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INVITED REVIEW

Molecular-based phenotype variations in amelogenesis imperfecta

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Abstract

Amelogenesis imperfecta (AI) is one of the typical dental genetic diseases in human. It can occur isolatedly or as part of a syndrome. Previous reports have mainly clarified the types and mechanisms of nonsyndromic AI. This review aimed to compare the phenotypic differences among the hereditary enamel defects with or without syndromes and their underlying pathogenic genes. We searched the articles in PubMed with different strategies or keywords including but not limited to amelogenesis imperfecta, enamel defects, hypoplastic/hypomaturation/hypocalcified, syndrome, or specific syndrome name. The articles with detailed clinical information about the enamel and other phenotypes and clear genetic background were used for the analysis. We totally summarized and compared enamel phenotypes of 18 nonsyndromic AI with 17 causative genes and 19 syndromic AI with 26 causative genes. According to the clinical features, radiographic or ultrastructural changes in enamel, the enamel defects were basically divided into hypoplastic and hypomineralized (hypomaturated and hypocalcified) and presented a higher heterogeneity which were closely related to the involved pathogenic genes, types of mutation, hereditary pattern, X chromosome inactivation, incomplete penetrance, and other mechanisms.The gene-specific enamel phenotypes could be an important indicator for diagnosing nonsyndromic and syndromic AI.

KEYWORDS
amelogenesis imperfecta, heterogeneity, nonsyndrome, syndrome

1 | AMELOGENESIS IMPERFECTA

Amelogenesis imperfecta (AI) refers to a heterogeneous group of rare disorders characterized by inherited developmental enamel defects. AI enamel usually presents yellow or yellow-brown discoloration and pitted or grooved surface, and the enamel becomes abnormally thin or even complete loss, soft and fragile, and prone to attrition. The reduced hardness or thickness of enamel results in increased sensitivity to cold, hot, thermal changes, and physical stimuli. Secondary effects of AI may include susceptibility to caries, periodontitis, pulpitis, and early tooth loss. These function and aesthetics changes in AI teeth may cause the problems such as eating difficulties, pain, severe embarrassment, and even psychological trauma (Roma et al., 2021). The prevalence of AI varies from 1:700 to 1:14,000 in different populations (Bäckman & Holm, 1986; Crawford et al., 2007; Witkop, 1957).

2 | CLASSIFICATION

The earliest classifications of AI as hypoplastic and hypocalcified types were put forward in Weinmann et al. (1945). The later AI

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classifications have evolved to some extent but are unexceptionally derived from the earliest (Crawford et al., 2007). Some of them are based on phenotypes, and others combine the mode of inheritance in diagnosis (Rao & Witkop Jr, 1971; Sundell & Koch, 1985; Winter & Brook, 1975). Currently, the most cited classification was proposed by Witkop Jr (1988). AI can be classified into four main types include hypoplastic (type I); hypomaturation (type II); hypocalcified (type III); and hypomaturation-hypoplasia with taurodontism (type IV), which are based on clinical and radiographic appearance, while the 15 subtypes are related to the mode of inheritance such as an X-linked, autosomal-dominant, or autosomal recessive genetic trait (Witkop Jr, 1988). Online Mendelian Inheritance in Man (OMIM) subgroups AI into four main types and 19 subtypes (OMIM: PS104500) based on clinical appearance, genetic pattern, and causative genes.

AI also can be divided into nonsyndromic forms characterized by an isolated teeth phenotype, and syndromic forms characterized by multi-tissues or organs were affected and enamel phenotypes are part of them.

In this review, we used the classifications of hypoplastic and hypomineralized types proposed by Sundell et al. to describe the basic enamel changes in nonsyndromic or syndromic AI. Hypoplasia enamel refers to those thin but hard enamels, or complete loss of enamel in some extreme cases due to the secretory phase failure of enamel development. The dysfunctions in maturation phase usually cause hypomineralized AI, which have the full-thickness but weak enamel. According to the reviews from Smith and report of Sundell, hypomineralized type can be further divided into hypocalcified and hypomaturation subtypes (Smith, Poulter, et al., 2017; Sundell & Koch, 1985; Sundell & Valentin, 1986). Hypomaturation AI presents the brittle enamel resulting from incomplete removal of enamel matrix protein, while hypocalcified enamel is soft and prone to abrasion and attrition caused by insufficient delivery of calcium ions to the developing enamel (Aldred et al., 2003; Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017; Figure 1). These enamel changes may occur isolatedly or combined together in one tooth or different teeth of one individual.

3 | ISOLATED AI AND RELATED GENES

Currently, there are about 41 genes related to enamel defects (Duan et al., 2019; Simmer et al., 2021; Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017). According to the published data and our analysis, at least 17 genes (*LAMA3*, *LAMB3*, *ENAM*, *AMELX*, *AMBN*, *ITGB6*, *ACP4*, *SP6*, *KLK4*, *MMP20*, *WDR72*, *ODAPH*, *SLC24A4*, *GPR68*, *FAM83H*, *AMTN*, and *RELT*) are correlated with isolated AI (nonsyndromic AI). Here, we listed *LAMB3* as a causative gene of nonsyndromic AI because its biallelic mutations cause junctional epidermolysis bullosa (JEB), but the heterozygous variants usually cause few or no apparent skin lesions and only show dental anomalies manifested as hypoplastic AI (Kim et al., 2013; Lee et al., 2015).

According to the clinical features of tooth, radiograph, or ultrastructure changes, nonsyndromic AI phenotypes are

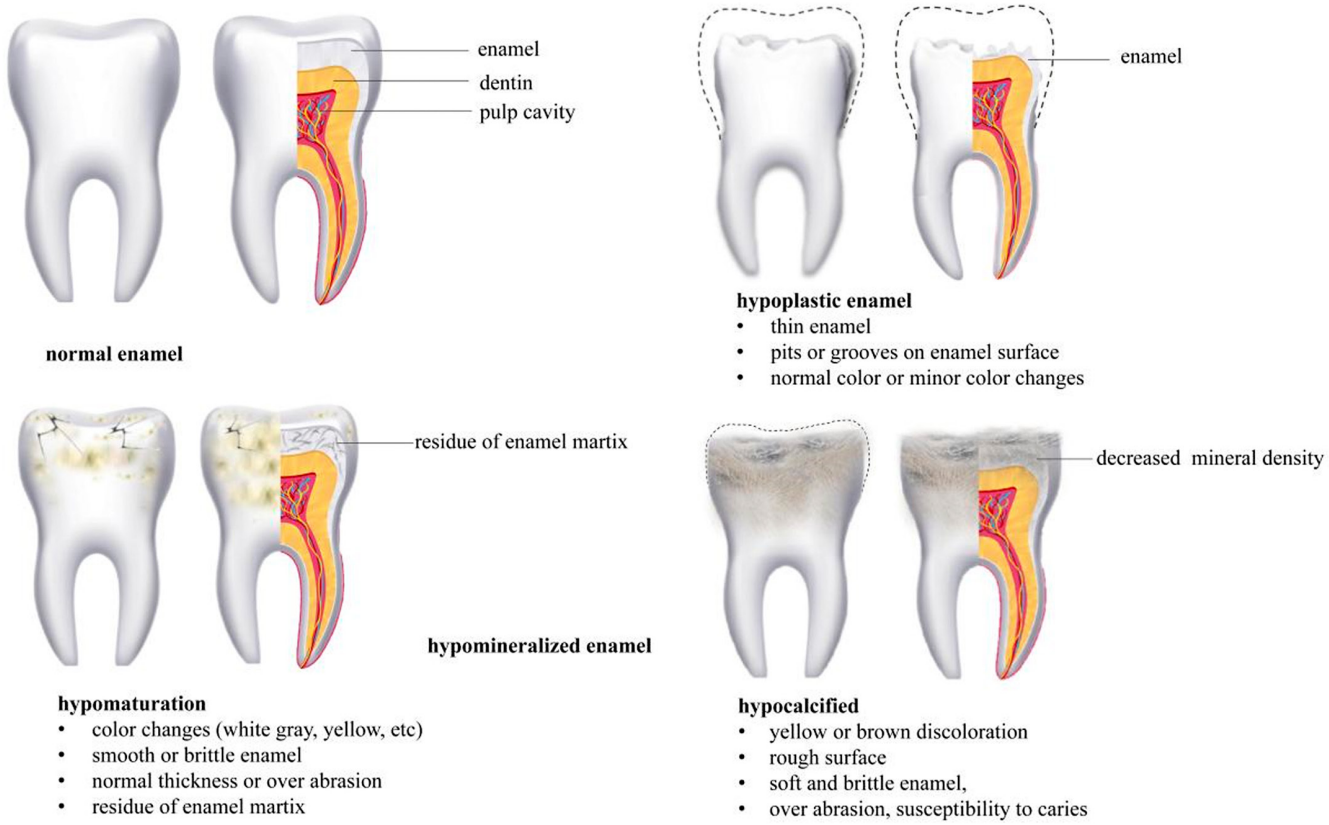

FIGURE 1 Basic characteristics of hereditary enamel defects.

classified into the hypoplastic and hypomineralized type (Sundell & Valentin, 1986).

Hypoplastic AI is characterized by thin enamel, or complete loss of enamel, and small pits or grooves but with normal color and hardness. Some affected AI individuals have abnormal morphology of teeth and malocclusion. The causative genes including *LAMA3*, *LAMB3*, *ENAM*, *AMELX*, *AMBN*, *ITGB6*, *SP6*, and *ACP4* (Table 1). The hypoplastic AI with the mutations in *ITGB6*, *ENAM*, and *AMELX* often show the combined hypomineralized enamel and anterior open bite malocclusion (Cho et al., 2014; Hart, Michalec, et al., 2003; Hart, Michalec, et al., 2003; Lee et al., 2011; Pavlic et al., 2007; Poulter, Brookes, et al., 2014; Wang, Choi, et al., 2014; Wang, Wrennall, et al., 2014). Besides enamel defects, taurodontism can be observed in some patients of *LAMB3*, *ACP4*, *ENAM*, and *SP6*-associated AI (Kim et al., 2013, 2021; Liang et al., 2022).

Hypomineralized AI is caused by the failed maturation stage, giving rise to a weak, premature enamel at full thickness. It can be further subdivided into hypomaturated and hypocalcified AI (Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017; Sundell & Koch, 1985; Sundell & Valentin, 1986). The former is characterized by brittle enamel with residual glaze matrix in the enamel. In contrast, the latter is caused by insufficient transport of calcium ions into the developing enamel and induce soft enamel prone to abrasion and attrition, and the microstructure showed a decreased density (Aldred et al., 2003; Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017). The mutations in *KLK4*, *MMP20*, *WDR72*, *ODAPH*, *SLC24A4*, and *GPR68* mainly cause hypomaturation, and *FAM83H*, *AMTN*, and *RELT* are related to hypocalcified AI. In addition, although mutations in *MMP20* and *ODAPH* cause hypomaturation AI, some of them also cause hypoplastic-hypomaturation AI as well, which characterized by hypoplastic enamel and/or poor contrast of enamel compared with dentine in panoramic radiograph (Gasse et al., 2017; Parry et al., 2012; Wang et al., 2020). Interestingly, almost all hypomineralized AI is associated with malocclusion; for example, anterior open bite in AI related to *MMP20*, *GPR68*, *KLK4*, *RELT*, *WDR72*, and *FAM83H* and deep overbite in AI related to *ACP4*, which might be due to the reduced hardness of enamel prone to abrasion (Kim et al., 2022; Kim, Simmer, et al., 2005; Kuechler et al., 2012; Lee et al., 2022; Parry et al., 2016; Wang et al., 2020).

4 | SYNDROMES WITH ENAMEL DEFECTS

Many dental abnormalities including enamel defects are the telltale symptoms of some syndromes. They may be used as one of diagnostic criteria or as a useful auxiliary diagnostic criterion aid. Some systemic genetic diseases or syndromes with AI phenotypes usually have the malformations or dysfunctions in eye, ear, skin, bone, and nervous system. OMIM listed 19 syndromic disorders with enamel abnormalities (Table 2).

4.1 | Kohlschütter-Tönz syndrome

Kohlschütter-Tönz syndrome (KTZS, OMIM# 619229) was first described clinically in 1974. AI, epilepsy, and neurodevelopmental delays are representative manifestations of KTZS and are present in all the patients reported. As an autosomal recessive neurodegenerative disease, KTZS presents several clinical manifestations including epilepsy, spasm, ataxia, neuromotor degeneration, severe systemic developmental delay, and cerebellar vermis dysplasia (Kohlschütter et al., 1974). KTZS cases have yellowish-brown discolored teeth and are prone to have caries. Both primary and permanent teeth are affected. Schossig et al. found that the biallelic mutations in rogdi atypical leucine zipper gene (*ROGDI*) on chromosome 16p13 cause KTZS (Schossig et al., 2012). Later, the solute carrier family 13 member 5 (*SLC13A5*) on chromosome 17p13.1 was also reported to cause KTZS (Schossig et al., 2017). The cases with *SLC13A5* mutation and *ROGDI* mutation present the clinical differences. In KTZS-associated *ROGDI*, seizures are rarely detected in the neonatal period and may be as late as 3 years of age, and the enamel is hypocalcified (Schossig et al., 2017). In contrast, seven out of 10 cases with *SLC13A5* mutation had seizures in the first few days of life and the enamel is hypoplastic (Thevenon et al., 2014).

4.2 | Nephrocalcinosis syndrome

Nephrocalcinosis syndrome (OMIM#204690), also known as an enamel-renal syndrome (ERS) or MacGibbon syndrome, is characterized by enamel defect and nephrocalcinosis. In 1972, MacGibbon reported a sibling with enamel loss, renal calcareosis, and normal calcium metabolism (MacGibbon, 1972), which was later confirmed by Lubinsky et al. (Lubinsky et al., 1985). ERS patients exhibit a unique oral phenotype, including generalized hypoplastic AI on primary and secondary dentitions, pulp stones, delayed or failed eruption of secondary dentition, gingival overgrowth, hyperplastic dental follicles, and calcified nodules (de la Dure-Molla et al., 2014).

MacGibbon syndrome is caused by homozygous or compound heterozygous mutations in the family with sequence similarity 20, member A gene (*FAM20A*) on chromosome 17q24 (Jaureguiberry et al., 2012). FAM20A controls the phosphorylation of enamel peptides and mineralization (Lignon et al., 2017). *Fam20a*$^{-/-}$ mice present with the dental phenotype such as enamel defects, microdontia, and flat molars (Vogel et al., 2012).

The mutations in *MSX2* cause hypomatured AI, cleft lip and palate, and polycystic kidney disease leading to nephrocalcinosis (Suda et al., 2006). MSX2 is a morphogenetic substance of tooth enamel. The expression patterns of Msx2 and amelogenin are converse and MSX2 contributes to enamel thickness inhibition in vivo (Babajko et al., 2014; Molla et al., 2010). *Msx2* and *Sp6* concertedly form a

TABLE 1 Summary of causative genes and associated phenotypes of nonsyndromic amelogenesis imperfecta.

Type of AI	OMIM	Tooth features	Radiograph	Ultrastructure	Inheritance	Gene	Reference
Hypoplastic	600805	Deep pits and vertical grooves, localized rough, horizontal bands with chalky-whiteness	Thin enamel, normal contrast between enamel and dentin	Pits and grooves confined within the enamel layer, reduced mineralization close to the DEJ	AD	*LAMA3* (laminin alpha-3)	Gostyńska et al. (2016) and Wang et al. (2022)
	104530	Pits and vertical grooves with yellow-brown pigmentation, multiple cusps in molar, sensitivity to thermal changes	Thin enamel, normal contrast between enamel and dentin, taurodontism	Laminar arranged crystallites in DEJ	AD	*LAMB3* (Laminin beta-3)	Kim et al. (2013), Lee et al. (2015), Wang, Hu, et al. (2015), Wang, Zhao, et al. (2015) and Smith et al. (2019)
	104500	Horizontal row of pits or linear depressions or grooves	Thin enamel, normal contrast between enamel and dentin, taurodontism	Lack of normal prismatic structure, laminar arranged crystallites, glass-like appearance of prisms	AD	*ENAM* (Enamelin)	Mårdh et al. (2002), Hart, Michalec, et al. (2003), Hart, Hart, et al. (2003), Kim, Seymen, et al. (2005), Kim, Simmer, et al. (2005), Pavlic et al. (2007), Shore et al. (2010), Simmer et al. (2013) and Yu et al. (2022)
	204650	Thin enamel or completely absent, decreased enamel mineralization, yellow-brown discoloration, anterior open bite malocclusion	Extremely thin enamel	Irregular and disorganized enamel rods, undistinguishable prisms	AR	*ENAM* (Enamelin)	Hart, Michalec, et al. (2003), Hart, Hart, et al. (2003) and Koruyucu et al. (2018)
	301200	Hypomineralized and soft enamel, hard and thin enamel with generalized pits and vertical ridges, rough teeth with discoloration, wide spacing between teeth, snow-capped appearance, anterior open bite	Extremely thin enamel, normal or lower contrast between enamel and dentin, more enamel on the cusp tips	Crater-shaped voids and amorphous shape of prisms in pits and ridges areas	XLD	*AMELX* (Amelogenin)	Kim et al. (2004), Lee et al. (2011), Hu et al. (2012), Cho et al. (2014), Kim, Kang, et al. (2017), Kim, Kim, et al. (2017) and Duan et al. (2019)
	616270	Enamel easily peels off, yellow or gray or brownish-blue discoloration, rough tooth surface	Thin or even no enamel	Reduced numbers of enamel prisms with normal structure, increased width and straight line in DEJ	AR	*AMBN* (Ameloblastin)	Poulter, Brookes, et al. (2014), Poulter, Murillo, et al. (2014), Lu et al. (2018) and Liang et al. (2019)
	608613	Hypoplastic enamel with rough surface, small teeth with wide space	Thin enamel, blunt root apex, enlarged pulp chambers, taurodontism	—	AD	*SP6* (Epiprofin)	Smith et al. (2020) and Kim et al. (2021)

(Continues)

TABLE 1 (Continued)

Type of AI	OMIM	Tooth features	Radiograph	Ultrastructure	Inheritance	Gene	Reference
	616221	Loss of enamel after tooth eruption, hypomineralized enamel with yellow-brown discoloration, a shoulder of remaining enamel at the cervical margin, rough tooth surface, sensitivity to thermal changes, anterior open bite	Thin enamel, normal contrast between enamel and dentin	Grossly disorganized prism architecture of inner enamel layer, less distinction of Hunter–Schreger bands	AR	*ITGB6* (Integrin-β6)	Poulter, Brookes, et al. (2014), Poulter, Murillo, et al. (2014), Wang, Choi, et al. (2014), Wang, Reid, et al. (2014), Wang, Wrennall, et al. (2014) and Seymen, Lee, et al. (2015), Seymen, Park, et al. (2015)
	617297	Yellow to black discoloration, multiple dental caries, sensitivity to thermal changes, deep overbite, wide teeth space	Extremely thin enamel , normal or lower contrast between enamel and dentin, taurodontism	—	AR	*ACP4* (Acid phosphatase 4)	Hytönen et al. (2019), Kim et al. (2022) and Liang et al. (2022)
Hypomaturated	204700	Enamel prone to chipping and attrition, yellow-brown discoloration, sensitivity to hot and cold, susceptibility to dental caries, anterior open bite	Normal thickness and shape of unerupted tooth, lower contrast between enamel and dentin	Organic matrix in the inner enamel layer, increased enamel porosity	AR	*KLK4* (Kallikrein 4)	Wright et al. (2006), Wang et al. (2013), Seymen, Lee, et al. (2015), Seymen, Park, et al. (2015), Smith, Kirkham, et al. (2017), Smith, Poulter, et al. (2017) and Lee et al. (2022)
	612529	Opaque and chalky white enamel easy to breakdown in the post-erupted tooth, yellow-brown discoloration, rough tooth surface and sensitivity to thermal changes, hypoplastic-hypomaturation	Normal thickness and shape of unerupted tooth, lower contrast between enamel and dentin	Absence or loss of interprismatic enamel, lower mineral density along the periphery of the rods in the inner and middle enamel	AR	*MMP20* (Matrix metalloproteinase 20)	Kim, Seymen, et al. (2005), Kim, Simmer, et al. (2005), Ozdemir, Hart, Firatli, et al. (2005), Ozdemir, Hart, Ryu, et al. (2005), Papagerakis et al. (2008), Lee, Seymen, Kang, et al. (2010), Lee, Seymen, Lee, et al. (2010), Gasse et al. (2013), Wang et al. (2013), Seymen, Lee, et al. (2015), Seymen, Park, et al. (2015), Gasse et al. (2017), Kim, Kang, et al. (2017), Kim, Kim, et al. (2017) and Wang et al. (2020)
	613211	Loss of surface enamel after tooth eruption, opaque and creamy enamel, rough and soft surface, yellow-brown discoloration, sensitivity to thermal changes and physical stimuli	Normal size and shape of unerupted tooth, irregular surface in erupted molar tooth, poor contrast between enamel and dentin	Lack of enamel rods decussation	AR	*WDR72* (WD repeat domain 72)	El-Sayed et al. (2009), Lee, Seymen, Kang, et al. (2010), Lee, Seymen, Lee, et al. (2010), El-Sayed et al. (2011), Kuechler et al. (2012), Hentschel et al. (2016), Zhang, Koruyucu, et al. (2019) and Khandelwal et al. (2021)

TABLE 1 (Continued)

Type of AI	OMIM	Tooth features	Radiograph	Ultrastructure	Inheritance	Gene	Reference
	614832	Loss of enamel after tooth eruption with yellowish to brown discoloration, susceptibility to dental caries	Poor contrast between enamel and dentin	—	AR	*ODAPH* (Odontogenesis-associated phosphoprotein)	Parry et al. (2012)
	615887	Irregular grooves and pits with yellow-brown discoloration, enamel attrition, soft surface, and susceptibility to caries	Normal size and shape of unerupted tooth, poor contrast between enamel and dentin	Irregular enamel prisms with missing of Hunter–Schreger lines		*SLC24A4* (Solute carrier family 24 member 4)	Parry et al. (2013), Seymen et al. (2014), Herzog et al. (2015), Khan et al. (2020), Lepperdinger et al. (2020) and Seymen et al. (2021)
	617217	Localized surface roughness with yellow-brown discoloration, creamy opaque enamel, fractured enamel, anterior open bite	Poor contrast between enamel and dentin	—	AR	*GPR68* (G protein-coupled receptor 68)	Parry et al. (2016) and Seymen et al. (2021)
Hypocalcified	130900	Small enamel islands in cusp and/or cervical area, vertical grooves, soft and easily disintegrated surface, yellow or black-brown discoloration, susceptibility to caries, anterior open bite, Class III malocclusion	Normal size and shape of unerupted tooth, thin enamel after tooth eruption, poor contrast between enamel and dentin	Prismatic structures with cracks or crevices in DEJ, irregular, broken, and collapsing enamel rods, decreased rods number, widened inter-rod spaces, enamel matrix residue	AD	*FAM83H* (Family with sequence similarity 83 member H)	Hart et al. (2009), Wright et al. (2009), El-Sayed et al. (2010), Urzúa et al. (2015), Xin et al. (2017), Yu et al. (2018) and Alvarez et al. (2022)
	617607	Soft enamel, yellow-brown discoloration	Poor contrast between enamel and dentin	Reduced mineral density, gnarled appearance of prismatic structure	AD	*AMTN* (Amelotin)	Smith et al. (2016)
	618386	Rapid attrition of occlusal enamel, hypoplastic enamel, yellow discoloration , rough surface, anterior open bite	Unusual crown contours after eruption, poor contrast between enamel and dentin	Non-prismatic with an abnormal lamellar structure of inner enamel layer, abnormal prisms of outer layer	AR	*RELT* (RELT TNF receptor)	Kim et al. (2019) and Nikolopoulos et al. (2020)

Abbreviations: AD, autosomal-dominant; AR, autosomal-recessive; DEJ, dentin–enamel junction; XLD, X-linked-dominant.

TABLE 2 Syndromes with enamel defects.

Name	Abbreviation	Alias	OMIM	Inheritance	Main characteristics	Oral and dental characteristics	Mutation	Reference
Tricho-dento-osseous syndrome	TDO I		#190320	AD	Curly hair, dolichocephaly, radial dense bones, occasionally brittle nails, thickening chondrocranium	Delayed eruption of teeth, thin and/or pitted enamel, hypomaturation-hypoplasia AI, increased dental caries	*DLX3* (17q21.33)	Robinson and Miller (1966), Lichtenstein et al. (1972), Quattromani et al. (1983), Shapiro et al. (1983), Price et al. (1998) and Duverger et al. (2017)
	TDO II				Sparse as well as curly hair, more striking nail changes, thickening and sclerosis of the calvaria, males show narrowing of the ear canal	Precocious eruption of teeth, dentin defects, thin and/or pitted enamel hypomaturation-hypoplasia AI		
	TDO III				Macrocephaly, increased calvarial bone density and thickening, obliterated frontal sinuses, poorly pneumatized mastoid, and obliterated diploe of calvarial	Hypoplastic-hypocalcified enamel, and enamel pitted, small teeth and widely spaced with signs of attrition and frequent abscesses, short roots, taurodontism		
Cone-rod dystrophy with amelogenesis imperfecta		Jalili syndrome	#217080	AR	Photophobia, night blindness, macular degeneration and hyperpigmentation, pigment disorders, nystagmus, reduced vision, and color vision deficits	Hypoplastic or hypocalcified AI, yellow or brown teeth, barely visible enamel, rough surfaces and irregular defects, premature tooth loss, dental caries	*CNNM4* (2q11.2)	Michaelides et al. (2004), Parry et al. (2009) and Maia et al. (2018)
Kohlschütter-Tönz syndrome	KTZS		#226750	AR	Severe global developmental delay, early-onset intractable seizures, spasticity, ataxia, neuromotor degeneration, vermis dysplasia of the cerebellum	Hypocalcified or hypoplastic AI, yellow or brown discoloration of the teeth, thin, soft, and rough enamel	*ROGDI* (16p13.3) *SLC13A5* (17p13.1)	Kohlschütter et al. (1974), Schossig et al. (2012), Thevenon et al. (2014) and Schossig et al. (2017)

TABLE 2 (Continued)

Name	Abbreviation	Alias	OMIM	Inheritance	Main characteristics	Oral and dental characteristics	Mutation	Reference
Kohlschütter-Tönz syndrome-like	KTZSL		#619229	AD	Global developmental delay, impaired intellectual development, moderate to profound short stature, poor overall growth, brachycephaly	Delayed tooth eruption, oligodontia, widely spaced teeth, yellow teeth, hypoplasia AI, thick lips, drooling	*SATB1* (3p24.3)	den Hoed et al. (2021)
Nephrocalcinosis syndrome		Enamel – renal syndrome/ McGibbon syndrome	#204690	AR	Nephrocalcinosis	Hypoplastic AI on primary and secondary dentition, pulp stones, delayed or failed eruption of secondary dentition, gingival overgrowth	*MSX2* (5q35.2) *FAM20A* (17q24.2)	MacGibbon (1972), Lubinsky et al. (1985), Suda et al. (2006), Molla et al. (2010), Jaureguiberry et al. (2012), Vogel et al. (2012), Babajko et al. (2014), de la Dure-Molla et al. (2014), Lignon et al. (2017) and Ruspita et al. (2020)
Vitamin D-dependent rickets			#264700	AR	Slow growth, hypotonia, skeleton deformity, midgetism	Short roots, enlarged pulp chambers with thin dentin, enamel hypoplasia on several incisors and/or canines, rough enamel surface and irregular structure, yellowish-brownish enamel, hypocalcified enamel	*CYP27B1* (12q14.1)	Zambrano et al. (2003) and Gjørup et al. (2018)
Vitamin D-resistant rickets			#277440	AR	Refractory hypocalcemia, elevated serum levels of 1,25-dihydroxy-vitamin D, retarded growth, sparse body hair (sometimes alopecia)	Multiple gum abscesses, periapical abscess, enamel hypoplasia, large pulp chambers with thin enamel and dentin, attrition, and exposure of abnormal dentin, enamel hypoplasia (thin, yellowish-brown), dentin defect, maxillofacial deformity, skull deformation, delayed tooth eruption	*VDR* (12q13.11)	Goodman et al. (1998)

(Continues)

TABLE 2 (Continued)

Name	Abbreviation	Alias	OMIM	Inheritance	Main characteristics	Oral and dental characteristics	Mutation	Reference
Rubinstein–Taybi syndrome	RSTS1		#180849	AD	Mental retardation, postnatal growth deficiency, microcephaly, broad thumbs and halluces, dysmorphic facial features	High-arched and narrow palate, dental crowding, talon cusps, crossbite, screwdriver-shaped permanent incisors, enamel hypoplasia, enamel discoloration	*CREBBP* (16p13.3)	Milani et al. (2015), Korzus (2017), Menke et al. (2018) and Martins et al. (2022)
Heimler syndrome	HS I		#234580	AR	Sensorineural hearing loss, nail abnormalities, retinal pigmentation abnormalities, macular dystrophy (rare)	Normal primary teeth, hypoplastic or hypomineralized AI in secondary teeth	*PEX1* (7q21.2)	Heimler et al. (1991), Ratbi et al. (2015) and Mechaussier et al. (2020)
	HS II		#616617	AR	Sensorineural hearing loss in early childhood, retinal pigmentation abnormalities, slightly broad thumbs, leukonychia of fingernails	Hypoplastic or hypocalcified enamel of secondary dentition, dental overcrowding, enlarged pulp chambers of maxillary molars (taurodontism)	*PEX6* (6p21.1)	
Zellweger spectrum disorders	ZSD		614873	AR	Isolated prelingual sensorineural hearing loss, nail and dental abnormalities, a mild cognitive impairment, learning disabilities, and poor feeding	White spots of the upper central incisors on the vestibular surfaces, high-arched palate and visible enamel hypoplasia of the first permanent upper molars, yellowish enamel, and irregular shape at the cusps	*PEX26* (22q11.21)	Klouwer et al. (2015) and Braverman et al. (2016)
Oculo-dento-digital dysplasia	ODDD	Oculo-dento-digital syndrome	#164200	AD	Typical facial appearance and variable involvement of the eyes, dentition, fingers	Enamel hypoplasia, selective tooth agenesis, microdontia, premature loss of teeth, dental caries	*GJA1* (6q22.31)	Pizzuti et al. (2004), Richardson et al. (2006) and Jamsheer et al. (2010)

TABLE 2 (Continued)

Name	Abbreviation	Alias	OMIM	Inheritance	Main characteristics	Oral and dental characteristics	Mutation	Reference
Epidermolysis bullosa	Dystrophic epidermolysis bullosa (DEB)		#226600	AR	Recurrent blistering at the level of the sublamina densa beneath the cutaneous basement membrane, poor growth due to poor nutrition	Enamel hypoplasia, oral blisters, lingual adhesions	*COL7A1* (3p21.31)	Bauer and Eisen (1978), Seltzer et al. (1989), Hovnanian et al. (1991), Colombi et al. (1992) and Titeux et al. (2008)
	Junctional epidermolysis bullosa (JEB)		#226650 /#226730 /# 619816 /#619787	AR	Sparse eyebrows and eyelashes, nail hypoplasia, oligotrichosis, alopecia, skin blistering (onset at birth), atrophic scarring, hyperpigmentation, milia	Enamel hypoplasia, prone to caries, pitting enamel, thin enamel, defective pits, and furrows	*LAMB3* (1q32.2) *LAMA3* (18q11.2) *LAMC2* (1q25.3) *ITGB4* (17q25.1) *ITGA6* (2q31.1) *COL17A1* (10q25.1)	Wright et al. (1993), Aberdam, Aguzzi, et al. (1994), Aberdam, Galliano, et al. (1994), Pulkkinen, Christiano, Airenne, et al., 1994; Pulkkinen, Christiano, Gerecke, et al., 1994, Wright et al. (1994), Kivirikko et al. (1995), McGrath et al. (1995), Vidal et al. (1995) and Kim et al. (2013)
	Simplex epidermolysis bullosa (SEB)		*601282	AR	Skin blistering at birth or shortly thereafter, progressive muscle weakness, and rarely by alopecia.	Enamel hypoplasia	*PLEC* (8q24.3)	Argyropoulou et al. (2018) and Vahidnezhad et al. (2022)
Developmental and epileptic encephalopathy with amelogenesis imperfecta	DEE		#615905	AR	Refractory seizures in early infancy, intellectual disability, poor speech and communication, ataxia, spasticity, abnormal involuntary movements	Hypodontia, delayed eruption, hypoplastic AI, enamel chipping, yellow surface, pits on teeth	*SLC13A5* (17p13.1)	
Autoimmune polyglandular syndrome	APSI	Whitaker syndrome	#240300	AD/AR	Addison disease, and/or hypoparathyroidism, and/or chronic mucocutaneous candidiasis, malabsorption and diarrhea, chronic active hepatitis, juvenile-onset pernicious anemia, alopecia, primary hypogonadism	Enamel hypoplasia with loss of normal enamel structure	*AIRE* (21q22.3)	Kahaly (2009), Michels and Gottlieb (2010) and Kahaly and Frommer (2018)
	APSII	Schmidt syndrome	%269200		Addison disease, autoimmune thyroid disease, or type I diabetes mellitus			

(Continues)

TABLE 2 (Continued)

Name	Abbreviation	Alias	OMIM	Inheritance	Main characteristics	Oral and dental characteristics	Mutation	Reference
Cystic fibrosis	CF		#219700	AR	Cor pulmonale, chronic bronchopulmonary infection, bronchiectasis, pulmonary blebs, pancreatic insufficiency in 80%	Enamel hypoplasia	*CFTR* (7q31.2)	Jagels and Sweeney (1976), Wright et al. (1996), Grubb and Boucher (1999), Arquitt et al. (2002), Bronckers et al. (2010) and Duan et al. (2011)
Morquio syndrome		Mucopoly-saccharidosis type IVA	#253000	AR	Short stature, skeletal dysplasia, dental anomalies, coarse facial features, mild, prognathism, corneal clouding, broad mouth, hearing loss	Enamel hypoplasia in both deciduous and permanent teeth, dull and grayish enamel, thin and pitted enamel with a tendency to fracture and flake off, widely spaced teeth, frequent caries	*GALNS* (16q24.3)	Gardner (1975), Sela et al. (1975) and Hendriksz et al. (2013, 2015) and Vinod et al. (2022)
		Mucopoly-saccharidosis type IVB	#253010	AR	Skeletal dysplasia, corneal clouding	Widely spaced teeth, grayish enamel, frequent caries	*GLB1* (3p22.3)	
Amelo-onycho-hypohidrotic syndrome			%104570		Seborrheic dermatitis (scalp), hypohidrosis, xerosis (buttocks, extensor surfaces of extremities), onycholysis	Hypocalcified-hypoplastic enamel, yellow-brown tooth discoloration, marked delay in eruption of permanent teeth	NA	
Pfeiffer-Palm-Teller syndrome			261560		Short stature, cup-shaped ears, narrow palpebral fissures, epicanthal folds, progressive joint stiffness	Enamel hypoplasia	NA	
Arthrogryposis and ectodermal dysplasia			601701		Brachycephaly, microcephaly, unusual facial appearance, cleft lip/palate, minor malformations of limbs, ectodermal dysplasia	Oligodontia, enamel abnormalities, cleft lip/palate	NA	

Abbreviations: AD, autosomal-dominant; AR, autosomal-recessive; NA, not available.

network of transcription factors controlling the ameloblast life cycle and amelogenesis during the late stages of tooth development (Ruspita et al., 2020). The knockout mice of *Fam20a* and *Msx2* share the similar dental phenotypes, raising the possibility that MSX2 and FAM20A function within a shared molecular pathway (Molla et al., 2010).

4.3 | Tricho-dento-osseous syndrome

Tricho-dento-osseous syndrome (TDO, #190320) is an autosomal-dominant disorder with complete penetrance characterized by abnormalities involving hair, teeth, and bone (Lichtenstein et al., 1972; Robinson & Miller, 1966).

Tricho-dento-osseous can be divided into three types: TDO I, TDO II, and TDO III (Quattromani et al., 1983; Shapiro et al., 1983). TDO I has been characterized by kinky or curly hair, dolichocephaly, radiodense bones, and occasionally brittle nails. Bones characteristics of TDO I include delayed skeletal maturation, premature closure of calvaria, poorly pneumatized mastoid of calvaria, dolichocephaly, and abnormal mandibular shape (Lichtenstein et al., 1972). Dental abnormalities include hypomaturation–hypoplasia enamel, impacted teeth, and delayed eruption. TDO II individuals also have abnormalities in the hair, teeth, and bones. The hair is woolly and sparse. Dental radiographs show obliteration of the pulp cavities, dysplastic dentin, and precocious eruption defects. Bones characteristics may include sclerotic of long bones, increased thickness of calvaria, and sclerosis of the skull. The nails are flat, thin, and brittle. Males also have the narrowing of ear canal. TDO III has prevalent macrocephaly together with increased density and thickness in calvarial bone. The dental findings include hypoplastic, hypocalcified, and pitted enamel, small and widely spaced teeth with signs of attrition and frequent abscesses, taurodontism, and short roots (Shapiro et al., 1983).

The heterozygous mutation in the *DLX3* gene is responsible for TDO (Price et al., 1998). The clinical phenotypes depend on the affected functional region of DLX3 protein. DLX3 is indispensable in regulating ion transporters and carbonic anhydrase during the mature stage of enamel formation and plays an important role in regulating pH oscillations during enamel mineralization (Duverger et al., 2017).

4.4 | Heimler syndrome

Heimler syndrome (HS; #234580, #616617) is a rare autosomal recessive disorder characterized by sensorineural hearing loss, retinal dystrophy, and AI. This syndrome was first documented by Heimler et al. (1991). Then, Ilham Ratbi found that homozygous or compound heterozygous mutations in *PEX1* and *PEX6* genes caused HS (Ratbi et al., 2015). HS is one of the less severe forms of peroxisome biogenesis disorders (PBDs). Sensorineural hearing loss is the most penetrant clinical sign of HS, even in the early childhood. All patients presented with bilateral prelingual or congenital hearing impairment. AI is one of the typical clinical signs of HS. Almost all the reported HS cases had hypoplastic/hypomineralized AI in the permanent dentition, and those posterior teeth (premolar and molar) were more severely affected than anterior teeth (incisors) (Mechaussier et al., 2020). Accordingly, recognition of AI is key for diagnosing HS.

4.5 | Cone-rod dystrophy with amelogenesis imperfecta

Cone-rod dystrophy (CORD) with amelogenesis imperfecta (#217080), also known as Jalili syndrome, is an autosomal recessive disorder caused by the mutations in the ancient conserved domain protein 4 gene (*CNNM4*) on chromosome 2q11 (Maia et al., 2018; Parry et al., 2009). Significant visual impairment with nystagmus and photophobia is present in CORD cases from infancy or early childhood and progresses with age. Teeth of CORD patients are yellow or brown. The enamel of primary and secondary dentitions is grossly abnormal and barely visible in part, reflecting hypomineralized or hypoplastic/hypomineralized AI changes (Michaelides et al., 2004).

4.6 | Epidermolysis bullosa

Epidermolysis bullosa (EB) is an inherited, heterogeneous genetic skin disease characterized by mucocutaneous fragility and blister formation. EB is mainly divided into four types: simplex, junctional, dystrophic, and Kindler, and each type has its own subtypes (Fine et al., 2014; Has et al., 2020; Intong & Murrell, 2012). The enamel abnormalities could be found in dystrophic, junctional, and simplex types of EB (Argyropoulou et al., 2018; Vahidnezhad et al., 2022).

Junctional epidermolysis bullosa (JEB; #226650, #226730, #619816, and #619787) is an autosomal recessive blistering disease with skin and mucous abnormalities. The causative genes of JEB include *LAMA3*, *LAMB3*, *LAMC2*, *COL17A1*, *ITGB4*, and *ITGA6*. Defects in bialleles of *LAMA3*, *LAMB3*, *LAMC2*, and *COL17A1* cause JEB, while defects in bialleles of *ITGA6* and *ITGB4* cause JEB with pyloric atresia (Aberdam, Aguzzi, et al., 1994; Aberdam, Galliano, et al., 1994; Kivirikko et al., 1995; McGrath et al., 1995; Pulkkinen, Christiano, Airenne, et al., 1994; Pulkkinen, Christiano, Gerecke, et al., 1994; Vidal et al., 1995). The defective single allele in *LAMB3* and other genes usually causes autosomal-dominant JEB with AI and little or no apparent skin fragility. In other words, the above genes cause skin abnormalities in an autosomal recessive manner and enamel defects in an autosomal-dominant pattern, respectively (Kim et al., 2013). The affected enamel of JEB is generalized hypoplasia characterized by thin and full of pits and furrows, easily causing dental caries (Wright et al., 1994). All JEB-related genes such as *COL17A1* and *LM332* are both important for oral and skin basement membranes and ameloblastic adhesion and enamel mineralization (Umemoto et al., 2012; Wright et al., 1994).

Simplex epidermolysis bullosa simplex with muscular dystrophy (SEB-MD) is an autosomal recessive disease, characterized mainly

by skin blistering at birth or shortly thereafter, progressive muscle weakness, and rarely by alopecia. SEB-MD is caused by mutations in the *PLEC* gene (OMIM *601282), which encodes plectin, a structural protein expressed in several tissues such as epithelia and muscle. SEB mainly causes enamel hypoplasia (Argyropoulou et al., 2018; Vahidnezhad et al., 2022).

Autosomal recessive dystrophic epidermolysis bullosa (DEB; #226600) is a severe skin disorder beginning at birth and characterized by recurrent blistering at the level of sublamina densa beneath the cutaneous basement membrane. DEB is caused by homozygous or compound heterozygous mutations in the gene encoding type VII collagen (*COL7A1*) on chromosome 3p21. *MMP1*, encoding matrix metalloproteinase type I, is a possible candidate modifier gene of recessive DEB although its causative role in DEB was not identified by linkage analysis (Bauer & Eisen, 1978; Colombi et al., 1992; Hovnanian et al., 1991). MMP1 is secreted by basal keratinocytes and dermal fibroblasts and degrade type VII collagen and other substrates (Ala-aho & Kähäri, 2005; Seltzer et al., 1989). The increased activity of MMP1 could aggravate the disease through enhanced degradation of type VII collagen (Titeux et al., 2008).

Dystrophic epidermolysis bullosa patients will present with enamel defects, but not all develop enamel abnormalities, and some reports claim that recessive DEB patients may have enamel surface defects with the similar frequency and distribution to those in healthy controls (Umemoto et al., 2012; Wright et al., 1993).

4.7 | Other syndromes with enamel abnormalities

Vitamin D-dependent rickets type 1A (VDDR1A; #264700), also known as hereditary selective deficiency of the active form of vitamin D (1,25-dihydroxyvitamin D3), is caused by the mutation in the gene encoding 25-hydroxyvitamin D3-1-alpha-hydroxylase (*CYP27B1*) on chromosome 12q13. The patient demonstrated slow growth, hypotonia, rickets, enamel hypoplasia, and dentin problems. Some patients had yellow-brown enamel on their permanent teeth and periodontal disease (Gjørup et al., 2018; Zambrano et al., 2003).

Vitamin D-resistant rickets (VDRR; #277440) are also known as Vitamin D-dependent rickets type II, and vitamin D receptor (*VDR*) is the causative gene. The clinical features of VDDR are as follows: hypocalcemia, retarded growth, sparse body hair (sometimes alopecia), premature tooth loss, enlarged pulp chambers, thin dentine, and hypoplastic enamel (Goodman et al., 1998).

Oculodentodigital syndrome (ODDD; #164200) is characterized by a typical facial appearance and variable involvements of eyes, teeth, and limbs. Dental features include enamel hypoplasia with yellow discoloration, small teeth, and premature tooth loss. The mutations in the gene coding connexin 43 (*GJA1*) may cause ODDD mainly in autosomal-dominant form and rarely in autosomal recessive way (Jamsheer et al., 2010; Pizzuti et al., 2004; Richardson et al., 2006).

Cystic fibrosis (CF; #219700) is classically described as a triad of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, and elevation of sodium and chloride concentration in sweat. Between 5% and 44% of CF patients had variable enamel hypoplasia (Duan et al., 2011; Jagels & Sweeney, 1976). CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) (Grubb & Boucher, 1999). *Cftr* knockout mice have enamel with crystallite defects, retained protein, and hypomineralization, suggesting a role for CFTR in enamel formation and mineralization (Arquitt et al., 2002). CFTR immunostaining is not present in secretory ameloblasts but highly prominent in the apical plasma membranes of maturation ameloblasts, which are severely affected in *Cftr* null mice (Bronckers et al., 2010; Wright et al., 1996). CFTR functional deficiency may lead to pathological endocytosis of ameloblasts, leading to increased protein content in mature enamel and eventually leading to enamel abnormalities (Duan et al., 2011).

Online Mendelian Inheritance in Man also provides the information on the following syndromes related to enamel abnormalities: autoimmune polyglandular syndrome (#240300), Rubinstein-Taybi syndrome (#180849), and Morquio syndrome (#253000, #253010).

To sum up, the enamel phenotypes linked to the above syndromes can be divided into three categories: hypoplastic, compound, and unstated enamel characteristic. Hypoplastic enamel defects such as thin enamel and discoloration were found in 19 syndromes. Among these 19 syndromic enamel defects, patients with Vitamin D-resistant rickets have dentin abnormalities, oculodentodigital syndrome shows selective tooth agenesis, microdontia, and premature loss of teeth.

Abnormal tooth eruption are also found in Kohlschütter-Tönz-like syndrome, nephrocalcinosis syndrome, and Vitamin D-resistant rickets. Isolated hypocalcified enamel has not been found in any reported syndromic AI, while the combined hypoplastic-hypocalcified was more common in seven syndromes. Among these, Vitamin D-dependent rickets also shows short roots, enlarged pulp chambers with thin dentin. Three types of TDO syndrome and Heimler Syndrome type II have the symptoms of taurodontism. Amelo-onycho-hypohidrotic syndrome has the delayed eruption of permanent teeth. The details of enamel changes are not described in arthrogryposis and ectodermal dysplasia, so we grouped it as unstated enamel phenotypes (Figure 2). The dentists and other clinicians may use these enamel changes and other combined dental abnormalities as telltale symptoms to diagnose systemic hereditary diseases.

5 | DEVELOPMENT OF TOOTH ENAMEL AND MOLECULAR PATTERN OF AI

5.1 | Enamel development

Enamel formation is a dynamic process showing a specific spatial and temporal pattern. When the tooth germ develops to the late bell stage, the inner enamel epithelium differentiates into ameloblasts,

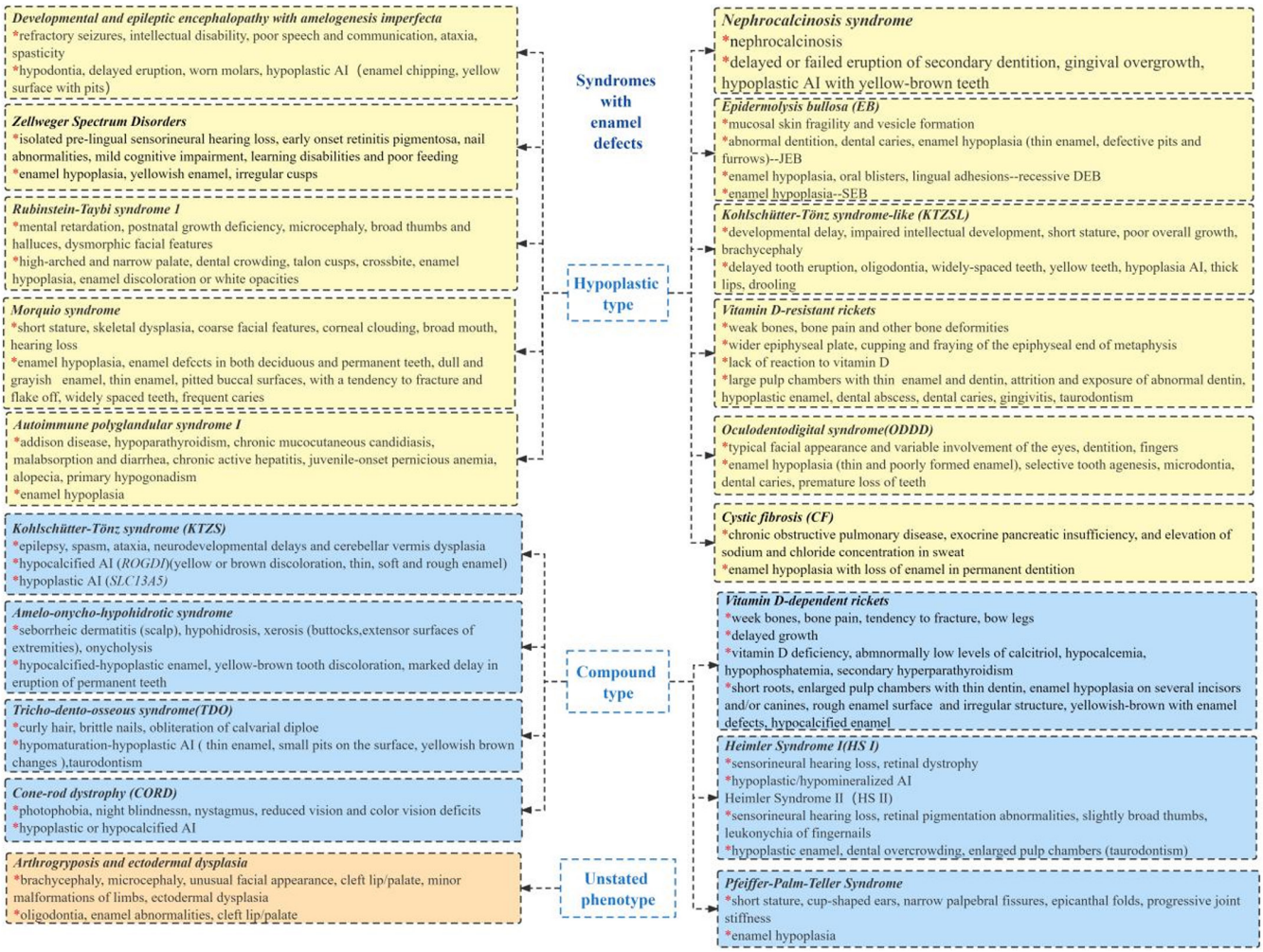

FIGURE 2 Classification of syndromes with enamel defects.

marking the initiation of enamel development (Lacruz et al., 2017). Once the inner enamel epithelial cells differentiate into ameloblasts, the cells gradually become taller and form Tomes' processes. The ameloblasts in the secretory phase secrete enamel matrix proteins through Tomes' processes. The secretory phase is responsible for enamel morphogenesis. After the enamel reaches its final thickness at the end of secretory stage, the ameloblasts stop secreting and Tomes' processes disappear (Bronckers, 2017; Smith, 1998). The crystal growth and deposition appear in the secretory stage and become the main activity in the mature phase (Bronckers, 2017; Moradian-Oldak, 2012). Ameloblasts in maturation stage change between smooth-ended and ruffled-ended. Most matrix proteins and water are absorbed, the crystals are formed and deposited, and finally the mature enamel contains up to 96% of minerals (Figure 3).

5.2 | Molecular pattern of AI

Amelogenesis imperfecta is a clinically and genetically heterogeneous group of diseases characterized by enamel and its study has helped to define the processes and genes involved in amelogenesis (Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017; Urzúa et al., 2015). Currently, 41 genes were reported related to enamel defects (Simmer et al., 2021). These genes includes *AMELX*, *ENAM*, and *AMBN* that encodes enamel matrix proteins (EMPs) and makes up the bulk of enamel organic matrix; *MMP20* and *KLK4* that degrades the enamel matrix proteins during the secretory and maturation stage respectively; *ITGB6*, *LAMA3*, *LAMB3*, *COL17A1*, *COL7A1*, *AMTN*, *ODAPH*, and *FAM83H* that functions the cell–cell and cell-matrix adhesion; *WDR72*, *SLC24A4*, *GPR68*, *CNNM4*, *SLC13A5*, and *CFTR*, encoding ion channels, transporters or pH sensors, that may control the active transport of mineral ions between ameloblasts and enamel space to support crystallite growth in maturation stage; transcript factors *DLX3*, *MSX2*, *SP6*, and *CREBBP* that regulates enamel-related gene expression; *FAM20A* and *VDR* regulates enamel mineralization; *GJA1* affects intercellular communication; *PEX1* and *PEX6* protects ameloblasts against oxidative injuries and regulates lipid homeostasis; *SATB1* influences ameloblast differentiation, as well as *RELT* and *ACP4* regulates enamel development with unclear mechanism (Figure 4).

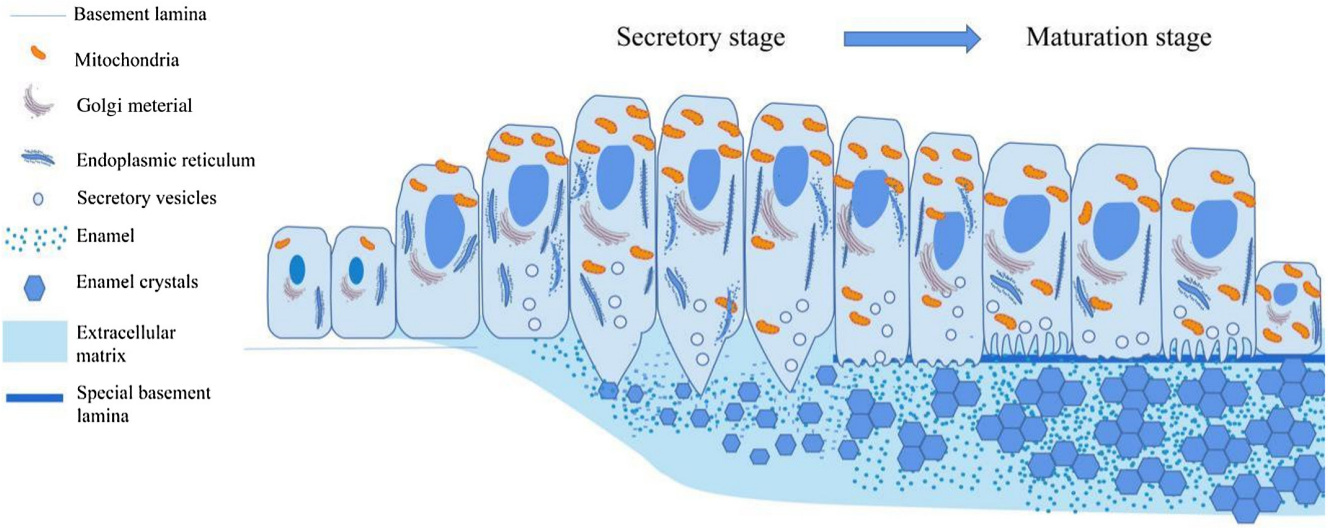

FIGURE 3 Schematic map of ameloblasts and enamel in different development stages. In the secretory phase, ameloblasts secrete enamel matrix and few crystals are deposited. Then ameloblasts gradually become short and transform into mature stage. Matrix proteins are degraded and endocytosed, and large amount of mineral content are increased during maturation stage.

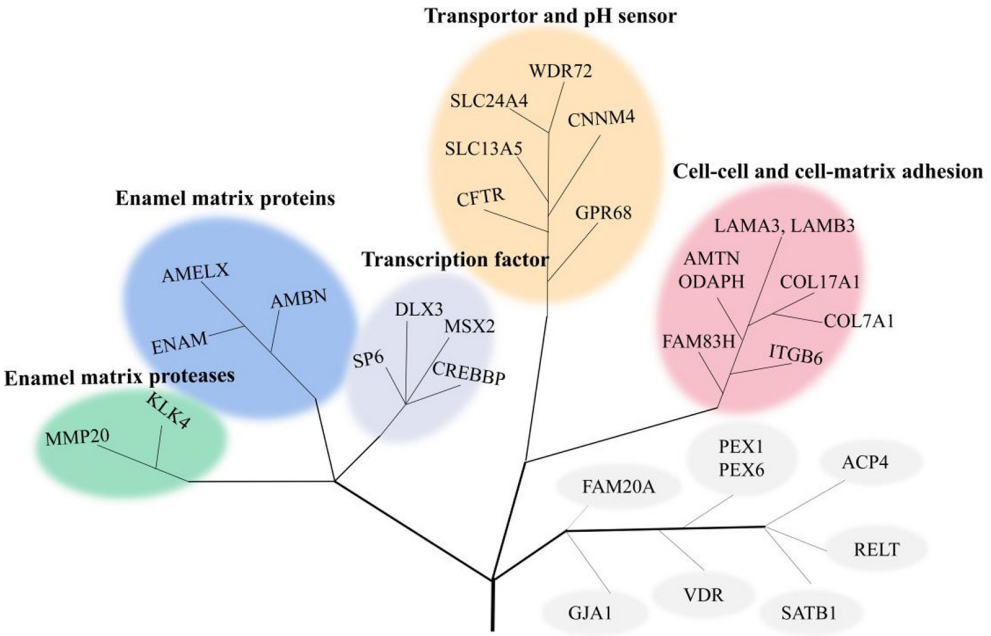

FIGURE 4 Subgroups of the moleculars underlying amelogenesis imperfecta.

5.2.1 | Amelogenin (AMELX)

Amelogenin, the only AI pathogenic gene located on the X chromosome, encodes the enamel-specific protein secreted by ameloblasts during secretory stage enamel. Amelogenin accounts for almost 90% of enamel matrix proteins (Termine et al., 1980) and provides the scaffold for the spacing and growth of enamel crystallites (Chen et al., 2011). Additionally, unprotonated amelogenins rich in hydrophobic, proline, and histidine can bind to protons, suggesting amelogenin could regulate the pH in enamel (Guo et al., 2015). After being secreted, amelogenin undergoes intensive extracellular proteolytic processing (Brookes et al., 1995).

The mutations in *AMELX* cause X-linked AI. The affected individuals present various clinical heterogeneity, which are related to the location of mutations in signal peptide region, N-terminal region, or C-terminal region of amelogenin protein, or the effects of mutation on the function and expression (Aldred et al., 1992). For example, large deletions and N-terminal variants usually cause hypomaturation AI with variable focal hypoplasia, while mutations in the signal peptide and the C-terminal result in smooth hypoplastic

AI (Hart et al., 2002; Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017).

The skewed X inactivation could attribute to the variable phenotypes in females with *AMELX*-linked AI (Duan et al., 2019). The homozygous *AMELX* mutation in females and hemizygous *AMELX* mutation in males presented the same enamel malformations, such as thin enamel and pit defects, while the heterozygous *AMELX* mutation in females showed vertical bands of opaque white enamel and thinner translucent enamel, due to the coexisted ameloblasts secreting normal and defective amelogenin (Duan et al., 2019).

5.2.2 | Enamelin (ENAM)

ENAM is primarily expressed by secretory stage ameloblasts and involved in the nucleation, growth, and organization of hydroxyapatite crystals (Hu & Yamakoshi, 2003). ENAM cleavage products have a high affinity for HA crystals and accumulate within enamel prisms, while the uncleaved protein presents in the outermost layer of newly secreted enamel matrix (Hu & Yamakoshi, 2003).

Mutation in *ENAM* causes hypoplastic AI in humans. The affected enamel showed a clear dose-dependent effect and variable expressivity. Patients with a homozygous mutation exhibited severe generalized enamel imperfecta or even loss of enamel, while the heterozygous *ENAM* mutation displayed localized enamel defects (Kim, Seymen, et al., 2005; Kim, Simmer, et al., 2005; Yu et al., 2022). ENAM is usually expressed in an amount approximately appropriate for enamel formation. Haploinsufficiency of *ENAM* causes a localized dysplastic enamel characterized by horizontally oriented pits, grooves, or large hypoplasia. The substantial alteration in ENAM protein structure will lead to more severe phenotypes through dominant negative effects of toxic defective protein matrix (Hart, Hart, et al., 2003; Hart, Michalec, et al., 2003).

5.2.3 | Ameloblastin (AMBN)

AMBN, the second most abundant nonamelogenin enamel matrix protein, is a phosphorylated glycoprotein expressed throughout amelogenesis with the peak amount in the secretory stage (Fukumoto et al., 2004; Lee et al., 1996). AMBN is localized to Tomes' processes, the enamel matrix, and the dentino-enamel junction (DEJ) (Krebsbach et al., 1996). During teeth development, AMBN can be cleaved into C-terminus and N-terminus fragments by MMP20, and its cleavage products bounds to the sheath space surrounding enamel prisms (Poulter, Brookes, et al., 2014; Poulter, Murillo, et al., 2014). Subsequently, ameloblastin plays a role in crystal nucleation and the linkage between ameloblasts and the enamel extracellular matrix. Clinical heterogeneity of *AMBN*-associated AI is related to the type and location of the mutations in *AMBN*. A homozygous inframe deletion (c.294+139_531+478del) induces the reduced mineral density and thickness of enamel (Poulter, Brookes, et al., 2014; Poulter, Murillo, et al., 2014), and a homozygous mutation in splice-junction (c.532-1G>C) only causes thin enamel without any pits (Prasad et al., 2016). Moreover, a heterozygous missense mutation (c.1069C>T) in *AMBN* results in autosomal-dominant hypoplastic human AI and dentin defects (Lu et al., 2018).

5.2.4 | Matrix metalloproteinase 20 (MMP20)

MMP20 is located in chromosome 11q22.2 and encodes a 483-amino-acid protein, previously called enamelysin (Llano et al., 1997). MMP20 is secreted by ameloblasts during the secretory stage and is responsible for processing the enamel matrix protein into functional fragments (Hu, Smith, Richardson, et al., 2016; Kim, Kang, et al., 2017). MMP20 plays an important role in enamel mineralization by replacing the organic matrix with mineral crystals (Uskoković et al., 2011) and regulating crystal elongation, the normal structure of dentin–enamel connection, and the organization and maintenance of enamel prisms (Lu et al., 2008).

The severity of clinical phenotype of MMP20-related AI is related to the reduced functional activity of MMP20 (Kim et al., 2020; Kim, Kang, et al., 2017; Kim, Kim, et al., 2017). The mutations with total loss of MMP20 function present severe enamel phenotype such as severe discoloration and hypoplastic–hypomaturation (Gasse et al., 2013; Kim, Kang, et al., 2017; Kim, Kim, et al., 2017; Papagerakis et al., 2008), while the mutations with retained functional activity show mild discoloration compared with nullifying mutations (Gasse et al., 2013; Kim, Kang, et al., 2017; Kim, Kim, et al., 2017; Kim, Seymen, et al., 2005; Kim, Simmer, et al., 2005; Lee, Seymen, Kang, et al., 2010; Ozdemir, Hart, Ryu, et al., 2005; Seymen, Lee, et al., 2015; Seymen, Park, et al., 2015; Wang et al., 2013). The degree of discoloration could be an indicator of the enamel porosity and reflects an altered level of enamel maturation.

MMP20 has five domains including signal peptide, prodomain, catalytic domain, linker, and hemopexin domain. Almost all the reported *MMP20* mutations to date were associated with MMP20 hemopexin-like (PEX) domain and catalytic domain (Gasse et al., 2013, 2017; Kim, Kang, et al., 2017; Kim, Kim, et al., 2017; Kim, Seymen, et al., 2005; Kim, Simmer, et al., 2005; Lee, Seymen, Kang, et al., 2010; Lee, Seymen, Lee, et al., 2010; Ozdemir, Hart, Firatli, et al., 2005; Ozdemir, Hart, Ryu, et al., 2005; Papagerakis et al., 2008; Seymen, Lee, et al., 2015; Seymen, Park, et al., 2015; Wang et al., 2013, 2020).

5.2.5 | Kallikrein 4 (KLK4)

KLK4 is one of the 15 kallikrein subfamily members located in a cluster on chromosome 19, and plays important role in the degradation of enamel proteins. During the transition and maturation stages, the remaining enamel matrix was degraded by KLK4, removed by endocytosis, and further replaced by tissue fluid for the enamel crystals to grow in width (Yamakoshi et al., 2013). *KLK4* mutation

mainly causes hypomaturation AI, which may be related to the loss or reduction in KLK4 activity (Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017; Wright et al., 2006). Cleavage of KLK4 enables the degraded enamel matrix protein to move from deep enamel (Bartlett & Simmer, 2014). KLK4-related AI remains organic matrix in the inner enamel layer but normal in the outer layer, suggesting that KLK4 is more required for the mineralization of inner enamel than outer enamel (Núñez et al., 2016; Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017).

5.2.6 | LAMA3, LAMB3, COL7A1, and COL17A1

Laminin 332 (LM332) is a basement-membrane protein composed of three heterotrimeric polypeptide chains, α3, β3, and γ2, which are encoded by the *LAMA3*, *LAMB3*, and *LAMC2*, respectively (Smith et al., 2019). LM332 expression is observed in secretory ameloblasts and Tomes' processes. Therefore, defective LM332 may interrupt the secretory stage of amelogenesis, leading to a reduction in the enamel matrix volume and impaired crystal rod growth. LM332 may participate in controlling ameloblast differentiation and adhesion to enamel matrix (Yoshiba et al., 1998). LM332 can anchor ameloblasts to the enamel matrix, which is required for crystal rod orientation, structure, and mineralization (Aberdam, Aguzzi, et al., 1994; Aberdam, Galliano, et al., 1994). The C-terminal domain of LAMB3 contributes to the complete heterotrimers which enables LM332 to be secreted (Matsui et al., 1995), thus *LAMB3* truncates in the C-terminal domain may induce loss function of LM332. Biallele *LAMB3* mutations are bound up with JEB, while *LAMB3*-related AI is caused by a defect of a single allele (Kim et al., 2013).

Type VII collagen (COL7) is a major component of anchoring fibrils in the epidermal basement membrane and plays a crucial role in anchoring fibril formation and mediates derma-epidermal adherence (Christiano et al., 1994; Sakai et al., 1986). Mutations in *COL7A1* lead to DEB in an autosomal recessive manner. COL7A1 is expressed throughout enamel formation and essential for forming Tomes' processes (Umemoto et al., 2012). COL7 interacts with laminin 332 at the epithelial–mesenchymal junction. The deficiency of COL7 disrupts the interaction between COL7 and laminin 332, and laminin 332 regulated ameloblast differentiation (Rousselle et al., 1997; Sakai et al., 1986).

Collagen type XVII, alpha-1 (*COL17A1*) is an integral component of hemidesmosomes at the dermal-epidermal junction, belongs to transmembrane collagen expressed in stratified and complex epithelia, and it plays a crucial role in hemidesmosome stability and epithelial–mesenchymal attachment (McGrath et al., 1995). COL17A1 plays a role in enamel formation and ameloblast differentiation. The *Col17* gene is involved in the interaction between enamel epithelium and underlying mesenchymal through the epithelial–mesenchymal junction (Asaka et al., 2009). *Col17*$^{-/-}$ mice lack Tomes' processes in ameloblasts or exhibit malformed ameloblasts and reduced production of enamel matrix (Asaka et al., 2009; Umemoto et al., 2012). Compared with the COL7 deficiency-related deleterious effects on ameloblast differentiation, COL17 deficiency appears to have a more damaging effect on enamel epithelium.

5.2.7 | Integrin, β6 (ITGB6)

ITGB6 is a member of the integrin superfamily, containing α and β subunits and acts as a receptor on the cell surface (Hynes, 2002). Members of integrin family are involved in cell–cell, cell–matrix, and cell–pathogen interactions by facilitating interaction with the cytoskeleton (Zhang & Chen, 2012). ITGB6 expression is localized in the distal membrane of differentiated and pre-ameloblasts and then internalized by the secretory stage ameloblasts, while the strongest expression appeared in the maturation stage ameloblasts (Wang, Choi, et al., 2014; Wang, Reid, et al., 2014; Wang, Wrennall, et al., 2014). Studies showed that inefficient ITGB6 could result in the impaired cell–matrix interaction, ameloblast–ameloblast interactions, and proteolytic processing of extracellular matrix proteins via MMP20 (Munger et al., 1999; Poulter, Brookes, et al., 2014; Poulter, Murillo, et al., 2014). Clinical phenotypes of *ITGB6*-related AI are related to the types of mutations. p.Arg616* and p.[Ala143Thr];[His275Gln] causes generalized hypoplastic AI (Wang, Choi, et al., 2014; Wang, Reid, et al., 2014; Wang, Wrennall, et al., 2014), p.Gly173Arg mainly causes pitted hypoplastic-hypomineralized enamel (Seymen, Lee, et al., 2015; Seymen, Park, et al., 2015), and p.Pro196Thr results in pitted hypomineralized AI (Poulter, Brookes, et al., 2014; Poulter, Murillo, et al., 2014).

5.2.8 | The family with sequence similarity 83 member H (FAM83H)

FAM83H encodes an intracellular protein associated with keratin cytoskeleton and desmosome (Fulcher et al., 2018). FAM83H is expressed by several cell types, especially in the pre-secretory and secretory ameloblasts (Kim et al., 2008). Affect enamel of *FAM83H*-related AI shows a reduced mineral density, suggesting the defects in calcification process during amelogenesis.

In vitro studies have shown that FAM83H locates to keratin filaments and regulates the organization of the keratin cytoskeleton and maintains the formation of desmosomes in ameloblastoma cells (Kuga et al., 2016). The functional truncations of FAM83H could disturb the organization of keratin cytoskeleton and desmosomes of ameloblastoma cells, which suggests that AI caused by the FAM83H mutation might be mediated by the disorganization of the keratin cytoskeleton and subsequent disruption of desmosomes in ameloblasts (Kuga et al., 2016). In addition, overexpression or *Fam83h* null mice did not show distinct enamel phenotypes (Wang et al., 2016); thus, it is believed that *FAM83H*-related AI is likely caused by the gain of function or dominant negative effect of mutated *FAM83H*

rather than loss of function or haploinsufficiency (Nowwarote et al., 2018).

5.2.9 | Amelotin (AMTN)

AMTN is a proline, leucine, threonine, and glutamine-rich protein and specifically expressed in maturation-stage ameloblasts (Moffatt et al., 2006). The protein localizes to the ameloblast basal lamina, where it participates the attachment between the maturation stage ameloblasts and the mineralizing enamel (Bartlett & Simmer, 2015; Holcroft & Ganss, 2011; Moffatt et al., 2014). A vitro study indicates that *AMTN* plays a critical role in the formation of compact surface aprismatic enamel during maturation (Abbarin et al., 2015). Therefore, *AMTN* is thought to be possibly bi-functional, with roles in both cell–matrix attachment and mineral nucleation (Smith, Kirkham, et al., 2017; Smith, Poulter, et al., 2017). Deletion in *AMTN* mainly presents a lower mineral enamel (Smith et al., 2016), which is also observed in mouse mode (Nakayama et al., 2015; Núñez et al., 2016), suggesting an important role of *AMTN* in the mineralization of enamel.

5.2.10 | Odontogenesis-associated phosphoprotein (ODAPH)

Chromosome 4 open reading frame 26 (C4orf26) is now defined as odontogenesis-associated phosphoprotein (ODAPH) because it was reported to be inactivated in toothless placental mammals (Springer et al., 2016). Human *ODAPH* encodes a protein of 130 amino acids, including a signal peptide and a secreted protein of 107 amino acids. Mutation in *ODAPH* has been reported to cause recessive hypomineralized AI in human (Parry et al., 2012). The affected enamel is yellowish-brown and hypomineralized, which was prone to rapid attrition after tooth eruption. Severe attrition of enamel and reduced enamel mineralization were also observed in *Odaph*$^{-/-}$ mice, which is consistent with the pattern of human hypomaturation AI phenotype (Ji et al., 2021).

Previous researches shown that ODAPH was located on the sBL between the distal ends of ameloblasts and the enamel surface in the maturation stage (Li et al., 2022). sBL is a specialized basement membrane and is located the distal portion of the ameloblasts, which forms after the formation of the enamel body when ameloblasts become shorter and lose their Tome's processes (Mu et al., 2022). It has been reported that sBL includes three specific constituents AMTN, ODAM, and SCPPPQ1 as well as rich in LAMC2, which is thought to participate in the adhesion and of ameloblasts to the tooth surface (Fouillen et al., 2017; Li et al., 2022). ODAPH is a newly discovered constituent of sBL. In *Odaph*-deficient mice, the integrity of the sBL is impaired and the maturation stage fails entirely (Ji et al., 2021; Liang et al., 2021). In addition, in vitro studies showed phosphorylated ODAPH has the capacity to promote nucleation of hydroxyapatite, which further prove ODAPH may play a vital role in adhesion of ameloblast and enamel at maturation stage (Parry et al., 2012).

5.2.11 | WD repeat domain 72 (WDR72)

WDR72, an intracellular protein, forms a β propeller structure that acts as a scaffold for protein–protein interactions (Jawad & Paoli, 2002; Katsura et al., 2014). WDR72 is widely expressed during tooth development and mainly in maturation-stage ameloblasts (El-Sayed et al., 2009). Mutations in *WDR72* mainly cause hypomatured AI. The affected enamel presents rough and soft surface with yellow-brown discoloration and easy to break after tooth eruption. WDR72 is thought to might be transported and secreted into immature enamel by vesicles and to remove cleaved enamel matrix proteins via endocytosis. Defects in *WDR7* could impair clathrin-mediated endocytosis in ameloblasts, resulting in impaired enamel mineralization (Wang, Hu, et al., 2015). *Wdr72* knockout mice present residual enamel matrix and the disruption of connection between ameloblasts and enamel matrix, suggesting WDR72 serves critical functions specifically during the maturation stage of amelogenesis and is required for both protein removal and enamel mineralization (Katsura et al., 2014; Wang, Hu, et al., 2015; Wang, Zhao, et al., 2015).

5.2.12 | Solute carrier family 24 member 4 (SLC24A4)

SLC24A is a member of the potassium-dependent sodium/calcium exchanger family (SLC24A). During the maturation stage of enamel development, SLC24A is involved in the active transport of Ca^{2+} and K^{+} from ameloblasts into the enamel matrix in exchange for Na^{+} (Khan et al., 2020). *SLC24A4*-related AI mainly exhibits soft enamel with yellow-brown discoloration and irregular enamel prisms, which might be related to decreased transporter activity or the loss of function of SLC24A4 mutant (Khan et al., 2020; Parry et al., 2013).

5.2.13 | Cyclin M4 (CNNM4)

CNNM4 encodes a putative metal transporter and transports Mg^{2+} from the enamel-forming areas (Yamazaki et al., 2013). It is localized to the basolateral membrane of ameloblasts and intestinal epithelia. CNNM4 is highly expressed during amelogenesis in the transition and maturation stages instead of secretion stage (Parry et al., 2009). Both SLC41A1 and CNNM4 are involved in regulating Mg^{2+} targeted transport in intestinal epithelial cells, but extrusion speed of Mg^{2+} by CNNM4 is faster than by SLC41A1, suggesting a specialized role of CNNM4 in the intestinal epithelia (Kolisek et al., 2012).

5.2.14 | Cystic fibrosis transmembrane conductance regulator (CFTR)

CFTR encodes an ATP-binding cassette (ABC) transporter that functions as a chloride channel regulated by cyclic AMP-dependent protein phosphorylation (Bronckers et al., 2010; Wang, Choi, et al., 2014; Wang, Reid, et al., 2014; Wang, Wrennall, et al., 2014). Meanwhile, CFTR controls the activity of other channels and transporters, including Na^+/H^+ exchangers (NHE), HCO_3^-/Cl^- exchangers and cotransporters, and Ca^{2+} and volume-activated Cl^- channels (Linsdell, 2006; Steward et al., 2005). CFTR is expressed in maturation stage ameloblasts, odontoblasts, and bone cells and plays an important role in pH regulation during enamel formation and maturation, and regulates receptor-mediated endocytosis in ameloblast-like PABSo-E cells by changing the intracellular acidic environment (Bronckers et al., 2010; Duan et al., 2011). Loss of CFTR function leads to the increased enamel matrix protein retention and reduced enamel mineralization.

5.2.15 | Solute carrier family 13 member 5 (SLC13A5)

SLC13A5 (a sodium-dependent citrate transporter) encodes a membrane citrate channel providing citrate influx proximally and efflux distally (Simmer et al., 2021). Citrate is highly enriched in bone and other mineralized organs, and has been demonstrated to be essential for the organization of the bone apatite nanocrystals (Costello et al., 2012; Dickens, 1941; Hu et al., 2010; Rhee & Tanaka, 1999; Xie & Nancollas, 2010). Osteoblasts, odontoblasts, and ameloblasts are responsible for synthesis of the citrate incorporated into the apatite nanocrystals in bone and teeth (Franklin et al., 2014). *Slc13a5* deficiency resulted in abnormalities in the enamel and bone, demonstrating the importance of the transporter in amelogenesis and osteogenesis (Irizarry et al., 2017). SLC13A5 delivers citrate into the enamel matrix, stabilizing the thin mineral belt. *Slc13a5*$^{-/-}$ mice could not form mature enamel, and the amount of enamel matrix was less formed, and the degree of mineralization was also reduced (Irizarry et al., 2017).

5.2.16 | G protein-coupled receptor 68 (GPR68)

GPR68 is a proton-sensing G protein-coupled receptor (GPCR) (Ludwig et al., 2003). The expression of GPR68 in ameloblasts is throughout the whole stage of amelogenesis, with the strong expression at the ameloblast pole in contact with the enamel matrix (Parry et al., 2016). Mutation in *GPR68* causes hypomaturation AI in human, which is characterized by brownish-yellow discoloration with increased opacity and poorly mineralized enamel prone to fracture and attrition (Parry et al., 2016; Seymen et al., 2021).

G protein-coupled receptor 68 is a recognized pH sensor in osteoblasts and osteocytes. In vitro studies have suggested that GPR68 could change barrier function of epithelial cells and inhibits migration in an acidic environment (de Vallière et al., 2015), as well as regulate the expression of Na^+/H^+ antiporters and H^+-ATPase transporters in epithelial cells (Mohebbi et al., 2012). Both crystal growth and protease activity are sensitive to extracellular pH in enamel development (Lacruz et al., 2010; Smith et al., 1996; Takagi et al., 1998). And during the maturation stage of amelogenesis, cyclic changes in ameloblasts morphology between ruffle-ended ameloblasts (RAs) with mildly acidic (pH 6.1–6.8) and smooth-ended ameloblasts (SAs) with physiological pH (pH 7.2–7.4) is also likely to be dependent upon a pH-sensing mechanism (Parry et al., 2016; Smith et al., 1996). Given the location in ameloblasts and the function of pH sensor, therefore, GPR68 is thought to function as a pH sensor and a potential switcher between ruffle-ended and smooth-ended ameloblasts during the maturation stage (Parry et al., 2016).

5.2.17 | Distal-less homeobox 3 (DLX3)

The transcription factor DLX3 is expressed in bone and ectodermally derived skin, hair, and teeth, and may play a role in craniofacial patterning and morphogenesis. The dysfunction of DLX3 both affects enamel and dentin (Choi et al., 2010; Robinson & Mahon, 1994). DLX3 is expressed in the ameloblasts throughout enamel formation, with a strong expression in the secretory phase but relatively weak in the pre-secretory and mature stages (Lézot et al., 2008; Zhang et al., 2015). DLX3 is involved in the expression of keratin sets, which contribute to enamel rod formation, and DLX3 contributes to the coordinated migration of ameloblasts in the enamel secretion process (Duverger & Morasso, 2018). ChIP-Seq analysis shows that DLX3 binds to the proximal promoters of several ion transporters and carbonic anhydrases known to regulate enamel pH during maturation. Thus, DLX3 plays a crucial regulatory function on pH oscillations during enamel mineralization (Duverger et al., 2017), while other reports showed that DLX3 also binds to enhancer regions of *Amelx* and *Enam* and positively regulates their expression (Zhang et al., 2015).

5.2.18 | Sp6 transcription factor (SP6)

SP6 belongs to a family of transcription factors that contains three classical zinc finger DNA-binding domains with a zinc atom, two cysteines, and two histidines (C2H2 motif). During teeth development, SP6 is expressed in the secretory stage of amelogenesis and inner enamel epithelium (Muto et al., 2012). SP6 promotes the proliferation of inner enamel epithelium and stimulates these cells to differentiate into ameloblasts, which further secret enamel matrix, which may explain hypoplastic enamel with *SP6* mutations (Utami et al., 2011). SP6 also regulates the expression of enamel-related gene such as *AMBN*. SPR study suggested the reduced binding of *SP6* mutant to the *AMBN* proximal promoter, which resulted in less *AMBN* protein present in the enamel matrix (Smith et al., 2020).

5.2.19 | Msh homeobox 2 (MSX2)

MSX2 belongs to a small family of chromosomally unlinked homeobox-containing genes related to the Drosophila gene muscle-segment homeobox (*msh*) (Babajko et al., 2014). During mid-gestation, Msx2 expression occurs at numerous interaction sites of epithelial–mesenchymal tissue, including tooth germ. *Msx2* deficient mice exhibit defects in the development of various ectodermal organs, including hair follicle, mammary gland, and dentition (Satokata et al., 2000). During enamel genesis, MSX2 inhibits the transition of outer enamel epithelium to keratinized stratified squamous epithelium and promotes properly differentiated enamel organs and subsequent enamel formation (Nakatomi et al., 2018). As a transcriptional regulator, Msx2 controls laminin 5 α3 expression in secretory ameloblasts, and ameloblasts from *Msx2* mutant mice exhibit defective cell–cell contacts (Ryan et al., 1999). Msx2 controls ameloblast terminal differentiation and the expression pattern of *Msx2* in ameloblasts is inversely related to amelogenin abundance (Babajko et al., 2014; Molla et al., 2010).

5.2.20 | CREB-binding protein (CREBBP)

CREBBP is a general transcriptional co-activator that interacts with various transcriptional factors, including c-Fos, c-Jun, NF-κB, and nuclear receptors, CREB and AP-1 (Bannister et al., 1995; Chan & La Thangue, 2001; Kamei et al., 1996; Shiama, 1997; Zhong et al., 1998). CREBBP is localized in the nuclei of ameloblasts in the maturation zone but not in the secretion and transition zones. CREBBP may function as a co-factor that participates in transcriptional activation of AP-1 and/or other factors in the maturation ameloblasts and the other enamel organ-derived cells (Nishikawa, 2002).

5.2.21 | Family with sequence similarity 20, member A (FAM20A)

FAM20A encodes components of the Golgi casein kinase complex that would control the phosphorylation of enamel peptides and enamel mineralization. FAM20A is only present in the ameloblast at secretory stage (Wang, Choi, et al., 2014; Wang, Reid, et al., 2014; Wang, Wrennall, et al., 2014). The role of FAM20A in amelogenesis may be indirect, as FAM20A is a pseudokinase that forms a functional complex with FAM20C and allosterically activates FAM20C to promote the phosphorylation of enamel matrix proteins in vitro and in cells (Cui et al., 2015). During tooth development, *Fam20a* and *Fam20c* are both expressed in ameloblasts and odontoblast (Li et al., 2016; Wang et al., 2010). The severe enamel defects and widespread mineralization of muscular arteries in *Fam20a*$^{-/-}$ mice suggest a local role of FAM20A in enamel and systemic roles in other tissues (Vogel et al., 2012).

5.2.22 | Vitamin D receptor (VDR)

Vitamin D acts locally by binding to vitamin D receptors (VDRs) and affects the proliferation of osteoblasts (van Driel & van Leeuwen, 2014). It has been shown that disruption of the vitamin D pathway reduces bone mineralization and negatively affects tooth formation (Berdal et al., 1987; Lézot et al., 2002). VDR deficiency reduces dentin mineralization and leads to early enamel hypermineralization (Zhang, Beck, et al., 2009). The higher expression of steroid hormone receptors such as VDR in the maturation-stage ameloblasts suggests a hormonal control of final enamel mineralization and quality (Zhang, Beck, et al., 2009; Zhang, Rahemtulla, et al., 2009).

5.2.23 | Gap junction alpha 1 (GJA1)

GJA1 gene encodes connexin 43 gap junction protein (Cx43) (Shimura & Shaw, 2022). Mutations in *GJA1* result in the misassembly of channels, change channel conduction characteristics, affect gap junctions, reduce intercellular communication, and disrupt morphological patterns during development and normal intercellular coupling in mature tissues (Paznekas et al., 2003). Cx43 plays a role in normal enamel organ differentiation and enamel development (Al-Ansari et al., 2018). Cx43 is localized in all stages of ameloblasts with a higher expression level in secretion stage to maturation stage (Toth et al., 2010). Cx43 in the supporting cells and ameloblast layers allows the enamel organ to properly differentiate, secrete, and mineralize enamel. Decreased Cx43 lead to enamel organ morphological defects and enamel hypoplasia (Toth et al., 2010).

5.2.24 | Special AT-rich sequence-binding protein 1 (SATB1)

Special AT-rich sequence-binding protein 1 (SATB1) is a genome organizer selectively binding to a special AT-rich sequence context where one strand consists of mixed A's, T's, and C's, excluding G's (ATC sequences). SATB1 is reported to be expressed predominantly in the thymus and selectively bound to nuclear matrix/scaffold-associating DNAs (MARs/SARs) (Dickinson et al., 1992). SATB1 is essential for establishing secretory ameloblasts polarity by affecting actin filament assembly, the formation of tight junction, and Tomes' processes. Several transcriptional regulators are recruited and assembled by the SATB1 network at specific gene loci to achieve

large-scale gene regulation and enable ameloblast differentiation (Zhang, Zheng, et al., 2019).

5.2.25 | Peroxisome biogenesis factor 1 (PEX1), peroxisome biogenesis factor-6 (PEX6)

As the members of the AAA family of ATPases, both PEX1 and PEX6 contain two ATPase domains in a single polypeptide chain and form hexameric double rings, are necessary for peroxisome biogenesis (Blok et al., 2015; Ratbi et al., 2015). PEX6 is expressed in the secretory ameloblasts (Zaki et al., 2016). The apically localized peroxisomes near the mineralized area might be involved in the degradation of reactive oxygen species to protect ameloblast and odontoblast processes. Furthermore, peroxisome-derived membrane lipids may defend the plasma membranes of ameloblasts and odontoblasts against oxidative injuries and regulate lipid homeostasis (Stelzig et al., 2013).

5.2.26 | RELT TNF receptor (RELT)

RELT is a member of the tumor necrosis factor (TNF) receptor superfamily, commonly regulates inflammation, cell proliferation, apoptosis, and morphogenesis (Aggarwal et al., 2012). Kim et al. (2019) first reported that variants in *RELT* could cause recessive AI as part of a syndrome encompassing small stature and severe childhood infections. Recently, Nikolopoulos et al. (2020) found that variants in RELT cause nonsyndromic hypomineralized AI in four Pakistani families. The affected individuals present reduced enamel mineralization with yellow discoloration and rough surface (Kim et al., 2019; Nikolopoulos et al., 2020). During tooth development, RELT is expressed during the secretory phase ameloblasts (Kim et al., 2019). In vitro studies have suggested that RELT stimulates the proliferation of T cells and can induce apoptosis (Cusick et al., 2010; Moua et al., 2017). However, proliferation and apoptosis are not normal activities of secretory stage ameloblasts. Therefore, RELT involved signaling molecule was thought to may not belong to the TNF superfamily during teeth development (Kim et al., 2019).

5.2.27 | Acid phosphatase 4 (ACP4)

ACP4 belongs to the histidine phosphatase superfamily with a conserved histidine active site (Rigden, 2008). During tooth development, ACP4 is located in secretory stage ameloblasts, follicular cells, odontoblasts, and osteoblasts (Choi et al., 2016). Mutation in *ACP4* has been reported to cause recessive hypoplastic AI in human. The affected individuals present extremely thin enamel with yellow-to-black discoloration and sensitivity to thermal changes (Kim et al., 2022; Liang et al., 2022).

Acid phosphatase 4 localizes to the Tomes' processes of secretory stage ameloblasts. A possible reduction in ENAM and AMBN was detected in the Tomes' processes in $Acp4^{R110C/R110C}$ mice model (Kim et al., 2022), indicating that ACP4 plays a critical role in appositional growth of dental enamel formation probably through regulating secretion or turnover of EMPs. At a molecular level, however, as an acid phosphatase, how ACP functions during appositional growth of enamel formation remains to be elucidated (Figure 5).

6 | CONCLUSIONS

Herein, we summarize the clinical characteristics of nonsyndromic AI and syndromic AI and the underline pathogenic genes. These AI causative genes play different roles in enamel development, which directly lead to various gene-specific enamel phenotypes.

Some genes cause the similar enamel abnormalities; thus, the basic AI phenotypes could be grouped as hypolastic, hypomaturation, and hypocalcification. However, genetic differences can lead to some subtle differences in abnormal enamel phenotypes even in the same type of AI. The phenotype characteristics of AI are totally gene-dependent. For example, the mutation in *LAMB3 and AMBN* is both associated with hypoplastic AI that mainly exhibits reduced enamel thickness with normal radiodensity. However, besides thin enamel, *AMBN*-related AI mainly showed an exfoliated enamel that results in a rough tooth surface with yellow, gray, or brownish-blue discoloration and incisor enamel attrition (Lu et al., 2018; Poulter, Brookes, et al., 2014; Poulter, Murillo, et al., 2014), while *LAMB3*-related AI mainly displays deep pits and vertical grooves and may also be accompanied with multiple cusps in molars and taurodontism.

The types of mutation may also determine genetic heterogeneity of AI. For example, enamel defects of *ENAM*-related AI are dose-dependent (Ozdemir, Hart, Firatli, et al., 2005; Ozdemir, Hart, Ryu, et al., 2005). The affected enamel with homozygous *ENAM* mutation is either completely absent or appears as a very thin mineral layer partially covering the crown (Hart, Hart, et al., 2003; Hart, Michalec, et al., 2003; Wang, Hu, et al., 2015; Wang, Zhao, et al., 2015; Yu et al., 2022). The patients with heterozygous *ENAM* mutation varied from a lack of penetrance to mild enamel defects (Koruyucu et al., 2018). In its mildest form, the enamel defects are well-circumscribed enamel pits, often arranged in horizontal lines (Simmer et al., 2013). With the increasing severity, the enamel defects appear as horizontal grooves, usually in the cervical third of crown (Masuya et al., 2005; Zhang, Hu, et al., 2019; Zhang, Koruyucu, et al., 2019; Zhang, Zheng, et al., 2019).

Furthermore, the phenotypic diversity of AI is associated with another genetic or epigenetic regulation mechanism such as X chromosome inactivation (Duan et al., 2019). The gender difference in enamel phenotypes has been found in *AMELX*-related AI cases or in mouse model (Barron et al., 2010; Duan et al., 2019; Hu, Smith, Cai, et al., 2016; Hu, Smith, Richardson, et al., 2016). The affected male enamel mainly exhibits multiple crown resorptions with a moth-eaten

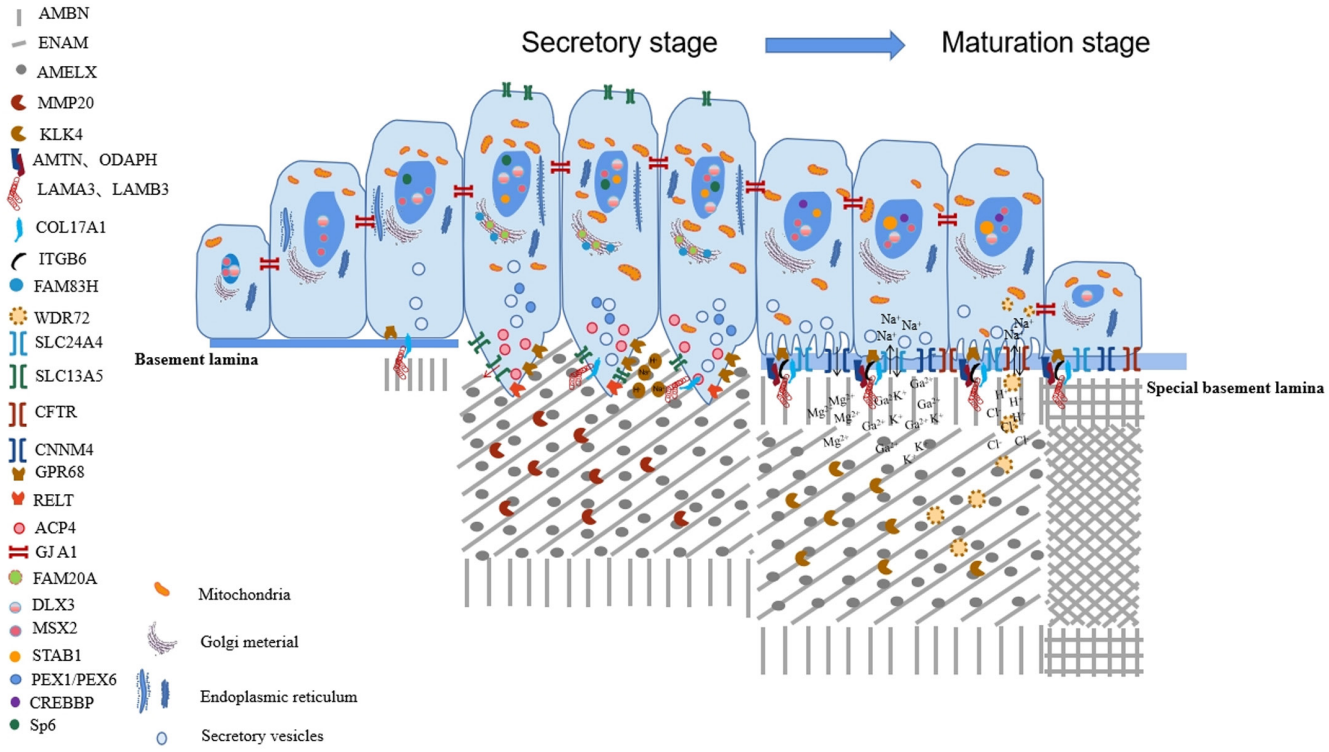

FIGURE 5 Schematic location of causative genes of nonsyndromic amelogenesis imperfecta (AI) and syndromic AI in different amelogenesis stage.

appearance (Lee et al., 2011) or snow-capped appearance with more radiographic enamel on the cusp tips than on the lateral and occlusal surfaces (Hu et al., 2012). The female *AMELX*-related AI cases present the variable enamel phenotypes from generalized thin and pitted enamel to vertical ridges with brown pigmentation, which turned out to be the difference between homozygous and heterozygous mutations in *AMELX* and the effect of skewed inactivated *AMELX* in X chromosome (Duan et al., 2019).

To sum up, the gene-specific enamel phenotypes could be one of the important indicators for diagnosing nonsyndromic and syndromic AI. It is recommended to pay attention to the general condition of AI patients to reduce the missed diagnosis of syndromic AI. Genetic testing is necessary to make a further molecular diagnosis. Overall, the increased understanding of genetic variants responsible for AI provides new insights into several cellular and extracellular biological processes critical for enamel formation, enables the clinicians to get a better understanding of isolated or syndomic AI and future improves the diagnosis and treatment level.

AUTHOR CONTRIBUTIONS

Jing Dong: Writing – original draft; writing – review and editing. **Wenyan Ruan:** Writing – original draft; writing – review and editing. **Xiaohong Duan:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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