TOR1A variants cause a severe arthrogryposis with developmental delay, strabismus and tremor

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Mutations in TOR1A cause dystonia 1

An autosomal dominant disease with incomplete penetrance (Ozelius and Lubarr, 1993; Ozelius et al 1997)

Dystonia is a neurological movement disorder characterised by repetitive and sustained involuntary muscle contractions resulting in severe twisting movements and abnormal postures involving one or more sites of the body
Most cases of DYT1 dystonia identified so far are caused by heterozygous in frame trinucleotide deletion (c.907-909delGAG) resulting in the loss of a glutamic acid residue, a 3-bp deletion.

One intriguing aspect of the DYT1 dystonia associated with this 3-bp deletion is that it displays greatly decreased penetrance.
Material & Methods

- Next generation Sequencing (NGS) in 25 cases with arthrogryposis multiplex congenita, which is defined as congenital contractures in more than two joints and in multiple body areas (Hall 1997).
Three Iranian families had homozygous variations in TOR1A
Family 1

- Case 1
- 4 year old male
- Developmental delay
- Severe Intellectual disability
- Strabismus
- Tremor in limbs
- Increased tone
- Contractures in elbows
- Clenched hands
- hammertoes
Family 1

- Case 2
- 2 year old male
- Developmental delay
- Severe Intellectual delay
- Strabismus
- Tremor in limbs
- Clenched hand
- Hip dislocation
- Limited movement in knees
- Hammertoes
Family 2

- 2 ½ year old girl
- Developmental delay
- Severe Intellectual disability
- No speech
- Strabismus
- Increased tone
- Tremor in hands and feet
- Contracture in elbows
- Clenched hands
Clinical features

- Hip dislocation
- Limited movement in knees
- Hammertoes
- Improvement in contractures with age
Family 3

- 2 ½ year old girl
- Developmental delay
- Moderate Intellectual disability
- 50 words vocabulary
- Intermittent strabismus
- Increased tone
- Tremor in thighs
- Contractures in elbows
- Kyphoscoliosis
- Limited movement in knees
Clenched hands
Hammertoes
Clubfeet
Improvement in contractures with age
Exome sequencing was performed for Families 1 and 3.
A novel homozygous missense mutation in exon 5 of TOR1A was identified in Case 1 (Family 1).
The common three base pair deletion in TOR1A (exon 5, c.907_909delGAG, p.Glu303del) was identified in homozygous state in TOR1A case 4 (Family 3).
Targeted sequencing of 33 known neurogenetic disease genes of Family 2 identified the same the base pair deletion c.907_909delGAG in homozygous state in TOR1A.
Genetic findings

- The TOR1A variants were validated by Sanger sequencing.
- The parents were heterozygous for the variants.
- Heterozygous mutations in TOR1A are associated with dystonia (DYT1) parents and their siblings, thirteen from family 1, eight from family 2, and fifteen from family 3 did not have movement disorders.
Wild-type torsinA is localised in the endoplasmic reticulum.

The p.Gly318Ser torsinA variant was abnormally concentrated in the nuclear envelope as has been previously reported for the disease associated p.Glu303del and p.Phe205Ile substitution.
Homozygous mutation in \textit{TOR1A}

- Homozygous \textit{Tor1a} p.glu303del mutation cause 100% mortality of mice after 48 hours (Cookson and Clarimmon, 2005; Dang et al., 2005; Goodchild et al., 2005).

- Homozygous torsinA knock-out mice as well as homozygous knock-in mice with two copies of the p.Glu303del allele died shortly after birth, suggesting that torsinA is indispensable for development.
Current Study

- Four Cases from three unrelated families
- Severe arthrogryposis, strabismus and tremor and \textit{TOR1A} variants
Clinical features

- Contractures of large and small joints including elbows, wrists, fingers, knees, ankles, and toes which improved with age.
- Congenital hip dislocation was seen in 2/4 patients.
- Strabismus gets worse in the patients.
- Developmental delay and intellectual disability were present in all patients, however, the degree was variable.
Case 1 and younger brother were severely delayed and had not developed the ability to speak or communicate verbally.

Case 3 had not started to communicate verbally but had started to communicate not verbally.
- Increased muscle tone in all patients
- Follow-up necessary
- A report by Clark et al., 2016 with arthrogryposis with homozygous frameshift variant in TOR1A
CONCLUSION

- We suggest homozygous variants in TOR1A cause a severe arthrogryposis phenotype including contractures of large and small joints, with developmental delay, progressive strabismus and infantile tremor.
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