

BeSHG

Interuniversity course

Yves Sznajer

Center for Human Genetic



Development Genetics and Birth defects

Refer to Thompson / Thompson 8th Edit Chapter 14

Framework

- Rationale in medical genetics
- Tool I: Registry - Epidemiology - Database
- Tool II: Definitions and Nosology
- Tool III: Distinct approaches
 - Dysmorphology
 - Syndromology

Rationale in medical genetic

*Clinical geneticist seeks a consistent approach
to lead to the diagnosis in a patient with birth defect*

Aims

- diagnostic assessment
- more precise delineation on natural history
- follow-up and prognosis
- open to precise genetic counselling

- Evidence derived from

Embryology: chronologic and stepwise mechanisms leading to ab-/normal development

Epidemiology - Population Genetics

Animal models

Prediction tools

Registries and Databases

Tool I - Congenital Anomalies Registry

Specific public health problem indicators EUROCAT

tribute to Professor Yves Gillerot

Central Registry – Project Management Committee
Reliable, Available and Comparable on quantitative or qualitative parameters - Dataset Registries



JRC TECHNICAL REPORT

European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2008 - 2017)

Agnieszka Kinsner-Ovaskainen, Joan Morris, Ester Garnier, Maria Loane, Monica Lanzoni

2020

EUROCAT is a European network of population-based registries for the epidemiological surveillance of congenital anomalies

The JRC-EUROCAT Central Registry maintains the EUROCAT Central Database

The database is dynamic, and is updated bi-annually with data from over 40 registries

The JRC-EUROCAT Central Registry reports and disseminates on a dedicated website updated data on the surveillance of congenital anomalies

The following information is provided: prevalence for **104** congenital anomaly subgroups, prenatal detection rates for **18 selected subgroups of congenital anomalies**, and **perinatal mortality associated with congenital anomalies**

<https://op.europa.eu/en/publication-detail/-/publication/cc2ffa13-d854-11ea-adf7-01aa75ed71a1/language-en>

example: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/ppe.12776>
Epidemiology of Pierre-Robin sequence in Europe: A population-based EUROCAT study

Tool I - Congenital Anomalies (CA) Registry

The Objectives of EUROCAT

- provide essential epidemiologic information on CA in Europe
- facilitate the early warning of new teratogenic exposures
- evaluate the effectiveness of primary prevention
- assess the impact of developments in prenatal screening
- act as an information and resource center for the population health professionals and managers regarding clusters or exposures or risk factors of concern
- provide a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children
- act as a catalyst for the setting up of registries throughout Europe collecting comparable and standardised data



EUROCAT Network

Overview of the EUROCAT network, its organisation and committees



Member Registries

Information about the EUROCAT member registries, coverage and how to apply for membership



Data and surveillance

Prevalence tables, prenatal detection rates and reports on statistical monitoring of congenital anomalies



Data Collection



Prevention and risk factors



Research



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Access to Joint Research
Centre's publications



publications.jrc.ec.europa.eu/repository/handle/JRC120236

[European Commission](#) > [JRC](#) > [JRC Publications Repository](#) > European Monitoring of Congenital Anomalies

2020

Technical reports

Health and consumer protection

European Monitoring of Congenital Anomalies: JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2008 - 2017)

Abstract: Worldwide, congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. According to the EUROCAT estimates, of the 5.1 million births in the European Union (EU) each year approximately 127,000 (2.5%) have a congenital anomaly. EUROCAT is a European network of population-based registries whose objectives are to provide essential epidemiologic information on congenital anomalies in Europe, to facilitate the early warning of new teratogenic exposures and to evaluate the effectiveness of primary prevention. Each year, EUROCAT performs statistical monitoring for both trends and clusters in time on 84 anomaly subgroups. The results of the statistical monitoring are the basis for instigating possible further investigations at the local registry level. The present report shows the results of the monitoring performed on data for the birth years 2008-2017 by the JRC-EUROCAT Central Registry. Cases of congenital anomaly among livebirths, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly following prenatal diagnosis at any gestational age were included. We report both the statistical results and, where available, the outcome of the preliminary investigations conducted by registries.



JRC TECHNICAL REPORT

European Monitoring of Congenital
Anomalies

JRC-EUROCAT Report on Statistical
Monitoring of Congenital Anomalies
2008 - 2017

Author(s): Michaela Kretschmer, Jean-Marc
Bégin, Sophie Moret-Lafon, Monique Létourneau

EUROCAT Prevalence Data Tables

Cases and prevalence (per 10,000 births) of all congenital anomaly subgroups for all registries, from 2011 - 2015

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	LB+FD+TOPFA N	Excluding Genetic Conditions LB+FD+TOPFA Rate
All Anomalies	59179	1433	14619	75231	253.31 (251.51 - 255.13)	60392	203.35 (201.73 - 204.98)
Nervous system	3402	270	4040	7712	25.97 (25.39 - 26.55)	6558	22.08 (21.55 - 22.62)
Neural Tube Defects	621	102	2334	3057	10.29 (9.93 - 10.66)	2862	9.64 (9.29 - 10.00)
Anencephalus and similar	67	58	1074	1199	4.04 (3.81 - 4.27)	1155	3.89 (3.67 - 4.12)
Encephalocele	82	8	249	339	1.14 (1.02 - 1.27)	291	0.98 (0.87 - 1.10)
Spina Bifida	472	36	1011	1519	5.11 (4.86 - 5.38)	1416	4.77 (4.52 - 5.02)
Hydrocephalus	815	66	711	1592	5.36 (5.10 - 5.63)	1327	4.47 (4.23 - 4.72)
Microcephaly	658	36	97	791	2.68 (2.49 - 2.87)	640	2.16 (2.00 - 2.34)
Arhinencephaly/holoprosencephaly	67	17	364	448	1.51 (1.37 - 1.65)	271	0.91 (0.81 - 1.03)
Eye	1036	15	99	1150	3.87 (3.65 - 4.10)	935	3.15 (2.95 - 3.36)
Anophthalmos/microphthalmos	195	8	61	264	0.89 (0.78 - 1.00)	188	0.63 (0.55 - 0.73)
Anophthalmos	35	2	28	65	0.22 (0.17 - 0.28)	53	0.18 (0.13 - 0.23)
Congenital cataract	361	1	4	366	1.23 (1.11 - 1.37)	312	1.05 (0.94 - 1.17)
Congenital glaucoma	95	0	0	95	0.32 (0.26 - 0.39)	89	0.30 (0.24 - 0.37)
Ear, face and neck	420	21	84	525	1.77 (1.62 - 1.93)	409	1.38 (1.25 - 1.52)
Anotia	55	0	4	59	0.20 (0.15 - 0.26)	53	0.18 (0.13 - 0.23)
Congenital heart defects	19889	380	2440	22709	76.46 (75.47 - 77.47)	19309	65.02 (64.10 - 65.94)
Severe CHD §	5267	193	1489	6949	23.40 (22.85 - 23.95)	5523	18.60 (18.11 - 19.09)
Common arterial truncus	141	9	60	210	0.71 (0.61 - 0.81)	151	0.51 (0.43 - 0.60)
Double outlet right ventricle §	327	19	116	462	1.56 (1.42 - 1.70)	387	1.30 (1.18 - 1.44)
Transposition of great vessels	840	15	136	991	3.34 (3.13 - 3.55)	953	3.21 (3.01 - 3.42)
Single ventricle	123	5	111	239	0.80 (0.71 - 0.91)	210	0.71 (0.61 - 0.81)
Ventricular septal defect	10098	123	637	10858	36.56 (35.88 - 37.25)	9543	32.13 (31.49 - 32.78)
Atrial septal defect	4587	30	100	4717	15.88 (15.43 - 16.34)	3983	13.41 (13.00 - 13.83)
Atrioventricular septal defect	913	55	381	1349	4.54 (4.30 - 4.79)	612	2.06 (1.90 - 2.23)
Tetralogy of Fallot	825	22	181	1028	3.46 (3.25 - 3.68)	825	2.78 (2.59 - 2.97)
Tricuspid atresia and stenosis	133	10	70	213	0.72 (0.62 - 0.82)	198	0.67 (0.58 - 0.77)
Ebstein's anomaly	108	9	14	131	0.44 (0.37 - 0.52)	124	0.42 (0.35 - 0.50)
Pulmonary valve stenosis	1140	6	49	1195	4.02 (3.80 - 4.26)	1073	3.61 (3.40 - 3.84)
Pulmonary valve atresia	218	1	73	292	0.98 (0.87 - 1.10)	266	0.90 (0.79 - 1.01)
Aortic valve atresia/stenosis §	364	7	66	437	1.47 (1.34 - 1.62)	393	1.32 (1.20 - 1.46)
Mitral valve anomalies	337	5	55	397	1.34 (1.21 - 1.47)	351	1.18 (1.06 - 1.31)
Hypoplastic left heart	393	36	381	810	2.73 (2.54 - 2.92)	710	2.39 (2.22 - 2.57)
Hypoplastic right heart §	86	9	67	162	0.55 (0.46 - 0.64)	153	0.52 (0.44 - 0.60)

LB = Live Births

FD = Fetal Deaths / Still Births from 20 weeks gestation

TOPFA = Termination of pregnancy for fetal anomaly following prenatal diagnosis - - = Data not available

§ = Incomplete or missing specification of ICD 9 codes

Source: EUROCAT Website Database: <http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables> (data uploaded 07/04/2017)

Copyright: University of Ulster, 2012



English EN

Search

European Commission > EU Science Hub > European Platform on Rare Disease Registration > EUROCAT > EUROCAT data > Prevalence

Prevalence charts and tables

Country/Registry
None Selected

Anomaly
All anomalies

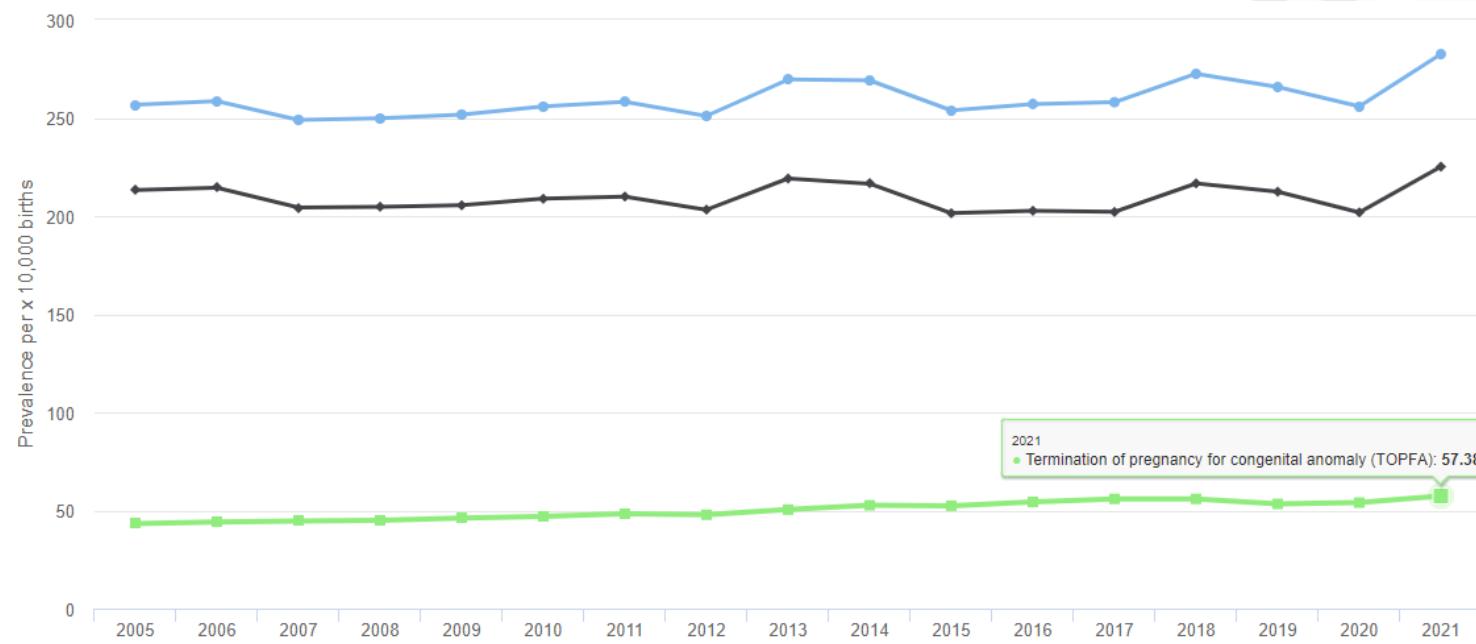
Years
2005 to 2021

Case with genetic conditions
Including genetic anomalies

[Export the raw data](#)

Prevalence rates by year

Prevalence per 10,000 births. All anomalies - 2005 to 2021 - All full registries - Including genetic anomalies



Legend

All cases

Live births + Still births from 20 weeks gestation

Termination of pregnancy for congenital anomaly (TOPFA)

Selected categories

Country/Registry

All full registries

Anomaly

All Anomalies

Years

2011 to 2017

- All countries and registries
- All registries
- All full registries
- All associate registries (A)
- All past registries (P)
- Manual selection

- Belgium
 - Antwerp
 - Hainaut
- Denmark
 - Odense
- France
 - Auvergne
 - Brittany
 - French West Indies
 - Isle de la Reunion
 - Paris
 - Rhone-Alps (A)
 - Central East France (P)
 - Strasbourg (P)
 - Italy
- Italy
 - Emilia Romagna
 - Tuscany
 - Campania (P)
 - North East Italy (P)
 - Sicily (P)
 - eland
 - Cork and Kerry
 - Dublin
 - SE Ireland
 - Galway (P)
 - L
 - N Netherlands

Eurocat adaptable tool

Anomalies

<input type="checkbox"/> All anomalies <input type="checkbox"/> Nervous system anomalies <input type="checkbox"/> Neural Tube Defects <input type="checkbox"/> Anencephaly and similar <input type="checkbox"/> Encephalocele and meningocele <input type="checkbox"/> Spina Bifida <input type="checkbox"/> Hydrocephaly <input type="checkbox"/> Severe microcephaly <input type="checkbox"/> Arhinencephaly / holoprosencephaly <input type="checkbox"/> Agenesis of corpus callosum <input type="checkbox"/> Eye anomalies <input type="checkbox"/> Anophthalmos / microphthalmos	<input type="checkbox"/> Gastro-intestinal anomalies <input type="checkbox"/> Oesophageal atresia with or without trachea-oesophageal fistula <input type="checkbox"/> Duodenal atresia or stenosis <input type="checkbox"/> Atresia or stenosis of other parts of small intestine <input type="checkbox"/> Ano-rectal atresia or and stenosis <input type="checkbox"/> Hirschsprung's disease <input type="checkbox"/> Atresia of bile ducts <input type="checkbox"/> Annular pancreas <input type="checkbox"/> Anomalies of intestinal fixation <input type="checkbox"/> Diaphragmatic hernia <input type="checkbox"/> Abdominal wall defects <input type="checkbox"/> Gastroschisis
--	---

Include cases with known genetic conditions Exclude cases with known genetic conditions Display both

Years


Year from 2000 to 2016

Individual years Combined years Display both

Fields

<input checked="" type="checkbox"/> Number of cases <input checked="" type="checkbox"/> Total prevalence <input checked="" type="checkbox"/> Fetal death prevalence <input checked="" type="checkbox"/> Livebirth proportion <input checked="" type="checkbox"/> TOPFA proportion	<input checked="" type="checkbox"/> Population <input checked="" type="checkbox"/> Live prevalence <input checked="" type="checkbox"/> TOPFA prevalence <input checked="" type="checkbox"/> Fetal death proportion
---	---

Another example – Selected categories

Chromosomal				
– Down Syndrome	43.58 (42.99 - 44.17)	16.67 (16.30 - 17.04)	1.54 (1.43 - 1.66)	25.37 (24.92 - 25.83)
– Patau syndrome/trisomy 13	24.14 (23.71 - 24.59)	9.74 (9.46 - 10.03)	0.50 (0.44 - 0.56)	13.91 (13.57 - 14.24)
– Edward syndrome/trisomy 18	2.18 (2.05 - 2.31)	0.30 (0.25 - 0.35)	0.12 (0.09 - 0.15)	1.76 (1.64 - 1.88)
– Turner syndrome	5.94 (5.72 - 6.16)	0.69 (0.62 - 0.77)	0.45 (0.39 - 0.52)	4.79 (4.59 - 4.99)
– Klinefelter syndrome	2.48 (2.34 - 2.63)	0.57 (0.51 - 0.65)	0.16 (0.12 - 0.20)	1.75 (1.64 - 1.87)
	0.65 (0.58 - 0.73)	0.44 (0.38 - 0.50)	0.01 (0.00 - 0.03)	0.20 (0.16 - 0.24)

Tool I - Congenital Anomalies Registry(ct'd)

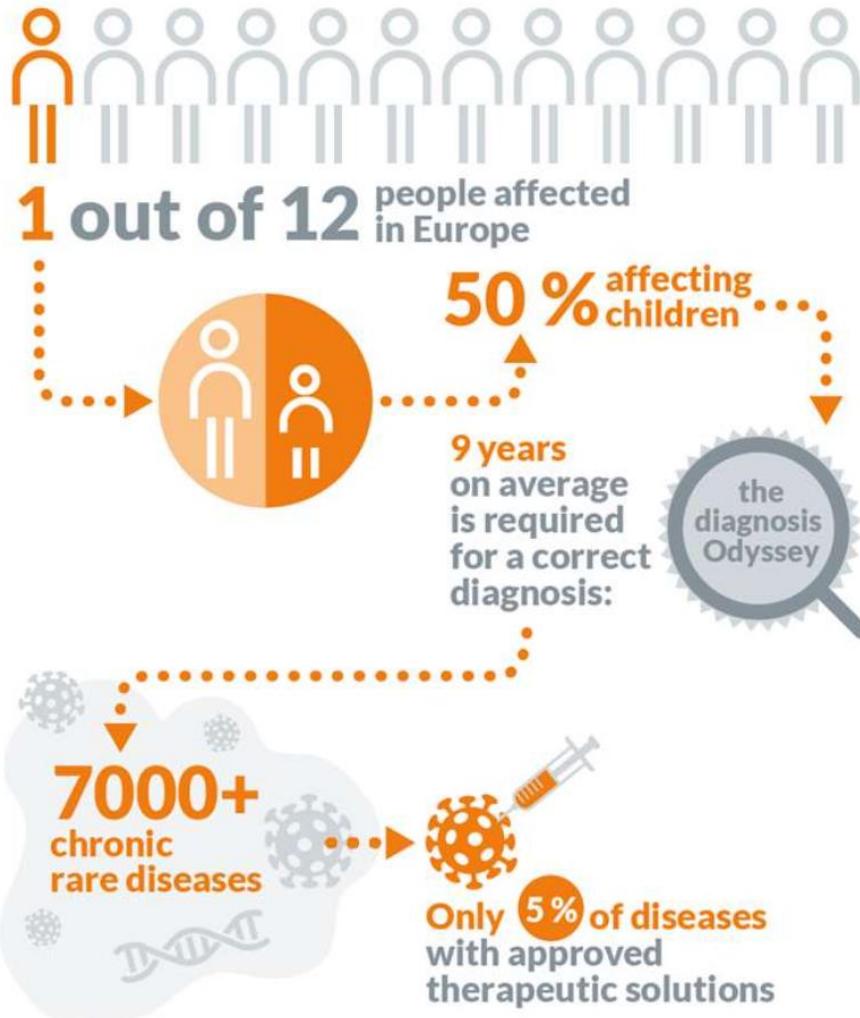
Networks of action for 'Rare diseases'*

- have been supported under the Program for Community Action on Rare Diseases in 1999-2003; the EU Public Health Program 2003-2007 and the second EU Health Program 2008-2013

The aims

- **improve exchange of information** via existing European networks
- **promote better classification**, develop strategies and mechanisms for exchanging information between people affected by a rare disease volunteers and professionals
- **define relevant health indicators**
- **develop comparable epidemiologic data at EU level**
- **support and exchange of best practice**
- develop measures for patient groups
- network and infrastructure for research into the causes and prevention of congenital anomalies and treatment/ care of affected children
- survey policies and practices with regard to periconceptional folic acid supplementation

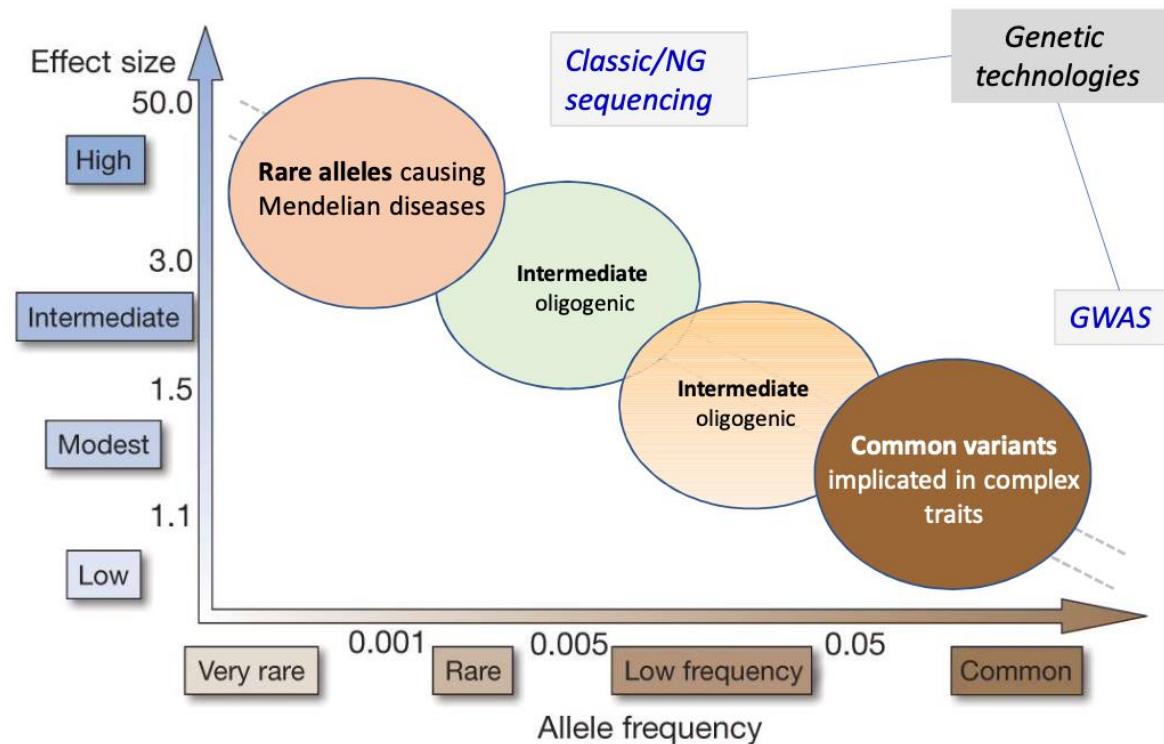
Rare diseases - definition



Rare diseases impact

- >80% with genetic origin
- Early onset , lifelong burden
- Difficult to diagnose and treat
- Often multisystemic – alter QOL
- Impact on social environment
- Fragmented support and research

Rare diseases – *The basics*



Manolio et al. Nature 461, 2009

Rare diseases – not limited to a concept



Belgisch plan voor
zeldzame ziekten



Bruxelles,
décembre 2013

TABLE DES MATIERES

Introduction

Domaine 1: Diagnostic et information au patient

Action 1: Remboursement des tests nécessaires au diagnostic et au suivi des maladies rares, effectués en Belgique ou à l'étranger

Action 2: Système de qualité au sein des centres de génétique humaine

Action 3: Introduction d'une consultation de conseil génétique dans les centres d'expertise pour maladies rares

Action 4: Consultation multidisciplinaire

Action 5: Communication centrée sur le patient

Action 6: Europlan

Domaine 2: Optimisation des soins

Action 7: Concentration de l'expertise et renforcement des centres de référence pour pathologies rares spécifiques existants : introduction d'un coordinateur de soins

Action 8: Création de centres d'expertise pour l'hémophilie

Action 9: Fonction maladies rares

Action 10: Réseaux maladies rares

Action 11: Nouveaux centres d'expertise

Action 12 : Alimentation médicale pour maladies rares

Action 13: Communication rapide des besoins médicaux : utilisation du dossier patient multidisciplinaire informatisé

Action 14: Unmet medical need

Action 15: Inventaire des besoins non couverts

Domaine 3: Connaissances et information

Action 16: Registre central des maladies rares

Action 17: Orphanet Belgium

Action 18: Formation des prestataires de soins

Action 19: Codification et terminologie

Domaine 4: Gouvernance et durabilité

Action 20: Evaluation et monitoring du Plan

The screenshot shows the homepage of the Institut des Maladies Rares website. At the top, there is a logo with a green leaf-like shape and the text "INSTITUT DES MALADIES RARES". Below it, it says "Cliniques universitaires SAINT-LUC | UCL Bruxelles". A banner at the top right features a smiling doctor in a white coat holding a clipboard, with a colorful confetti trail behind him. The main navigation bar includes links for "Accueil", "Présentation", "Centres", "Séminaire pratique", "Enseignement", and "Contact". A search bar is also present. The main content area has several sections: "Centres experts" (with a photo of a team in a lab), "Centres conventionnés INAMI" (with a photo of a group in a meeting room), "Consultations multidisciplinaires" (with a photo of a team at a table), and "Centre de génétique" (with a photo of a person using a microscope). Each section has a list of specific conditions or services. A sidebar on the left lists various rare diseases. The bottom right corner contains a green box with the text "Laboratoire de référence Screening prénatal".

2008: M-F. Vincent, M-C. Nassogne

Bienvenue sur le site de l'Institut des Maladies rares des Cliniques universitaires Saint-Luc !

Une maladie est dite rare lorsqu'elle affecte moins de 1 personne sur 2000. Entre 6000 à 8000 maladies rares sont identifiées. En Belgique, environ 700 000 personnes en sont atteintes. Souvent, les patients et leur médecin traitant se retrouvent démunis face aux pathologies et aux difficultés qu'elles impliquent. Afin d'aider les patients dans leur recherche du meilleur référencement et leur permettre un accès plus aisé aux consultations, les Cliniques universitaires Saint-Luc ont mis en place une structure organisationnelle : l'Institut des maladies rares.

Centres experts

- Affections pancréatiques de l'enfant
- Malformations vasculaires (angiomes)
- Centre labio-palatin Albert de Coninck
- Hémopathies cellulaires héréditaires ou congénitales
- Maladies autoimmunes et autoinflammatoires de l'enfant
- Maladies cardiaques rares
- Maladies endocrinienrées rares
- Maladies hépatiques de l'enfant
- Maladies neuro-cutanées congénitales
- Maladies neurogénétiques et neurodégénératives de l'enfant
- Maladies rhumatismales systémiques
- Pneumopathies infiltrantes diffuses

Centres conventionnés INAMI

Spécifiques aux maladies rares

- Hémophilie
- Maladies métaboliques héréditaires
- Maladies neuromusculaires
- Maladies rénales rares
- Mucoviscidose

Non spécifiques aux maladies rares

- Epilepsie réfractaire
- Infirmité motrice cérébrale (IMOC)
- Spina bifida
- Troubles du spectre autistique

Centre de génétique

Consultations multidisciplinaires

- Chiari type 1
- Dysplasie fibromusculaire
- Lupus Clinic
- Malformations vasculaires complexes et/ou syndromiques
- Naevus géant
- Ostéogénèse imparfaite (maladie des os de verre)
- Pathologies malformatives de l'œsophage
- Pied de Charcot
- Sclérose systémique
- Sclérose tubéreuse de Bourneville
- Syndrome de Marfan
- Syndrome de microdélétion 22
- Syndrome de Prader-Willi
- Syndrome de Williams
- Trisomie 21

Laboratoire de référence
Screening prénatal

> 20.000 patients



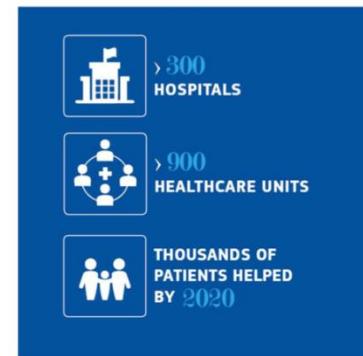
European
Reference
Networks

Rare diseases: european umbrella



European
Reference
Networks

>2016: 24 ERNS involving 25 European countries, over 300 hospitals with over 900 healthcare units and covering all major disease groups. http://ec.europa.eu/health/ern/policy_en

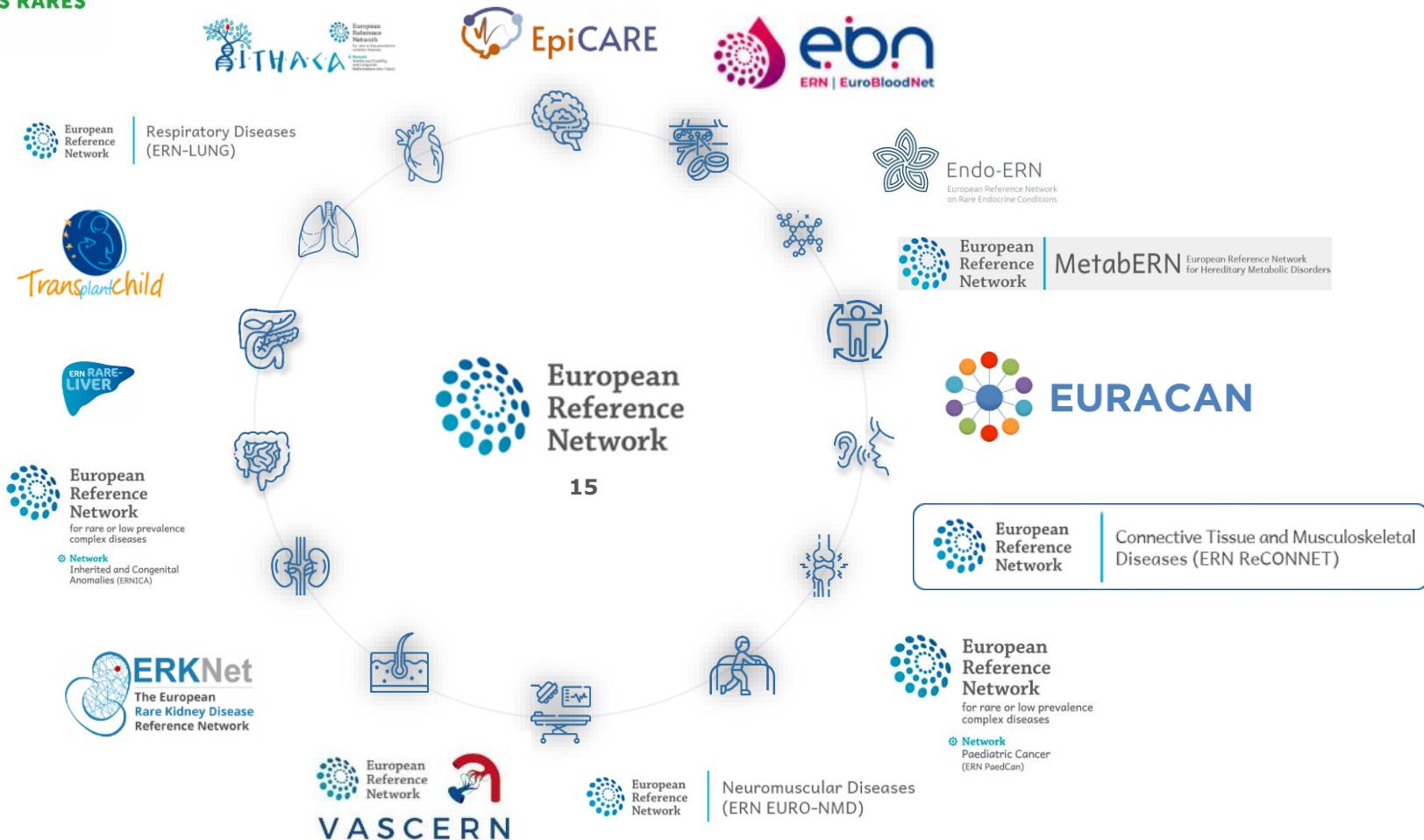


EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW-PREVALENCE AND COMPLEX DISEASES
Share. Care. Cure.



European
Reference
Networks





Evolutionary

ERN RARE-LIVER

Réseau européen de référence dédié aux maladies hépatiques

ERN TRANSPLANT-CHILD

Réseau européen de référence dédié à la transplantation chez l'enfant

Endo-ERN

Réseau européen de référence dédié aux maladies endocrinien

VASCERN

Réseau européen de référence dédié aux maladies vasculaires rares avec atteinte multi systémique

ERN EURO-NMD

Réseau européen de référence dédié aux maladies neuromusculaires

ERN ReCONNECT

Réseau européen de référence dédié aux maladies des tissus conjonctifs et musculosquelettiques

MetabERN

Réseau européen de référence dédié aux troubles héréditaires du métabolisme

ERKNet

Réseau européen de référence dédié aux maladies rénales

ERN EuroBloodNet

Réseau européen de référence dédié aux maladies hématologiques

ERNICA

Réseau européen de référence dédié aux anomalies congénitales et héréditaires

ERN EpiCARE

Réseau européen de référence dédié aux épilepsies

ERN ITHACA

Réseau européen de référence dédié aux malformations congénitales et aux handicaps intellectuels rares

ERN LUNG

Réseau européen de référence dédié aux maladies pulmonaires

ERN PAEDCAN

Réseau européen de référence dédié au cancer pédiatrique (hémato-oncologie)

ERN EURACAN

Réseau européen de référence dédié aux cancers chez les adultes (tumeurs solides)

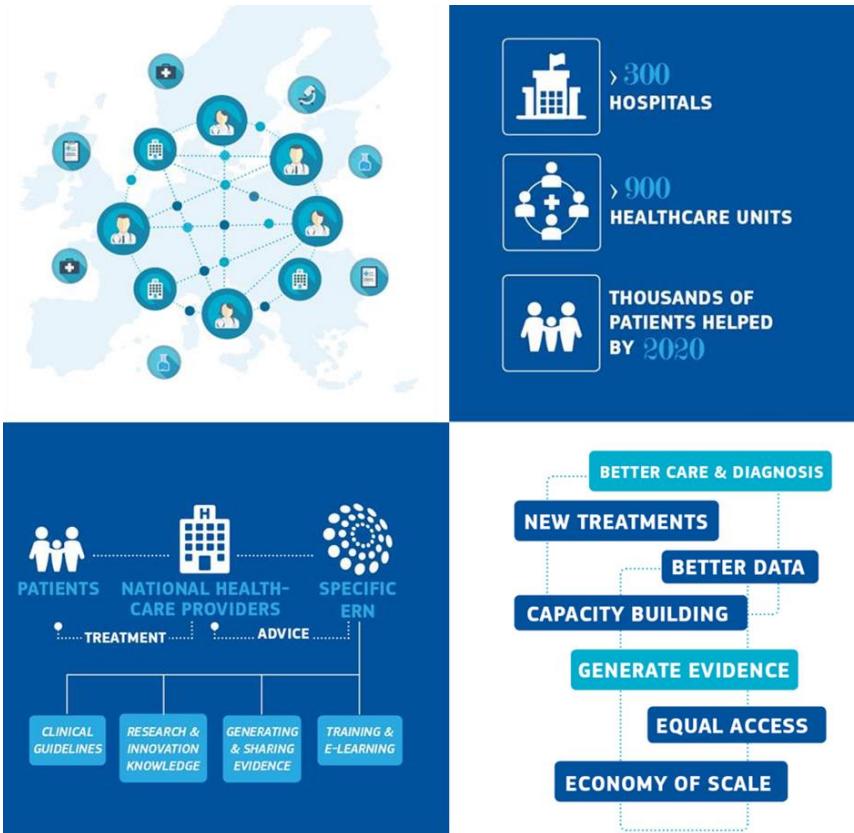
2017

9 ERNs

2022

+ 6 ERNs

European Reference Networks



- « Build guidelines, education and traineeship; peer review process
- Ease access to large cohorts /clinical trial – better understand on natural history of these conditions;
- **Collect data for development on drugs and pharmacotherapy as medical device ;**
- Update medical care and support – upgrade logistics and computer systems for better care

Source:

https://health.ec.europa.eu/european-reference-networks/work-erns_fr



EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW-PREVALENCE AND COMPLEX DISEASES

Share. Care. Cure.



Rare diseases : information sources

<https://www.orpha.net/consor/cgi-bin/index.php>



Aide

Nous contacter FR ▾

EN

ES

DE

IT

PT

NL

PL

CS

Le portail des maladies rares et des médicaments orphelins

« Aucune maladie n'est trop **rare** pour ne pas mériter attention »

Accédez à nos Services



Inventaire, classification et encyclopédie des maladies rares, avec les gènes associés



Inventaire des médicaments orphelins



Répertoire des associations et services aux patients



Répertoire des professionnels et institutions



Répertoire des centres experts



Répertoire des laboratoires médicaux fournissant des tests diagnostiques



Répertoire des projets de recherche en cours, essais cliniques, registres et biobanques



Collection de rapports thématiques : les Cahiers d'Orphanet



Chercher une maladie

Chercher

...informations



Associations de patients

Associations

Fédérations/Alliances

Lignes directes d'information

Accueil > Associations de patients > Associations

Rechercher une association de patients

Nom de maladie

(*) Champ obligatoire

Tous les pays

*

Chercher

Autre(s) option(s) de recherche ▲

› [Chercher par nom d'association](#)

Aide



[Data collection and registration of patient organisations in Orphanet](#)

Orphanet fournit des informations sur les associations de patients, les regroupements d'associations et les alliances dédiées à une maladie rare ou à un groupe de maladies rares.

Entrez le nom de la maladie recherchée pour accéder à cette information.

Les résultats peuvent être triés géographiquement (par pays, région et ville, par ordre alphabétique) ou par pertinence (les résultats spécifiques de la maladie apparaissent en premier, ceux relatifs aux groupes de maladies en second).



Avertissement

Patient support

EDITORIAL

Patient Organizations and Research on Rare Diseases

Julie R. Ingelfinger, M.D., and Jeffrey M. Drazen, M.D.

N Engl J Med 2011; 364:1670-1671 | April 28, 2011 | DOI: 10.1056/NEJMMe1102290



RaDiOrg.be
Rare Diseases Organisation



RE(ACT)
Community | The scientific knowledge sharing
and crowdfunding platform
for rare diseases

**BLACKSWAN
FOUNDATION**

 Fondation
Roi Baudouin
Agir ensemble pour une société meilleure

 **ABMM**
Maladies neuromusculaires

orphanhealthcare
Foundation for Rare Diseases

 **RARE DISORDERS**
Maladies Rares
Belgium
Alliance d'associations
et de patients concernés
par les Maladies Rares

 Member of
EURORDIS
Rare Diseases Europe



**SHORT GUIDE
ON PATIENT PARTNERSHIPS
IN RARE DISEASE
RESEARCH PROJECTS**

BASIC
PRE-CLINICAL
TRANSLATIONAL & SOCIAL

Written by the members
of the working group PENREP.
Guide first
published in July 2020
on www.ejprarediseases.org

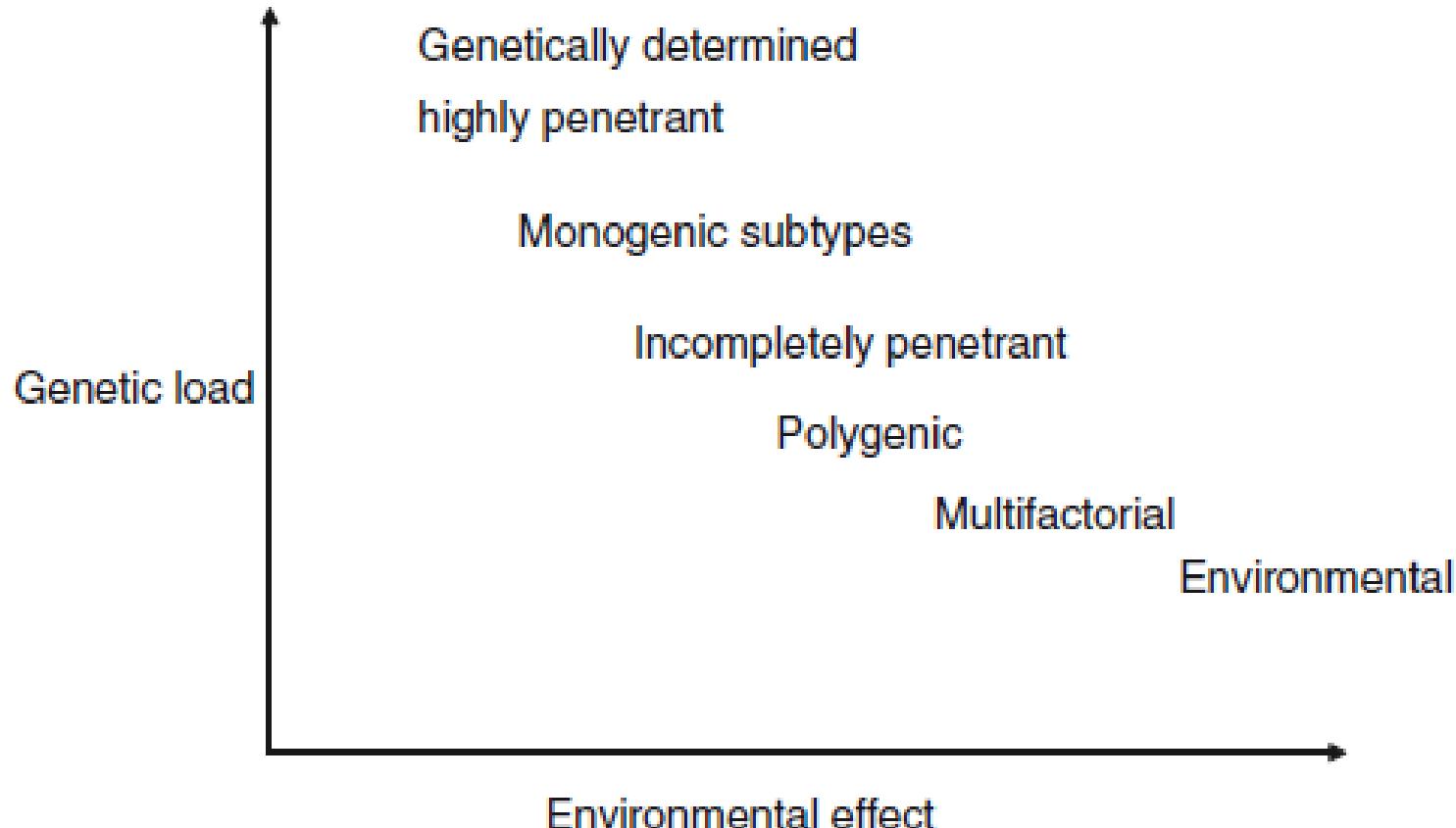
• Patient Engagement in
Biomedical Research Projects.

 EUROPEAN JOINT PROGRAMME
RARE DISEASES

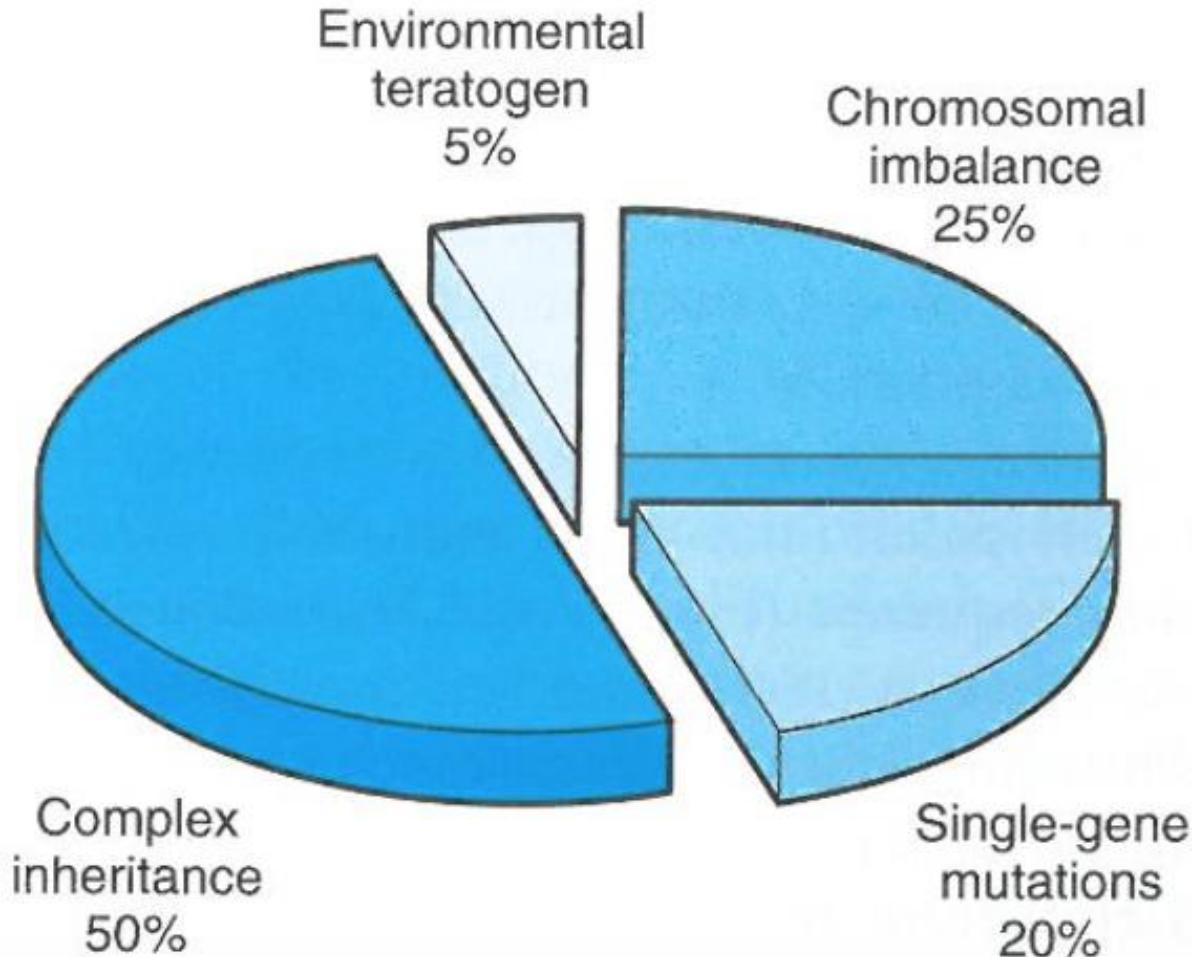


Birth defect - congenital anomaly

- Prevalence – 3%



Birth defect – ‘main categories’



Tool II - Birth defect - Nosology

- **Deformation** consequence of extrinsic factors that modify/alter physical devlpt (histology nl)
- **Disruption** destruction of irreplaceable fetal tissue (vascular, trauma, teratogen)
- **Dysplasia** abnormal shape, structure, composition and/ or histology during devlpt ectoderm structure and derivates leading to a wide range of phenotype bone/skeletal
- **Malformation** result from intrinsic abnormalities in one or more genetic program operating during development (e.g. polydactyly)

Illustration



(a)



(b)



(c)



(d)



(e)



(f)

Box figure 14.1 – Clinical photographs of the main types of dysmorphic features.

- (a) Cleft lip, a **malformation** representing failure of fusion of components of upper lip.
- (b) Meningomyelocele, talipes and hydrocephalus, a **malformation sequence** due to failure of closure of the neural tube and consequent effects.
- (c) Trisomy 13, a baby with a **malformation syndrome** consisting of holoprosencephaly, midline cleft lip and palate, polydactyly and heart defects.
- (d) Talipes, abnormal position of the feet, a **deformation** due to extreme lack of liquor *in utero*.
- (e) Amniotic bands **disruption** of a normal hand by constriction with strands of amnion leading to amputation and secondary fusion of finger tips (syndactyly).
- (f) Femur bones with multiple fractures and **abnormal modeling** due to osteogenesis imperfecta, a skeletal **dysplasia**.

Nosology (ct'd)

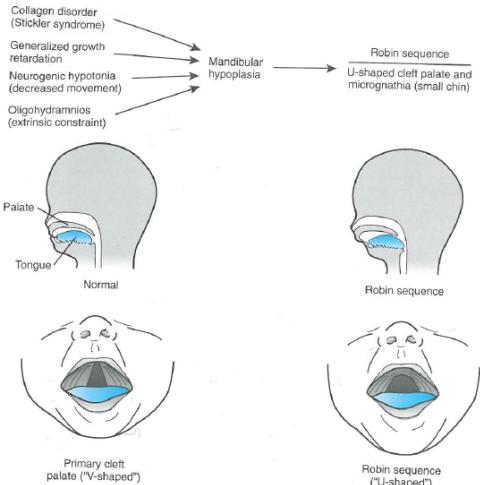
• Association

similar birth defects - different embryologic fields - inability so far to identify a genetic cause 'V.A.T.E.R', 'VACTER', 'VACTERL' cervico auriculo vertebral /'Goldenhar'

• Sequence

phenotype description of alteration of structures inside an embryonic field during development - *pleiotropic: effect on a single organ/system* - precise moment

NOT a diagnosis 'Pierre Robin', Potter'



Nosology (ct'd)

- **Syndrome**

combination of birth defects that occur secondarily to cytogenetic and/or a gene anomaly

- **Spectrum**

monogenic or cytogenetic anomaly leading to a modification in a signaling pathway during devlpt - possibly responsible for a range of signs that may be overlooked as distinct



Holoprosencephaly Sonic Hedgehog pathway *SHH*, *ZIC2*, *PATCH*,...

Tool III Clinical approach Dysmorphology

David Smith's contribution in 1966

- defines the distinctive clinical approach to look for distinct and/or minor signs in a patient to possibly obtain a diagnosis and orientate strategy to complete genotype definition – cytogenetic and/or molecular
- 'dysmorphologist' diagnoses a child with a birth defect, suggests appropriate work-up, guarantees follow-up and integrates pedigree and family history to published clinical reports to basic science literature

Path for reasoning

Clinical feature
of
congenital/birth defect



Clue for
syndrome identification



Orientate
Confirmatory diagnosis
Cytogenetic - molecular
cell biology - pathway

Dysmorphologist's 'textbook'

"Elements of Morphology: Standard Terminology"

John C. Carey*

International group of clinicians working in dysmorphology

Aims:

- initiate standardization of terms used to describe human morphology
- reach consensus regarding their definitions
- increase the utility of descriptions of the human phenotype
- facilitate reliable comparisons of findings among patients
- improve discussions with other related workers (pathologists, devlpt biology, molecular genetics) which will become more precise

Dysmorphology 'textbook'

"Elements of Morphology: Standard Terminology"

John C. Carey*

« These six articles provide **recommendations for the description and definition of human phenotypic variations** ... *in the same way that the International Standing Committee on Human Cytogenetic Nomenclature accomplished this for human cytogenetics [ISCN, 2005]* the *Nomenclature Working Group proposed the description of human sequence variations* [den Dunnen and Antonarakis, 2001]

Standard Terminology

- For Head and Face: pg 1- 23

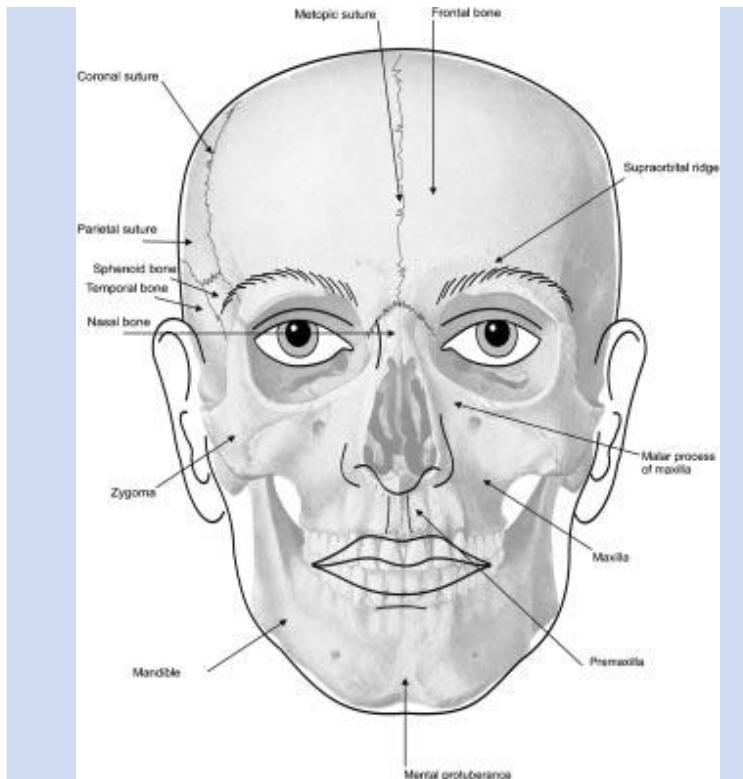


FIG. 1. An antero-posterior view of the cranium and face shows bony landmarks.

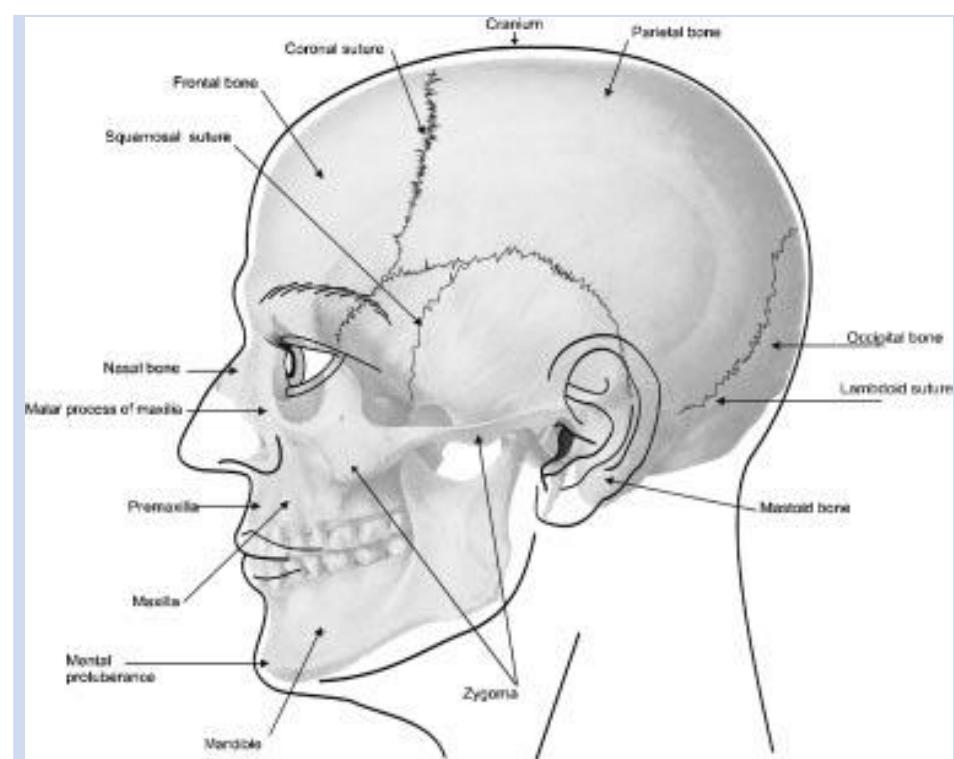


FIG. 2. A lateral view of the cranium and face shows bony landmarks.

Standard Terminology

- For Head and Face



FIG. 7. Macrocephaly. Note the increased size of the cranium. Differences in size are difficult to appreciate but increased head size in this child is notable because of comparison with the smaller face.

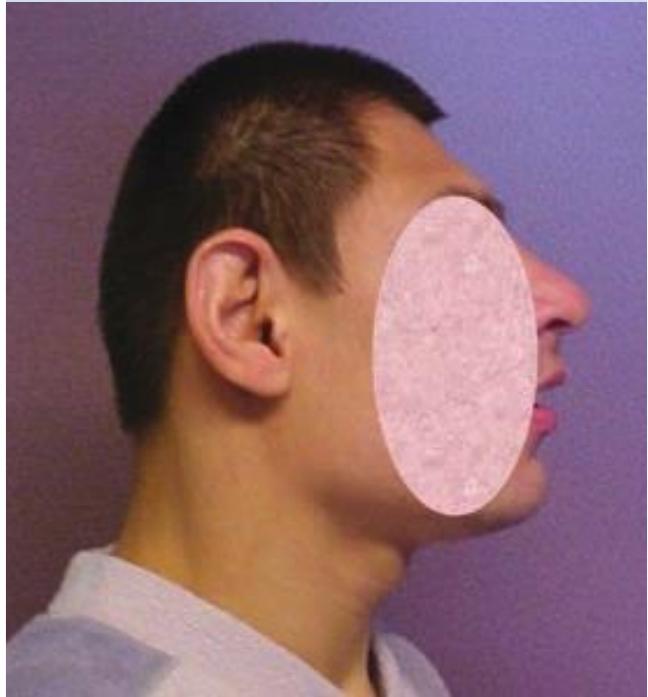
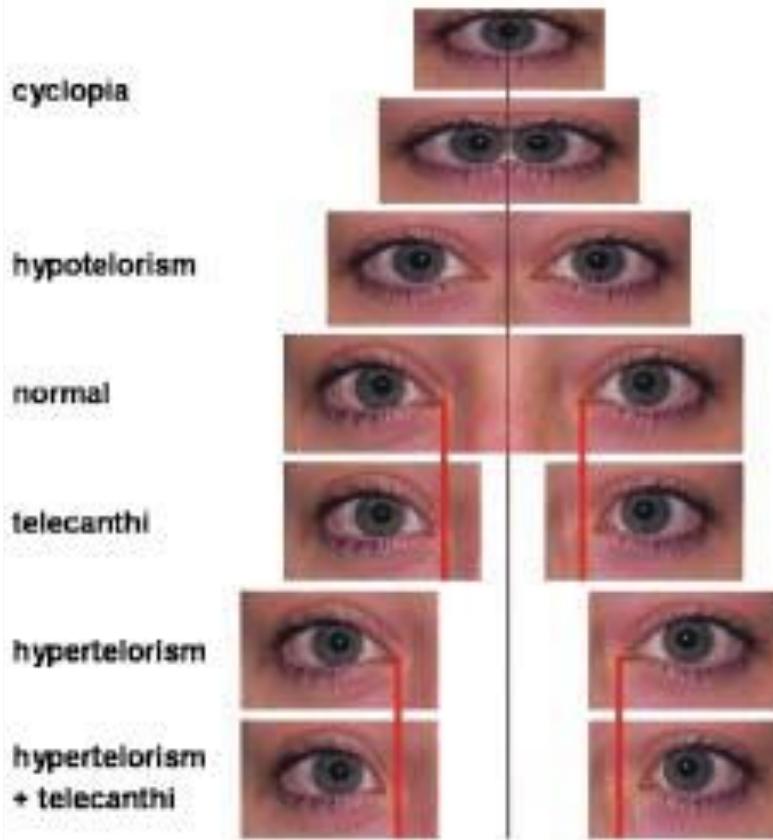
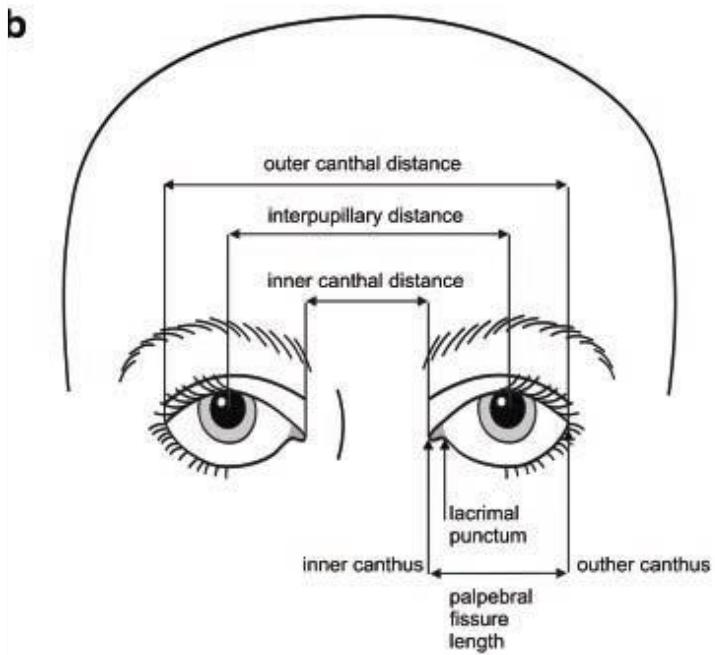
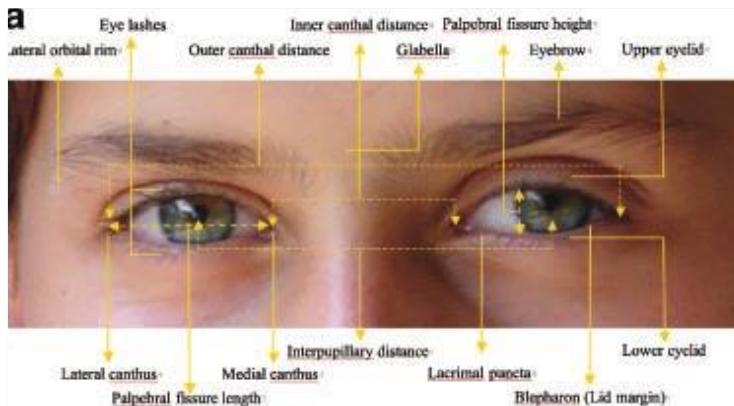


FIG. 8. Microcephaly. Decreased size of the cranium is accompanied by marked posterior sloping of the forehead.

Standard Terminology For Peri orbital Region – pg 29-39



Eyebrows

Orientation

- high
- horizontal



Shape

- arched
- heavy



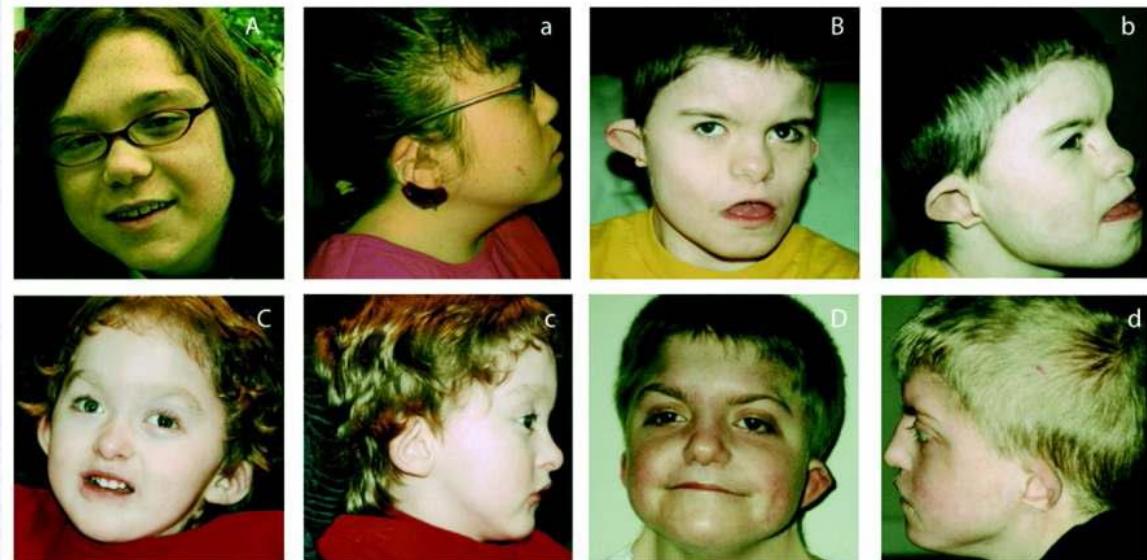
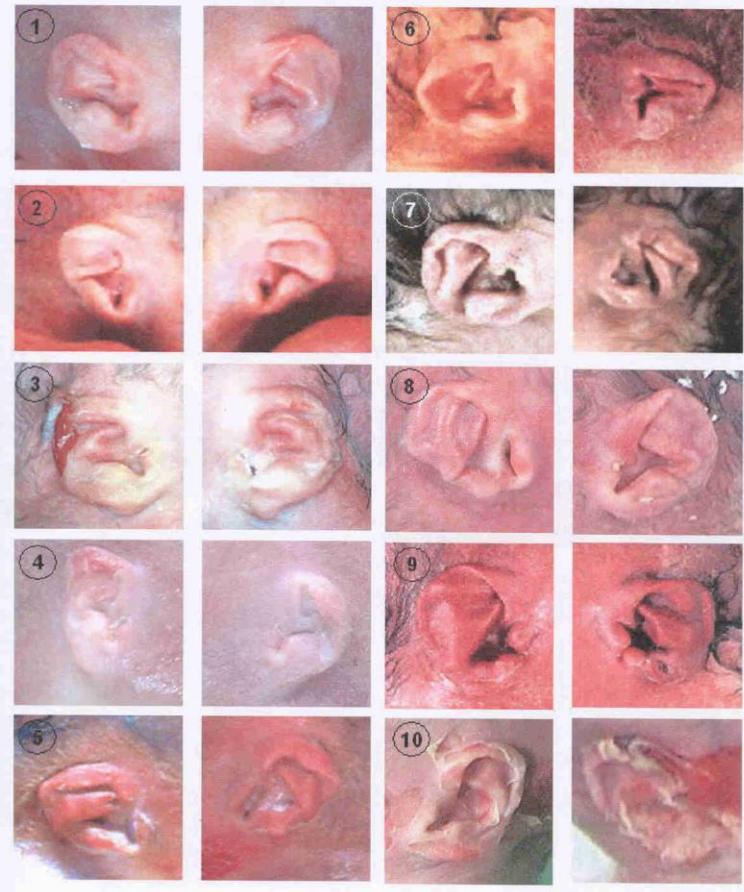
Distinctive

- Synophris (+ deafness,...)



External ears

...pathognomonic for a syndrome



From

'Face'

To

Gene'...

From Face to Gene ?...

FDNA



Smart Phenotyping. Better Genetics.

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It's
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CLINIC

Enhanced Patient Evaluation with Deep Phenotyping

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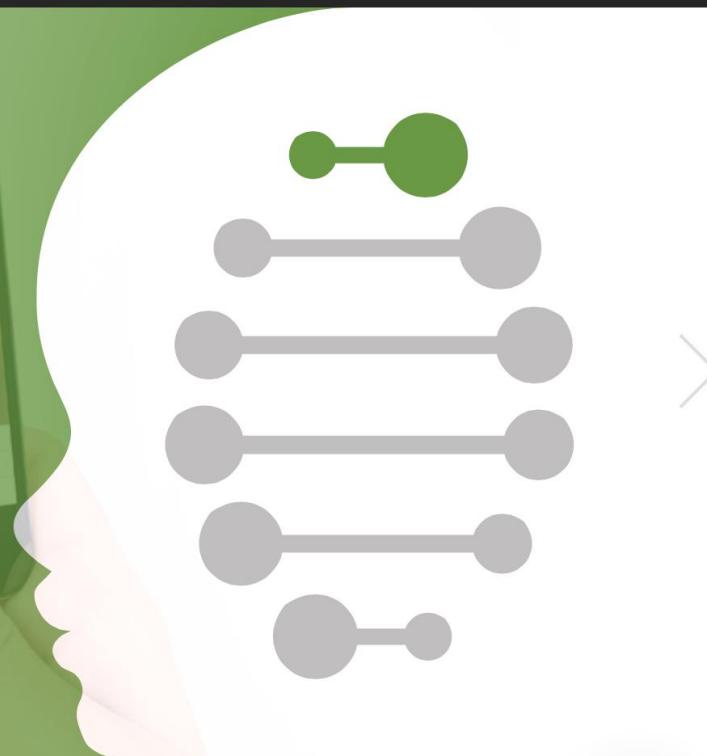
APPS

HOW IT WORKS

HELP CENTER

ABOUT FDNA

PUBLICATIONS



<http://www.face2gene.com>

Enhanced patient evaluation with Next-Generation Phenotyping

The Genetics Resource

Search for Syndromes

Review Photos & Features

Up-to-date Content through Genetics Community Curation

Ct'd



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Trusted Dysmorphology

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Aarskog Syndrome

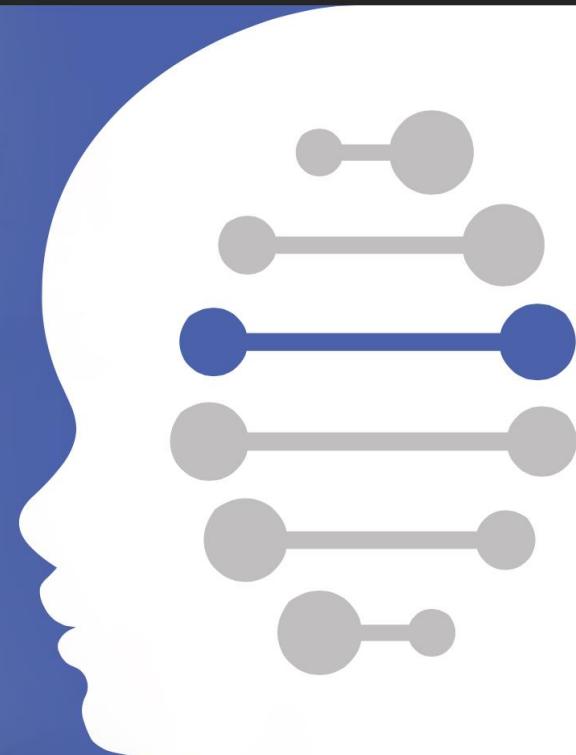
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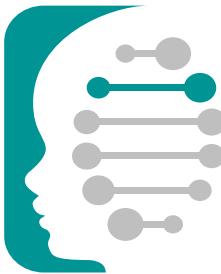
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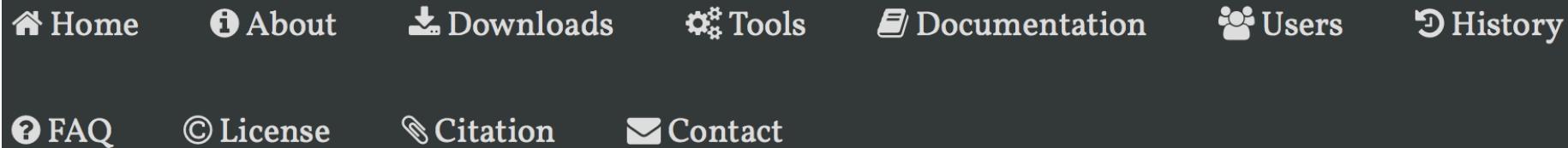
FORUMS

Collaborative Case Review for Diagnostic
Dilemmas

START USING FACE2GENE ([HTTP://APP.FACE2GENE.COM/FORUMS](http://app.face2gene.com/forums))

- ! Access the renowned [Expert Review Panel](#)
[\(/forums-diagnostic-dilemmas/expert-review-panel/\)](#)
 - detect phenotypes
 - reveal relevant facial and non-facial features
 - review relevant syndrome matches
 - access Best-in-class Resources
 - give and Receive Clinical Feedback

Human Phenotype Ontology



This page is split into:

- [Introduction](#)
- [Annotation guide](#)
- [Logical definitions](#)

An Introduction to the Human Phenotype Ontology

The Human Phenotype Ontology (HPO) intends to offer a tool that will allow large-scale computational analysis of the human phenotype. The HPO currently contains over 11,000 terms, each of which describes an individual phenotypic anomaly. The terms are arranged in a directed acyclic graph and are connected by **is-a** (subclass-of) edges, such that a term represents a more specific or limited instance of its parent term(s). All relationships in the HPO are **is-a**.

Human Phenotype Ontology

HPO Browser

The HPO Browser has a separate page for every term in the HPO. The following page, for instance, is for the root term: <http://www.human-phenotype-ontology.org/hpoweb?id=HP:0000118>.

PhenExplorer: The PhenExplorer has been superceded by the new HPO browser, which has all the functionalities of PhenExplorer and has additional features such as Excel-Exports

Clinical diagnostics using the HPO

Phenomizer:

The Phenomizer is available at <http://compbio.charite.de/phenomizer>.

It is a web-based application for clinical diagnostics in human genetics. It performs semantic similarity searches in ontologies [Köhler et al., AJHG, October 2009](#). The Manual for the Phenomizer can be found [here](#).

Catalog – Features on keywords

Insert/select keywords based on features

Menu. ▾ Support the Phenomizer. Help.

Features. Diseases. Ontology.

Enter feature... search. reset.

HPO id.	Feature.
HP:0010704	1-2 finger syndactyly
HP:0005767	1-2 toe complete cutaneous syndactyly
HP:0010711	1-2 toe syndactyly
HP:0010706	1-3 finger syndactyly
HP:0001459	1-3 toe syndactyly
HP:0010707	1-4 finger syndactyly
HP:0010712	1-4 toe syndactyly
HP:0006088	1-5 finger complete cutaneous syndactyly
HP:0010708	1-5 finger syndactyly
HP:0010713	1-5 toe syndactyly
HP:0030300	10 pairs of ribs
HP:0000878	11 pairs of ribs
HP:0030306	11 thoracic vertebrae
HP:0001233	2-3 finger syndactyly
HP:0005709	2-3 toe cutaneous syndactyly
HP:0004691	2-3 toe syndactyly
HP:0010709	2-4 finger syndactyly
HP:0005768	2-4 toe cutaneous syndactyly
HP:0010714	2-4 toe syndactyly
HP:0010692	2-5 finger syndactyly
HP:0010715	2-5 toe syndactyly
HP:0008083	2nd-5th toe middle phalangeal hypoplasia
HP:0011939	3-4 finger cutaneous syndactyly
HP:0006097	3-4 finger syndactyly
HP:0009779	3-4 toe syndactyly
HP:0010710	3-5 finger syndactyly
HP:0010716	3-5 toe syndactyly

Page 1 of 424 | Features 1 - 27 of 11442

Patient's Features.

HPO.	Feature. ▲	Modifier.	Num diseases
------	------------	-----------	--------------

Select if 'keyword' 'observed' vs 'mandatory'

News

Info

- The Phenomizer is developed and maintained by [Sebastian Köhler](#) (see [group website](#) for more info).
- The [Phenomizer_Orphanet](#) uses the latest Orphanet date and a different algorithm for ranking the differential diagnoses.

Please cite the following papers when you use this tool/HPO in your publications.

Köhler et al., [Clinical diagnostics in human genetics with semantic similarity searches in ontologies](#). Am J Hum Genet (2009) vol. 85 (4) pp. 457-64

Köhler et al., [The Human Phenotype Ontology in 2017](#). Nucleic Acids Research (2017) doi: <https://doi.org/10.1093/nar/gkw1039>

Clear. Mode of inheritance.

Tool IV - 'Syndromology'

derived from syndrome: clinical approach to occurrence multiple congenital anomalies



Ped Cardiology clinic

First description

9 patients with pulmonary valve stenosis, short stature

Hypertelorism, mild intellectual disability and ptosis cryptorchidism, 'skeletal malformations'

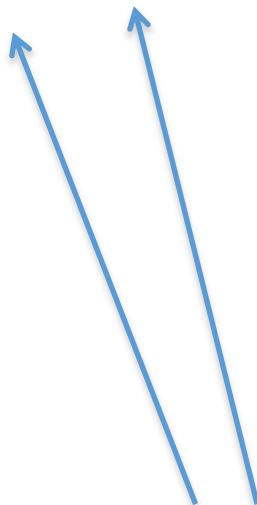


Noonan J and Ehmke D. J Pediatr 1963;63:468-470

Noonan JA. and Lexington K. Am J Dis Child 1968;116:373-380

Variability in phenotype

Large front, hypertelorism; down slanting palpebral fissures,
low set posteriorly rotated ears



Remnant of prenatal nuchal translucency and hygroma



pectus carinatum

Distinct patient...similar dysmorphic features

Large front, Hypertelorism; down slanting palpebral fissures, low set posteriorly rotated ears

and variable degree of lymphedema (unconstant)

pectus carinatum

...similar phenotypes

Same syndrome...

8 months

4 years

Congenital heart defect « pulm atresia»

IUGR

Hypertelorism

Macrocephaly (relative)

Curly hair

Failure to thrive

...

Evolving phenotype with age

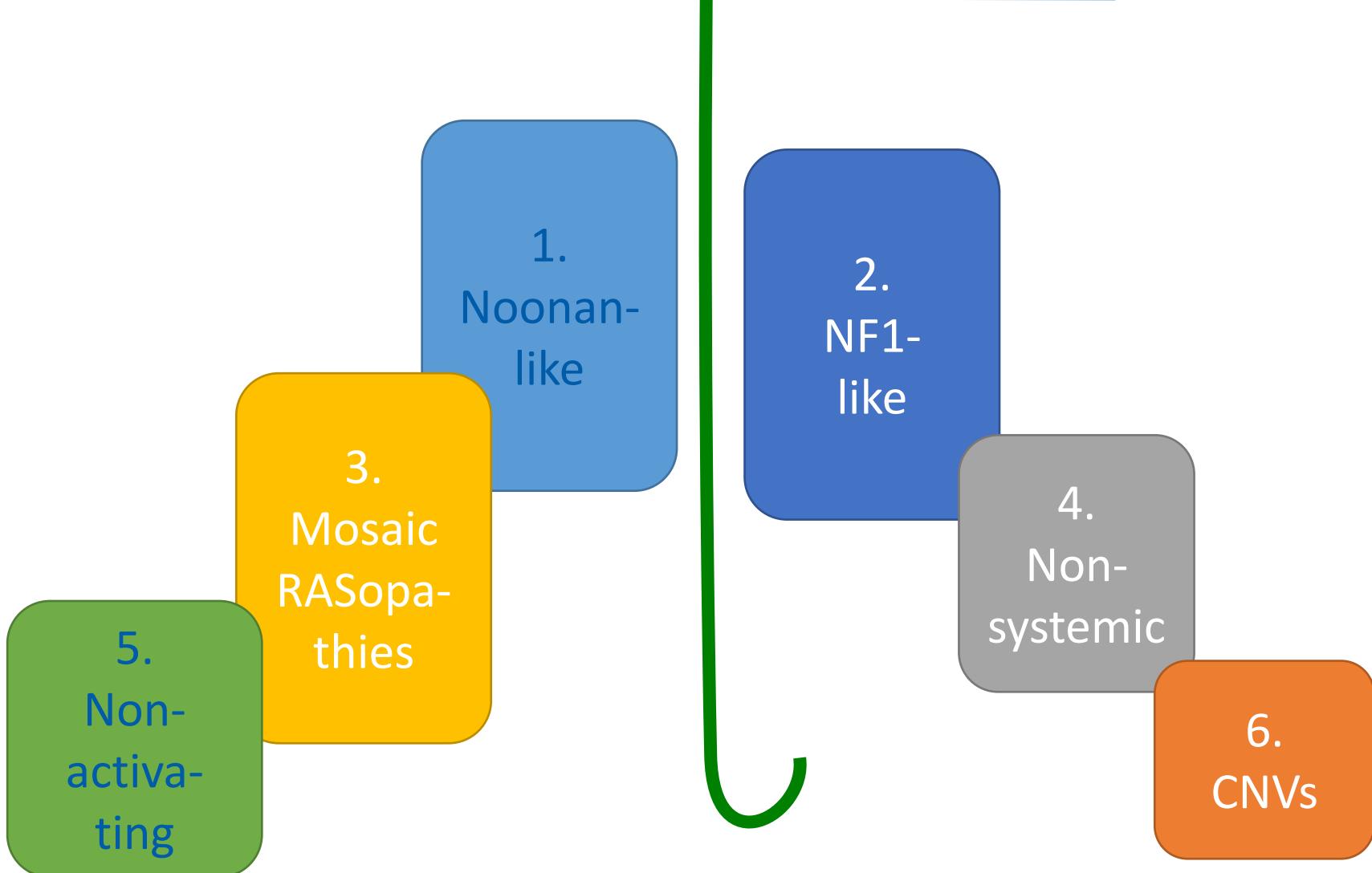
...Knowledge on natural history

...to adulthood

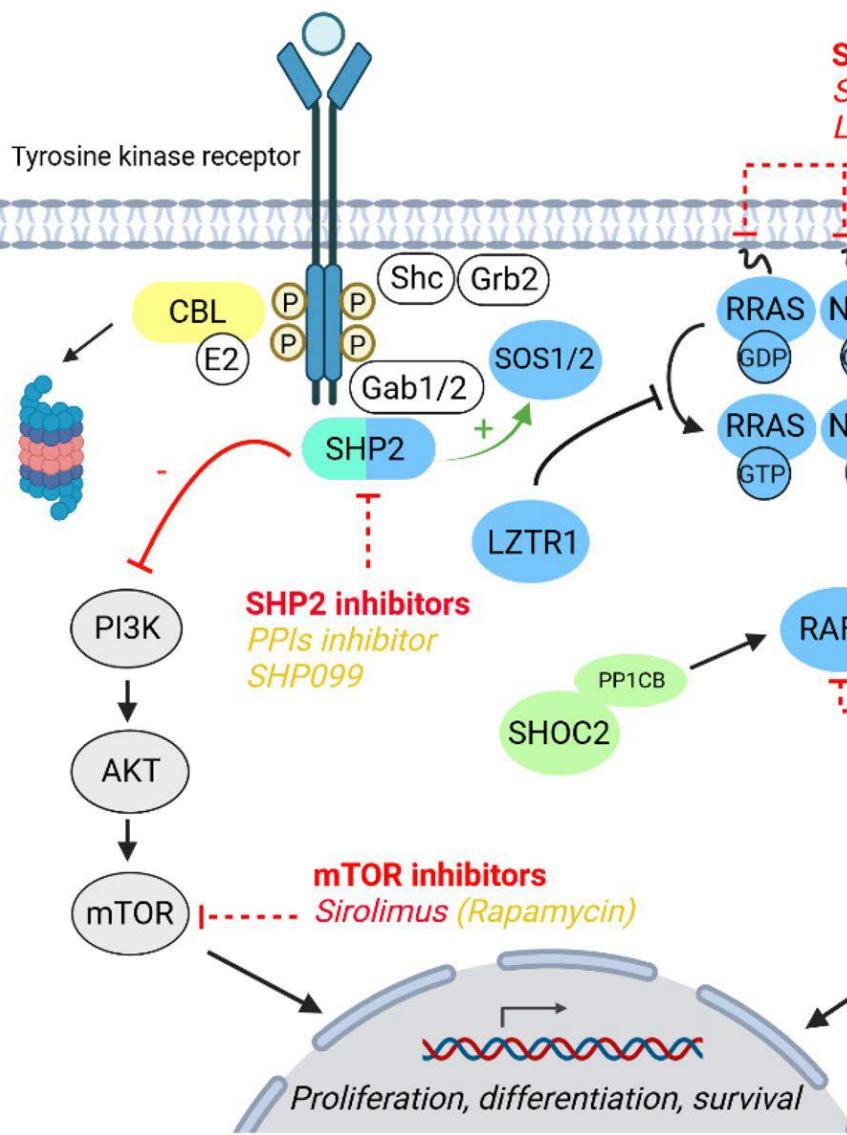
...to adulthood

- Sporadic
- Pulmonary valve stenosis
- Post natal growth retardation
- GH deficiency - therapy

RASopathies

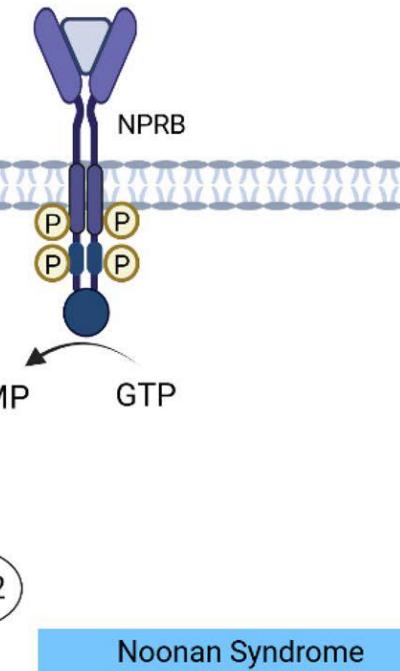


Insulin, IGF1...



PMID: 37863846

CNP
Vosoritide
TransCon CNP



Noonan Syndrome
NS with multiple lentigines
NS with loose anagen hair
CBL syndrome
CFC syndrome
Costello syndrome
Neurofibromatosis type 1
Legius syndrome

Gene	Highest RASopathy Association Achieved	Specific Conditions				
		Noonan	CFC	Costello	NSML	NS/LAH
<i>BRAF</i>	Definitive	Moderate(10.5)	Definitive(13.5)	Disputed	Limited(5.5)	-
<i>HRAS</i>	Definitive	-	-	Definitive(14.5)	-	-
<i>KRAS</i>	Definitive	Definitive(14)	Strong(12.5)	Disputed	-	-
<i>MAP2K1</i>	Definitive	Limited(3.5)	Definitive(12.5)	Disputed	Limited(2.5)	-
<i>MAP2K2</i>	Definitive	Limited(1)	Definitive(12.5)	-	-	-
<i>NRAS</i>	Definitive	Definitive(13.5)	Limited(0.5)	Limited(1)	Limited(3.5)	-
<i>PTPN11</i>	Definitive	Definitive(13.5)	Disputed	Disputed	Definitive(15)	-
<i>RAF1</i>	Definitive	Definitive(13.5)	Disputed	Disputed	Limited(4.5)	-
<i>RIT1</i>	Definitive	Definitive(13.5)	-	-	-	-
<i>SHOC2</i>	Definitive	Disputed	Disputed	Disputed	-	Definitive(12.75)
<i>SOS1</i>	Definitive	Definitive(12.5)	Limited(1.5)	Disputed	-	-
<i>LZTR1^T</i>	Strong	Strong(12)	-	-	-	-
<i>PPP1CB</i>	Strong	Strong(12.5)	-	-	-	Strong(12)
<i>SOS2^T</i>	Moderate	Moderate(9.5)	-	-	-	-
<i>LZTR1^(AR)</i>	Limited	Limited(8.75)	-	-	-	-
<i>MRAS</i>	Limited	Limited(4.5)	-	-	-	-
<i>RRAS</i>	Limited	Limited(3.25)	-	-	-	-
<i>RASA2</i>	Limited	Limited(1.5)	-	-	-	-
<i>A2ML1</i>	Disputed	Disputed	-	-	-	-
<i>RASA1</i>	Disputed	Disputed	-	-	-	-

From
M. Zenker

... Genotype

c.922A>G (p.N308D) *PTPN11* c.305C>G *SOS1* *RAF1*

BRAF

SHOC2

LZTR1

...first recessive form

...*SPRED2*

PMID: 38254922

Management of Noonan Syndrome

A Clinical Guideline

Noonan Syndrome Guideline Development Group

Recommended baseline investigations in Noonan Syndrome

Clinical Features of Noonan Syndrome	Baseline investigations
(where an investigation is not indicated for a specific clinical feature, please refer to the relevant age group-specific page for management recommendations)	
<ul style="list-style-type: none">□ Congenital heart defects (e.g. pulmonary stenosis, hypertrophic cardiomyopathy, atrial septal defect)□ Failure to thrive/slow growth rate/feeding problems□ Short stature□ Developmental delay and neuropsychological/behavioural issues□ Minor renal anomalies□ Bleeding disorders□ Visual problems (e.g. posterior segment ocular changes and anterior segment ocular abnormalities)	<ul style="list-style-type: none">□ Full cardiac evaluation at diagnosis.□ Monitor and plot growth on appropriate NS and age-based growth chart.□ Refer patient in second half of first year or at diagnosis for formal developmental assessment.□ Baseline neuropsychological assessment at primary school entry.□ Refer for renal ultrasound at diagnosis.□ Carry out baseline coagulation screening in patients aged 5+, or earlier if major procedure to be undertaken. (Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPPT) and FXI assay.)□ Refer for specialist ophthalmology assessment at the point of diagnosis.

Remaining questions...

on bench side:

caveats: level of evidence from whole exome sequencing
for variants in ‘Rasopathy’

at bedside – genetic counselling Index patient and family

How to explain penetrance ?

How to explain intra familial variable expressivity ?

c.922A>G (p.N308D) ***PTPN11***

Prevalent gene inside RASopathies- 40%

Prevalent mutation – heart defect 60%

To precise updated Genetic counselling in patients

Index patient with very mild phenotype

'de novo' autosomal dominant condition / 50% transmission

Large expressivity

...

access to PGD

Birth defect to genetic counselling

Building evidence since WES in daily practice and in near future WGS ?

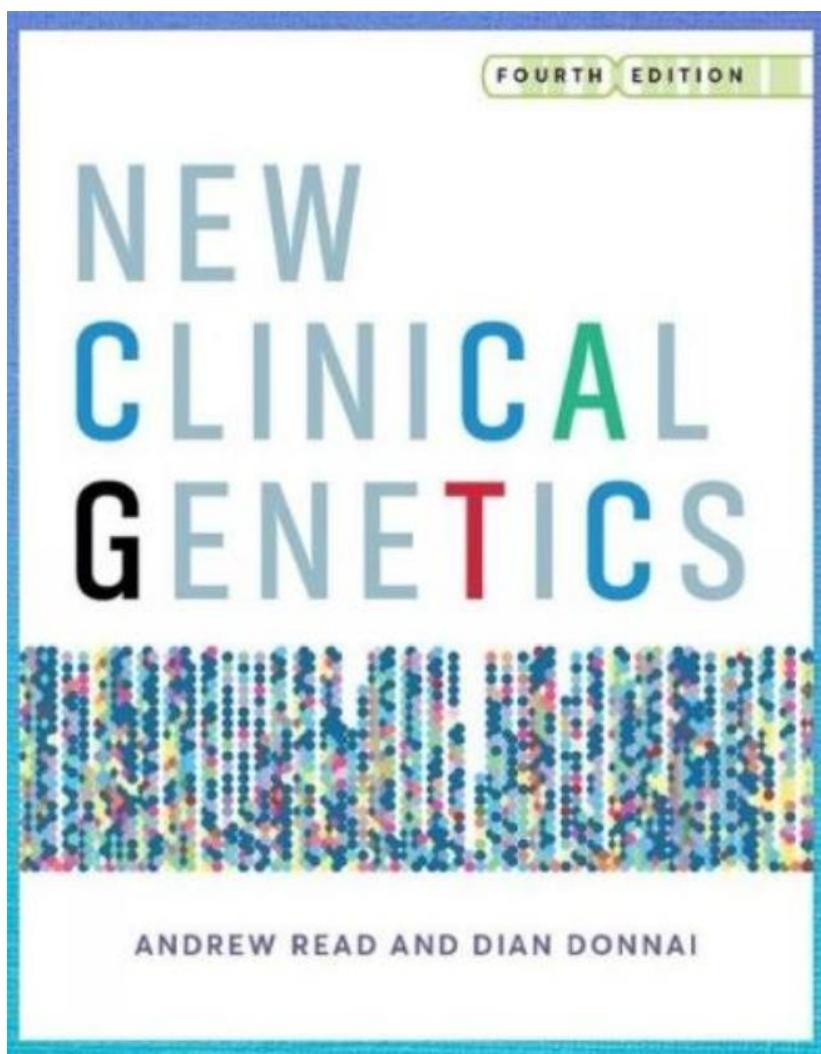
Clinical Geneticists are far less pertinent than thought
Human Hardware/brain memory on 4.000 mendelian disorders and phenotypes ?

Integrate balance : targeted/non selective approaches

Filtering on variants of unknown significance

When genetics approach become reverse ('unusual phenotype'), genotype identification ... « From Gene to Face »

Suggested Readings



Thank you for your attention

Open to your question



yves.sznajer@uclouvain.be