

# From mouse to patient

## Non-syndromic rare oral and dental diseases

### Are they really non-syndromic?

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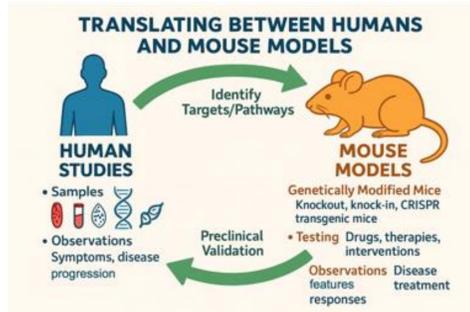
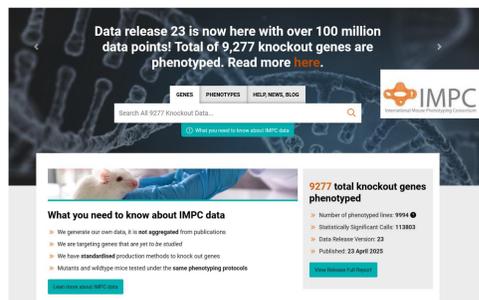
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## Mouse models are good models to study tooth development/anomalies in rare diseases



## International Mouse Phenotyping Consortium (IMPC) <https://www.mousephenotype.org>

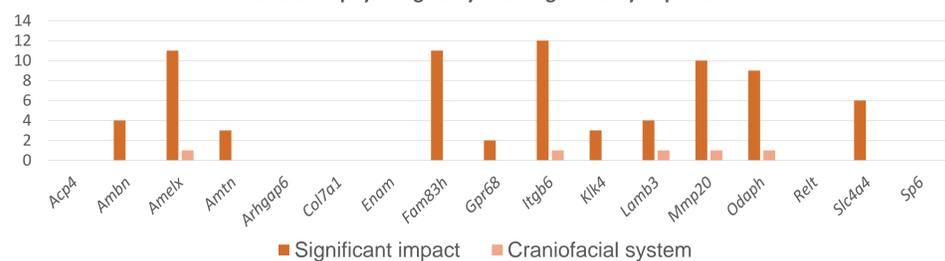
➢ 17 genes of interest (non-syndromic amelogenesis imperfecta): **ACP4, AMBN, AMELX, AMTN, ARHGAP6, COL7A1, ENAM, FAM83H, GPR68, ITGB6, KLK4, LAMB3, MMP20, ODAPH, RELT, SLC24A4, SP6**

➢ Analysis of the phenotypic data from 13 mouse models inactivated for the genes of interest, provided by the IMPC.

- **Arhgap6, Col7a1, Relt, Sp6** – no mouse models generated
- **Acp4, Enam** – no significant impact in either of the 24 systems tested
- Phenotypes are described using standardized mammalian phenotyping ontology terms developed by the Mouse Genome Informatics group
- Presence of associated extra-oral symptoms

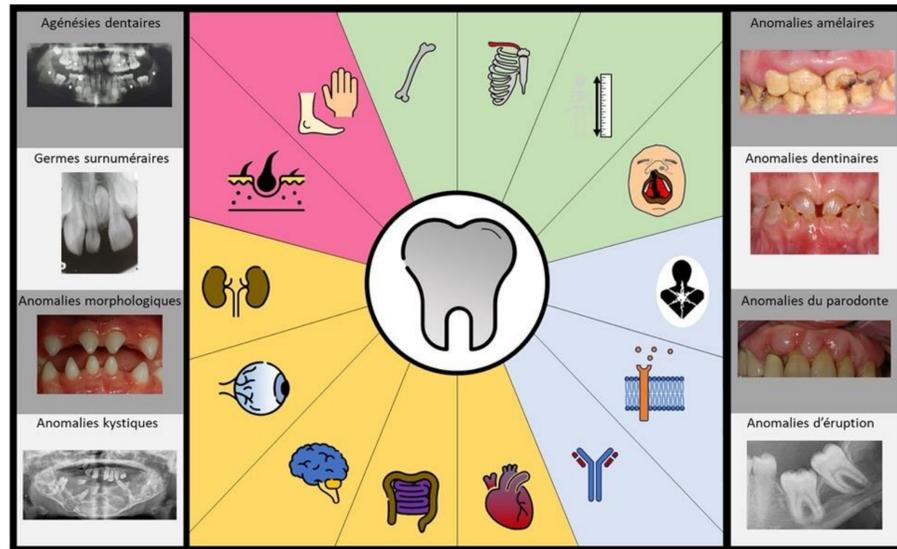
## Preliminary results

Number of physiological systems significantly impacted



SYSTEM/GENE	Ambn	Amelx	Amtn	Fam83h	Gpr68	Itgb6	Klk4	Lamb3	Mmp20	Odaph	Slc4a4
Adipose tissue											
Behavior/neurological											
Cardiovascular system											
Craniofacial											
Digestive											
Embryo											
Endocrine system											
Growth/size											
Hearing/vestibular/ear											
Hematopoietic system											
Homeostasis/metabolism											
Immune system											
Integument system											
Limbs,digits,tail											
Liver/biliary system											
Mortality											
Muscle											
Nervous system											
Pigmentation											
Renal/urinary system											
Reproductive system											
Respiratory system											
Skeleton system											
Vision/eye											

## Dental anomalies are participating to the clinical synopsis of more than 1000 rare diseases



La dent : un marqueur d'anomalies génétiques du développement (The tooth: A marker of developmental abnormalities), de La Dure-Molla M, Gaucher C, Dupré N, Bloch Zupan A, Berdal A, Chaussain C. Med Sci (Paris). 2024 Jan;40(1):16-23.

Dental anomalies are diagnostic clues for rare diseases. Teeth abnormality can be isolated or may be associated with other symptoms in other organs or systems, which leading us to the diagnosis of syndromic diseases.

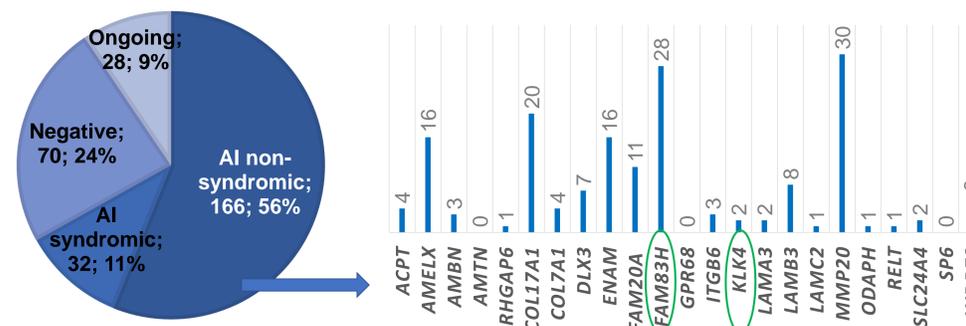
## Amelogenesis imperfecta (AI) : rare oral genetic diseases affecting the development of enamel



- prevalence varies from 1/700 to 1/1400
- modes of inheritance - autosomal dominant (AD), recessive (AR) or X-linked
- more than 70 genes are involved
- different forms
  - hypoplastic - quantitative defect: thin or even absent, hard, pitted or striae enamel
  - hypomineralized - qualitative defect: enamel of normal thickness, softer, intrinsic yellow-brown and rapidly cleaves
  - hypomature - qualitative defect: enamel of normal thickness, relatively hard, from chalky white to yellow-brown



## GenoDENT PANEL – NGS (next-generation sequencing) - 296 AI patients



## Reviewing in details patient's medical history

### Fam83h

**FAM83H NM\_198488.5: c.1072G>T hzt**

**KLK4 NM\_004917.4:c.212A>G hnz**

### Klk4

11 Significantly impacted by the knock-out

- ⚡ Homeostasis/metabolism
- 🧠 Reproductive system
- 🛡️ Immune system
- 👤 Endocrine/exocrine gland
- 👤 Integument
- 🍲 Liver/biliary system
- 👤 Hematopoietic system
- 🧠 Behavior/neurological
- 👤 Mortality/aging
- 👤 Cardiovascular system
- 👤 Renal/urinary system



AD Hypomineralized AI + Nephrocalcinosis

3 Significantly impacted by the knock-out

- 🛡️ Immune system
- 👤 Respiratory system
- 👤 Hematopoietic system



AR Hypomature AI + kidney stones + diabetes + infections