A novel COL1A1 mutation in a family with osteogenesis imperfecta associated with phenotypic variabilities

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Osteogenesis imperfecta (OI) is a heterogeneous disorder that is characterized by bone fragility and systemic complications, and is mainly caused by gene mutations in COL1A1 or COL1A2. A novel COL1A1 splicing mutation, c.750+2T>A, was identified in a Japanese OI family. Only the proband in this family showed various complications, such as heart valve diseases and severe scoliosis. The clinical heterogeneity in the family is discussed in this study.

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to a splicing abnormality. Although the same variant has never been reported previously or registered in the Database of Collagen Mutations (http://www.le.ac.uk/genetics/collagen/), similar splicing donor site variants were frequently identified in OI patients. Therefore, the identified variant was considered a causative mutation.

Figure 1. Clinical information and the results of the molecular analysis. (a) The family tree of the proband’s relatives. The proband (III-7) is a patient with OI. His grandfather (I-1), mother (II-5), and aunt (II-1) are suspected to have OI based on their clinical features, including a short stature, a history of long bone fractures, and blue sclera, although they did not exhibit scoliosis or heart disease. Causes of death: (I-1) death in action, (I-2) blood disease at 84 years, (II-1) traffic accident at 72 years, (III-2) heart disease at 25 years, (III-4) accident at 18 years. (b) Severe scoliosis (Cobb angle: right ~ 70° at T5-T10, left 60° at T11-L3). There is no obvious progression after adolescence. (c) The IGV (http://www.broadinstitute.org/igv/) shows the identified COL1A1 variant in ~ 50% of the reads. (d) Electropherograms of Sanger sequencing. The heterozygous variant in the consensus sequence in the splicing donor site of intron 10 is shown in the proband and his mother. The wild-type sequence is observed in the father. IGV, Integrative Genomics Viewer; OI, osteogenesis imperfecta.

Table 1. Summary of the clinical features in the family members

|                | Aunt (II-1) | Mother (II-5) | Proband (III-7) |
|----------------|-------------|---------------|-----------------|
| Short stature  | – 4.5       | – 4.5         | – 5.5           |
| Walking        | No problem  | No problem    | Crutch using    |
| Frequency of bone fracture | > 10 times | < 10 times | > 30 times |
| Bone deformity | –           | –             | Secondarily     |
| Blue sclera    | +           | +             | +               |
| Basal skull compression | NT     | NT            | –               |
| Heart disease  | NT          | NT            | MR, AR          |
| Fragility of capillary | Unknown | Easy occurrence of subcutaneous hemorrhage | Easy occurrence of subcutaneous hemorrhage |
| Scoliosis      | NT          | –             | Severe          |
| Tendon relaxity| +           | +             | +               |
| Dentinogenesis imperfecta | NT     | NT            | Spontaneous teeth fracture |
| COL1A1 mutation| NT          | +             | –               |
| Other complications | –      | –             | Chronic gastritis, esophageal hiatal hernia, gastroesophageal reflux disease, bronchial asthma |
| Treatment      | Unknown     | Alfacalcidol, teriparatide, calcium lactate | Eldecalcidol, carbethidol, esomeprazole, aspirin, budesonide/efomoterol |

Abbreviations: AR, aortic regurgitation; MR, mitral regurgitation; NT, not tested.
The clinical features observed in the proband are serious in comparison with those of the other family members. It may be due to clinical variability. Although significant phenotypic differences within one family are rare, there are some reports of intra-familial variability. Furthermore, it is known that the clinical severity is not exactly the same between OI patients with the same mutation from unrelated families. Somatic mosaicism has often been reported as an explanation of intra-familial variability in OI phenotypes. However, the family members in three generations were hypothesized to have the same condition in the present study, and this inheritance pattern is inconsistent with the finding of somatic mosaicism.

One of the possible reasons for the intra-familial variability in this study may be the patient’s lifestyle. The proband reported his active lifestyle as follows: a traumatic accident by slipping on a rainy day; increasing the range of his activities; and carrying or lifting heavy things, such as books or other weights, in addition to participating in exercise such as swimming for 15 years since his school days. An unidentifiable genetic modifier may be another reason.

In addition to these activities, weight gain and a diet lacking in protein, vitamins and calcium might exacerbate bone fractures in OI patients. Connective tissues that are too flexible and systemic muscles that are too thin to support bones may also accelerate the development of valve regurgitation and scoliosis. The recognition of the natural history of OI patients is important for supporting their quality of life. It is predicted that if we know how to avoid these risks, we may be able to improve the disease prognosis. In the future, it is necessary to elucidate the exact elements needed for a better quality of life. Therefore, we should collect long natural histories of OI patients, including possible factors that may affect the prognosis, in association with the genotypic data.

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.figshare.hgv.950.

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REFERENCES
1. Shapiro JR, Byers PH, Glorieux FH, Sponseller P (eds). Osteogenesis Imperfecta: A Translational Approach to Brittle Bone Disease. Academic Press: Cambridge, MA; 2013.
2. Takagi M, Matsuhashi M, Nishimura G, Hasegawa T. Osteogenesis imperfecta IIC caused by a novel heterozygous mutation in the C-propeptide region of COL1A1. Hum Genome Var 2014; 1: 14025.
3. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet 2016; 387: 1657–1671.
4. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979; 16: 101–116.
5. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A 2014; 164A: 1470–1481.
6. Van Dijk FS, Palc G, Van Rijn RR, Nikkels PG, Cobben JM. Classification of osteogenesis imperfecta revisited. Eur J Med Genet 2010; 53: 1–5.
7. Arvai K, Horvath P, Balla B, Tobias B, Kato K, Kirshner G et al. Next-generation sequencing of common osteogenesis imperfecta-related genes in clinical practice. Sci Rep 2016; 6: 28417.
8. Yamamoto T, Shimojima K. A novel MED12 mutation associated with non-specific X-linked intellectual disability. Hum Genome Var 2015; 2: 15018.
9. Dalgleish R. The human type I collagen mutation database. Nucleic Acids Res 1997; 25: 181–187.
10. Dalgleish R. The Human Collagen Mutation Database 1998. Nucleic Acids Res 1998; 26: 253–255.
11. Moraes MV, Milanez M, Almada BV, Sipolatti V, Reboucas MR, Nunes VR et al. Variable expressivity of osteogenesis imperfecta in a Brazilian family due to p.G1079S mutation in the COL1A1 gene. Genet Mol Res 2012; 11: 3246–3255.
12. Liu HY, Huang J, Wu D, Li T, Guo LJ, Guo QN et al. Collagen type I alpha 1 mutation causes osteogenesis imperfecta from mild to perinatal death in a Chinese family. Chin J Med (Engl) 2016; 129: 86–91.
13. Cohen-Solal L, Zylberberg L, Sangalli A, Gomez Lira M, Mottes M. Substitution of an aspartic acid for glycine 700 in the alpha 2(I) chain of type I collagen in a recurrent lethal type II osteogenesis imperfecta dramatically affects the mineralization of bone. J Biol Chem 1994; 269: 14751–14758.
14. Tsimicalis A, Denis-Larocque G, Michalovic A, Lepage C, Williams K, Yao TR et al. The psychosocial experience of individuals living with osteogenesis imperfecta: a mixed-methods systematic review. Qual Life Res 2016; 25: 1877–1896.

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