European Commission
Directorate-General for Health and Food Safety (DG SANTE)

ITHACA

ITHACA Board Meeting

2020 December 10th – 12th

Satellite Meetings : Friday Dec. 11th

WG 7 Research

From 9 to 10:50 AM

European Reference Networks

(WG7) Work Groups / Satellite Meetings : Friday December 11th

	WG7 Research M Tartaglia	SPEAKER PM contact : Anne Hugon
9h00	EJPRD & ERN fellowship Call Organization of candidate selection Clinical Bursaries : Sponsoring of workshops or clinical Research with Ithaca. Use calls and involve trainees	Marco Tartaglia, F. Clementina Radio
9h20	**Follow up on research collaborative Calls** Syntelencephaly cohort Pai/OAFNS syndrome IQSEC2 related phenotype Clinical-research-QRICH1 *DLG4 (not in ITHACA list)* *POGZ mutations (not in ITHACA list)*	Alinoe Lavillaureix Laurence Faivre Caterina Lo Rizzo Zeynep Tumer Zeynep Tumer Agnese Feresin
10h00	Orphanet news on productions of rare syndromes	Gemma Milman
10h20	Next expected deliverables and projects for the group	Marco Tartaglia, F. Clementina Radio
10h40 - 10h50	New members, Looking for new co-deputy chair	All attendees

European Reference Network
for rare or low prevalence complex diseases
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Calls and Mangement

EJPRD & ERN fellowship Call

- EJPRD consortium brings over 130 institutions (including all 24 ERNs) from 35 countries to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation in the rare disease field.
  The centralised collaboration between different stakeholders aims to speed up advances rare disease research for the benefit of patients.
- Training activities are supported by initiatives and competitive calls under the EJPRD's Pillar 3.

ERN fellowship Call

- The overall objective is to deliver research training programs for the European Reference Networks (ERNs) focusing on cross-cutting and overarching research themes. The training activities comprise fellow exchanges and workshops. The primary audience are healthcare professionals from ERNs interested or active in research.
- Target audience: Academic clinicians and researchers involved in ERNs.

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ERN fellowship Call 2020

EJP RD: CALLS IN THE ERN INTERNAL TRAINING AND SUPPORT PROGRAM

RESEARCH MOBILITY FELLOWSHIP

MAIN FEATURES

- Financially support young investigators to undertake short scientific visits (secondments) fostering specialist research training outside their countries of residence and within one of the ERN host institutions
- The research mobility fellowships cover stays of 4 weeks up to 3 months
- Applicants' profile:
  - PhD students with a minimum of one year of research experience OR
  - Physicians having finished their first year of specialist training
  - Affiliated to an ERN institution
- 2 calls per year: Next call for Research mobility fellowships will be open from **1 October until 13 November 2020**
- Contacts:
  fellowships@erknet.org;
  genturis@radboudumc.nl

RESEARCH TRAINING WORKSHOP

MAIN FEATURES

- Identify the most suitable topics for the organization of research training workshops with a cross-ERN added value
- Training topics may include: innovative research methodologies, diagnostic research topics, interdisciplinary treatment approaches (e.g. gene therapy, transplantation)
- Financing covers the organization of a 2 days workshop (e.g. venue, catering & travel and accommodation of speakers and participants)
- Applicant's profile:
  - Affiliated to an EJP RD beneficiary institution *or*
  - Affiliated to ERN-Full Member *or* ERN-Affiliated Partner institution
- 2 calls per year: Current call is **open from 31 August until 12 October 2020 (apply now!)**
- Contacts:
  RareEndoERN@Lumc.nl;
  sanja.hermanns@med.uni-tuebingen.de

The aim of the call is in compliance with the vision and goals set by the **International Rare Diseases Research Consortium (IRDiRC)**, which fosters international collaboration in rare diseases research

EJP RD

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ERN fellowship Call 2020

- Manage EJP-RD calls with a candidate selection jury (members TBD)
- Research mobility fellowships are meant to cover 4 weeks to 3 months within 18 months from the application approval (COVID-19 related extension). The exchange will be accomplished exclusively within member institutions of the same ERN or between member institutions of different ERNs.
- Fellowship exchanges can only be facilitated between ERN full members or ERN affiliated partners. Their travel and accommodation expenses will be covered, up to fixed maximum amounts.
- Define the selection criteria and evaluation scale
  - Strength of the proposed research/training program
  - Applicant's qualifications (Early-career, post-doctoral, other?)
  - Mentor's qualifications
- Jury's volunteers
- HCPs available to guest the fellows (maximum number of trainee, activities' plan)

- Bursaries: Sponsoring of workshops or clinical research within ITHACA (about 30,000€ for each workshop)

- New calls in 2021: use calls and involve trainees
- Strengthen the link with WG8

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Research collaborative Calls

- 10/12/2020 – Description of a patients 'cohort with homozygous or compound heterozygous mutations in CDK10 in order to better delineate the clinical spectrum and the natural history of Al Kaissi syndrome.
- 02/12/2020 – Search for patients with a deletion of the first 2 non-coding exons of the RAI1 gene
- 30/11/2020 – FOREIGN (FOSL2-related signs)
- 30/11/2020 – Search for patients with biallelic variants in genes implicated in the ufmylation
- 24/11/2020 – KMT2B-related disorders without dystonia
- 16/11/2020 – Search for patients with de novo variants in DCAF15
- 12/11/2020 – KLHL11 pathogenic variant in patients with lichen planus, abnormalities of the nails and tumour proneness
- 10/11/2020 – Phenotype-genotype study of TAF2
- 09/11/2020 – Phenothype-Genotype relationships in 3q29-microduplication syndrome
- 02/11/2020 – De novo missense variants in EIF3I cause a novel neurodevelopmental disorder with midline brain defects and skeletal abnormalities.
- 28/10/2020 – Implication of missense variants in the NSD1 gene in Sotos-like phenotype
- 27/10/2020 – CAMK2A-related neurodevelopmental disorder
- 26/10/2020 – Osteopathia striata with cranial sclerosis – A further insight
- 20/10/2020 – Expanding the phenotype related to de novo missense variants in HNRNPH2
- 05/10/2020 – A novel X-linked syndromic neurodevelopmental disorders associated with WDR44 pathogenic variants
- 29/09/2020 – RAB10: a candidate gene for a severe neurodevelopmental syndrome
- 29/09/2020 – B4GALT5 as potential candidate gene for a novel sphingolipid disorder.
- 24/09/2020 – Clinical and molecular characterization of a novel MYCN related syndrome – A mirror phenotype and molecular of the Feingold syndrome.
- 27/08/2020 – SCA2 in children
- 19/08/2020 – Functional studies of variants in RBM10
- 17/08/2020 – Lysosomal Storage and Albinism Due to Effects of a De Novo CLCN7 Variant
- 06/07/2020 – CHAMP1 Clinical Spectrum (MRD40 – OMIM 616579)
- 26/06/2020 – Syntelencephaly cohort
- 23/06/2020 – QRICH1 related disorders
- 22/06/2020 – Further delineate the clinical and molecular spectrum of recessive pathogenic SLC6A9 variants
- 09/06/2020 – Neurodevelopmental delay associated with KDM6B gene variants: description of the clinical and neurological phenotype
- 26/05/2020 – Search for patients with Pai/OAFNS syndrome
- 05/05/2020 – YY1 related disorder : clinical phenotype, neuropsychological profile, brain MRI characteristics and epigenetic signatures
- 05/05/2020 – CDK13 related disorder : clinical phenotype, neuropsychological profile, brain MRI characteristics and epigenetic signatures
- 05/05/2020 – Search for patients with Wildervanck syndrome
- 28/04/2020 – Understanding the New BRD4-related Syndrome

Call for collaborative clinical research on developmental disorders

- 34 Research collaborative Call since april 2020
- Selection process
- Publication

The principle behind this initiative is simple:

ITHACA

Call for collaborative clinical research on developmental disorders

These calls for collaborative projects typically aim to rapidly build up consistent clinical series for rare monogenic disorders, in order to better delineate the clinical spectrum and natural history of recently identified entities in the field of ITHACA. The call will be disseminated to the mailing list of ITHACA and will be posted on the web site, with regular reminders.

ITHACA Team will follow up the success of the call during the year that follows its publication. Any publication issued from this call should acknowledge ITHACA.

- Short title of the study:
- Targeted gene(s)/phenotype/disorder under study (to be quoted in the newsletter(s)) (OMIM # or ORPHA code)
- Summary (1000 letters max):
- Coordinating clinician;
- Institution (dept, hospital, City);
- Contact email:
- Specific requirements beyond clinical data and genotype data sharing:
  1- Re-analysis of DNA samples: Y/N
  2- Resampling of patients: Y/N
  3- Linked to a translational/basic research project? Y/N

- ✓ Any ITHACA member can submit a call for collaboration on a gene, a group of functionally related genes, a CNV…
- ✓ The call is forwarded to the entire network and remains visible for 6 months.
- ✓ We will limit calls to 2 genes per applicant per year (can be more than 2 per HCP, of course !)
- ✓ These calls are not necessarily based on fundamental or translational research, but assume that the project leader already has at least 2 or 3 families to start the work.
- ✓ The project leader is committed to bring this work to completion (one publication), and to keep the ITHACA ExCom informed of the progress of the work.
- ✓ ITHACA's role as facilitator will be highlighted in the acknowledgements in the article.
- ✓ This type of article could be furthermore entrusted to young geneticists (as part of our collaboration with the European group).
- ✓ You will find the submission template on the ECP Platform, or here : please complete it according to the established criteria and send it back to : alain.verloes@aphp.fr and coordination@ern-ithaca.eu

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Follow up on research collaborative Calls

Call for collaborative clinical research on developmental disorders

1. **Syntelencephaly cohort** **Alinoe Lavillaureix**
2. **Pai/OAFNS syndrome** **Laurence Faivre**
3. **IQSEC2 related phenotype** **Caterina Lo Rizzo**
4. Clinical-research-QRICH1 Zeynep Tumer
5. DLG4 (not in ITHACA list) Zeynep Tumer
6. **POGZ mutations (new)** **Agnese Feresin**

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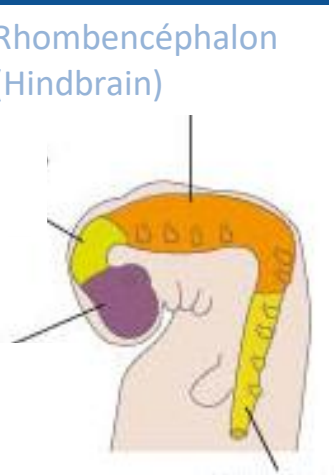
Holoprosencephaly
Syntelencephaly
DISP1

Alinoë Lavillaureix
Clinical Genetics (Pr Sylvie Odent) CHU Rennes
« Genetics of Development Related Pathologies »
Valérie Dupé & Marie de Tayrac
UMR 6290 CNRS France

Holoprosencephaly and midline defects

Holoprosencephaly (HPE):

- Incomplete cleavage of the forebrain
  - Between the 18th and 28th day of gestation
- Craniofacial and eye defects



Genetic Factors: *SHH signaling deficiency*

French cohort = unique

French National Reference Center
> 2000 Patients
Lab diagnosis (University Hospital)

Experts:
Clinical diagnosis (Pr Sylvie Odent)
Molecular diagnosis (Dr Christele Dubourg)
Bioinformatics (Dr Marie De Tayrac)
Functional studies (Dr Valérie Dupé)

CENTRE DE REFERENCE
Anomalies du développement
et syndromes malformatifs

CHU Rennes

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SHH: familial midline defects

p.(Tyr158*)

Odent et al.
1999

Arhinia

Alobar **HPE**

Growth failure, microcephaly, **hypotelorism**, mild ID, single median incisor, corpus callosum dysgenesis

Growth failure, microcephaly (-7DS), choanal stenosis, pituitary hypoplasia

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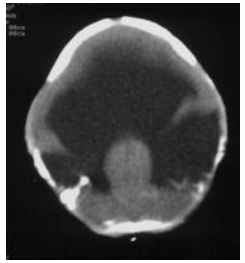
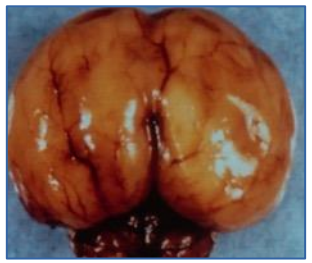
Brain, Facial and Eye anomalies



Alobar HPE

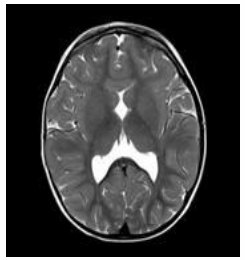
unique ventricule



Semilobar HPE

incomplete

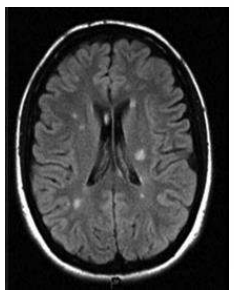
interhemispheric scissure



Lobar HPE

complete scissure

non-separation of frontal cortex on the midline



Microform

Complete separation of cortex

Facial anomalies :
cyclopia,
proboscis

Facial anomalies :
hypotelorism,
microphtalmia,
cleft lip and palate

Facial anomalies :
coloboma
epicanthus
single solitary
median central
incisor

phenotypic heterogeneity

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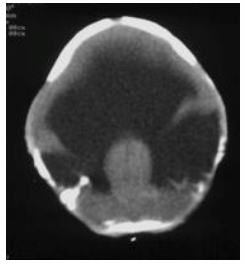
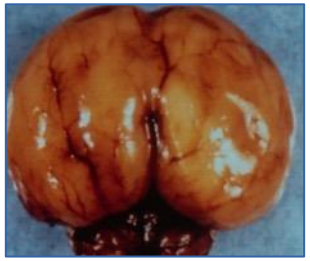
Syntelencephaly = Midline interhemispheric fusion (MIH)



Alobar HPE

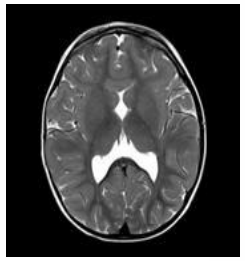
unique ventricule



Semilobar HPE

incomplete

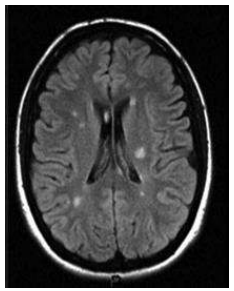
interhemispheric scissure



Lobar HPE

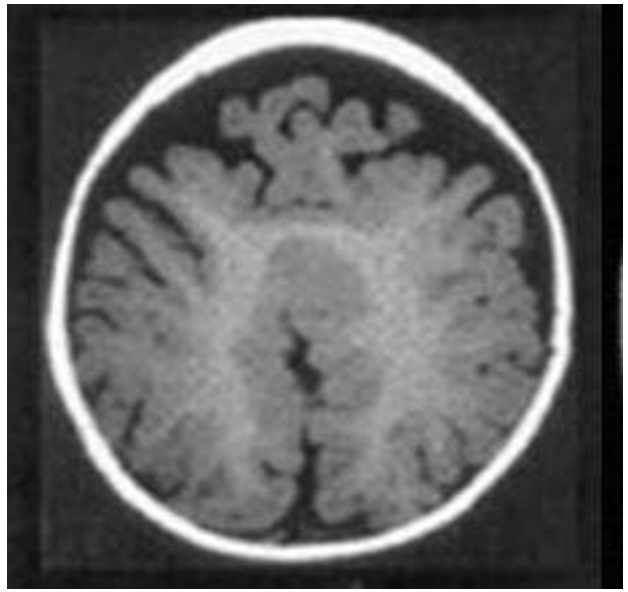
complete scissure

non-separation of frontal cortex on the midline



Microform

Complete separation of cortex



Syntelencephaly

hemispheric fusion does not occur at rostral forebrain but rather across posterior frontal region

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Syntelencephaly = Midline interhemispheric fusion (MIH)

Syntelencephaly: MRI appearance

Axial T1-weighted inversion recovery (IR) sequence shows **absence of septum pellucidum with fusion of the cingulate gyrus** (white arrow) (A) and continuous white matter across middle part of interhemispheric region (B). Sagittal T1-weighted IR sequence (C) with **absence of midbody of corpus callosum** (black arrows) and presence of genu and splenium (white arrows).

Arundeep Arora et al. Neurology 2012;79:e86

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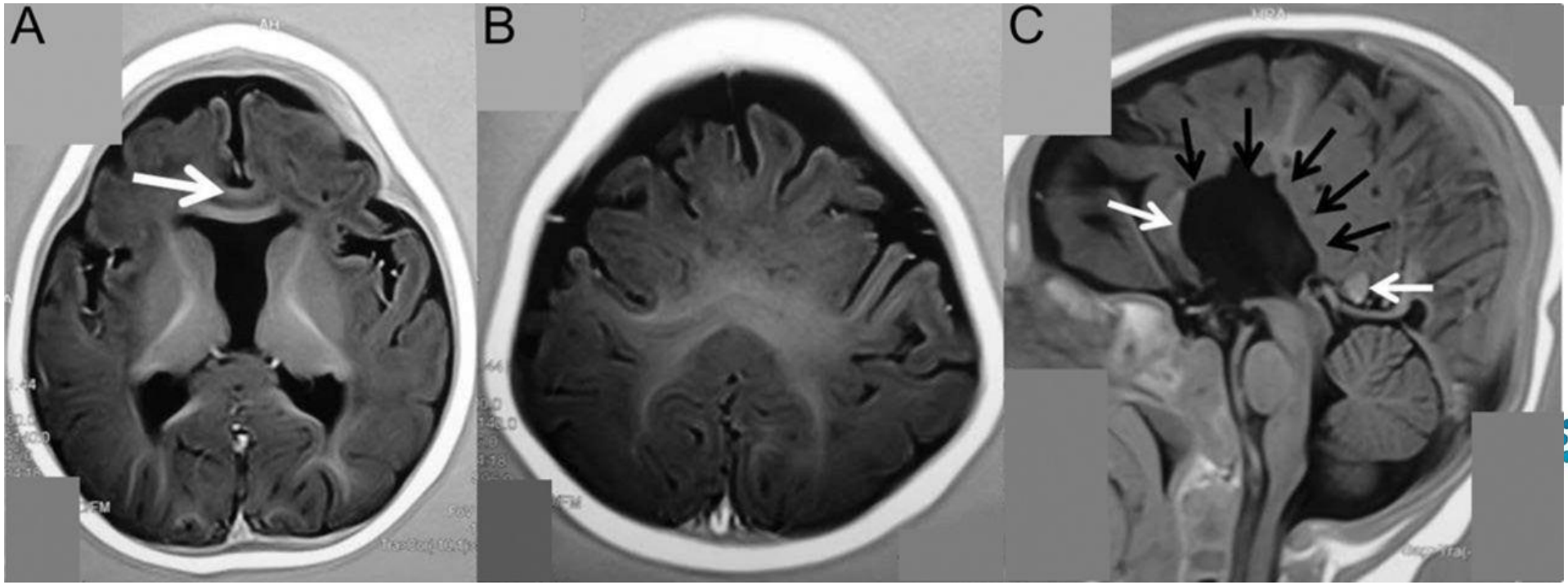
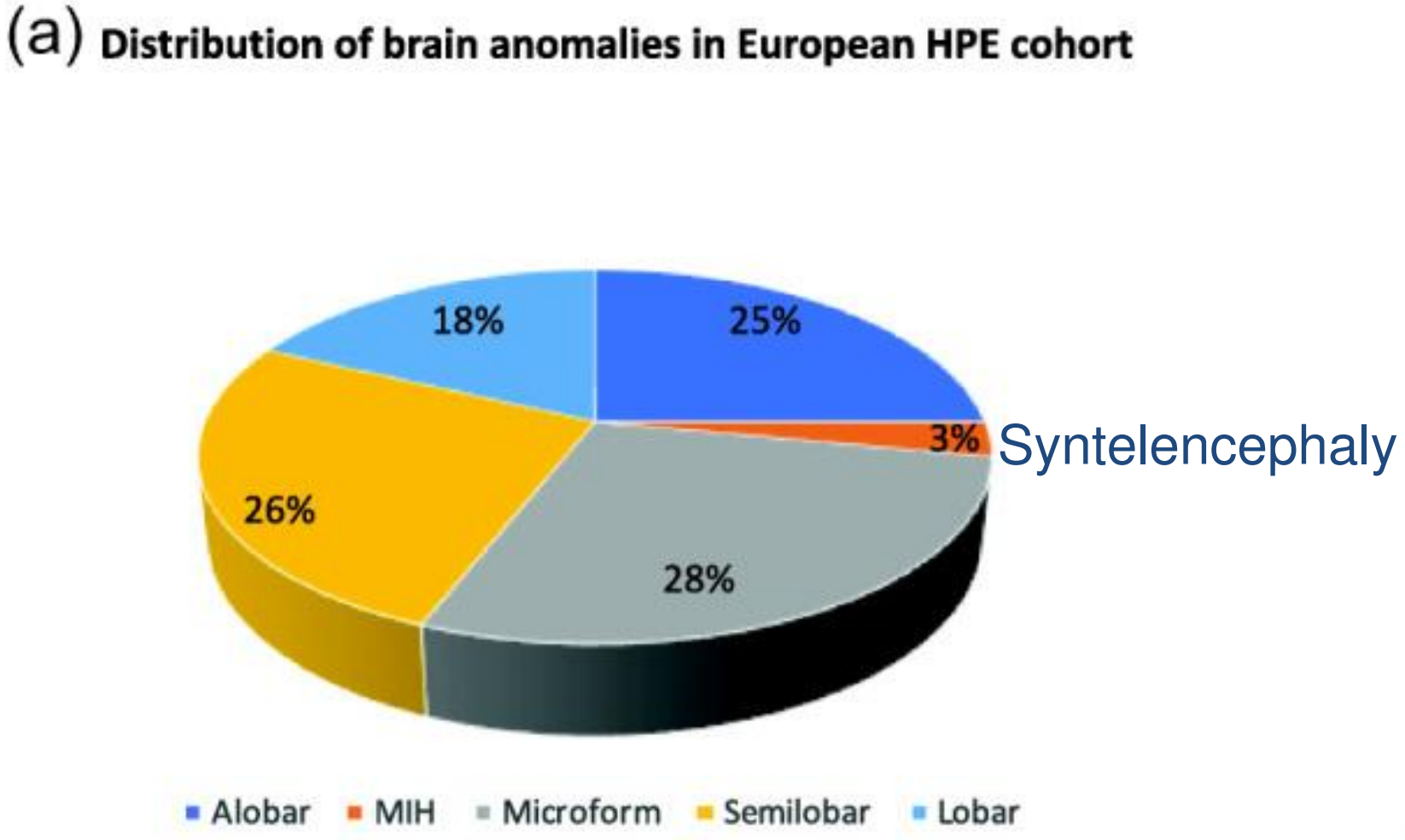


Syntelencephaly = Midline interhemispheric fusion (MIH)



Syntelencephaly

Dubourg, 2018

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Syntelencephaly = Midline interhemispheric fusion (MIH)

Genetics:

- *ZIC2*+

- Gene panel only for the majority of patients:

-> new genes with WES / WGS?

Neurodevelopment:

- Highly variable depending on the patients
- Syntelencephaly antenatally : future prognosis ?

-> Recruitment of patients to allow correlation between neuroimaging and neurodevelopment / neurologic symptoms

(collaboration with Pr Laurent Guibaud, Lyon, France)

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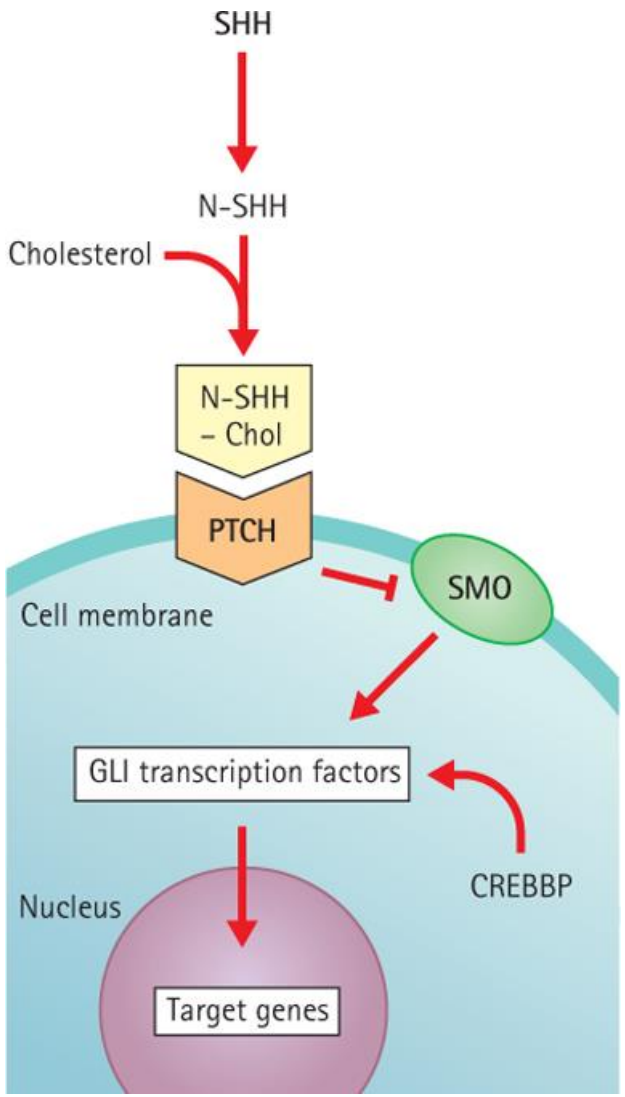
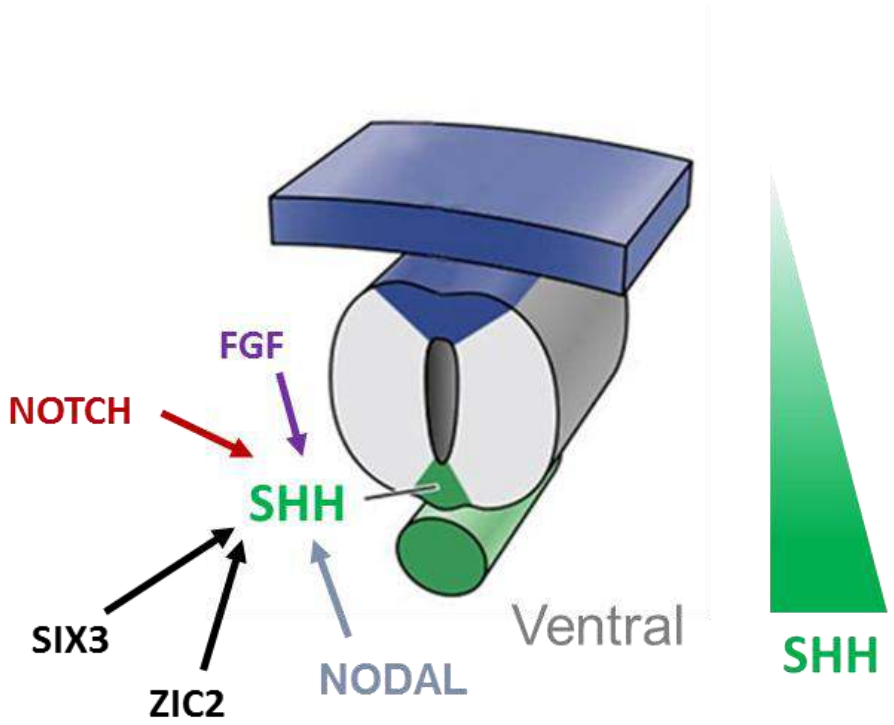
SHH Pathway and genetic heterogeneity in HPE





Adapté de Gilbert, 2010

These genes belong to the major pathways of brain and eye development (SHH, NODAL, FGF)

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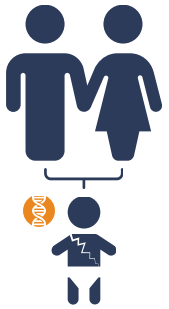
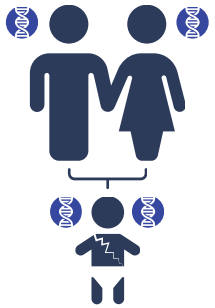
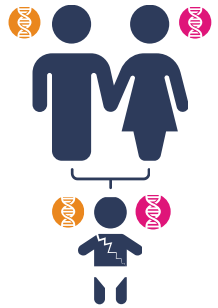
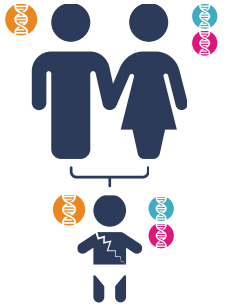
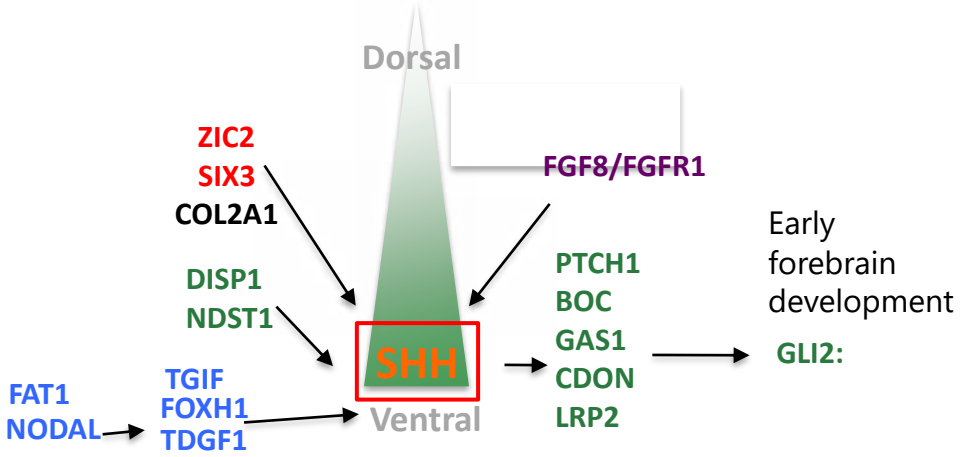
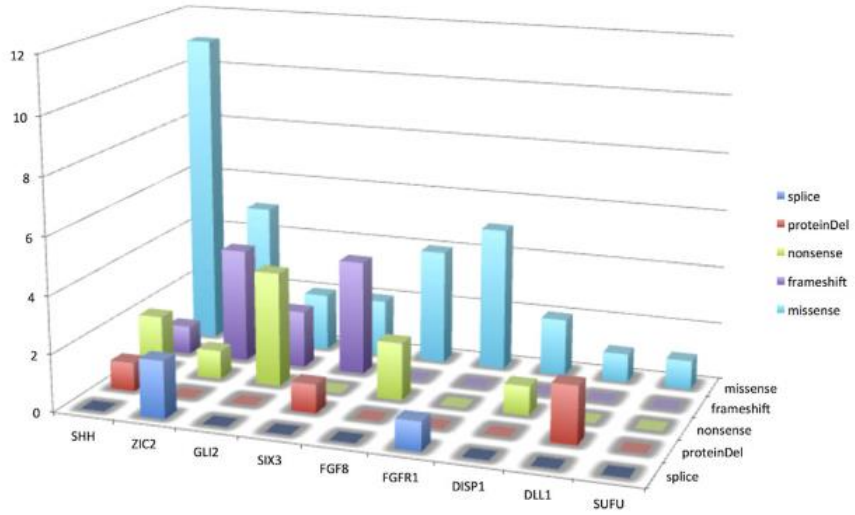
All HPE genes are involved in the regulation of SHH activity

Dubourg et al., 2016; Dubourg et al., 2018; Kim et al., 2019

Autosomal dominant *(de novo)*	**Autosomal recessive**	**Digenism**	**Oligogenism**
~35 %	*<1 %*	*? %*	*? %*
			
SHH (30%) *ZIC2 (70%)* *FGFR1 (50%)* *SIX3 (30%)*	*STIL/STIL* *DISP1/DISP1* *TGIF1/TGIF1* *FGF8/FGF8* *…*	*SHH/DISP1* *SIX3/PTCH1* *SHH/DLL1* *FGF8/FGFR1* *…*	*SHH/FAT1/NDST1* *HIC1/BOC/SCUBE2* *LRP2/COL2A1/FAT1* *…*





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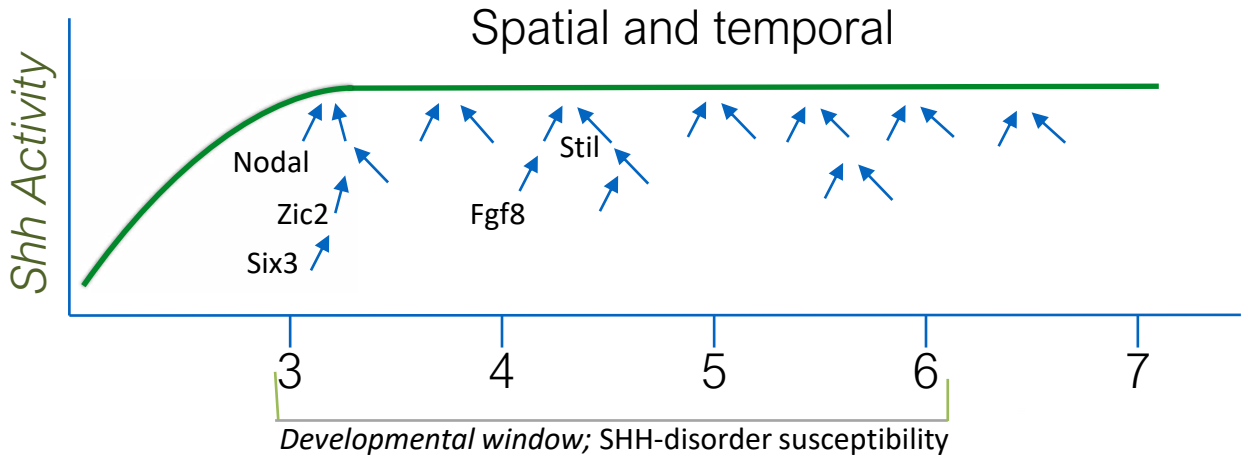
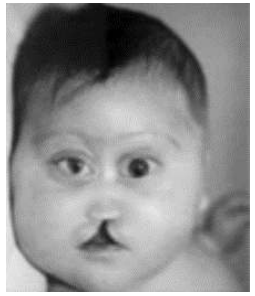
A tight control of SHH activity is crucial during craniofacial development



The genetic contribution to HPE is shaped by the interplay between multiple genes



Our hypothesis : accumulation of rare variants of genes implicated in SHH activity would lead to craniofacial malformations

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Craniofacial midline anomalies: microform HPE

- ***Craniofacial anomalies:***
  - Hypotelorism
  - Coloboma
  - Microphtalmia
  - **Solitary median maxillary central incisor (SMMCI)**
  - **Median cleft** (palate and/or lip)
  - **Pyriform aperture stenosis**
  - Choanal atresia / stenosis
  - Microcephaly
  - **Arhinencephaly**
  - Hypothalamic pituitary dysfunction
  - Corpus callosum anomalies

Cassidy & Allenson, 2005

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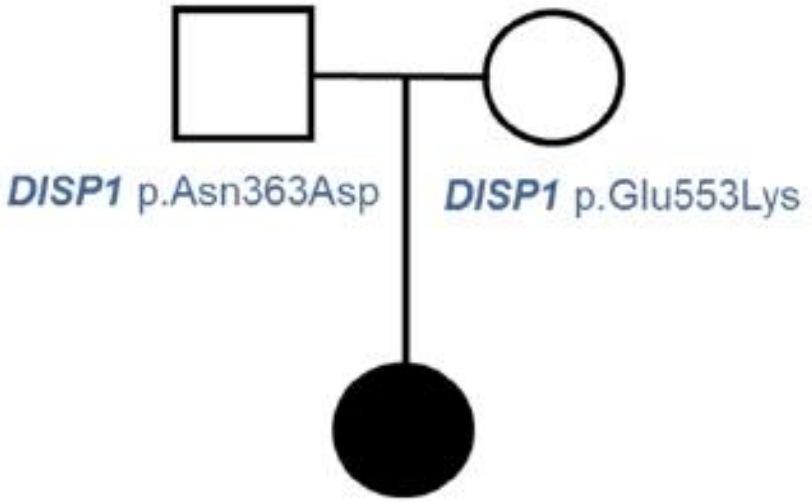
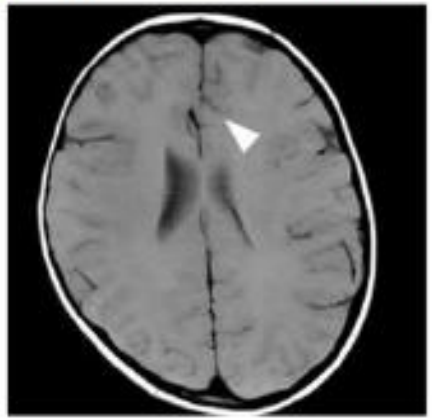
Disp1: recessive inheritance

Patient with cleft palate, mild learning difficulties





mild form of **lobar HPE** with a very localized fusion of hemispheres in the forebrain

DISP1 (NM_032890)

Mouden et al, *Clinical Genetics* 2016

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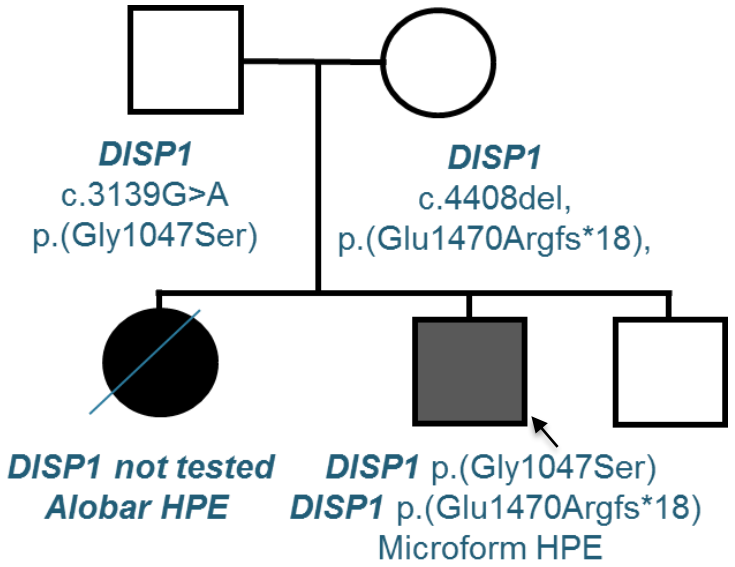
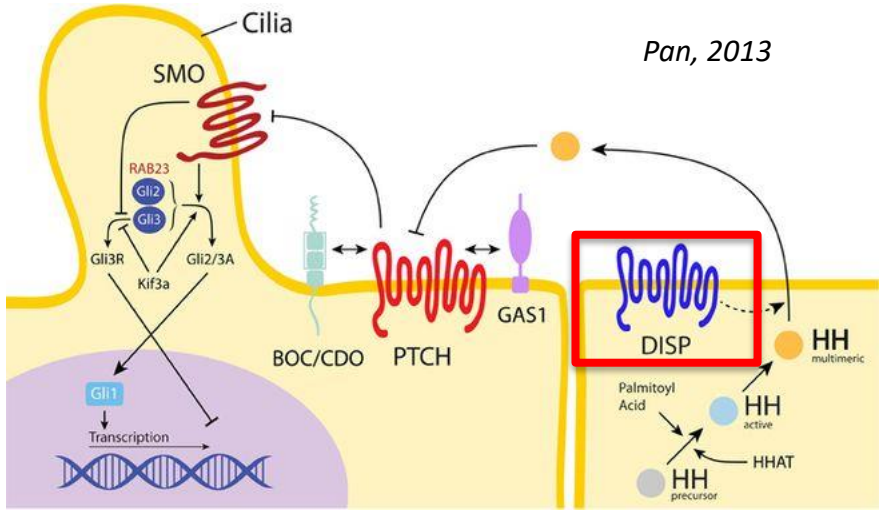
Disp1: recessive inheritance





Pan, 2013

<u>Microform HPE:</u>

Eye coloboma with impaired vision

Cleft lip and palate

Regular schooling with visual adaptations

Normal brain MRI

Unpublished data

In collaboration with Dr S. Whalen, Dr B. Keren (Paris)

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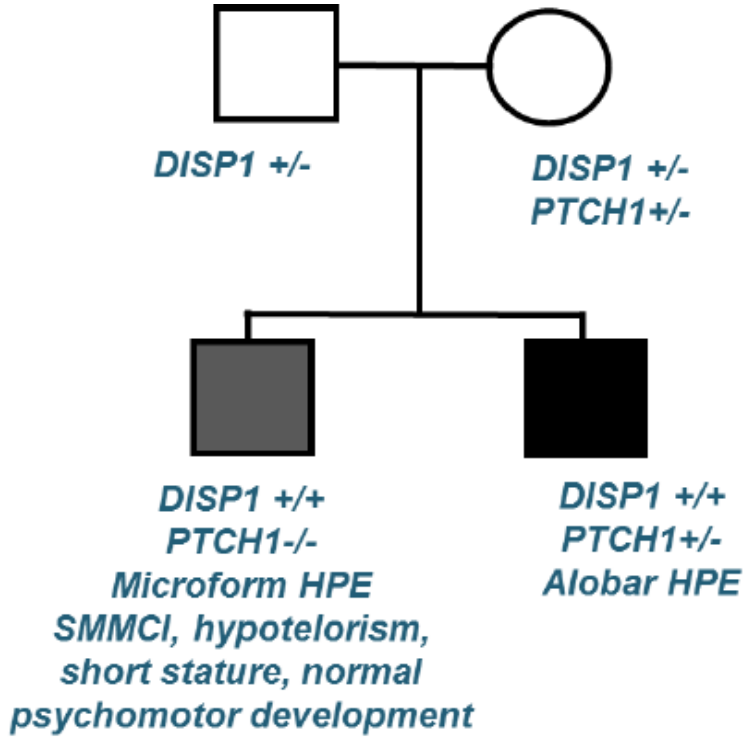
Disp1: recessive inheritance

- ***DISP1 variants:***
  - **c.2558T>C, p.(Ile853Thr)**
  - **c.3128C>T, p.(Ser1043Leu)**

We identified an additional variant in the affected boy with alobar HPE:
-heterozygous variant in *PTCH1* :
NM_000264.4:c.1318A>T or p.(Ile440Phe) inherited from the mother
This variant is absent in public databases, is predicted as damaging (score CADD = 24.2, score DANN = 0.98) and involves a very conserved residue (score GERP = 4.51 >> threshold = 2).

This additionnal variant combined with the *DISP1* variants (oligogenism) might explain the phenotypic variability in this family



Unpublished data in collaboration with Dr J Bos , Dr Y Hendriks Amsterdam

Conclusion / Call for collaborative clinical research

Shh deficiency syndrome

Syntelencephaly: very rare

Recruitment of patients

Correlation neuroimaging / neurodevelopment

Genetic causes

DISP1:

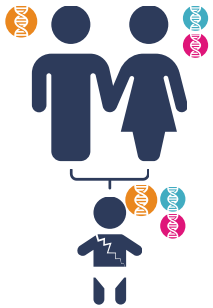
Recessive inheritance

Functional studies soon: we recruit patients!

New funding:

Exome/genome sequencing for microform HPE patients

Oligogenism? New genes?



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GPLD Team

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M. De Tayrac
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Thanks!

Patients and families
Clinicians, Fetopathologists
And all colleagues

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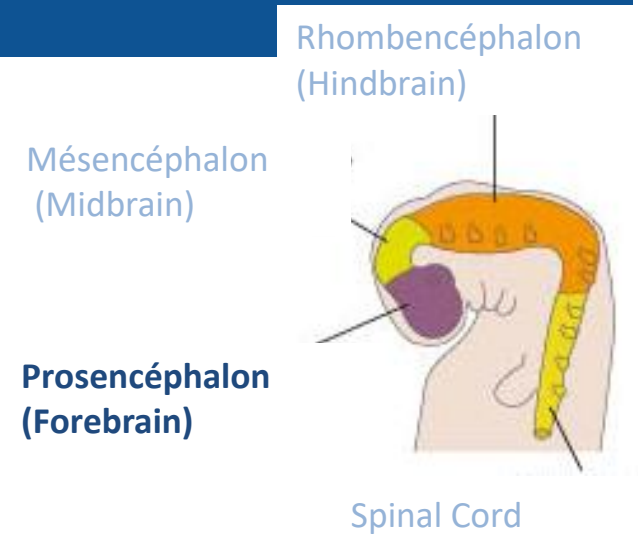
Holoprosencephaly and midline defects

Holoprosencephaly (HPE):

- Incomplete cleavage of the forebrain
  - Between the 18th and 28th day of gestation
- Craniofacial and eye defects



Genetic Factors: *SHH signaling deficiency*

French cohort = unique

French National Reference Center
> 2000 Patients
Lab diagnosis (University Hospital)

CENTRE DE REFERENCE
Anomalies du développement
et syndromes malformatifs

CHU Rennes

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2/ Pr Laurence Faivre
Collaborative call – Pai OAFNS

- First call as soon as the collaborative call initiative was launched in May

Targeted gene(s)/phenotype under study: Pai/OAFNS syndrome, ideally after negative exome

Abstract : The Solve-RD project is aiming at identifying genes in diseases resistant to exome sequencing. Pai and OAFNS are overlapping syndromes, belonging to the unsolvable cohorts in solve-RD, taking into account that exomes have remained negative in a number of patients. Multiomics are proposed to identify the molecular bases of these entities. New samples are required, including blood, urine and saliva of the proband and parents, and ideally tissue of affected area if available.

Coordinating clinician: Pr Laurence Faivre

Institution (dept, hospital, City): CHU Dijon/France

Contact email: laurence.faivre@chu-dijon.fr

Specific requirements beyond clinical data and genotype data sharing:

- Re-analysis of DNA samples : **N**
- Resampling of patients No if the trio is available : **Y**
- Linked to a translational/basic research project? **Y, Solve-RD**

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Collaborative call – Pai OAFNS

Pai syndrome and **oculo-auriculo-fronto-nasal syndrome** (OAFNS) hypotheses

Constitutional monogenic disease	Mosaic disease	Oligogenic disease
Coding or non-coding (regulatory) variation not detectable by short read sequencing	Variation not detectable in blood	Multiple genes belonging to the same pathway
→*Long read sequencing* →*RNA-seq* →*Proteome* →*Epigenome*	→*Tissue analysis*	→*Multiomics data integration*

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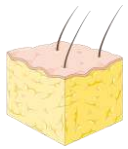
Collaborative call – Pai OAFNS

Analysis strategy for the Pai syndrome and OAFNS

Affected tissue available



Tissue
- SR GS
- Epigenome (methylation DNA)

Fibroblastes
- LR GS
- RNAseq
- Proteome

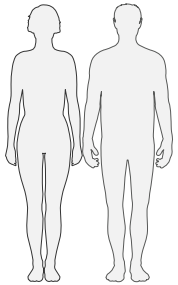
- SR GS
- Epigenome (methylation DNA)
- Proteome (plasma)

No affected tissue available

- SR GS
- LR GS
- RNAseq
- Epigenome (methylation DNA)
- Proteome (plasma)

- SR GS
- Deep ES

+/- Deep ES



- SR GS +/- LR GS
- RNAseq
- Epigenome (methylation)
- Proteome (plasma)

SR : short-read
LG : long-read

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Collaborative call – Pai OAFNS

	France	ITHACA
Pai/OAFNS included with tissue	4	0
Pai/OAFNS included with no tissue	4	0
Pai/OAFNS with no samples sent	5	8 (UK 2, Italy 1, Spain 1, Netherlands 1, Cyprus 1, New Zeland 2)
Replication cohort	5	3

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Dr Caterina Lo Rizzo - SIENA
IQSEC2-related phenotype

WE JOIN CALL!

Call for collaborative clinical research on developmental disorders

These calls for collaborative projects typically aim to rapidly build up consistent clinical series for rare monogenic disorders, in order to better delineate the clinical spectrum and natural history of recently identified entities in the field of ITHACA. The call will be disseminated to the mailing list of ITHACA and will be posted on the web site.

- Short title: ***IQSEC2*-related phenotype**
- Targeted gene(s)/phenotype under study (to be quoted in the newsletter): ***IQSEC2***
- Summary (1000 letters max): ***IQSEC2*** **is a new gene related to an X-linked intellectual disability, characterized by a highly variable phenotype partially overlapping Rett syndrome. To date the mechanisms underlying this broad clinical variability are not fully understood both in male and female patients. The aim of this study is to collect clinical and molecular data of patients harbouring a mutation in *IQSEC2* gene in order to better define the clinical wide spectrum of *IQSEC2* gene related phenotype.**
- Coordinating clinician: **Prof. Alessandra Renieri, MD, PhD**
- Institution (dept, hospital, City): **U.O.C. Genetica Medica, Università di Siena – Dipartimento di Biotecnologie Mediche; Azienda Ospedaliera Universitaria Senese – Ospedale Santa Maria alle Scotte Viale Mario Bracci, 53100 SIENA, ITALY**
- Contact email: **alessandra.renieri@unisi.it**

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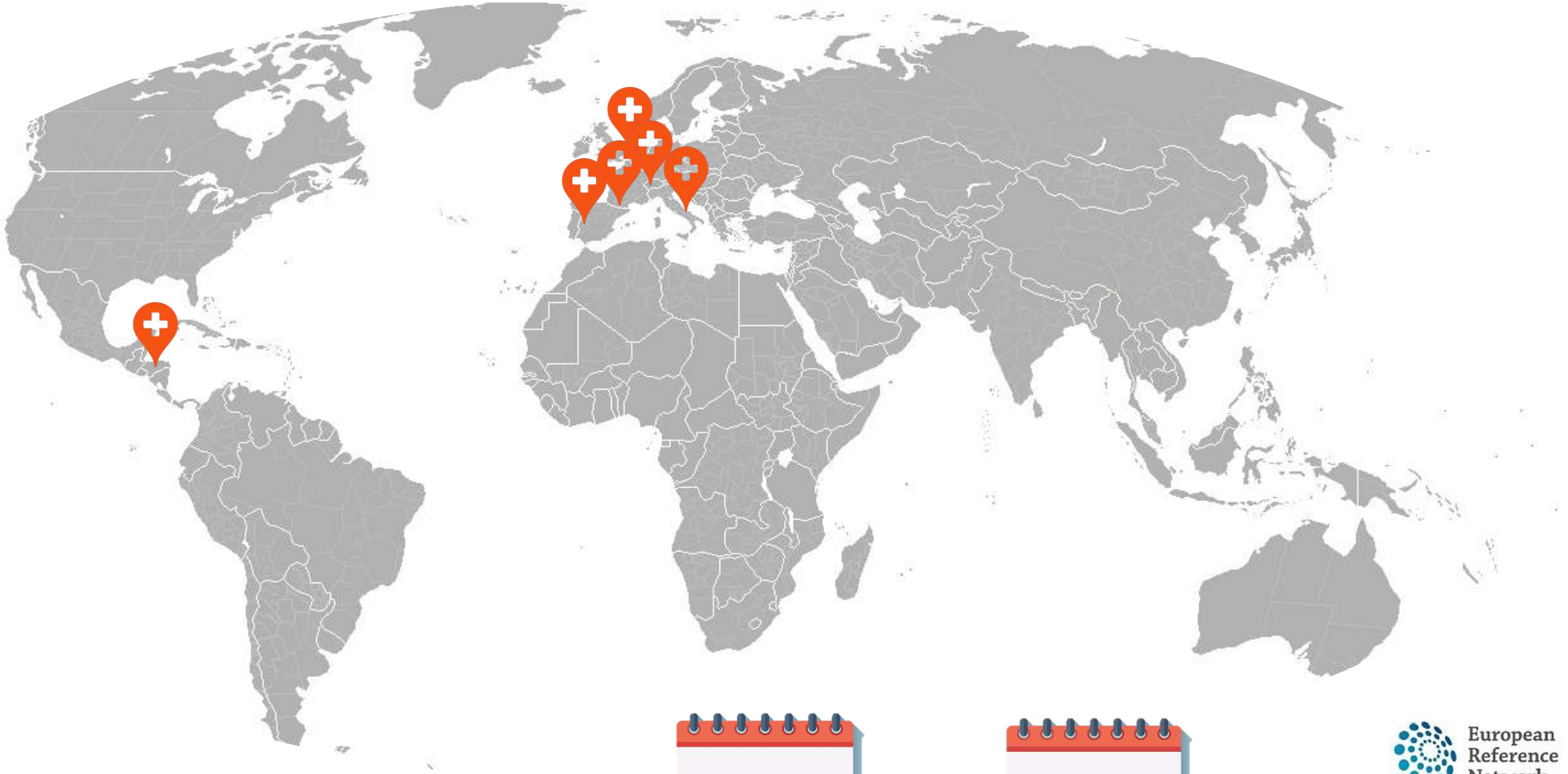
Dr Caterina Lo Rizzo - SIENA
IQSEC2-related phenotype



DATA COLLECTION from JUNE **to** SEPT.

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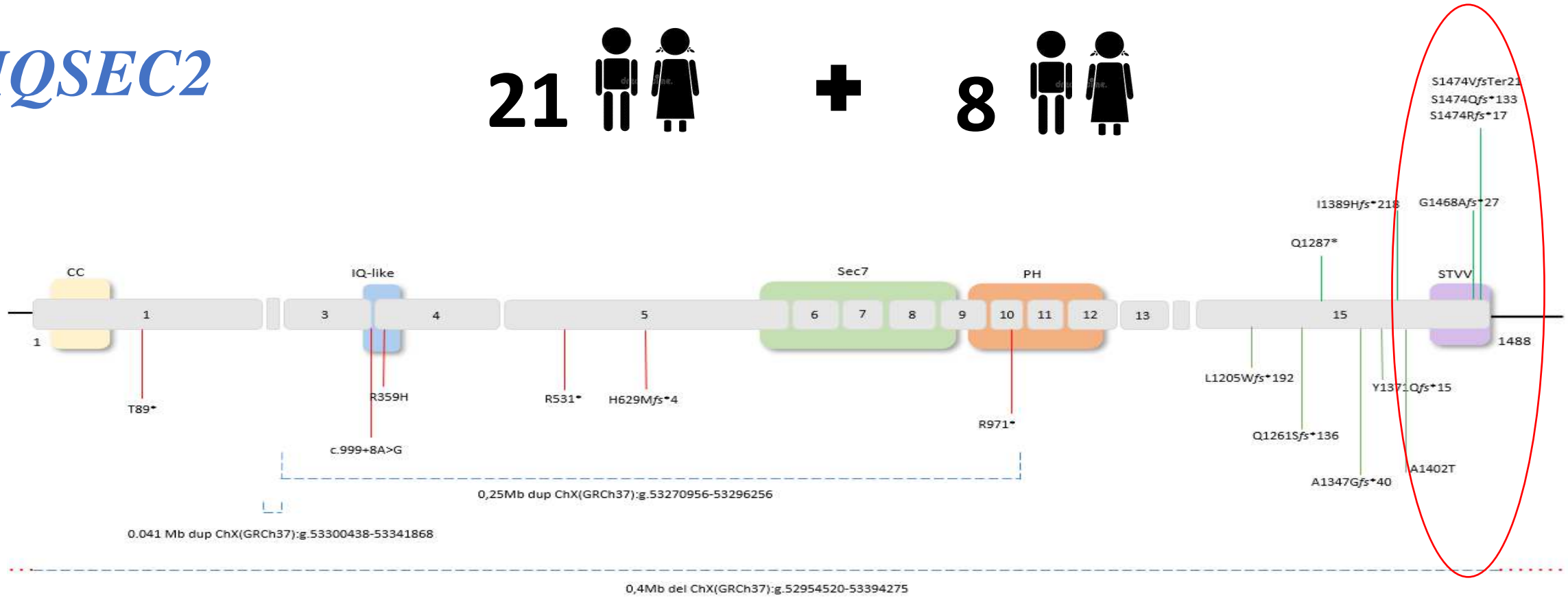
3/ Dr Caterina Lo Rizzo - SIENA
IQSEC2-related phenotype

IQSEC2

21 + **8**



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Dr Caterina Lo Rizzo - SIENA
IQSEC2-related phenotype

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Dr Caterina Lo Rizzo - SIENA
IQSEC2-related phenotype

Thanks for the collaboration!

European Reference Network
for rare or low prevalence complex diseases

Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

4/ Clinical-research-QRICH1 Zeynep Tumer

Department of Clinical Genetics
Copenhagen University Hospital - Rigshospitalet

QRICH1

Zeynep Tümer
Kennedy Center
Department of Genetics

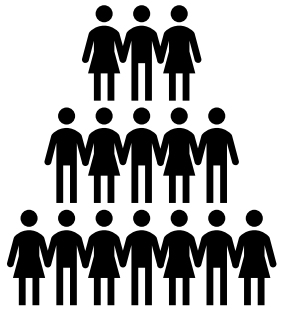
QRICH1-associated developmental delay and intellectual disability in 36 unrelated individuals

ANNOUNCEMENT 23. june 2020

Targeted gene(s)/phenotype under study : *QRICH1*

Abstract : *De novo* pathogenic variants of *QRICH1* (Glutamine-rich protein 1, OMIM #617387) has recently been described in five patients (Ververi et al. 2018; Lui et al. 2019). The variants have been associated with developmental delay and intellectual disability, mild facial dysmorphism and chondrodysplasia in some cases. Through Gene Matcher (Genematcher.org) we have now identified 19 further patients with *QRICH1*-variants. Currently, we are in the process of defining the phenotype-genotype spectrum of *QRICH1*-related disorders in the patient cohort (a total of 24 including the published cases) and preparing a manuscript. We welcome further cases to this study to reach a better understanding of this rare disorder. We aim to close inclusion of further cases 15th July 2020.

Coordinating clinician/researcher: Zeynep Tümer



CURRENT STATUS

- The current number of unpublished indivials are now 27 – two of the patients are through ITHACA collaboration (Prof. Favier's group)
- 4 new patients reported meanwhile (Föhrenbach et al. 2020).
- TOTAL number of individuals will be 36 (including 9 published)

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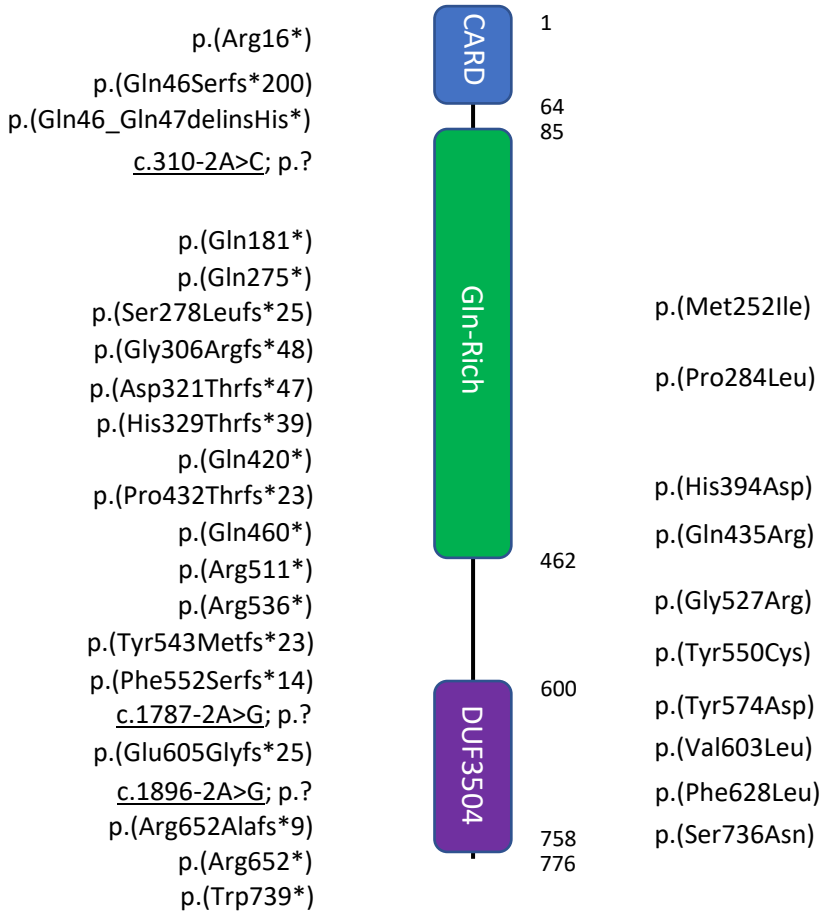
QRICH1 has 11 isoforms and all encode the same 776 amino acid protein.

- glutamine (Q) rich region
- **CARD domain** (Caspase activation and recruitment domain): uncharacterized
- **DUF3504 domain** (domain of unknown function): a protein-protein interaction domain found in several proteins involved in apoptosis, inflammation and immune responses.

Protein Truncating Variants: n=23



Missense Variants: n=10

28 *de novo*, 3 paternally inherited (c.961del, c.1655del, c.310-2A>C), 2 being investigated.

Collaborators from 27 different locations *(author list not complete yet and not in the final order)*

- Laurence Faivre, Anne-Sophie Denommé-Pichon - France
- Richard Finkel, Lindsay Rhodes - St. Jude Children's Research Hospital.
- Reymundo Lozano, Cassie Mintz, Isha Gupta - Mount Sinai, New York
- Anya Revah-Politi, Kwame Anyane-Yeboa - Columbia University
- Lindsay Rhodes, GeneDX
- Wendy Chung, Scott Robinson - New York Presbyterian Hospital
- Michael Ciliberto, Lillian H Howard - Iowa
- Sérgio B. Sousa, Belinda Campos-Xavier - Coimbra, Portugal
- Fernando Simarro-Santos - Madrid, Spain
- Julie Cohen, Anne Comi - Kennedy Krieger, Maryland
- Maria Palomares, Sixto García-Miñaúr - Madrid, Spain
- Alice Fievet, Marlene RIO - France
- Trevor Hoffman - Southern California Kaiser Permanente Medical Group
- Jill A. Rosenfeld (Jill Mokry), Jaya Punetha, Jennifer Pose, Lisa Emrick /UDN, Baylor, Texas
- Ausitin Larson, Michele Rapp - Colarado
- Nicholas Ah Mew - Children's National
- Sylvie Odent, Lena Damaj – France
- Sumit Parikh - Cleveland Clinic
- Mary Beth Fasano, Anna Paulson - Iowa University
- Anja Leiber, Henry Oppermann, Konrad Platzer, Institute of Human Genetics Leipzig University
- Amanda Gerard, Lorraine Potocki - Texas Children's Hospital.
- Cynthia Curry - UCSF
- Paul Benke - Joe DiMaggio Children's Hospital in Hollywood, Florida
- Alyssa Ritter, Kosuke Izumi - CHOP, Philadelphia
- Rikke Møller - Denmark
- Natasha Brown, Smitha Kumble - Australia
- Zeynep Tümer - Copenhagen, Denmark

Article is in preparation and not submitted yet

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Follow up on research collaborative Calls

Call for collaborative clinical research on developmental disorders

1. **Syntelencephaly cohort** **Alinoe Lavillaureix**
2. **Pai/OAFNS syndrome** **Laurence Faivre**
3. **IQSEC2 related phenotype** **Caterina Lo Rizzo**
4. Clinical-research-QRICH1 Zeynep Tumer
5. DLG4 (not in ITHACA list) Zeynep Tumer
6. **POGZ mutations (new)** **Agnese Feresin**

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5/ DLG4 (not in ITHACA list) Zeynep Tumer

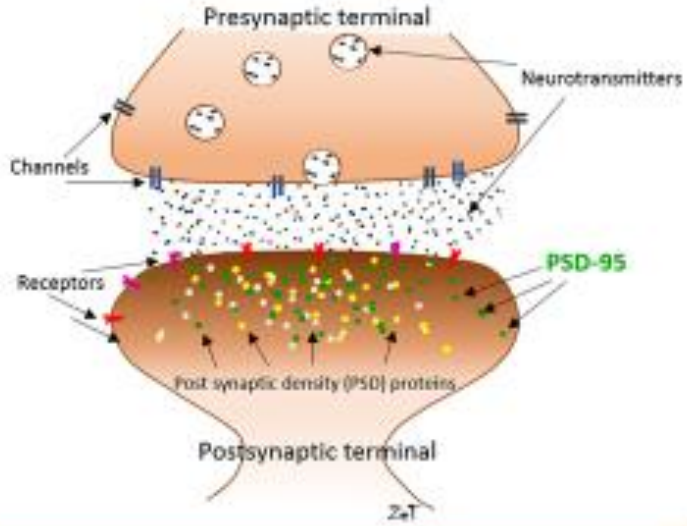
Department of Clinical Genetics
Copenhagen University Hospital - Rigshospitalet

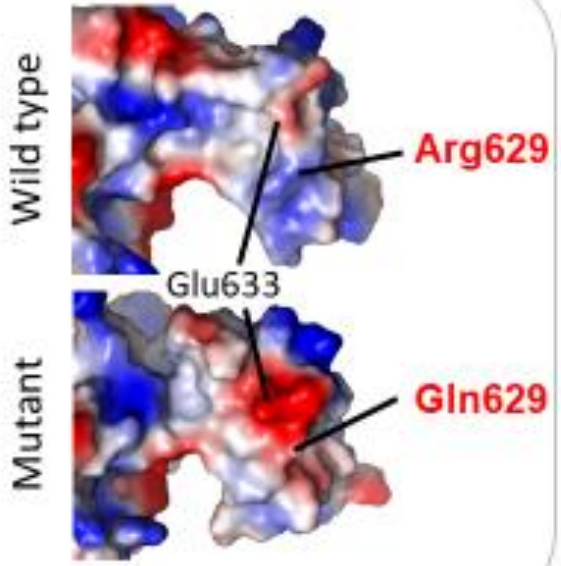
DLG4

Zeynep Tümer
Kennedy Center
Department of Genetics

DLG4-related synaptopathy as a new and rare brain disorder

Postsynaptic density protein-95 (PSD-95), encoded by *DLG4*, regulates excitatory synaptic function in the brain.





Molecular dynamics simulation

This study presents 53 individuals with 45 distinct *DLG4* variants, most of which are loss-of-function variants with *de novo* occurrence. The few missense variants are predicted to change structure or function of the protein using e.g. molecular dynamics simulation.

The clinical picture is predominated by early onset global developmental delay, intellectual disability, autism and attention deficit hyperactivity disorder.

CONCLUSION Haploinsufficiency of *DLG4* is likely to impair PSD-95 activity, and interfere with synaptic function during critical developmental windows.

Grafical abstract, Genetics in Medicine (accepted for publication)

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Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

DLG4-related synaptopathy: A new rare brain disorder

Agustí Rodríguez-Palmero, MD[1,2], Melissa Maria Boerrigter, MSc[3,4], David Gómez-Andrés, MD, PhD[5], Kimberly A Aldinger, PhD[6], Íñigo Marcos-Alcalde, PhD[7,8], Bernt Popp, MD[9,10], David B Everman, MD[11], Alysia Kern Lovgren, PhD[12], Stephanie Arpin, MD[13], Vahid Bahrambeigi, MSc[11,14], Gea Beunders, MD[15], Anne-Marie Bisgaard, MD, PhD[16], Bjerregaard VA, PhD[3], Ange-Line Bruel, MD[17], Thomas D Challman, MD[18], Benjamin Cogne, PharmD, PhD[19,20], Christine Coubes, MD[21], Stella A de Man, MD, PhD[22], Anne-Sophie Denommé-Pichon, MD[23], Thomas J Dye, MD[24,25], Frances Elmslie, MD, FRCP[26], Lars Feuk, PhD[27], Sixto García-Miñaúr, MD[28], Tracy Gertler, MD, PhD[29], Elisa Giorgio, PhD[30], Nicolas Gruchy, MD, PhD[31], Tobias B Haack, MD[32], Chad R Halderman-Englert, MD[33], Bjørn Ivar Haukanes, PhD[34], Juliane Hoyer, MD[9], Anna C E Hurst, MD[35], Bertrand Isidor, MD, PhD[19,20], Maria Johansson Soller, MD, PhD[36,37], Sulagna Kushary, MSc, CGC[38], Malin Kvarnung, MD, PhD[36,37], Yuval E Landau, MD, PhD[39,40,41], Kathleen A Leppig, MD[42], Anna Lindstrand, MD, PhD[36,37], Lotte Kleinendorst, MD[43], Alex MacKenzie, MD, PhD[44], Giorgia Mandrile, MD, PhD[45], Bryce A Mendelsohn, MD, PhD[46], Setareh Moghadasi, MD, PhD[47], Jenny E Morton, MB, FRCP[48], Sebastien Moutton, MD[23,49], Amelie J Müller, PhD[32], Melanie O'Leary, MSc[12], Marta Pacio-Míguez, MSc[28], Maria Palomares-Bralo, PhD[28], Sumit Parikh, MD[50], Rolph Pfundt, PhD[51], Ben Pode-Shakked, MD[41,52,53,54], Anita Rauch, MD, PhD[55], Elena Repnikova, PhD[56], Anya Revah-Politi, MSc, CGC[38,57], Meredith J Ross, MSc, CGC [58], Claudia A L Ruivenkamp, PhD[47], Elisabeth Sarrazin, MD[59,60], Juliann M Savatt, MSc[18], Agatha Schlüter, PhD[1,], Bitten Schönewolf-Greulich, MD, PhD[3], Zohra Shad, MD[61], Charles Shaw-Smith, MRCP, PhD[62], Joseph Shieh, MD, PhD[63], Motti Shohat, MD[64], Stephanie Spranger, PhD[65], Heidi Thiese, MSc[42], Frederic Tran Mau-Them, MD, PhD[23], Bregje van Bon, MD, PhD[51], Ineke van de Burgt, MD, PhD[51], Ingrid M B H van de Laar, MD, PhD[66], Esmée van Drie, MD[43], Mieke M van Haelst, MD[43], Conny M van Ravenswaaij-Arts, PhD[15], Edgard Verdura, PhD[1,], Antonio Vitobello, PhD[23], Stephan Waldmüller, PhD[32], Sharon Whiting, MBBS, FRCPC[44], Christiane Zweier, MD, PhD[9], Carlos E Prada, MD[25,67], Bert B A de Vries, MD, PhD[51], William B Dobyns, MD[6,68,69], Simone F Reiter, MD, PhD[34], Paulino Gómez-Puertas, PhD[7], Aurora Pujol, MD, PhD[1,70,*], Zeynep Tümer, MD, PhD[3,71,*]

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Accepted - Genetics in Medicine

Some facts – 85 contributing authors from 72 different locations Worldwide and more than 2000 mail correspondance.

Acknowledgements
We thank all the affected individuals and families for their collaboration.
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We refer to the publication in Genetics in Medicine for full acknowledgement, author affiliations and funding.

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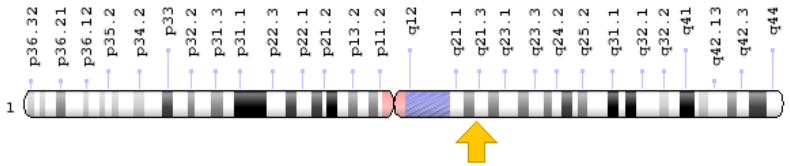
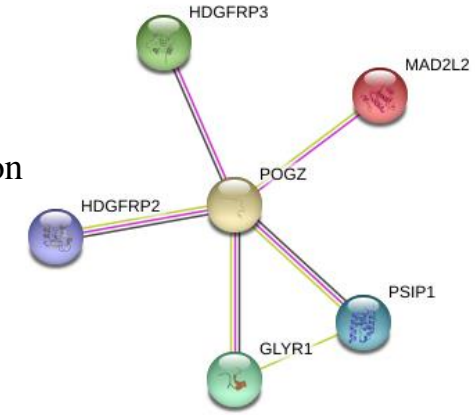
6/ Dr Agnese Feresin
POGZ mutations

POGO TRANSPOSABLE ELEMENT WITH ZNF DOMAIN; *POGZ* (*614787)



→ heterochromatin formation and chromosomal segregation mitotic progression

→ transcriptional regulator in functional neuronal network



616364

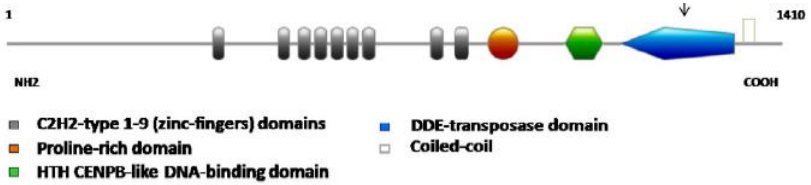
WHITE-SUTTON SYNDROME; WHSUS

Alternative titles; symbols

MENTAL RETARDATION, AUTOSOMAL DOMINANT 37; MRD37

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
1q21.3	White-Sutton syndrome	616364	AD	3	POGZ	614787



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Dr Agnese Feresin
POGZ patients

IRCCS Burlo Garofolo, **Trieste**

AUSL Genetica Medica, **Reggio Emilia**
Ospedale Pediatrico Bambino Gesù, **Roma**

Ospedale San Camillo-Forlanini, **Roma**

Ospedale Pediatrico Bambino Gesù, **Roma**

Azienda Ospedaliera San Pio, **Benevento**

IRCCS Oasi Maria SS, **Troina**

Neurodevelopmental disorder

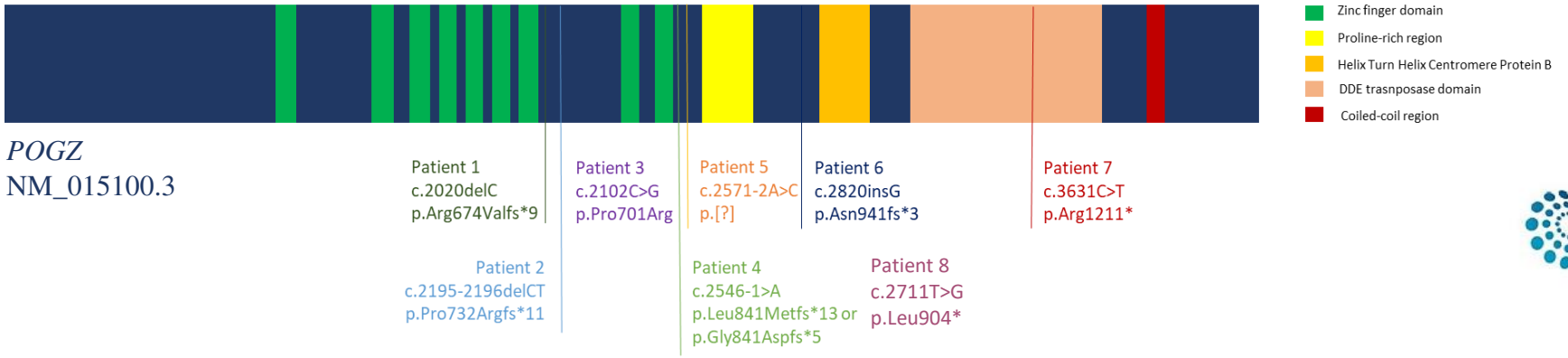
+

Neurological and other clinical manifestation

+

Facial features

- Chromosomal Microarray Analysis: **normal**
- Whole Exome Sequencing Analysis: **likely pathogenic / pathogenic *POGZ* variant**



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Dr Agnese Feresin
POGZ patients: clinical features

	Patient 1 c.2020delC p.Arg674Valfs*9	*Patient 2* c.2195-2196delCT p.Pro732Argfs*11	*Patient 3* c.2102C>G p.Pro701Arg	*Patient 4* c.2546-1>A p.Leu841Metfs*13 or p.Gly841Aspfs*5	*Patient 5* c.2571-2A>C p.[?]	*Patient 6* c.2820insG p.Asn941fs*	*Patient 7* c.3631C>T p.Arg1211*	*Patient 8* c.3631C>T p.Arg1211*	**Total**
Intellectual disability	Mild	Mild	Mild	Mild	Severe	Severe	Mild	Severe	**8/8**
Global developmental delay	+	+	+	+	+	+	+	+	**8/8**
Autism spectrum disorder	-	-	-	-	+	+	+	+	**4/8**
Other behavioural concern	Obsessive-compulsive disorder	-	Unspecified emotional disorder, anxiety, ADHD, hyperphagia	-	Stereotypies, hyperactivity, no ocular contact	Poor eye contact, stereotypic movement	Unspecified, various neurobehavioral anomalies	Absence of speech, autistic features	**6/8**
Seizures	-	-	-	-	-	+	-	+	**2/8**
Neurologic finding	-	-	High pain threshold, Sleep disorder	Hypotonia, synchronous movements, dystonia	Hypertonia, Clumsiness	Waddling gait with externally rotated feet	Hypotonia, motor coordination problems, High pain tolerance Severe sleep disorder	Hypotonia, Seizures, Clumsiness	**6/8**
Eye abnormality	Variable exophoria extropia	Right hyperopia and amblyopia	-	-	Strabismus, myopia	-	Astigmatism	-	**4/8**
Hearing loss	-	-	-	Bilateral, sensorineural, mild	-	Unilateral, profound	Absent cocleo-stapedial reflexes	Sensorineural, bilateral	**4/8**
Gastrointestinal involvement	-	-	Cyclic vomit	-	Swallowing, constipation, feeding difficulties	Constipation, gastroesophageal reflux	Dysphagia, feeding difficulties, hepatomegaly	Feeding difficulties	**5/8**
Genitourinary involvement	-	-	-	-	Undescended testes	Olygoamenorrhea	-	-	**2/8**
Cardiac involvement	-	-	-	Patent foramen ovale and ductus arteriosus	Atrial septal defect, aortic coarctation, ventricular septal defect	Atrial septal defect closed spontaneously	Aortic bicuspid valve with mild ascending aorta dilatation	Patent foramen ovale	**5/8**
Brain imaging (MRI)	-	Above and subtentorial gliotic foci	-	Blake's pouch cyst, reduction of supratentorial white matter, square ventricles and hippocampal malrotation	Dilated lateral ventricles, cerebellar vermis hypoplasia	Cerebellar atrophy, thin corpus callosum, abnormally simplified gyral pattern, mild brainstem hypoplasia	Partial hypoplasia of cerebellar vermis, wide communication between the IV ventricle and pericerebellar fluid spaces	Cerebral atrophy and slightly thinned aspect of the anterior part of the corpus callosum.	**6/8**
Other	-	Post-natal obesity	-	Bilateral adducted thumb	-	Vitiligo	Diastasis recti, drooling	-	

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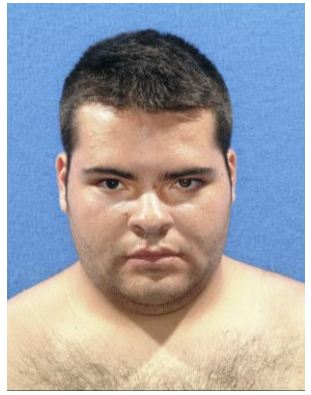
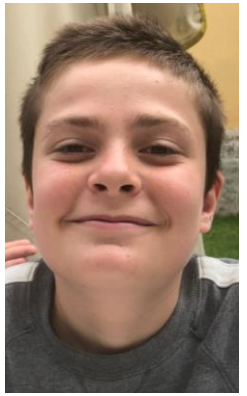
Dr Agnese Feresin
POGZ patients: phenotypic features

Facial features		Body features	
Midface		Head	
Midface hypoplasia	2/8	High, broad forehead	5/8
Prognathisms	3/8	Brachicephaly	2/8
Eyes		Hands	
Sparse eyebrows	3/8	Brachydactyly	1/8
Hypertelorism	2/8	Clinodactyly	1/8
Upslanting palpebral fissures	1/8		
Nose		Skeleton	
Broad nasal root	6/8	Large toes	4/8
Flat nasal bridge	4/8	Pes planus	3/8
Anteverted nares	1/8		
Ears		Growth	
Small ears	2/8	Overweight	3/8
Thick elices	2/8	Height (10-90°centile)	3/8
Mouth		Other	
Tented	3/8	Clubfoot	1/8
Smooth philtrum	3/8	Kiphosis	1/8
Thick upper lip	3/8	Congenital thumb adduction	1/8

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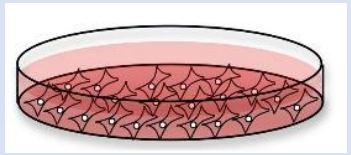
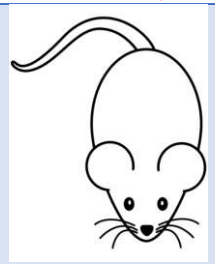
Dr Agnese Feresin
Perspectives for POGZ related conditions

Pathogenetic variant of *POGZ* is responsible on neurodevelopmental disorder, physical features and clinical manifestations



Definition of **pathogenic mechanisms of damaging variants in POGZ**: alteration of chromatin remodeling, neuronal proliferation and synaptic function



Knock-in mice show abnormally **elevated activation of excitatory neurons** resulting in impaired neuronal development, social deficit and altered behavioral performances

Elucidation of the improving role of **inhibition of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated synaptic transmission** in POGZ-dysregulated neural activity

Administration of an orally active, selective, non-competitive AMPA receptor agonist, to candidate POGZ patients to evaluate the **neurophysiologic response.**

nature COMMUNICATIONS

ARTICLE

OPEN

Pathogenic POGZ mutation causes impaired cortical development and reversible autism-like phenotypes

Kensuke Matsumura et al.

...Let's join!

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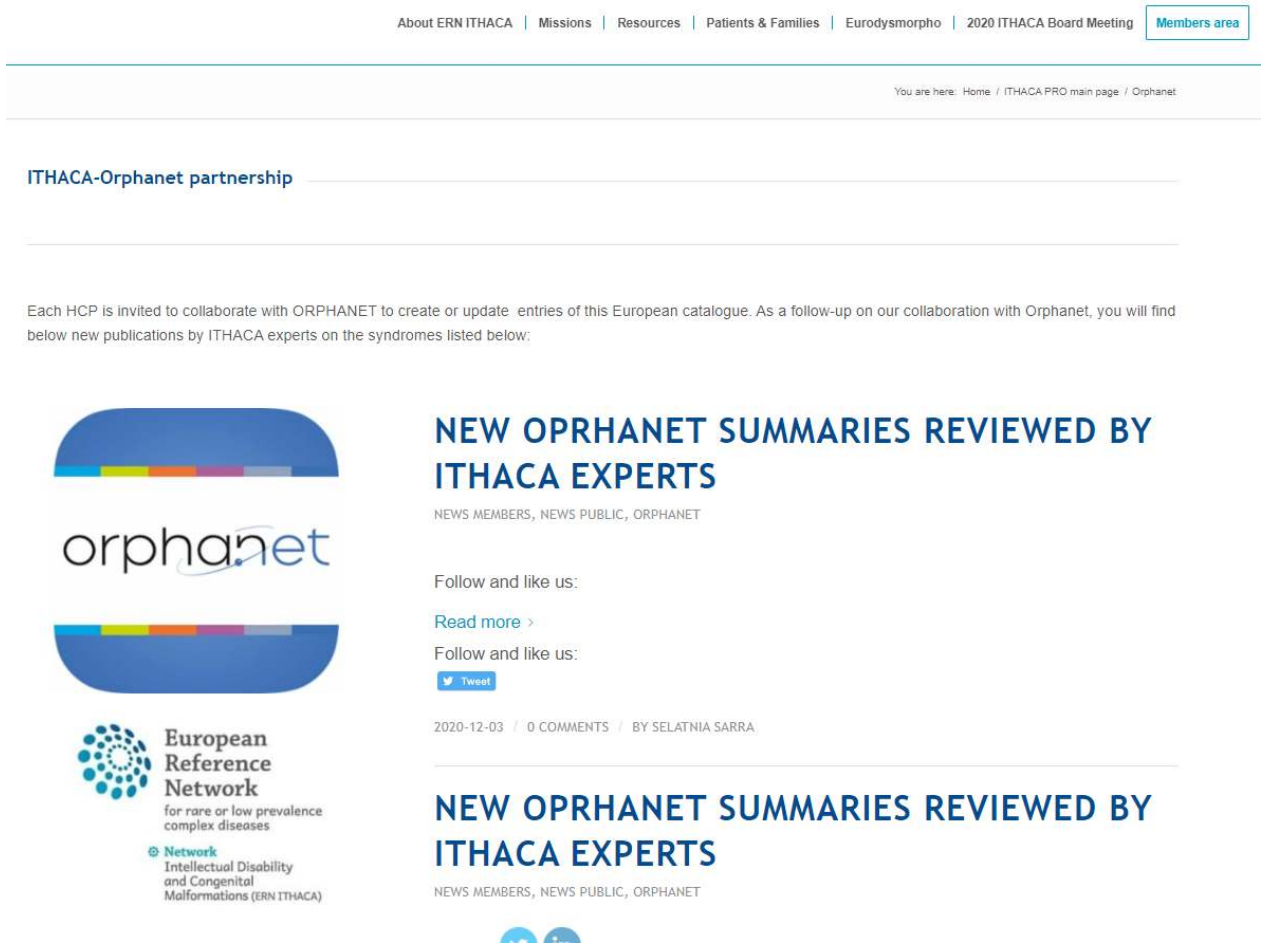
Orphanet news on productions of rare syndromes

Orphanet / ITHACA Collaborative
35 on dec 11th

- Dyggve-Melchior-Clausen disease
- Rubinstein-Taybi syndrome
- Noonan syndrome
- Inverted duplicated chromosome 15 syndrome
- Galloway-Mowat syndrome
- Hennekam syndrome
- Pitt-Hopkins syndrome
- Feingold syndrome type 1
- Feingold syndrome type 2
- 22q11.2 duplication syndrome
- 22q11.2 deletion syndrome
- Kabuki syndrome ENG
- Kabuki syndrome FR
- Nasopalpebral lipoma-coloboma syndrome
- KBG syndrome
- Mowat-Wilson syndrome
- Hypertelorism, Teebi type
- Tall stature-intellectual disability-renal anomalies syndrome
- Short stature-brachydactyly-obesity-global developmental delay syndrome
- Cerebellar-facial-dental syndrome
- Microcephalic osteodysplastic primordial dwarfism types I and III
- Holoprosencephaly
- L1 syndrome
- Simpson-Golabi-Behmel syndrome
- Freeman-Sheldon syndrome
- Developmental delay-facial dysmorphism syndrome due to MED13L deficiency
- Noonan syndrome-like disorder with loose anagen hair
- Opitz G/BBB syndrome
- Treacher-Collins syndrome
- Carpenter syndrome
- Smith-Magenis syndrome
- Sotos syndrome
- Fraser syndrome
- Oculocerebrofacial syndrome, Kaufman type
- THOC6-related developmental delay-microcephaly-facial dysmorphism syndrome
- Intellectual disability-microcephaly-strabismus-behavioral abnormalities syndrome



https://ern-ithaca.eu/ithaca-pro-blog/orphanet/

https://www.orpha.net/

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Update on the Orphanet-ITHACA collaboration for disease summary texts

Gemma Milman

Orphanet - Inserm US14, Paris, France

Gemma.milman@inserm.fr

11th December 2020

Content

Orphanet at a glance	Objective
	Nomenclature
	Organisation of knowledge base
Encyclopedia for professionals	Overview
Collaboration summary	Number of texts
	Classification
	Feedback

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Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

ORPHANET AT A GLANCE

European Reference Network
for rare or low prevalence complex diseases

Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Orphanet's missions

Improve the **visibility** of RD by providing **a common language** across healthcare and research systems (ORPHA nomenclature)

Provide **high-quality information** and **expertise** on RD

Contribute to **generating knowledge**

→ piecing together the parts of the puzzle for better understanding of RD

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The Orphanet nomenclature

- **The only nomenclature specific to RD**
- Each disease is assigned **a <u>unique</u> and <u>stable</u>** ORPHAcode
- Comprehensive, standardized, evidence-based
- Multi-lingual (**<u>EN</u>**, FR, DE, ES, IT, NL, PT, PL, CZ)

ORPHAcode	Preferred term	Synonyms	Keywords
ORPHA:73229	HANAC syndrome	Autosomal dominant familial hematuria-retinal arteriolar tortuosity-contractures syndrome Hereditary angiopathy-nephropathy-aneurysms-muscle cramps syndrome	Glomerular basement membrane disease due to a COL4A mutation
Definition: A rare multisystemic disease characterized by small-vessel brain disease, cerebral aneurysm, and extracerebral findings involving the kidney, muscle, and small vessels of the eye.			

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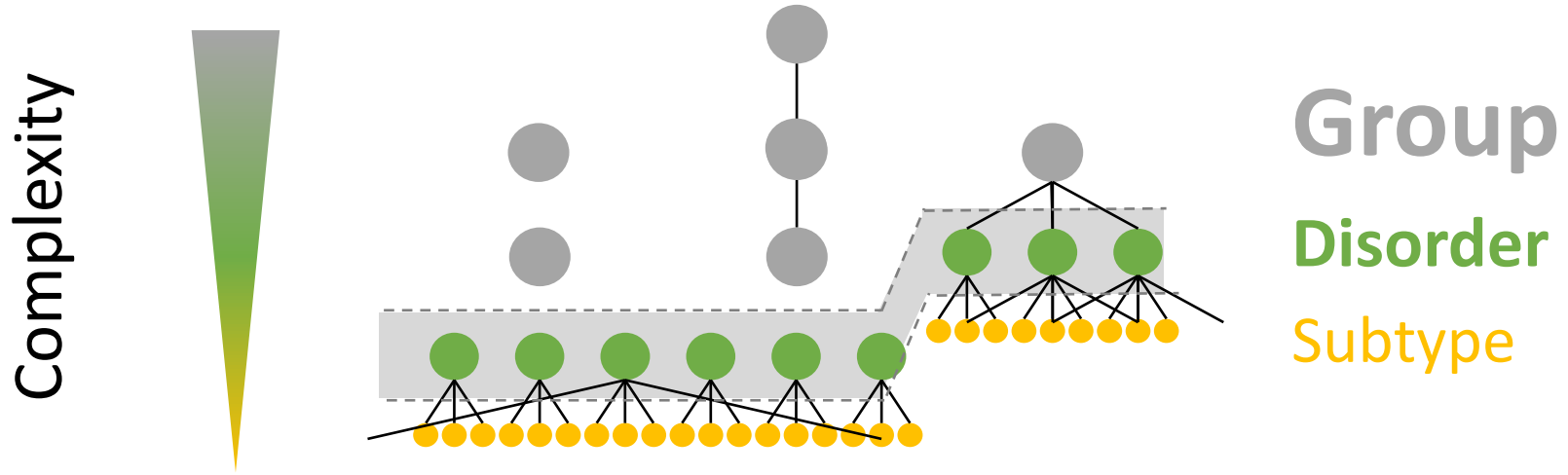
How are diseases organized in Orphanet?



Disorder:

- clinically homogeneous entity
- ≥ 2 independent individuals

(≠ incidental association of clinical signs)

More than **6,000 rare diseases** at the ''disorder'' level

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The Orphanet classification of RD

Multi-dimensional

Organized by **medical specialty**
As used in **clinical practice**
(if > 1 specialty →)

Stickler syndrome

- Orphanet classification of rare developmental anomalies during embryogenesis
- Classification of sucking/swallowing disorders
- Orphanet classification of rare genetic diseases
- Orphanet classification of rare eye diseases
- Orphanet classification of rare bone diseases
- Orphanet classification of rare otorhinolaryngological diseases
- Orphanet classification of rare surgical maxillo-facial diseases

"Preferential parent"
→ **Linearization for statistical purposes**

Hierarchical

Orphanet classification of rare bone diseases

- Rare bone disease ORPHA:93419
  - Primary bone dysplasia ORPHA:364526
    - Spondyloepiphyseal dysplasia and spondyloepimetaphyseal dysplasia ORPHA:253
      - **Stickler syndrome ORPHA:828**
        - Autosomal recessive Stickler syndrome ORPHA:250984
        - Stickler syndrome type 1 ORPHA:90653
        - Stickler syndrome type 2 ORPHA:90654

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Cross-referencing with other databases

→ Semantic interoperability

Ongoing collaborations:
SNOMED-CT, ICD-11 revision

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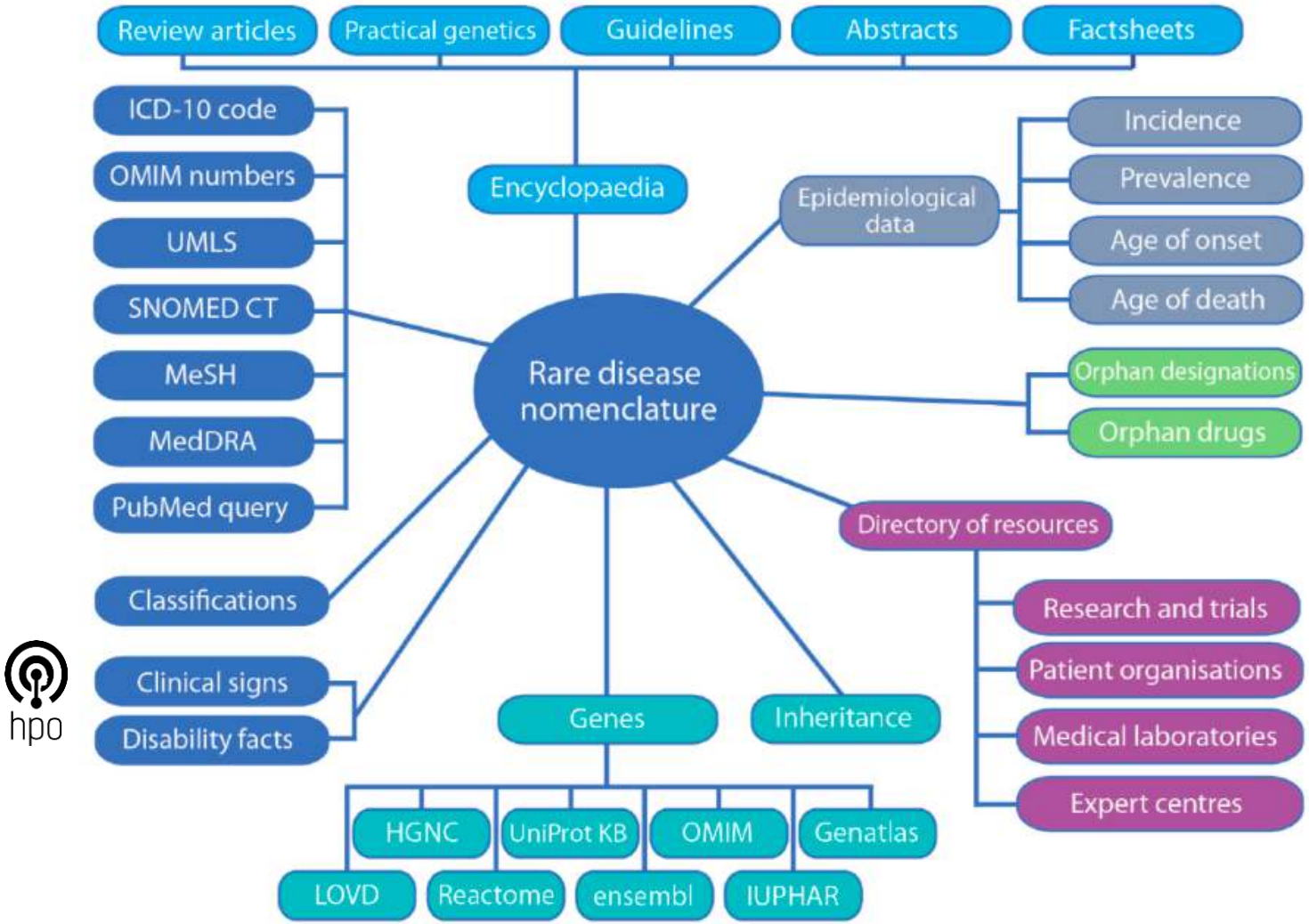
An exhaustive knowledge base



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THE ORPHANET ENCYCLOPEDIA FOR PROFESSIONALS

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Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Encyclopedia overview & characteristics

- Intended for healthcare professionals
- Clinical emphasis
- Use of HPO terms (where possible)
- Based on review of biomedical literature
- Texts are limited to **3,500-4,000** characters

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Types of text?

Definition

- **Forms part of nomenclature**
- Required for **all** disorders
- Historic entities (>25 years since last report)

Abstract

- According to priorities
- 8 – 10 sections (**3500 -4000 characters max**)
- >< historic entities
- Reviewed by experts in the disease/group of diseases

Standard text

- “This disease is described under…”
- Certain subtypes (e.g. etiological, histological) are described under clinical group or disorder
- Certain groups (e.g. category)

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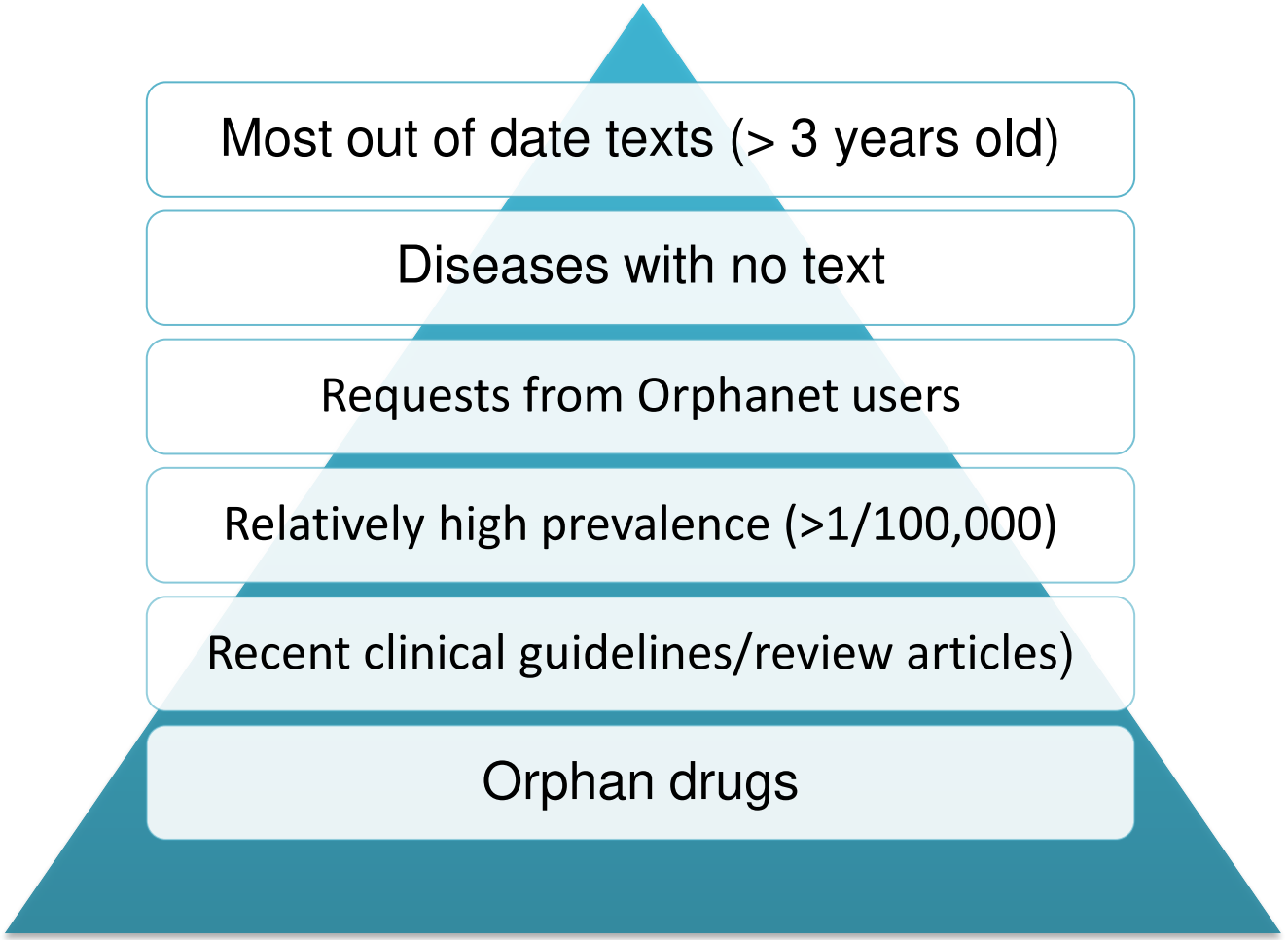
Which diseases to prioritise



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ITHACA-ORPHANET COLLABORATION OVERVIEW

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Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Orphanet/ERN collaboration: a mutual benefit

Scientific expertise

Data validation

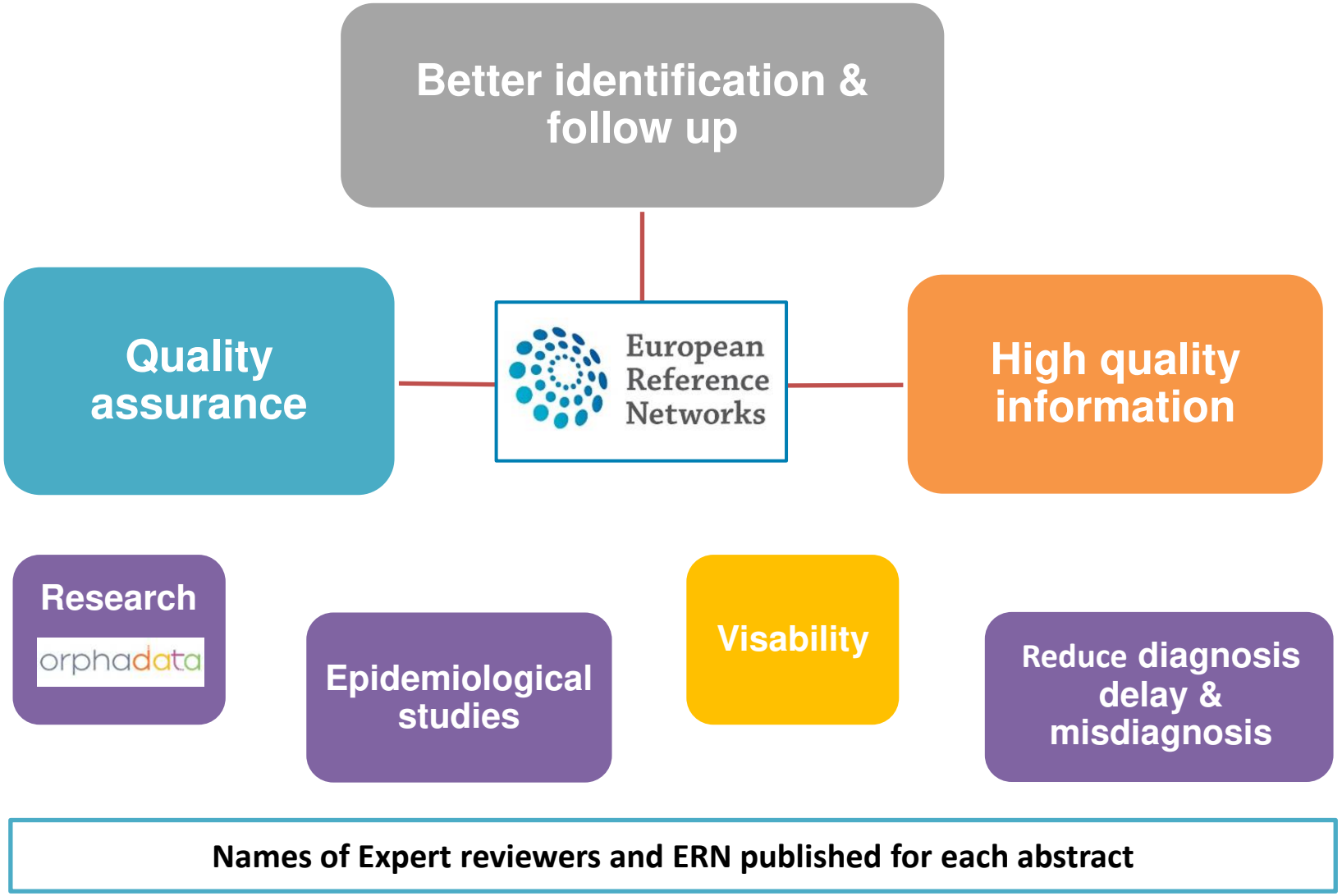
orphanet ⇌ European Reference Networks

Expertise on **databasing and classification**

→ Standardized structure of clinical information

Data for **analysis** of RD orphadata

Why is your contribution important?



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Proposed collaboration

Quality control of published definitions

Disease summary texts (abstracts)

Text translation

HPO annotation

Classification

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Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Quality control of disease definitions

Definitions form part of the Orphanet nomenclature.

To assure quality, experts were asked to verify that that the clinical characteristics (or where relevant the biochemical or imaging characteristics) that define the disease were correctly described.

Attributed to experts reviewing relevant diseases (i.e. same group)

Experts are acknowledged in the Orphanet Report Series

QC Status	Grand total
Completed	15
In progress	5
Total	**20**

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Disease summary texts

- From the experts invited 94 disease summary texts were accepted
- Includes updates, new texts and review of draft texts
- No action required (36):
  - recently published
  - ongoing with a different expert
- Pending
  - few patients reported
  - Disease creation to be evaluated
  - Awaiting confirmation of reviewer's expertise

Current Status	Grand Total
Published	**36**
In progress	**58**
New expert required	29
No action required	36
Pending	53
Grand Total	**212**

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Orphanet definition of an expert

A medical doctor or researcher with prominent experience in a rare disease or a group of rare diseases, and identified by Orphanet based on published articles (particularly reviews and guidelines), involvement in expert centers, expert networks, and/or in dedicated research activities including clinical trials.

Volunteers can of course write a text provided it is validated by an expert who fulfils the above criteria.

From the point of view of the reader: The expert reviewer is understood as the expert on the disease.

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Text translations (French)

- 2 translations of text in English to French

- Translations must be true to the original English text, and must not add or substract information

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Classification (reviewed as required)

KMT2D	KMT2D-related disorder	Created
CNTNAP2 / NRXN1	Pitt Hopkins-like syndrome	Ongoing
CHD3	Snijders Block-Campeau syndrome	Ongoing
KMT2C	KMT2C - Kleefstra syndrome	Ongoing
SPECC1L	Opitz GBBB syndrome	Ongoing
MECP2	MECP2 duplication syndrome	Ongoing
POR	Antley-Bixler syndrome	Ongoing
LZTR1	Noonan Syndrome, Autosomal Recessive	To be reviewed
DLG4	Intellectual developmental disorder 62 MRD62	To be reviewed
BRPF1	Intellectual developmental disorder with dysmorphic facies and ptosis (IDDDFP)	To be reviewed
PUM1	Pumilio-1-associated developmental disability, ataxia, and seizure (PADDAS)/ spinocerebellar ataxia 47	To be reviewed
TUBB2A	TUBB2A - tubulin beta 2A class IIa	To be reviewed
TBR1	Intellectual Developmental Disorder With Autism And Speech Delay; IDDAS	To be reviewed

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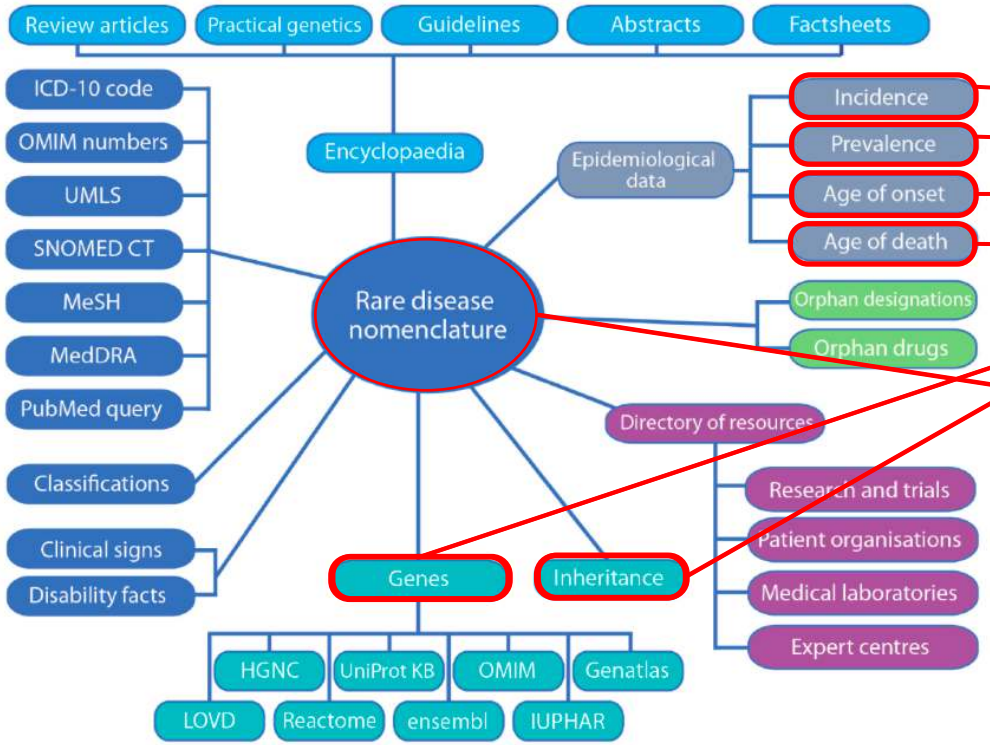
Update of associated disease data



ITHACA experts have also helped to update the associated disease data!

Validated information is displayed on the disease web page or exportable via Orphadata.org et ORDO

NB: References only required in order to link **new** data.

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Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Some Feedback

- Experts are very responsive and high rate of engagement
- Occasionally, abstracts too long
- Clinical vs etiological subtypes and OMIM
- Nomenclature/ synonyms – must correspond exactly to the disorder
- Differential diagnosis – sometimes entities included that are not created in ORPHANET.
- How to verify who is affiliated with the ITHACA? (e.g. text collaboration with colleagues should we associate everyone from the centre

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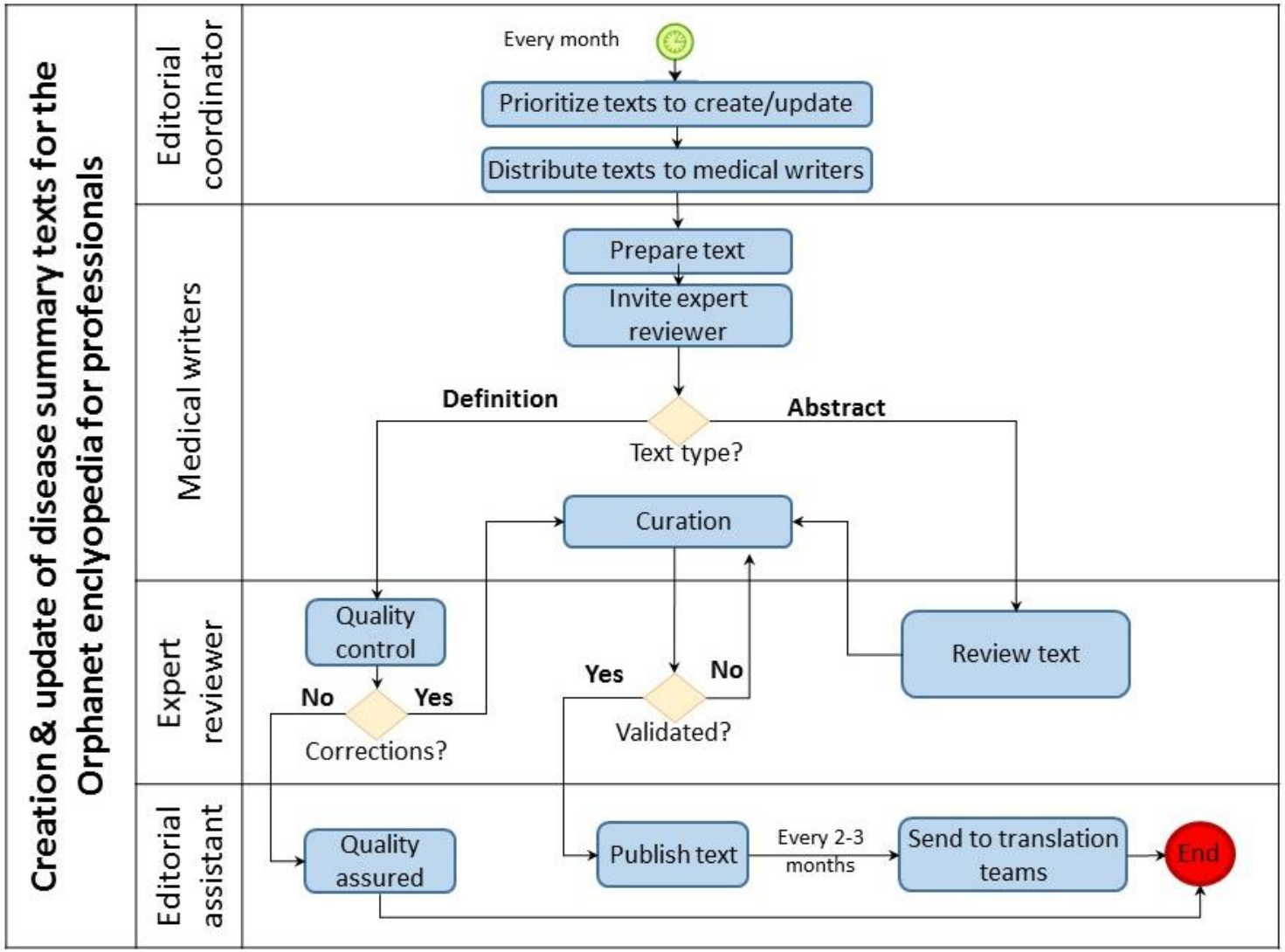
Orphanet encyclopedia for professionals



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Thank you for your attention!
Time for your feedback…

"THE BAD NEWS IS YOU HAVE A DISEASE UNKNOWN TO MEDICAL SCIENCE - THE GOOD NEWS IS I'M GOING TO NAME IT AFTER ME."

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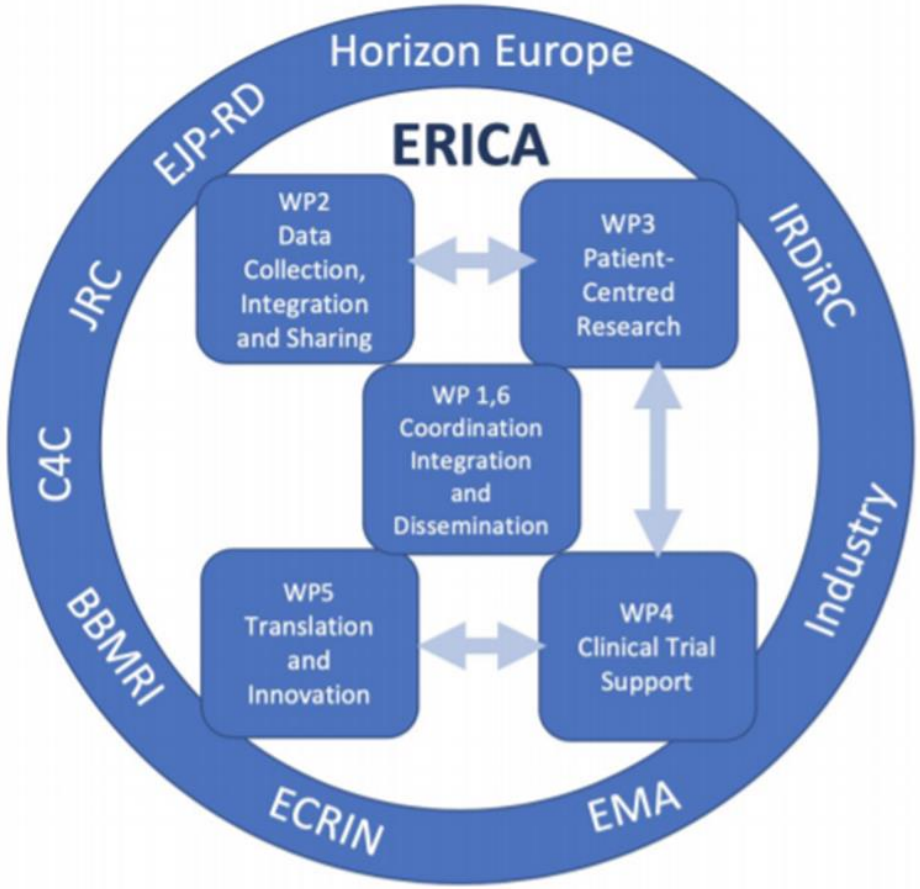
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Involvement in ERICA «European Rare disease research Coordination and support Action» project

- Coordinator: Alberto Pereira (Endo-ERN)
- ERICA consortium includes all 24 ERNs
- Objectives:
  - new intra- and inter-ERN rare disease competitive networks;
  - effective data collection strategies;
  - better patient involvement;
  - enhanced quality and impact of clinical trials;
  - enhanced quality and impact of clinical trials;
  - increased awareness of ERN's innovation potential;

- Strengthen the research and innovation capacity of the ERNs through integration of the ERN research activities outreach to European research infrastructures



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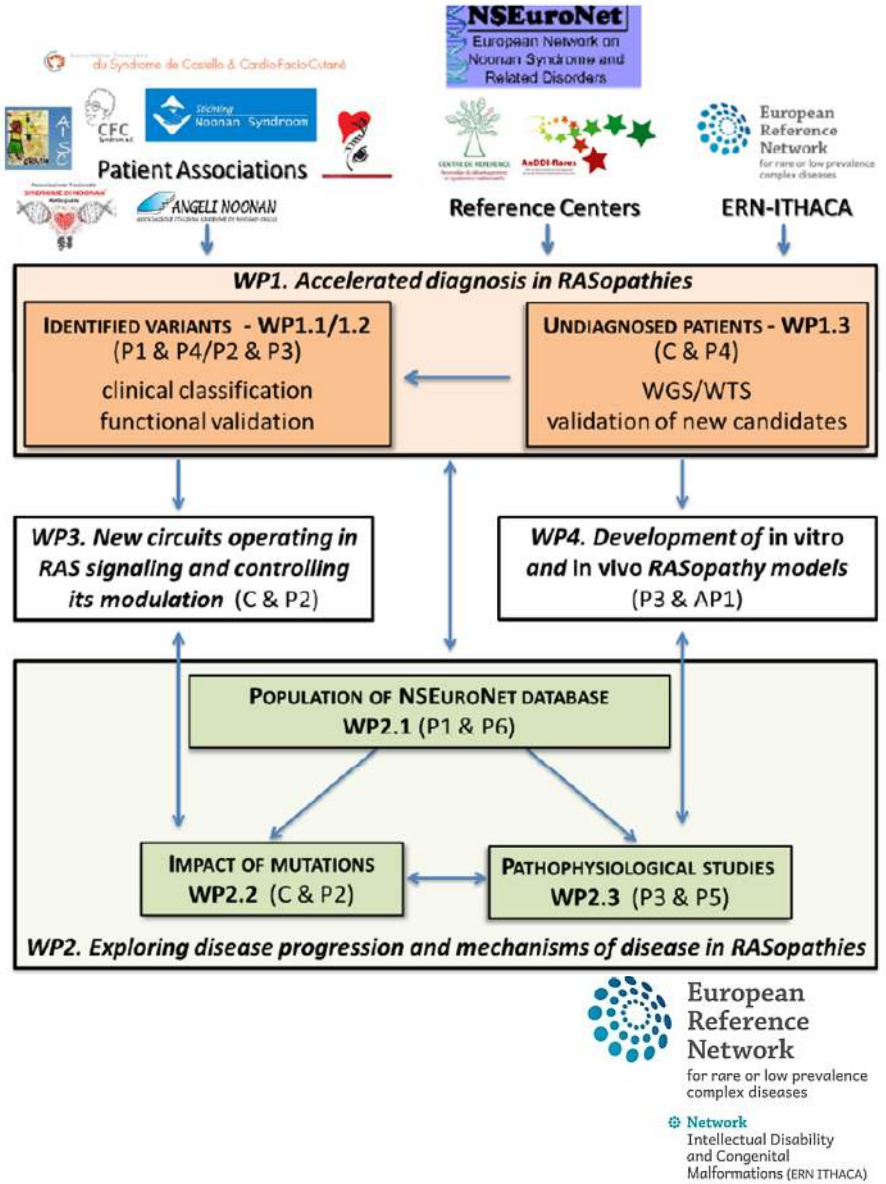
NSEuroNet «European network on Noonan syndrome and related disorders»

- Coordinator: Marco Tartaglia
- NSEuroNet consortium includes 7 partners from Italy, France, Germany, The Netherlands, Poland, and USA
- Objectives:
  - To resolve the functional consequences of a large panel of uncharacterized mutations
  - To generate *in vitro* and *in vivo* gene/mutation-specific models
  - To characterize novel circuits modulating RAS signaling
  - To explore the pathophysiology of key complications of these diseases
  - To identify novel disease genes
  - to populate a dedicated database (link with ILIAD project) that will be used for clinically oriented studies
- ERN-ITHACA contribution and planned activities:
  - Monthly/bimonthly session for the discussion of molecularly undiagnosed NS/RASopathies patients through CPMS or similar tool
  - Selection of cases
  - First level molecular analysis offered to East-European Countries
  - Each contribution is welcomed during the «Dysmorphology Meeting»



Next expected deliverables and projects for the group

WP7	D7.1	Produce collaborative research studies on a series of patients with unsolved disorders or on mechanisms of RD	At least 3 collaborative works (publications, conference papers, etc.) citing ITHACA and listed on the ERN website, describing new genes or pathogenic mechanisms	Report	Public	28 Feb 2022	Pending

- Urgent to have visibility
- Involvement in ERICA project
- Clinical research: use collaborative calls and involve trainees
- NOT IN DELIVERABLE
  - Manage EJP-RD calls
    - Selection of patients for EJP-RD exchange calls
    - Sponsoring of workshops

MONITORING
Items 5

MONITORING
Items 4b

Forecasts of the working group

- Discussion for Y 4-5 Future objectives
  - D7.1 Produce collaborative research studies on a series of patients with unsolved disorders or on mechanisms of RD
  - MS12 Exchange two trainees per year between participating HCPs to promote research: collaborations and knowledge sharing
  - MS13 Publish 1 collaborative research article per year on new disease genes or mechanisms

- Bimonthly TC to speed up the WG activities and promote collaborative projects
- New members expectations and major research topic(s)
- Looking for new co-deputy chair
- Agenda next meeting 2021

- Points to summarize for the afternoon plenary session
  - Manage of EJPRD-ERN fellowship Call 2020
  - Y4-5 objectives
  - Involvement of ERN-ITHACA in cross-ERN projects and initiatives
  - Ongoing collaborative clinical research

Do not hesitate to send your feed back
Thankyou for your participation – PM Contact anne.hugon@aphp.fr

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