Intra-familial variability in patients with dominant RYR1 variations: analysis of 10 families

Xingzhi Chang, Cuijie Wei, Jieyu Liu, Yanbin Fan

Department of Pediatric, Peking University First Hospital, Beijing, 100034,China

Introduction

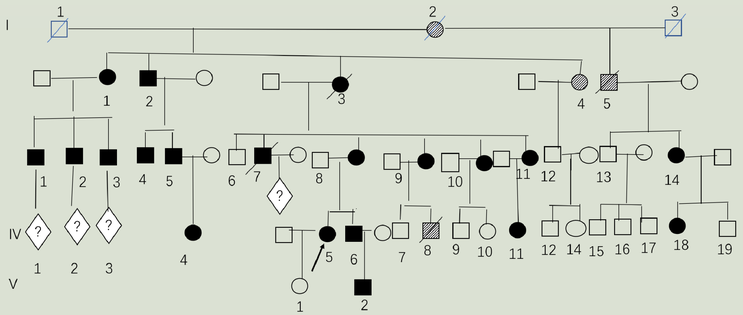
Pathogenic variation in RYR1 is the most common cause of congenital myopathy. Clinical heterogeneity was noted between patients with RYR1-related myopathies, both in dominant and recessive inheritance. While phenotype variance among family members with the same variation was not fully understood.

Patient and method

Patient

64 patients were identified with dominant RYR1 variations from 10 families, patients scattered in at least three generations in 8 families. In 5 large families, there was at least 5 members involved, with 24 patients in the largest family（Figure 1）.

Fig 1 the largest family tree in patients



Method

Clinical, muscle pathologic and gene test data were collected and analyzed.

Genomic DNA was extracted from leukocytes. RYR1 variations were screened through gene panel or whole exome sequencing strategy.

Result

The clinical spectrum was highly variable among family members. Hereditary anticipation appeared in 7 families, as probands had earlier onset and more severe manifestation than their parents, and the motor ability of child usually worse than that of their parents.

Ten missense pathogenic variations were identified, two out of them located in exons 95, one in exon 100, one in exon 101, and six in exon 102. All located in Pore forming and PVSD domains.

At least one member in eight families received muscle biopsy. Typical cores were identified in muscle specimens(Table 1).

Table 1. Genetic and pathologic data of patients

Pt	Pathology	Variants	Variation type	Origin	Pathogenicity	Protein	Exon
1	CCD	c.14678 G>A‡	missense	Paternal	P	P. Arg4893Gln	102
2	CCD	c.14741G>C‡	missense	Paternal	P	P. Arg4914Thr	102
3	CCD	c.G14719A ‡	missense	Paternal	P	p. Gly4907Ser	102
4	CCD	c.14693T>C‡	missense	Paternal	P	p. Ile4898Thr	102
5	CCD	c.13904A>G	missense	Maternal	LP	p. Glu4635Gly	95
6	CCD	c.14591A>C	missense	Paternal	LP	p. Tyr4864Ser	102
7	/	c.13909 A>G‡	missense	Maternal	P	p. Thr 4637ALa	95
8	/	c.14678G>A‡	missense	Maternal	P	p. Arg4893Gln	102
9	CCD	.14422_14423delinsAA‡	missense	Maternal	P	p. Phe4808Asn	100
10	CCD	c.14582G>A	missense	Maternal	P	p.Arg4861His	101

Note: RYR1 NM_000540.3 Pt, patient; ‡, previously reported; /, data unavailable; CCD, central core disease;

conclusion

Intra-family clinical diversity of RYR1 were observed in large families, and hereditary anticipation phenomenon was noticed with unknown mechanism. Modifying gene may exist encoding a protein nearing Pore forming domain of RyR1.

Contact

Email: changxingzhi7318@163.com