

## Case Report

# The First Case of *TNNT3* Related Distal Arthrogryposis Type 2B in Hong Kong

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### Abstract

Distal Arthrogryposis (DA), is a group of ten (DA1-DA10) rare, clinically and genetically heterogeneous autosomal dominant disorders primarily characterised by non-progressive congenital contractures of the distal limb joints without a neuromuscular disease. Among the ten subtypes, DA Type 2B (DA2B), known as Sheldon-Hall syndrome is considered to be the most common manifesting camptodactyly, talipes equinovarus, ulnar deviation of fingers, triangular face, small chin and short stature. However, individuals with a mutation in *TNNI2*, *TNNT3*, or *MYH3* have phenotypes that can hardly be distinguished from one another. Here we have reported the first molecularly confirmed *TNNT3* related distal arthrogryposis family in Hong Kong. The clinical phenotype and underlying mechanism have also been discussed.

### Key words

Distal arthrogryposis 2B; Sheldon-Hall syndrome; *TNNT3*

### Introduction

Arthrogryposis is a group of rare syndromes involving congenital, non-progressive contractures in two or more joints in different body areas,<sup>1</sup> subsequent to pathological basis such as recognisable genetic disorders, environmental insult or exposure to a teratogen. Distal Arthrogryposis (DA) is characterised as an autosomal dominant disorder of arthrogryposis with congenital contractures of distal limb joints. According to Bamshad's diagnostic criteria,<sup>2</sup> DA is diagnosed based on more than two clinical characteristics: (1) a consistent pattern of distal joint involvements (2) limited proximal joint involvement (3) an autosomal dominant inheritance pattern (4) reduced

penetrance and (5) variable expressivity. DA patients may commonly exhibit camptodactyly, ulnar deviation, talipes equinovarus, absent flexion finger creases, scoliosis or congenital hip dislocation and stiff elbows.<sup>3</sup> Up to date, ten different types of DA have been classified according to proportion of features they share with one another,<sup>2</sup> where only less than 100 cases of DA2 have ever been reported, the epidemiological data for prevalence, penetrance and expressivity remains uncertain in literature. Herein, we presented a case of a Chinese family with dominant *TNNT3* mutation clinically diagnosed with Distal Arthrogryposis Type 2B (DA2B), to provide more clues on genotype-phenotype correlations.

### Case Report

A full-term new-born Chinese baby boy was referred from the Department of Obstetrics and Gynaecology of a public hospital in October 2006 for Arthrogryposis Multiplex Congenita involving left rigid talipes equinovarus, right rocker-bottom foot with calcaneal deformity. It was noted that the baby had a strong maternal family history of multiple joint deformities involving eight affected family members over five generations (Figure 1).

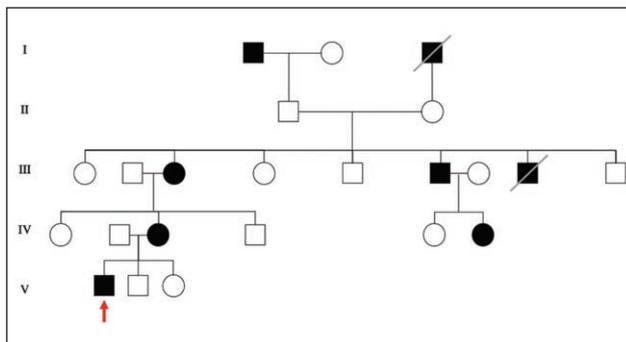
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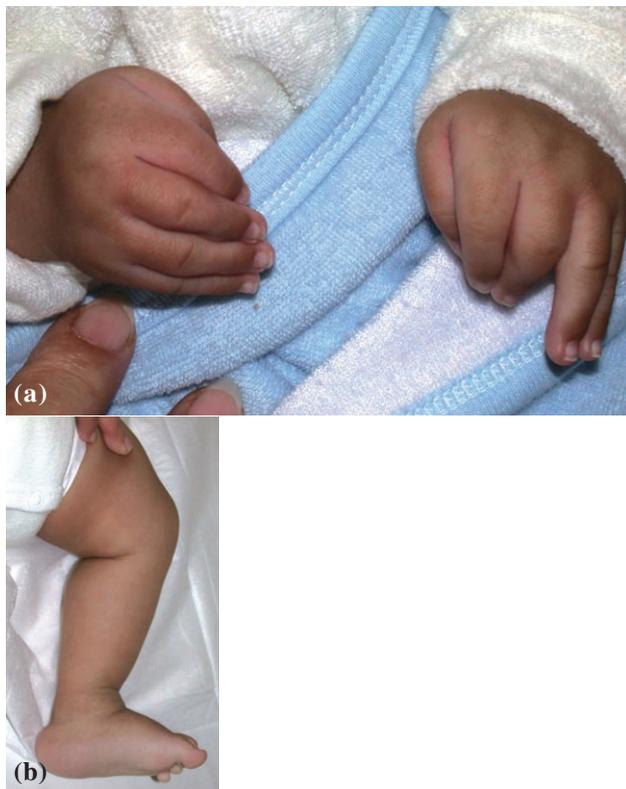
The proband was initially presented with right inguinal hernia, right torticollis, both hands with flexion deformity at proximal interphalangeal joints and incomplete flexion at distal interphalangeal joints, ulnar deviation of fingers and single transverse palm creases (Figure 2a). He also had a right rocker-bottom foot with talipes equinovarus and a cast on his left foot (Figure 2b). There was no dysmorphic facial feature and the neurological examination



**Figure 1** Pedigree of the family.

was normal. He had undergone multiple corrective surgeries for his inguinal hernia and distal joint deformities since the age of 2. There are multiple family members affected, yet the clinical features are highly variable. His mother had no feet contractures but had torticollis in childhood, presented with mild facial asymmetry, only index and middle fingers of her left hand showed flexion contractures at proximal interphalangeal joints and incomplete flexion at distal interphalangeal joints (Figure 2c). His maternal grandmother presented likewise with similar yet even milder contractures at both hands only and had no facial asymmetry. However, the detailed clinical features of other affected family members were not available.

Based on the clinical manifestations of multiple non-progressive distal joint contractures and a strong positive family history, the diagnosis of DA could be clinically ascertained according to Bamshad's criteria.<sup>2</sup> Blood samples were collected from the boy and his mother in February 2017 for gene panel testing that included *CHRNA*, *MYH3*, *TNNI2*, *TNNT3*, *TPM2* genes. The coding and splice site junction (+/-10bp) of the above genes were captured



**Figure 2** Distal joint contractures of the family. (a) Proband presented with bilateral flexion deformity at distal joints and ulnar deviation of fingers; (b) Proband's right rocker-bottom foot with talipes equinovarus; (c) Proband's mother presented with similar flexion contractures, most severe at index and middle fingers of her left hand.

and simultaneously sequencing by massively parallel sequencing on Illumina platform (MiSeq). The sequencing reads were then assembled and aligned to reference gene sequences based on human genome build GRCh37/USCS hg19. Variants were being called by Helicube bioinformatics analysis. All potential likely pathogenic or pathogenic variants were further confirmed by Sanger capillary sequencing. As a result, a heterogenous missense variant c.188G>A (p.Arg63His) in *TNNT3*{NM\_006757.3} gene was detected in both proband and his mother. This variant is a reported pathogenic variant in a disease database ClinVar and not present in population databases like ExAC and gnomAD. By the American College of Medical Genetics and Genomics (ACMG) guideline which provided interpretative categories of sequence variants, it is classified as pathogenic, thus the molecular diagnosis of *TNNT3* related Distal arthrogryposis 2B [OMIM 601680] was substantiated.

### Electronic-Database Information

Disease databases – primarily contain variants found in patients with disease and assessment of variants' pathogenicity:

- ClinVar, <http://www.ncbi.nlm.nih.gov/clinvar/>, a disease database of assertions about the clinical significance and phenotype relationship of human variations.

Population databases – generally contain frequencies of variants in large populations:

- Exome Aggregation Consortium (ExAC), <http://exac.broadinstitute.org/>, a population database of variants found during exome sequencing of 60,706 unrelated individuals sequenced as part of various disease-specific and population genetic studies, where paediatric disease subjects and related individuals were excluded.
- Genome Aggregation Database (gnomAD), <http://gnomad.broadinstitute.org/>, a similar population database with newer and larger size of datasets i.e. 125,748 exome sequences and 15,708 whole-genome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies.

### Discussion

Arthrogryposis, a rare condition with incidence of 1/3000 pregnancies,<sup>4</sup> has over 400 different specific conditions recognised and over 320 genes implicated over the past 40 years.<sup>1</sup> In Hall's review,<sup>5</sup> only 28% found to have genetic cause, the rest remained either unknown or attributed to environmental insult. Given the phenotypic variability, it has been classified into three groups<sup>5</sup> (i) primary limb involvement; (ii) limb involvement plus other malformations or anomalies; and (iii) limb involvement plus central nervous system dysfunction and mental retardation.

Upon unremarkable neurological examination without extra-articular involvement, our patient was suspected to have group 1 of arthrogryposis. Though epidemiological data indicates that amyoplasia congenita is the most classical form of arthrogryposis with sporadically occurring pattern,<sup>1</sup> the strong family history of our patient involving only multiple joint contractures without any neurological disorders, directed the cause to DA, which is as well the second most common form of arthrogryposis with an incidence of around 1/20,000 live births.<sup>3</sup>

Concerning the gene ontology of DA, mutations in genes that lead to sarcomeric protein or connective tissue dysfunction, such as *TNNI2*, *TNNT3*, *TPM2*, *MYH3*, and *MYH8* genes that encode components of the contractile apparatus of fast-twitch myofibres or *MYBPC1* gene that encodes myosin-binding protein C1 of slow-twitch myofibres or fibrillin gene *FBN2*, can all cause DA.<sup>3</sup> Among which, *TNNT3* gene mutation found in our patient was newly considered as a positional and functional candidate for causing multiple congenital contractures.<sup>6</sup> According to last update in October 2019 by NCBI gene (<https://www.ncbi.nlm.nih.gov/gene/7140>), *TNNT3* is located on chromosome 11p15.5 containing 22 exons and it encodes the fast-twitch skeletal muscle isoform of troponin T,<sup>6</sup> which forms part of the contractile apparatus of fast twitch myofibres by interacting with actomyosin ATPase inhibitory subunit troponin I, calcium binding subunit troponin C, tropomyosin and actin, to regulate muscle contraction and relaxation. *TNNT3* was later found to play a role in nuclear localisation of calcium channel Cav $\beta$ 1a subunit in skeletal muscle in the early differentiation of muscle progenitor cells.<sup>7</sup> In experimental

functional study, the mutation in our family with the substitution of the 63rd codon with Arginine to Histidine, leading to a gain of function with increased ATPase activity that disturbed troponin T's interaction with tropomyosin, which increased calcium sensitivity in the skeletal muscle and consequently muscle contractility, thus further caused the development of contractures.<sup>6</sup>

So far, only few pathogenic mutations of fast skeletal muscle TnT gene (*TNNT3*) have ever been reported,<sup>8,9</sup> most were clinically diagnosed as DA2B, yet exhibited wide intra-familial phenotypic variability and spectrum of clinical expressions, suggesting reduced penetration of pathogenic mutations. The observation that DA2B can be caused by mutations in either *TNNI2* or *TNNT3* confirms that DA2B is genetically heterogeneous.<sup>6</sup> Although the cause of DA2B can be distinguished by direct genetic testing of *TNNT3* and *TNNI2*, there is no strict genotype-phenotype correlations for distinguishing subtypes clinically. *TNNT3* gene has been conventionally mapped to cause DA2B, yet a study revealed that a *TNNT3* gene mutation is also able to cause DA1,<sup>10</sup> proposing that DA1 and DA2B may be regarded as a continuum of increasingly severe forms of myopathy. As the diagnosis of DA2B depends on the presence of non-limb findings and calcaneovalgus deformities,<sup>10</sup> our patient could be clinically classified as DA2B with facial and shoulder asymmetry, mild right ptosis, torticollis and right foot calcaneal deformity. However, ptosis, torticollis and inguinal hernia observed in our patient have rarely been reported in cases of *TNNT3* mutation, therefore we have expanded the phenotypic manifestations for *TNNT3* related disease.

The management for DA is mainly supportive care. Early intervention with occupational and physical therapy, serial casting or surgery would all help optimise the quality of life. Given the extreme spectrum of phenotypic expressivity, parental testing even in the absence of significant symptoms should be considered for reproductive risk assessment.

## Conclusion

We have reported the first case of *TNNT3* related DA family in Hong Kong. This highlights the clinical approach and importance of genetic testing in management of arthrogryposis.

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We are thankful to the family for their consent for the publication of their clinical photos.

## Declaration of Interest

None

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