Genotype-phenotype characteristics in four pedigrees of type II collagenopathy in our hospital

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Introduction

- Type II collagen is one of the essential elements for the cartilage, eye, and inner ear, and important in normal growth.
- Type II collagen is encoded by *COL2A1* gene, and the mutations cause type II collagenopathy, which is characterized by the symptoms of skeletal dysplasia, ocular abnormities, and hearing impairment.
- Type II collagenopathy is a generic name of the skeletal dysplasia caused by pathogenic variants of *COL2A1* and includes achondrogenesis type II, spondyloepiphyseal dysplasia, spondyloepimetaphyseal dysplasia, and stickler syndrome type1[1)].
- Since this is a rare disease (1/10,000 in Stickler syndrome type1, which is the most frequent type II collagenopathy)[1)], genotype-phenotype characteristics is still unknown.

Object

We describe the genotype-phenotype characteristics of type II collagenopathy about our patients.

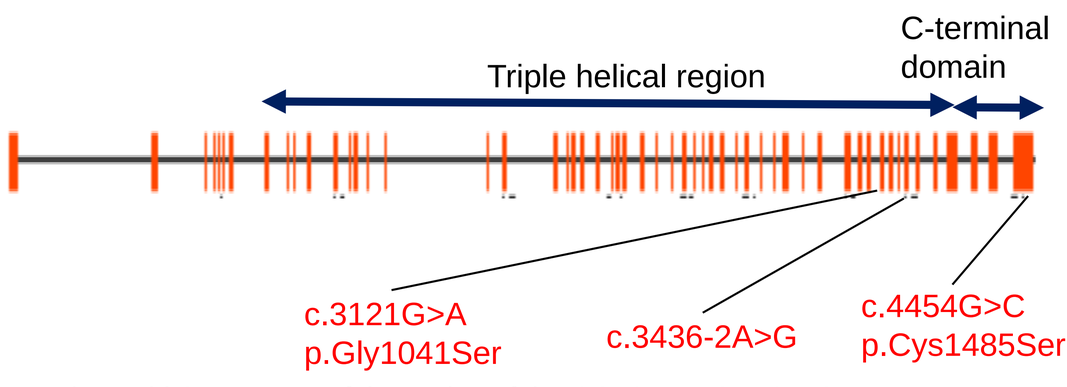
Method

- We recruited four pedigrees clinically suspected of type II collagenopathy.
- We conducted whole exome sequencing and detected pathogenic variants by bioinformatic analysis.
- We discussed genotype-phenotype characteristics of our type II collagenopathy compared with previous reports.

Patient characteristics

Family	I	II	III	IV
Proband	7 year-old girl	4 year-old boy	8 year-old boy	9 year-old boy
Family history	Father Younger sister	None	Younger sister	Father?
short statue with short trunk	yes	yes	yes	yes
Short statue	-4.1SD Father: -3.4SD Little sister: -3.4SD	-5.0 SD	-8.5 SD	-2.5 SD
Specific face	Round face Flat nose	Flat nose	Flat nose Small jaw	Hypertelorism Flat nose Small jaw
Cleft palate	no	no	no	no
Ocular abnormity	no	no	no	Myopia
Hearing impairment	no	no	no	no
Other symptoms	no	GHD	Tracheo-laryngomalacia	Brachydactyly Autism GHD
platyspondyly	yes	yes	Yes Ovoid vertebra	Yes Ovoid vertebra
Delayed ossification	no	yes	yes	yes
Long bone	Enlargement of metaphysis	No abnormity	Slightly dumbbell shape	Splaying epiphysis
Clinical diagnosis	SEMD SEDC	SEDC SEMD	Kniest dysplasia SEDC	SPD PLSDT
COL2A1 variant	c.3436-2A>G	c.3121G>A p.Gly1041Ser	c.3121G>A p.Gly1041Ser	c.4454G>C p.Cys1485Ser
Zygosity	heterozygous	heterozygous	heterozygous	heterozygous
Allele frequency (gnomAD)	none	none	none	none
Functional prediction	Damaging (Human Splicing Finder)	Damaging (SIFT, PROVEAN)	Damaging (SIFT, PROVEAN)	Damaging (PolyPhen2, PROVEAN)
Reported	Not reported	Reported as SEMD Strudwick type[2)]	Reported as SEMD Strudwick type[2)]	Not reported

GHD: growth hormone deficiency, SEMD: spondyloepimetaphyseal dysplasia, SEDC: spondyloepiphyseal dysplasia congenital, SPD: spondyloperipheral dysplasia, PLSDT: platyspondylic dysplasia Torrance type



Amino Acid Sequences of the region of the COL2A1 p.Gly1041Ser

human	1029	GPAGEPGREGSPGADGPPGRDGAA 1052
mouse	1029	GPAGEPGREGSPGADGPPGRDGAA 1052

Discussion

- The c.3426-2A>G is a novel splice site mutation. Several splice site mutations were reported in Stickler syndrome type 1[3)]. Although the height is considered to be relatively tall, our patient has severe short statue and SEMD Strudwick is suspected.

- The c.3121G>A is a missense variant in glycine position of the Gly-X-Y repeat motifs. Glycine substitution of the Gly-X-Y cause a disruption of triple helical formation (dominant negative) and lead to severe phenotype[3)]. The variant was reported in SEMD Strudwick type, but our patient, especially pedigree III has more severe phenotype and is suspected as knist dysplasia or SEDC clinically.

- The c.4454G>C is a novel missense variants in C terminal region. The mutation in C terminal region was reported to be related with PLSDT and SPD[4)]. Our patient has the symptoms fulfilled with SPD characteristics.

- Pedigree II and III have same pathogenic variant, but the severity is apparently different. The modifier variant may contribute, but we cannot detect it.

Conclusion

- Through the considerations of genotype-phenotype characteristics of our type II collagenopathy patients, we reassure the spectrum of the phenotype. Thus, the accumulation of the cases is required.

Reference

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