LAMA3, LAMB3, COL17A1, AMBN, ENAM and WDR72 Mutations Causing AI

Objectives: Amelogenesis imperfecta (AI) can be manifested as isolated (non-syndromic) enamel malformations, or as a phenotype in syndromes. To date, 18 genes have been implicated in the etiology of isolated AI (*LAMA3, LAMB3, COL17A1, FAM83H, DLX3, AMELX, ENAM, AMBN, AMTN, C4orf26, ODAM, MMP20, KLK4, WDR72 , ITGB6, SLC24A4, ACPT, GPR68*). In some cases, isolated AI is observed in the carriers of syndromes, as in the case of junctional epidermolysis bullosa (JEB). Syndromic AI patients are sometimes diagnosed as having isolated AI because the non-dental phenotypes go undetected or appear later in life. Genetic tests to determine the cause of AI can distinguish among isolated, carrier, or syndromic forms of AI, which improves patient management and prognosis. To identify the disease-causing mutations in families with AI.
Methods: AI families were analyzed by whole exome sequencing (WES) of genomic DNA from both parents and at least one affected offspring. Raw reads were aligned against human genome assembly GRCh37 using BWA. Variants were called and calibrated using GATK. High confidence variants were annotated and filtered by VarSeq. Potentially damaging mutations were prioritized, screened for each family member by Sanger sequencing to validate cosegregation of phenotype and genotype.
Results: The following AI-causing mutations were identified: heterozygous *LAMA3* (c.7367delG, p.Gly2456Alafs*22), heterozygous *LAMB3* (c.1705C>T, p.Arg569*), heterozygous *LAMB3* (c.3361G>T, p.Glu1121*), heterozygous *LAMB3* (c.3518G>T, p.*1173Leuext*56), *COL17A1* heterozygous (c.3327delT, pPro1110Argfs*21), compound heterozygous *AMBN* (c.1340C>T, p.Pro447Leu/c.1061T>C, p.Leu354Pro), *ENAM* heterozygous (c.588+1delG, splice junction), *ENAM* heterozygous (c.395dupA, p.Pro133Alafs*13), *WDR72* homozygous (c.377G>A, p.Trp126*), *WDR72* homozygous (c.1265G>T, p.Gly422Val) and *WDR72* homozygous c.1467_1468delAT, p.Val491fs*8).
Conclusions: We identified novel AI-causing mutations in multiple families with inherited enamel defects. Screening known AI candidate genes currently has a 40 to 50% chance of identifying the disease-causing mutation in a given family, suggesting that many more AI causing genes await discovery.

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