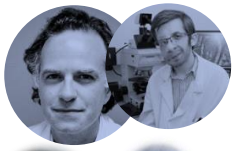
Genetics
From Phenotype to Gene to Cellular Network

Ariane Berdal team

Complex disease
Pathophysiology

Rare
to
Common
diseases

In silico disease (gene) selection

Dental-eye-kidney epithelial rare diseases

Phenotype-related genetic variants

Lrp2, Cubn, cldn19, Vsp13b, Fam20A, Ocrl, Apc

Cohort, Biobank

Animal models

Cubn-cKO; Lrp2-cKO; Cubn/Lrp2-cKO; Cubn-D ; FAM20A-KO

Genetic variants involved in molecular pathways

Exomes, proteomes, phospho-proteomes

Pathways involved in cellular networks

Interactome, metabolomes

Cellular Networks in systems pathobiology

Tooth decay/Enamel defects
Myopia – Retinal degeneration
Renal Ectopic calcification/Proteinuria

Renata Kozyraki team

Inserm Imagine Institute
Team V.Cormier-Daire
(M.De la Dure-Molla)
Team C.Antignac

CRC
Team F. Behar-Cohen
Team P. Crambert

CNRS Plateform PISSARO
Rouen University
P. Cosette

University British Colombia M MacDougall
COFECUB/EcosNord AC Acevedo

Inserm UMRS 1155 Tenon
C. Chatziantoniou

Genetics

Cohorts

collection

follow-up

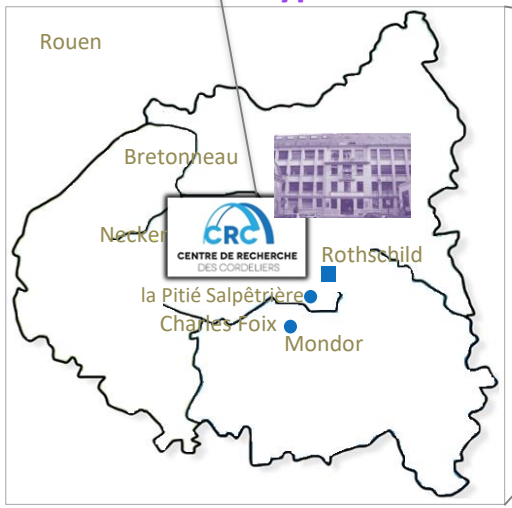
in silico

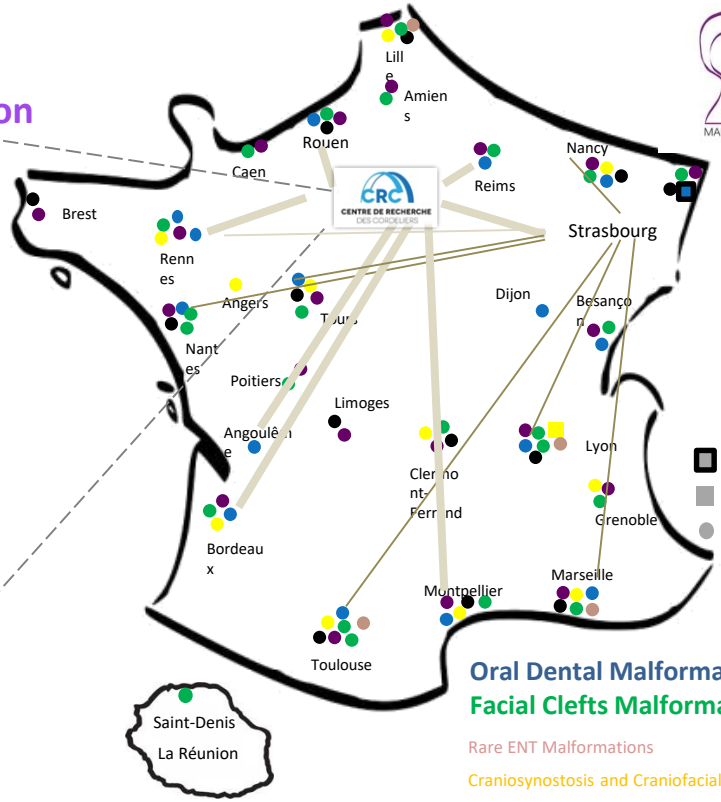
studies

Res

Réseau Environnement Santé

Molar Incisor Hypomineralization





ERN CRANIO

FILIÈRE SANTÉ MALADIES RARES TeteCou

MALFORMATIONS RARES TÊTE COU DENTS

50. 000 cases

Oral-Dental Rare diseases

Oral Dental Malformations ORares

Facial Clefts Malformations MAFACE

Rare ENT Malformations

Craniosynostosis and Craniofacial

Pierre Robin congenital sucking / swallowing disorders

Neurological and Craniofacial Vascular Anomalies

French Health Ministry

European Reference Network

CAPES CAMPUS FRANCE campusfrance.org

CRMR Rothschild 2007-12-17

CRMR Necker 2007-12-17

CCMR la Pitié-Salpétrière 2017

CCMR la Pitié Mondor Rouen 2017

Filière TETECOU Necker 2015

Rés 2015

ERN CRANIO 2017

COFECUB 2013-2016 / 2018-2020

EcosNord 2012-2015

Genetics

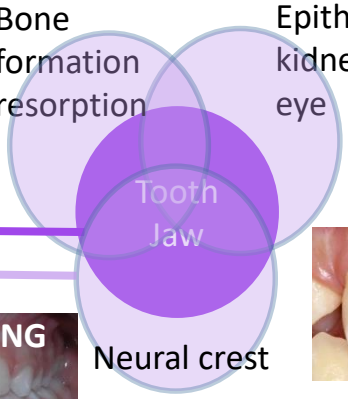
In silico Phenotype-genotype analysis & group definition

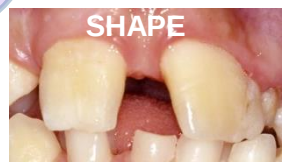
Rare Disease update (900 entities 2018)
Classification: pathophysiological groups
Nosology Data mining Diagnosis decision tree

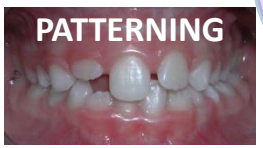
Mutation identification
-**Individual** (hypothesis issued from CRC bioresearch)
Amelogenin*, FAM20A*, claudins 16,* 19*, cubilin & megalin

-**Multiple (DNA array, exomics…)**
Whole Tooth-array 274 genes (40% diagnosis*)
Speific tooth array included in syndromic panels

Concrete clinical and scientific outputs
-**Diagnosis , Treatment**
-**Dental Omics** (specific and shared wiht other systems)
-**Annotated Biobanks** (tooth tissues, gingival cells…)







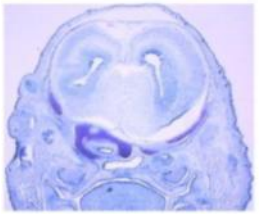
De la Dure Molla 2018, Yamaguti 2017, Friedlander 2017,Baudon 2016, Beres 2016, Marchac 2016, Prasad 2016, Kadlub et al 2016, 2015, 2014, 2013, Gordon 2015, Heikinheimo 2015, Coudert 2015, Bhatia 2015, Bacrot 2015, De la Dure-Molla 2014

Genetics

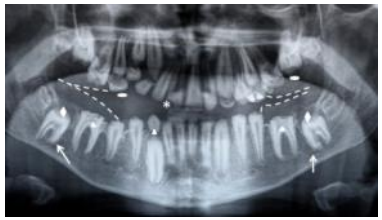
Pathophenome Association and cellular pathways

Oral

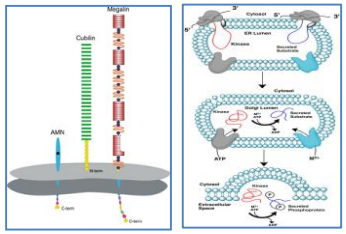
Enamel defects
Oligodontia
Tooth eruption



Cases et al., 2013

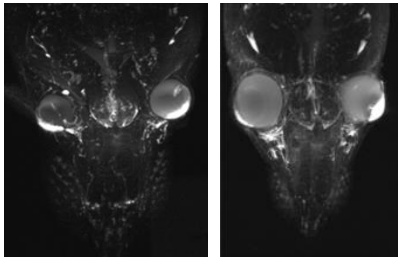


De la Dure-Molla et al., 2014
Lignon et al., 2017



Eye

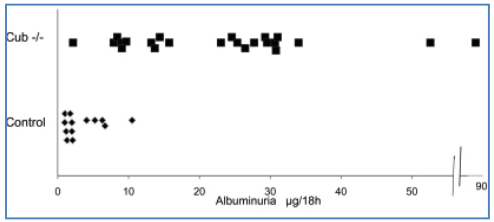
Severe myopia
Retinal detachment
Glaucoma



Cases et al., 2015
Cases et al., 2017

Kidney

Pathobiochemistry
Nephrocalcinosis
Renal Defects



Amsellem et al., 2010
Storm et al., 2013.

Eye-Renal-Oral Syndromes

DBS, IGS, ERS (FAM20A), Cohen, FPHHN, KS-2, Lowe, FAP, OSR

Pr Ariane Berdal
Head of the O-Rare Constitutive Site at Rothschild Hospital- Paris

Dr Muriel de la Dure Molla
Co-Head of the O-Rare Constituent Site at Rothschild Hospital -Paris

The Reference Centre was labelled by the National Plan for Rare Diseases 1 (PNMR1) as a constituent site of the CRMR MAFACE "Rare facial and oral cavity defects". Then, it joined the TETECOU Rare Disease Health Network as part of PNMR2, and also, the European Craniofacial Anomalies and ENT Disorders network.
In 2017, the National Labelling Campaign for Rare Disease Reference Centers enabled Rothschild Hospital to become a Reference Center for Rare Oral and Dental Diseases (O-Rare) - Constitutive Site.

The CRMR provides oral management of many rare, isolated (PFE Primary Failure of Eruption) and syndromic diseases, bone diseases (osteogenesis imperfecta, dermatological diseases (incontinentia pigmentia, ectodermic dysplasia), mucous membrans diseases (neurofibromatosis, Ehler-Danlos), muscular diseases, neurosensory diseases or malformations (Steiner muscular dystrophy, cleidocranian dysplasia).

From antenatal period to birth, in children, adolescents and adults, these pathologies require specialized dental care, involving all pediatric and adult dental disciplines throughout life. In the absence of a consensus of treatment, the CRMR has built both pediatric and adult therapies through the interaction of a multidisciplinary team allowing functional, morphological and aesthetic oral rehabilitation.
The geographical proximity of the CRMR in Paris to CRMRs sharing the management of common syndromic diseases (CRMR MAFACE, CRANIOST, OSCAR, MAGEC located at Necker Hospital) has enabled advanced multidisciplinary consultations and closed link were established to advance management and research.

The CRMR has thus acquired diagnostic expertise for mucosal, bone, muscular, sensorial and dental clinical phenotypes and their functional disabilities. The CRMR published the first international classification of rare oral malformations: “Classification of genetic dental disorders”.

The CRMR is also concerned with the patients’ economical and life-quality issues. Research works are carried out by the CRMR to support the need for recognition of oral disability and its extremely heavy financial burden for the patients (ORAQL study, steps and actions with the CNAM and MDPHs).

The CRMR relies on strong research teams with expertise in biology, genetics, engineering and biomaterials to support translational research and to find new therapeutic perspectives for patients.

Inserm
La science pour la santé
From science to health

Centre de Référence
O-RARES
PARIS - Rothschild

Rare Oral and Dental Diseases
Paris Rothschild Reference Center

Coordinator: Prof. Ariane Berdal,
Coordinator Assistant: Pr Muriel de La Dure - Molla

Filière Santé Maladies Rares
TeteCou
MALFORMATIONS RARES TÊTE COU DENTS

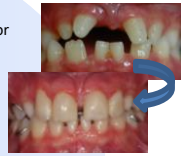
The O-Rare Paris Rothschild CRMR was created by its label in 2007. It has a dual objective: the diagnosis and therapeutic management of rare anomalies in the oro-facial sphere. It brings together a multidisciplinary team of experts: pediatric dentist, oral medicine specialist, dentofacial orthopaedics specialist, oral surgery and implantology specialist and maxillofacial surgeons.

Dental anomalies are a sign of the appeal of many genetic diseases

A National Network

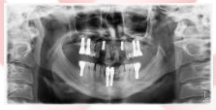
Our missions

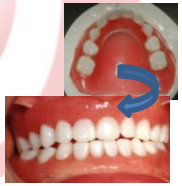
Facilitate diagnosis and define a strategy for therapeutic, psychological and social support
Define and disseminate care protocols, in conjunction with the HALDE Coordinate research work and participate in epidemiological surveillance
Participate in training and information activities for health professionals, patients and their families
Lead and coordinate networks of health and medico-social correspondents
Be privileged interlocutors for guardians and patient associations



Rare oral and dental diseases

Genetic diseases affecting the Orofacial sphere can be isolated or syndromic. The development of the face, jaws, tooth and its supporting tissues form a continuum. These rare congenital malformations affect one or more of these structures in a variable way: the skeletal bone, soft tissues, teeth and their supporting tissue including alveolar bone, as well as the vascularization and innervation of all these structures. Not all of them express themselves from birth. More than 1000 pathologies have been identified to date.





Région	Syndromes
Faciale	1080
Orale	837
Buccale	677
Dentaire	535

*London Dysmorphology Database, Oxford Medical Databases,Oxford University Press, version 2.2, 2000.

Our Research Projects

CLINICAL RESEARCH
Nosology of Genetic Dental Diseases
Definition of Dental Abnormalities (international consensus)
Quality of life
Genotype / Phenotype characterization (oligodontics, IAH)

FUNDAMENTAL RESEARCH
FAM20A and mineralization pathology
Craniofacial pathophysiology of IO
Matrisone's characterization of NCMs
Embryological origin of mucous membranes and craniofacial tissues

Family associations

Patient associations are key players in the network. Our annual meetings allow us to be as close as possible to families to answer their questions and concerns.

CRMR in a few figures

500 Patients in active line
2000 Annual consultations
100 Pathologies covered
16 Centers of expertise at national level
8 Partners research laboratories

Our partners