The involvement of the *DLX3* gene in isolated or syndromic amelogenesis imperfecta

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Introduction

Amelogenesis imperfecta (AI) is a heterogeneous set of rare genetic diseases affecting enamel development. Clinical phenotypes of enamel can be described as:

1. **Hypoplastic:** quantitative defect of the enamel, thinner, pitted or striated, up to agenesis of the enamel
2. **Hypomineralized:** sub-mineralization making the enamel softer, rougher, and more colorful
3. **Hypomature:** relatively hard enamel but not translucent or even coloured

AI can be **isolated** or **syndromic**. Currently, more than 100 causative genes have been identified, including the *DLX3* gene. It is involved in two distinct entities of autosomal dominant inheritance:

- Hypomature AI with non-syndromic taurodontism known as type IV (OMIM # 104510)
- Trichodento-bone syndrome (TDO) (OMIM #190320), a form of ectodermal dysplasia with curly hair and bone abnormalities

The *DLX3* gene (17q21.33, three exons) encodes a transcription factor involved in osteogenic differentiation, and more specifically in the **development of the forebrain and craniofacial mass**.

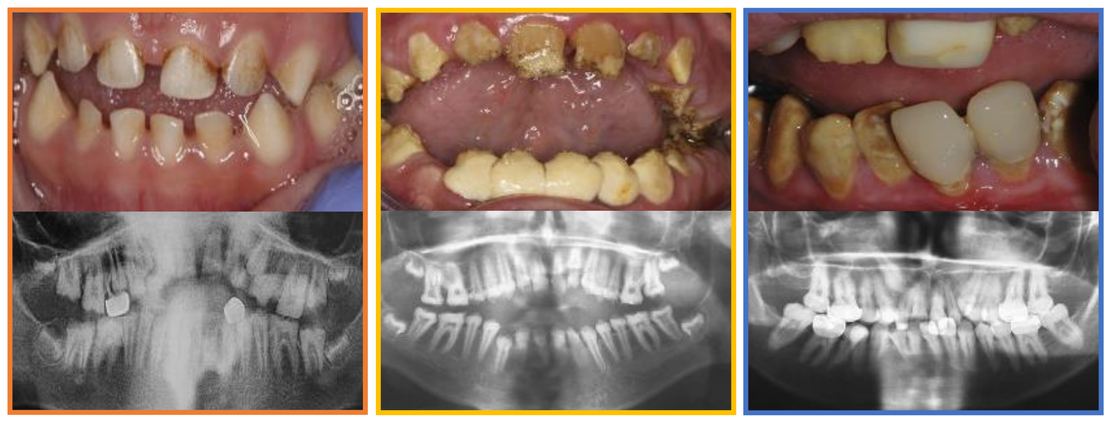

Figure 1 : Photos and X-rays depicting the different types of AI
From left to right: **hypoplastic**, **hypomineralized**, **hypomature**

Results

1. The NGS panel GenoDENT in the context of rare oral and dental diseases (Figure 2)

Individuals with AI can benefit from specific care in the O-Rares network including molecular diagnosis:

→NGS panel GenoDENT (Prasad *et al.*, 2016; Rey *et al.*, 2019)
v7 = 676 genes
→Exome sequencing

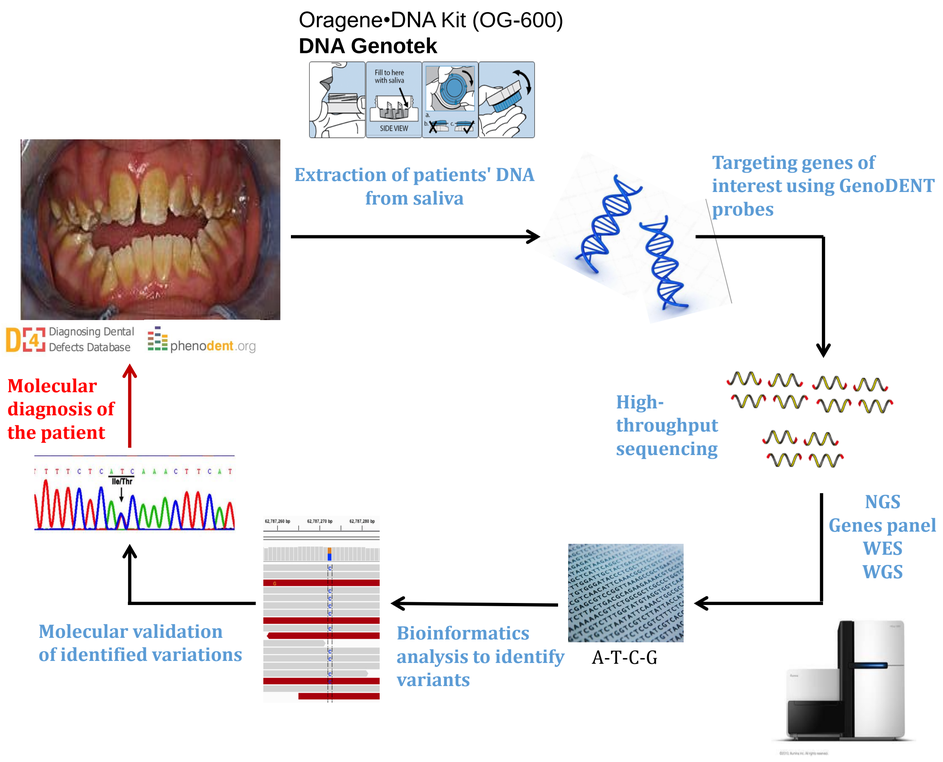

Figure 2: GenoDENT Panel Procedure
From patient care to diagnostic reporting

More than 500 individuals sequenced

2. Novel mutations identified in *DLX3*

We identified **five variations** (Figure 3 & Table 1), three of which were in 3 families with an isolated hypoplastic AI phenotype and two in 2 families with a syndromic AI phenotype. Clinically, the enamel is hypoplastic, thin with sometimes the presence of wells; the molars have a root morphological abnormality seen on radiographs called taurodontism (Figure 3).

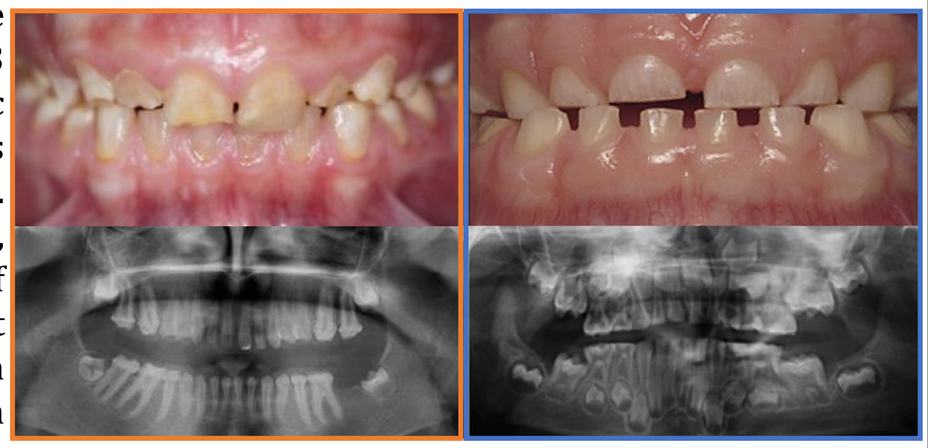

Figure 3: Photos and X-rays of patients with DLX3-related AI
Isolated AI (mutation c.537C>A, left) or syndromic AI (mutation c.561_562del, right)

Variant (c.)	Variant (p.)	Localization	Publication	Status	Effet of the mutation	Segregation	Phenotype
c.92C>G	p.(Thr31Ser)	Exon 1	Bloch-Zupan et al., 2023	heterozygous	missense	NA	Isolated AI
c.537C>A	p.(Asn179Lys)	Exon 3	Bloch-Zupan et al., 2023	heterozygous	missense	NA	Isolated AI
c.545C>T	p.(Ser182Phe)	Exon 3	No	heterozygous	missense	3 symptomatic carriers	syndromic (TDO)
c.561_562del	p.(Tyr188Glnfs*13	Exon 3	Dong et al., 2005	heterozygous	frameshift, STOP	3 symptomatic carriers	syndromic (TDO)
c.710A>G	(Tyr237Cys)	Exon 3	Bloch-Zupan et al., 2023	heterozygous	missense	NA	Isolated AI

Table 1: Variations in the *DLX3* gene (NM_005220.3) found in our cohort

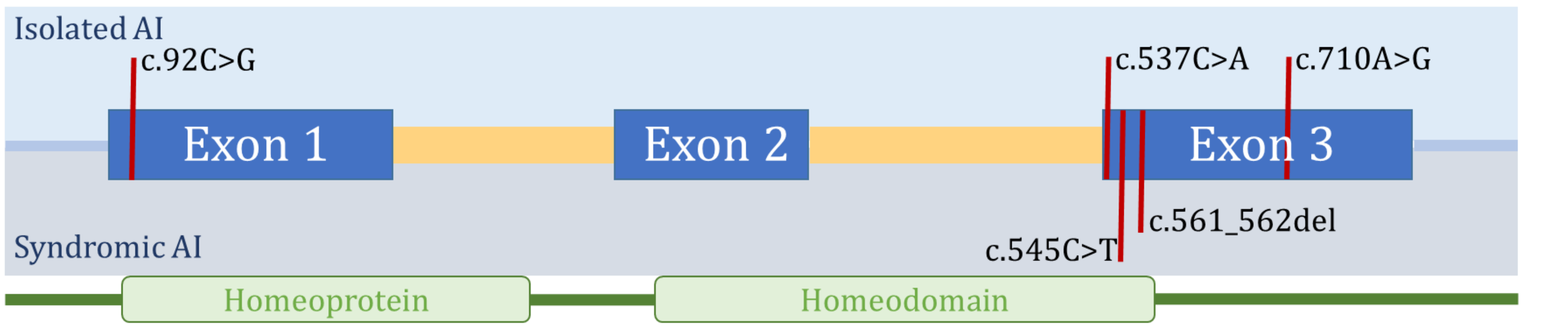

Figure 4: Schematic representation of the *DLX3* gene
Exons are shown in **dark blue**, introns in **yellow**, and UTRs in **light blue**. Major protein domains are shown below the gene, in **green**. The identified mutations are located in exons 1 and 3.

Conclusion

The use of diagnostic tools in molecular biology such as sequencing on a panel of genes and the exome has made it possible to identify **new genetic variants** involved in these hypoplastic AIs linked to *DLX3* and thus to **improve patient management**. AI with taurodontism and TDO could be two allelic diseases. Finally, if variants of unknown significance (VSI) are identified, they could be studied in **cell and/or organoid culture research** with a view to determining their impact and possibly reclassifying them as probably pathogenic (class 4) or pathogenic (class 5).

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