Ectopic mineralisation and tooth eruption defects related to *FAM20A/Fam20a* gene mutations

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Context and experimental strategies

The aim of this study is to define the natural history of a rare and handicaping dento-periodontal malformation (OMIM #204690) secondary to *FAM20A* mutations (for review: Nitavayardhana, Molecular Genetics Genomics 2020).This Enamel Renal Syndrome (ERS) combines tooth eruption failure, hypoplastic-aplastic amelogenesis imperfecta, gingival fibromatosis and ectopic mineralisation, unconstantly associated with nephrocalcinosis (De la Dure-Molla, Orphanet J Rare Diseases 2014). ERS requires detailed follow-up during growth and ends with heavy, painfull surgery and complex prosthetic rehabilitation in adults. (Mauprivez, Quintescence Int 2018). Our goal is to decipher some ERS physiopathological mechanisms to pave the way of less invasive treatments in the future.

The study compares these experimental data with the clinical, radiological and genetic parameters of patients at the Reference Centre. The ultrastructure of the continuously growing incisor of the Fam20a-/- mouse (Vogel, Vet Pathol. 2012) is studied using transmission electron microscopy, making it possible to trace the kinetics of amelar and peridental differentiation and mineralisation.

I. Retrospective analysis of ERS patient cohort (2006-2024)

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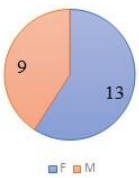
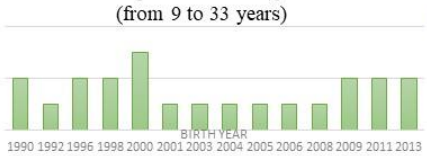
ERS population
n=22 in 16 families

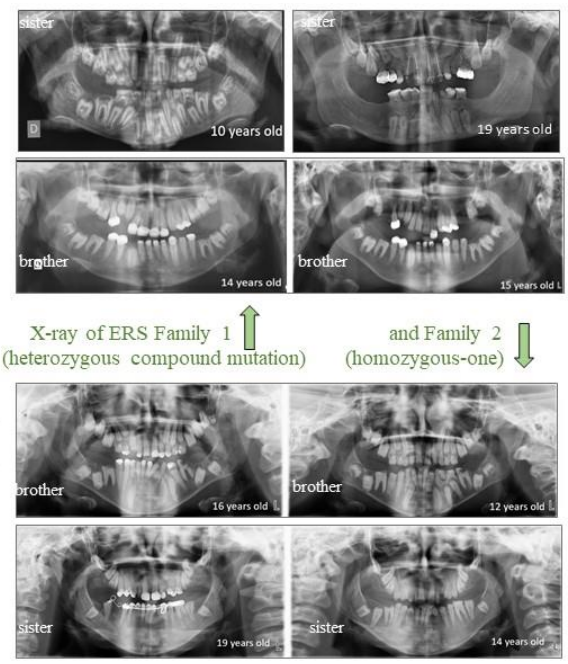


ERS patient's birth year
(from 9 to 33 years)

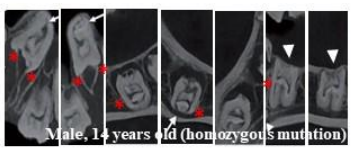


Cohort = 1/4 of published ERS cases

The cohort of ERS patient highlights a phenotypic heterogenity with different severities between and within the families, as illustrated here in the brother and sister of families 1&2.



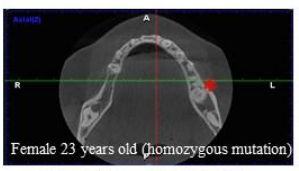
X-ray of ERS Family 1 (heterozygous compound mutation) and Family 2 (homozygous-one)



ERS Molar CBCT

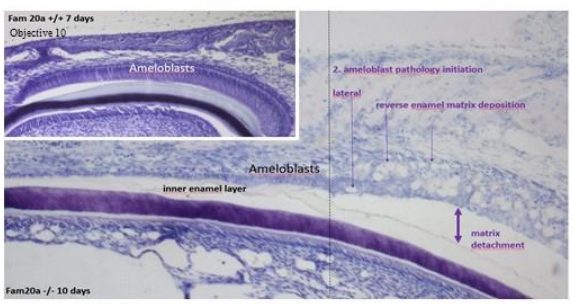
X-rays of the patients evidence different grades of:
- tooth impaction and adhesion with bone
- coronal resorption (white arrow head)
- intra-pulpal calcification
- root dilaceration (white arrows).

Interestingly, the fusion between tooth and bone is located at the coronal enamel *



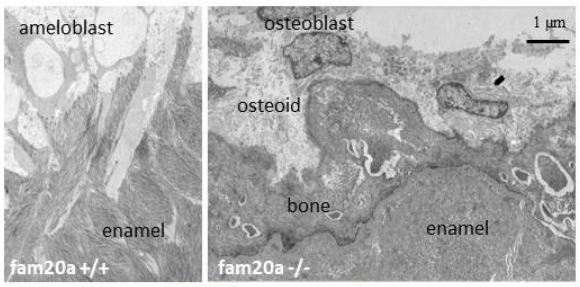
Mandibular ERS CBCT

II. Micro-analysis of fam20a -/- mice



Light microscopy of Incisor mouse enamel

- *Enamel organ and ameloblasts are desorganised*
- *Amelogenesis process stops*
- *Osteoblasts secrete bone onto enamel*



TEM of mouse enamel

Discussion and perspectives

This kinetic description of ERS in the Rothschild reference centre cohort and in its animal model (*Fam20a*-KO mice) gave some clues on the natural history of the disease, which has not been described to date. This layed the foundations for an interception strategy (separating enamel and bone to unlock tooth eruption) to share and develop within the collective dynamics of the O-Rares network.