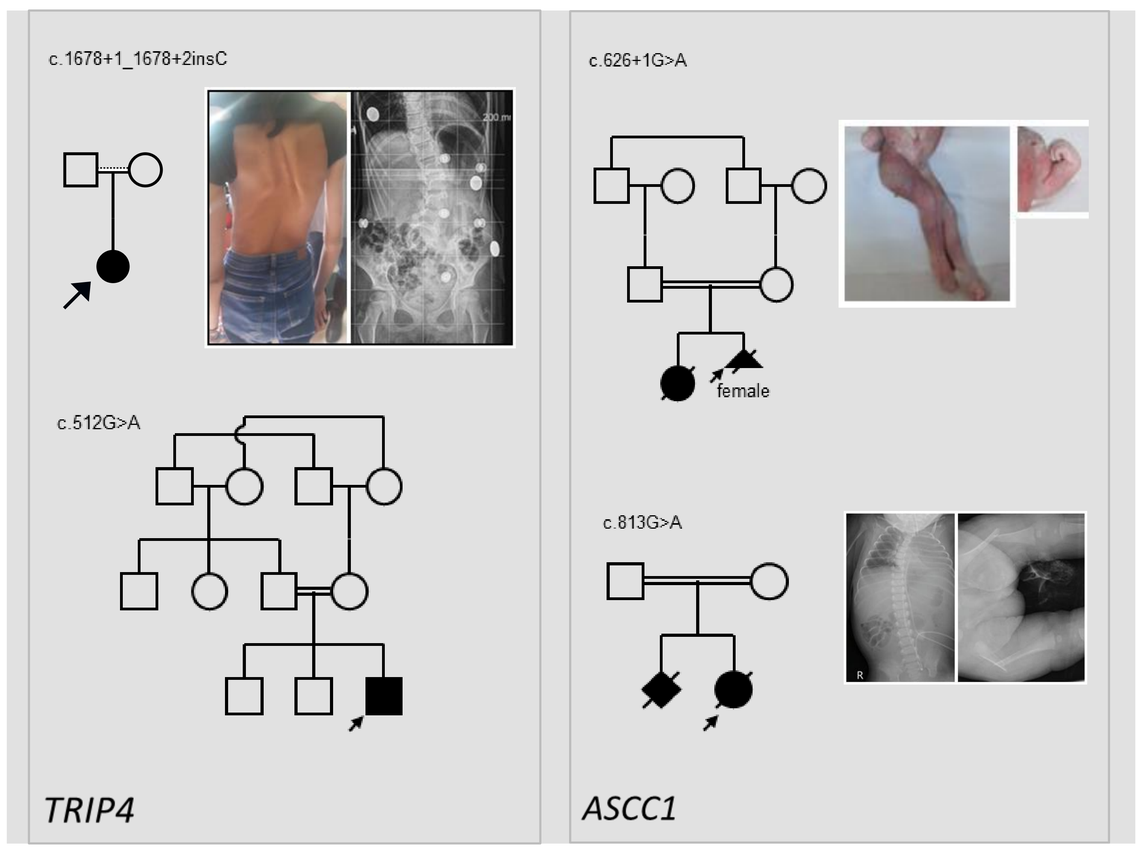

Figure 2: Pedigrees and photographs of novel patients homozygous for TRIP4 or ASCC1 variants. Displayed features: A) severe scoliosis, lipodystrophy, B) rigid knees, extended feet, clenched hands, arm fractures, C) scoliosis, thin ribs, fractures of femora and humerus

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Disclosure of conflict of interest:

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