CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2015: 87: 90–92
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CLINICAL GENETICS
doi: 10.1111/cge.12340

Letter to the Editor

Novel *LAMB3* mutations cause non-syndromic amelogenesis imperfecta with variable expressivity

To the Editor:

Amelogenesis imperfecta (AI) is a collective term referring to inherited malformation of tooth enamel without other non-oral symptoms. Junctional epidermolysis bullosa (JEB) is a group of recessive genetic disorders featuring skin fragility, easy blistering and AI. Carriers having only one defective allele usually have no disease phenotype; however, rarely, heterozygous conditions can cause autosomal-dominant AI (ADAI) with no or very mild skin fragility. Recently, *LAMB3* mutations causing non-syndromic AI have been identified in three families with an autosomal-dominant inheritance pattern (1, 2).

We recruited two families with generalized hypoplastic AI without any other medical conditions. The proband of family 1 was a 2-year-old girl presenting with generalized, irregular hypoplastic enamel in all her primary teeth. Newly erupted primary second molars showed small islands of enamel on the cusp tips and cervical areas. She inherited enamel hypoplasia from her mother. Other family members (a grandmother and uncle) were also affected similarly (Fig. 1a–d).

The proband of family 2 was an 8-year-old boy who also presented with enamel hypoplasia in all his primary and permanent teeth. Thermal sensitivity was not severe and hypoplastic grooves and pits accentuated the mamelon structures especially in the mandibular incisors. Interestingly, it was reported by his father that no one else in this family was affected by enamel defects. However, close examination of the father of the proband revealed hypoplastic grooves in several teeth (Fig. 1e–i).

Whole exome sequencings identified novel frameshift *LAMB3* mutations (NM_000228.2: c.3357_3358insC in family 1 and c.3463_3475delGAGCAGATCCGTG in family 2). The mutation in family 1 (c.3357_3358insC) was located only 25 bp away from the splicing donor site of exon 22. A shift in the reading frame would not generate an early termination codon within this exon and would not affect normal mRNA splicing. Therefore, the mutant transcript would escape non-sense-mediated mRNA decay (NMD) and generate a truncated protein with 39 novel amino acids instead of a C-terminal with 53 amino acids in the wild-type LAMB3 (p.Met1120fs*40). The mutation in family 2 (c.3463_3475delGAGCAGATCCGTG) would also escape NMD because of its location in the last exon producing a truncated protein with 50 novel amino acids replacing the C-terminal 18 amino acids of the wild-type LAMB3 (p.Glu1155fs*51) (Fig. 1J). The extremely mild clinical phenotype in the father and grandmother could be caused by the fact that the mutation replaced only 18 amino acids in the C-terminus.

JEB is caused by mutations in *LAMA3*, *LAMB3*, *LAMC2*, and *COL17A1*. Among them, *LAMB3* mutations are responsible for about 80% of all JEB cases. Laminin-332 is a basement membrane protein and a heterotrimer composed of three subunits encoded by the *LAMA3*, *LAMB3*, and *LAMC2* (3). Even though mutations in both alleles cause JEB with AI, a single defective allele in a carrier of JEB could result in AI with little or no skin phenotype. Two cases in *COL17A1* and one case in *LAMA3* heterozygous carrier have been reported to have ADAI with no or a mild skin phenotype (4, 5).

Recently, a heterozygous *LAMB3* mutation (c.3392_3393insG) has been reported to cause ADAI in a family (1). Subsequently, two more mutations (c.3446_3453delGACTGGAG and c.3431C>A) have been identified to cause ADAI in two families (2). All three mutations are non-sense or frameshift mutations, but the truncated proteins are expected to be expressed escaping NMD because of their location on the last exon.

Two novel *LAMB3* mutations identified in this study are also expected to escape NMD and be expressed as truncated proteins. Interestingly, highly variable expressivity was confirmed in family 2, while all the affected members of family 1 exhibited consistently a similar hypoplastic enamel phenotype. The mutation in family 2 replaces only 18 amino acids at the C-terminus and produces 1154 amino acids of wild-type LAMB3. This small replacement would explain the phenotypic variation in family 2 (Fig. 1j).

Acknowledgements

The authors are grateful to all family members who participated in this study. This work was supported by grants from the Bio

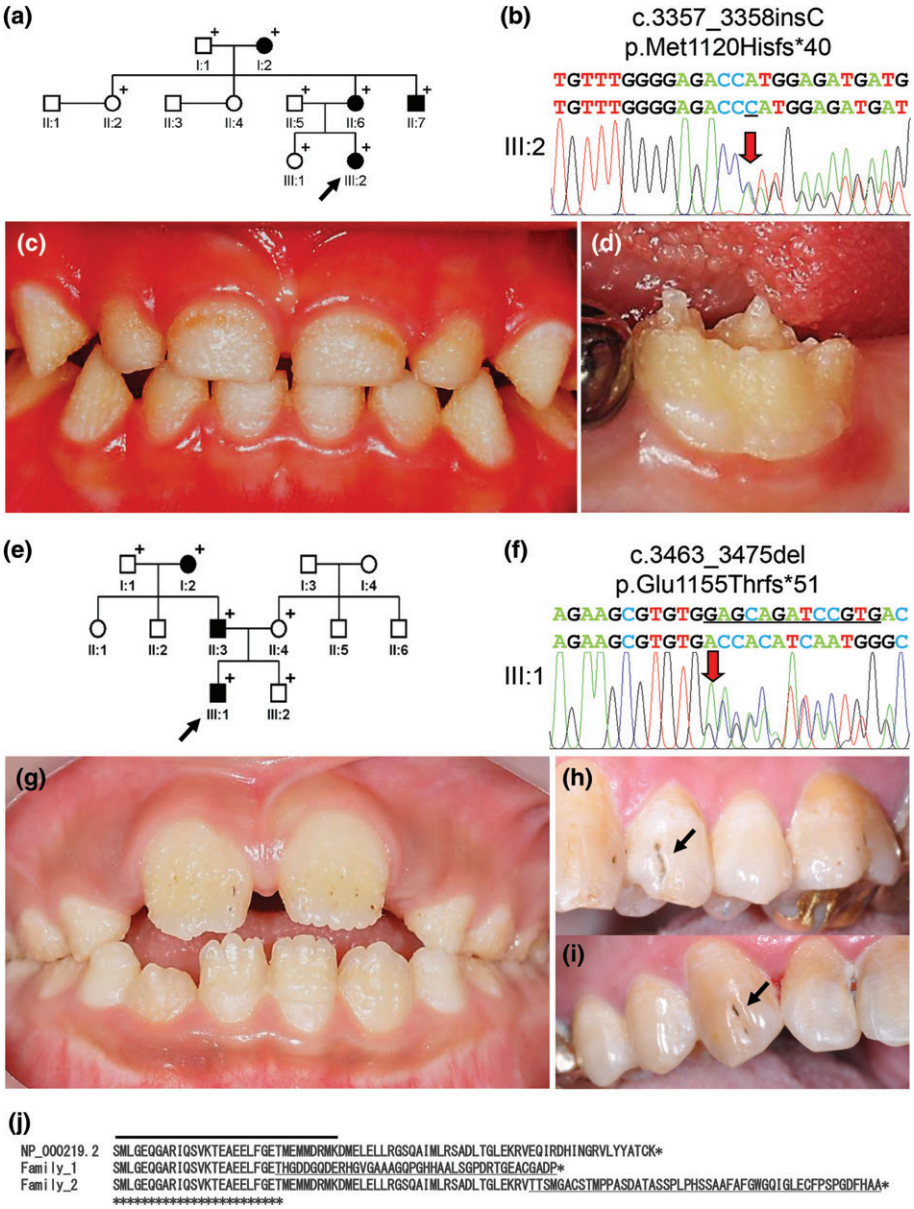

Fig. 1. (**a**) Pedigree of family 1. The 'plus' symbol indicates individuals recruited for this study. (**b**) DNA sequencing chromatogram of the PCR amplification products from the proband (III:2) of family 1. Wild-type (top) and the mutated sequences are shown in the chromatogram. Red arrow indicates the location of the mutation (c.3357_3358insC, p.Met1120Hisfs*40). (**c**) Frontal clinical photo of the proband taken at the age of 2 years 1 month. (**d**) Clinical photo of left mandibular deciduous second molar of the proband taken at the age of 3 years 2 months. (**e**) Pedigree of family 2. The 'plus' symbol indicates individuals recruited for this study. (**f**) DNA sequencing chromatogram of the PCR amplification products from the proband (III:1) of family 2. Wild-type (top) and the mutated sequences are shown in the chromatogram. Red arrow indicates the location of the mutation (c.3463_3475del, p.Glu1155Thrfs*51). (**g**) Frontal clinical photo of the proband taken at the age of 8 years 7 months. (**h**, **i**) Lateral clinical photos of the father (II:3) of the proband. Hypoplastic grooves in the maxillary left first premolar and right canine indicated by black arrows. (**j**) Alignment of the human wild-type LAMB3 (NP_000219.2) C-terminus sequence with the predicted truncated proteins of families 1 and 2. Black bar above the sequence indicates sequence encoded by exon 22. Sequences with underline indicate novel sequences by truncating mutations.

& Medical Technology Development Program (2013037491), the Science Research Center grant to Bone Metabolism Research Center (2008-0062614) by the Korea Research Foundation Grant funded by the Korean government (MEST).

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