DATA REPORT

Distal arthrogryposis with variable clinical expression caused by TNNI2 mutation

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Distal arthrogryposis (DA) is a clinically and genetically heterogeneous disorder characterized by congenital limb contractures with no primary neurological or muscular effects. DA is an autosomal dominant disorder with reduced penetrance and variable expression. DA is classified into 10 types, 1, 2A, 2B, 3–5, 7–10,1 and molecular diagnosis can help with the correct diagnosis of DA. DA2B (OMIM 601680) is one of the most common types.2 In DA2B, mutations have been found in genes encoding troponin I, fast skeletal type (TNNI2),3 troponin T3, fast skeletal type (TNNT3),4 myosin heavy chain 3, skeletal muscle, embryonic (MYH3)5 and tropomyosin 2 (TPM2).5 In this study, we describe the detailed clinical features and molecular diagnosis of a female DA patient.

The female patient was 3 years old and born after 40 weeks of gestation to non-consanguinean Croatian parents (Figure 1a). Apgar scores were 8/7 at 1/5 min and her birth weight was 3450 g (50th percentile) and she was 48 cm long (25th percentile). At birth, short neck, low posterior hairline, nevus flammeus on the forehead and asymmetric epicanthus were seen. Bilateral joint contractures were also observed at the wrists, elbows, hips and knees, together with right-sided torticollis. In addition, hand and foot deformities (talipes equinovarus) and skin-furrowed fingers were reported (Table 1). Serum amino acid and organic acid levels, peripheral blood lymphocyte karyotypes and electroencephalogram were all normal. During the first few months, the patient showed motor delay, bilateral hypertonia and vertical talus (Figure 1b, c). Her motor movements were slow, and closed fists and bilateral un abducted thumbs were observed (Figure 1d, e). Her head was tilted to the left and rotated to the right. The patient also presented with hypertonic upper limbs and a palmar grasp. In addition, she was unstable when standing on tiptoes. Physiological reflexes were present. Physical therapy was started immediately for neurodevelopmental delay and right-sided torticollis. Poor muscle tone, hypertonus of the upper limbs, and palmar grasp were consistently observed. Conservative orthopedic correction using the Dobbs method (high gypsum boots, replaced every 7 days) was started. At 4 months, the talus was surgically repositioned and the navicular bone was fixed with Kirschner wire. The patient wore orthoses for her ankles and feet during the day, but only at night on the hands and wrists. Physical therapy is currently ongoing.

Whole-exome sequencing (WES) was performed as previously described6 and 93.7% of RefSeq coding regions were covered by 20 or more reads. WES identified a novel TNNI2 mutation (c.485G>A, p.Arg162Lys) in the patient and her father. The father has no typical DA but hip dysplasia. This may explain the clinical features of DA2B in this family, but with variable clinical expression.

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methylenic group of the arginine is a component of the hydrophobic core and this can be replaced by the methylenic group of the mutated lysine residue (p.Arg162Lys). Therefore, this mutation does not affect the protein structure, but could impair the molecular interactions between TnI and actin filaments.

In conclusion, we describe a novel TNNI2 mutation in two family members: a young girl with DA2B and her father with hip dysplasia (but not typical DA). This mutation may explain the variable clinical expression of DA2B in this family.

Table 1. Clinical features of the patient and her father

| Physical features                  | Proband | Father |
|-----------------------------------|---------|--------|
| **Face**                          |         |        |
| Triangular face                   | +       | +      |
| Naeveus flammeus on forehead     | +       | +      |
| Long philtrum                    | +       | +      |
| Small prominent chin             | +       | −      |
| Small mandible                   | +       | +      |
| Micrognathia                     | +       | −      |
| Attached ear lobules             | −       | +      |
| Downslanting palpebral fissures  | −       | +      |
| Prominent nasolabial folds       | +       | +      |
| Broad nasal bridge               | −       | −      |
| Broad nasal root                 | +       | +      |
| Small mouth                      | +       | +      |
| High-arched palate               | +       | −      |
| **Skeletal**                      |         |        |
| Short stature                     | +       | +      |
| Mild neck webbing                | +       | +      |
| **Hands**                         |         |        |
| Overriding fingers               | +       | +      |
| Thumb adduction                  | +       | +      |
| Contractures of the proximal interphalangeal (PIP) joints | + | + |
| Contractures of the metacarpophalangeal joints | + | + |
| Hypoplastic or absent interphalangeal creases | + | + |
| **Feet**                          |         |        |
| Talipes equinovarus              | +       | +      |
| Calcaneovalgus deformities       | +       | +      |
| Vertical talus                   | +       | +      |
| Metatarsus varus                 | −       | −      |
| Clubfoot                         | +       | +      |

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.882.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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