Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

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

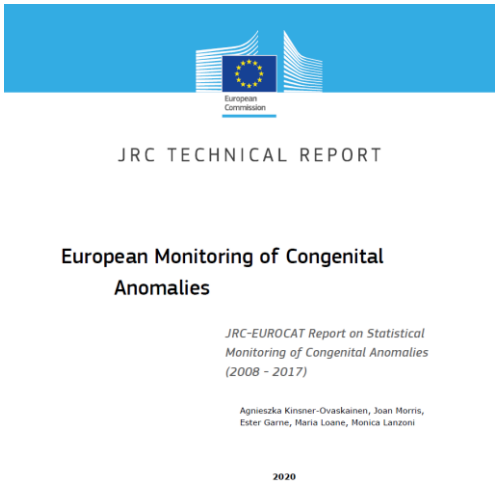
Registries and Databases

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



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

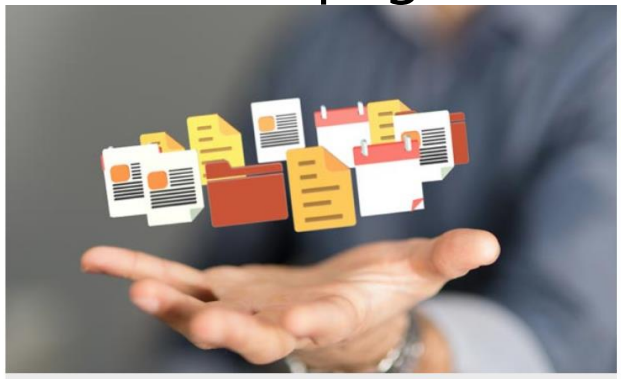
Tool I - Congenital Anomalies (CA) Registry

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

https://publications.jrc.ec.europa.eu/repository/handle/JRC136655
Frontpage

eurocat



EUROCAT Network

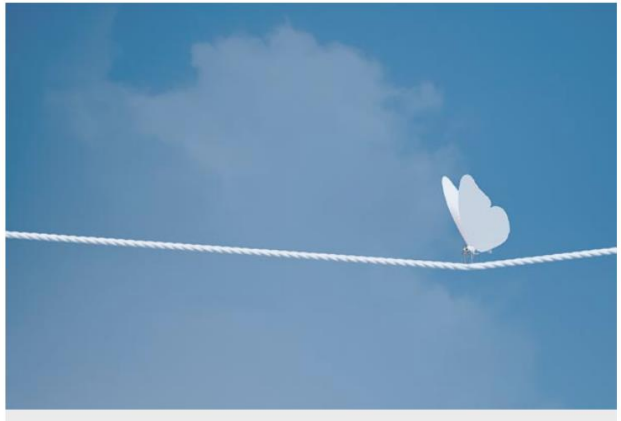
Overview of the EUROCAT network, its organisation and committees

Member Registries

Information about the EUROCAT member regsitries, 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

European Commision link

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

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European Commission

JRC Publications Repository

Home Search Help

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.

eurocat
european surveillance of congenital anomalies

http://www.eurocat-network.eu

EUROCAT Prevalence Data Tables

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

						Excluding Genetic Conditions	
Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	LB+FD+TOPFA N	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/micropthalmos	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)

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

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

https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence

European Commission | English EN | Search

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

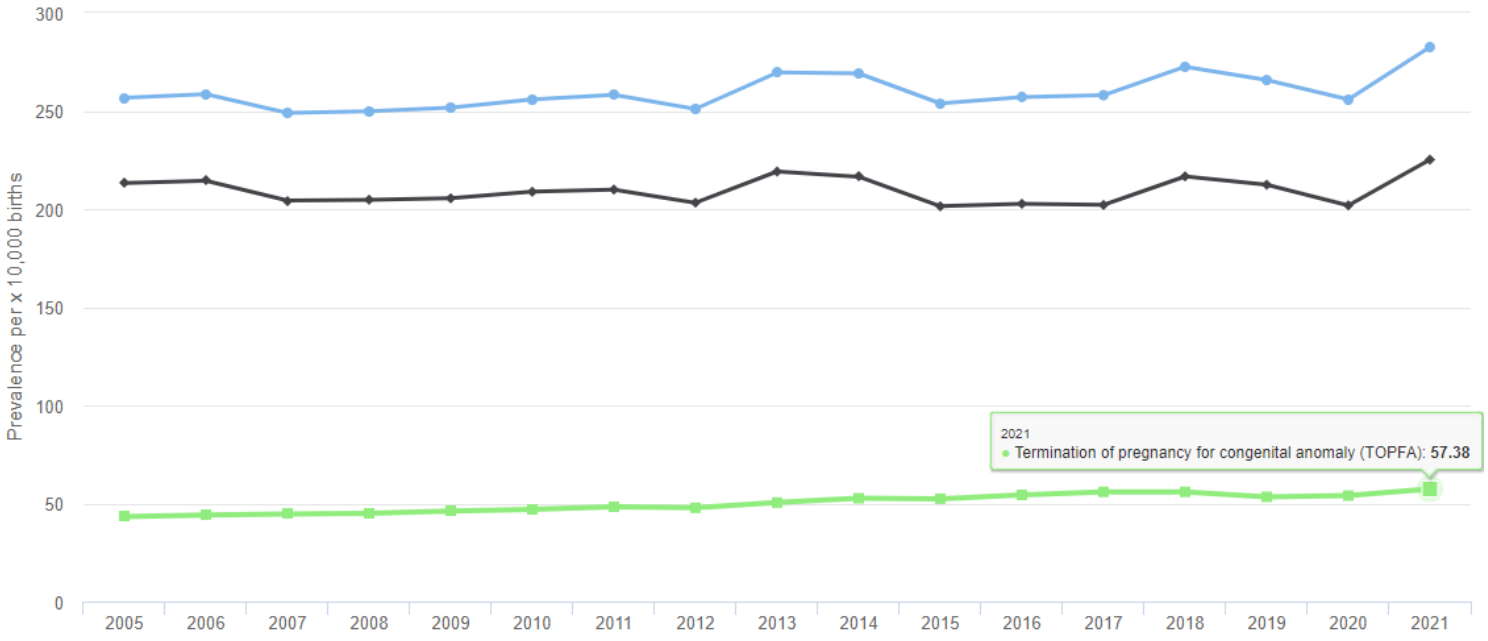
Prevalence charts and tables

Country/Registry	Anomaly	Years	Case with genetic conditions
None Selected	All anomalies	2005 to 2021	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	Anomaly	Years
All full registries	**All Anomalies**	**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

- Emilia Romagna
- Tuscany
- Campania (P)
- North East Italy (P)
- Sicily (P)

eland

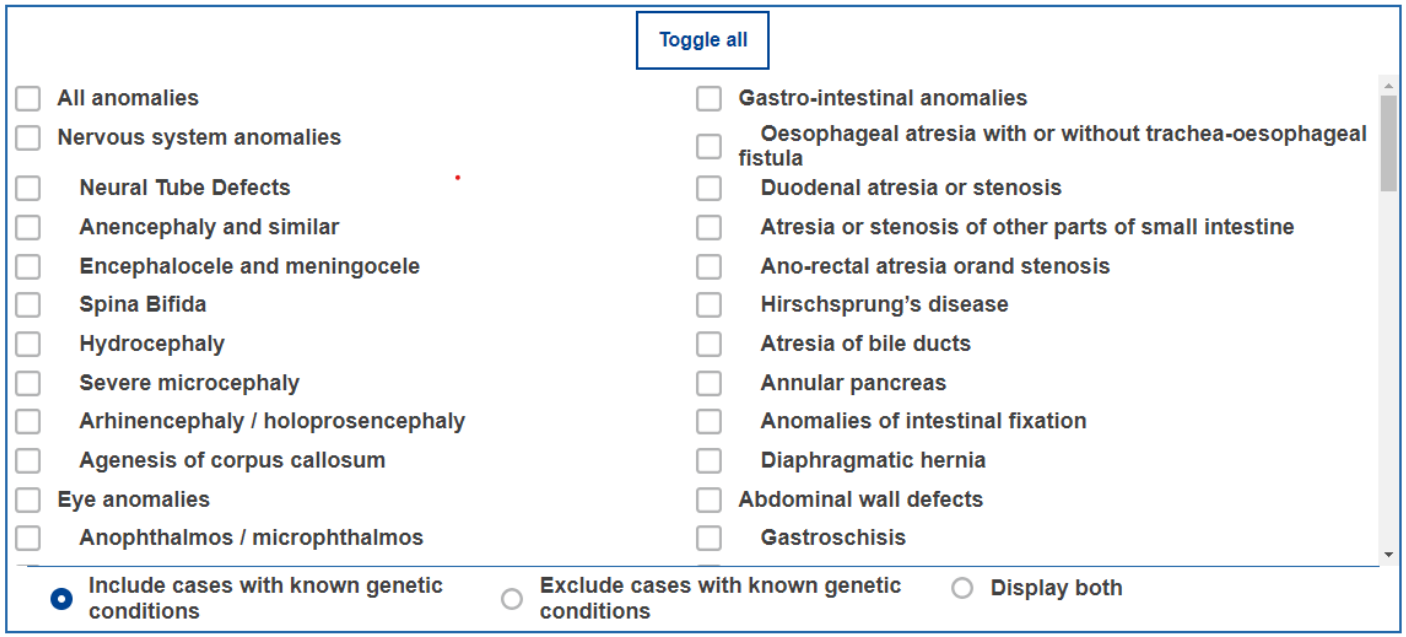
- Cork and Kerry
- Dublin
- SE Ireland
- Galway (P)

L

- N Netherlands

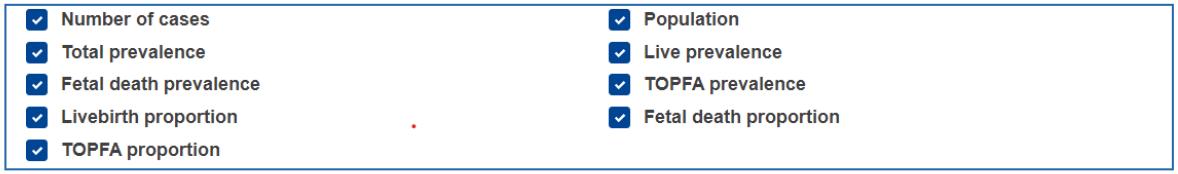
Eurocat adaptable tool

Anomalies



Years

Fields



Another example – Selected categories

Chromosomal	43.58 (42.99 - 44.17)	16.67 (16.30 - 17.04)	1.54 (1.43 - 1.66)	25.37 (24.92 - 25.83)
– Down Syndrome	24.14 (23.71 - 24.59)	9.74 (9.46 - 10.03)	0.50 (0.44 - 0.56)	13.91 (13.57 - 14.24)
– Patau syndrome/trisomy 13	2.18 (2.05 - 2.31)	0.30 (0.25 - 0.35)	0.12 (0.09 - 0.15)	1.76 (1.64 - 1.88)
– Edward syndrome/trisomy 18	5.94 (5.72 - 6.16)	0.69 (0.62 - 0.77)	0.45 (0.39 - 0.52)	4.79 (4.59 - 4.99)
– Turner 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)
– Klinefelter syndrome	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)

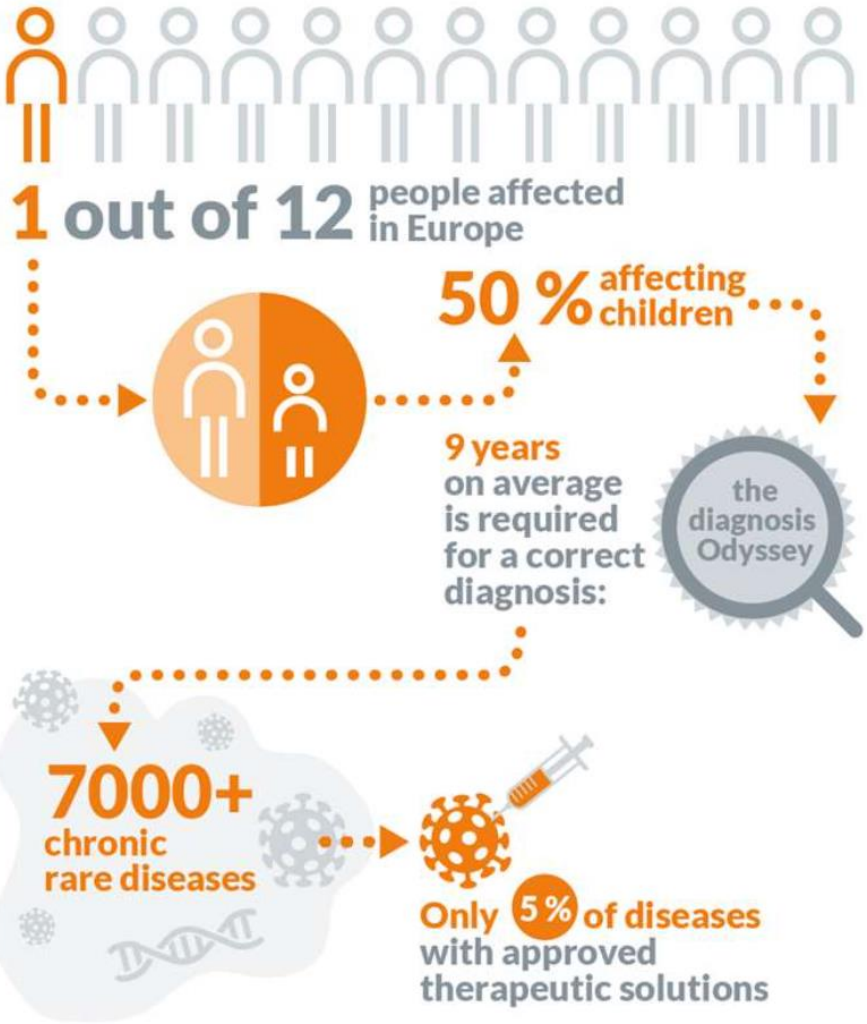
Networks of action for 'Rare diseases'*

- 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

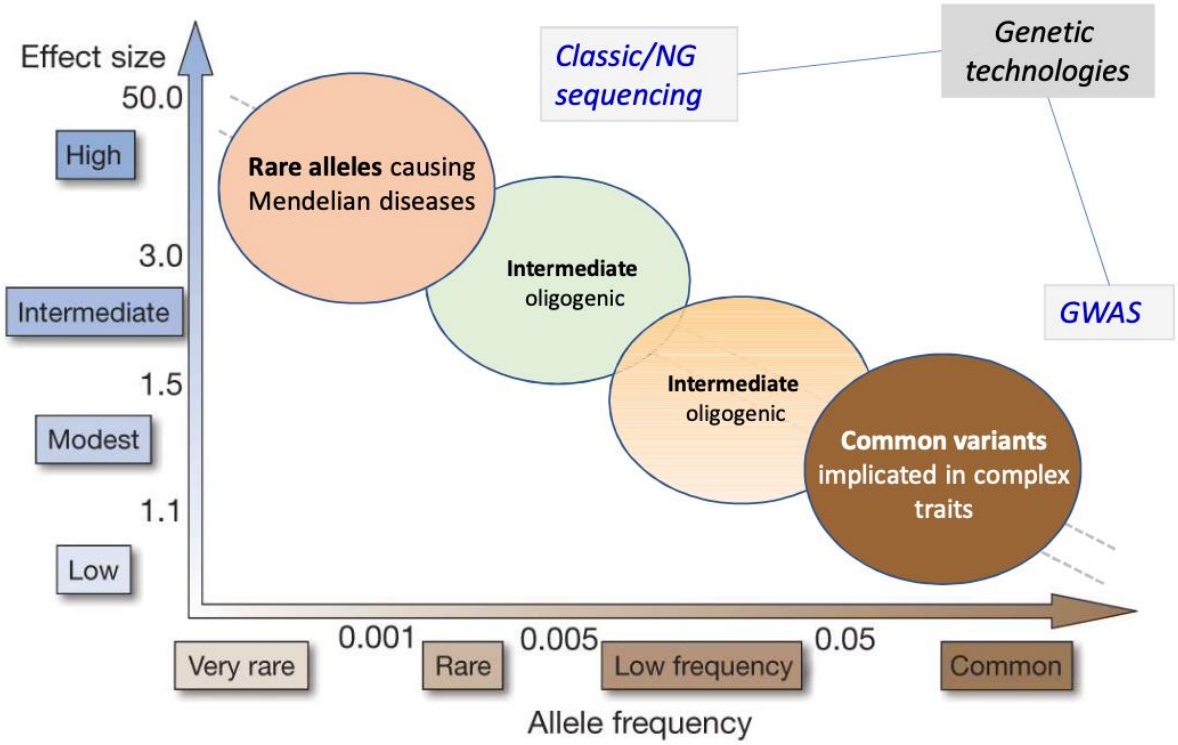


Rare diseases impact

- >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 define conditions with a prevalence <1/2.500 live births*

Rare diseases – *The* basics



Manolio et al. Nature 461, 2009

Rare diseases – not limited to a concept

Kidney International (2017) **92,** 796–808;

Belgisch plan voor zeldzame ziekten

Plan belge

Maladies rares /

Zeldzame ziekten

TABLE DES MATIERES

http://www.institutdesmaladiesrares.be

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 endocriniennes 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

> 20.000 patients

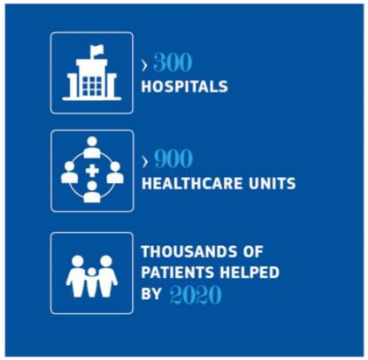
European Reference Networks

Laboratoire de référence
Screening prénatal

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

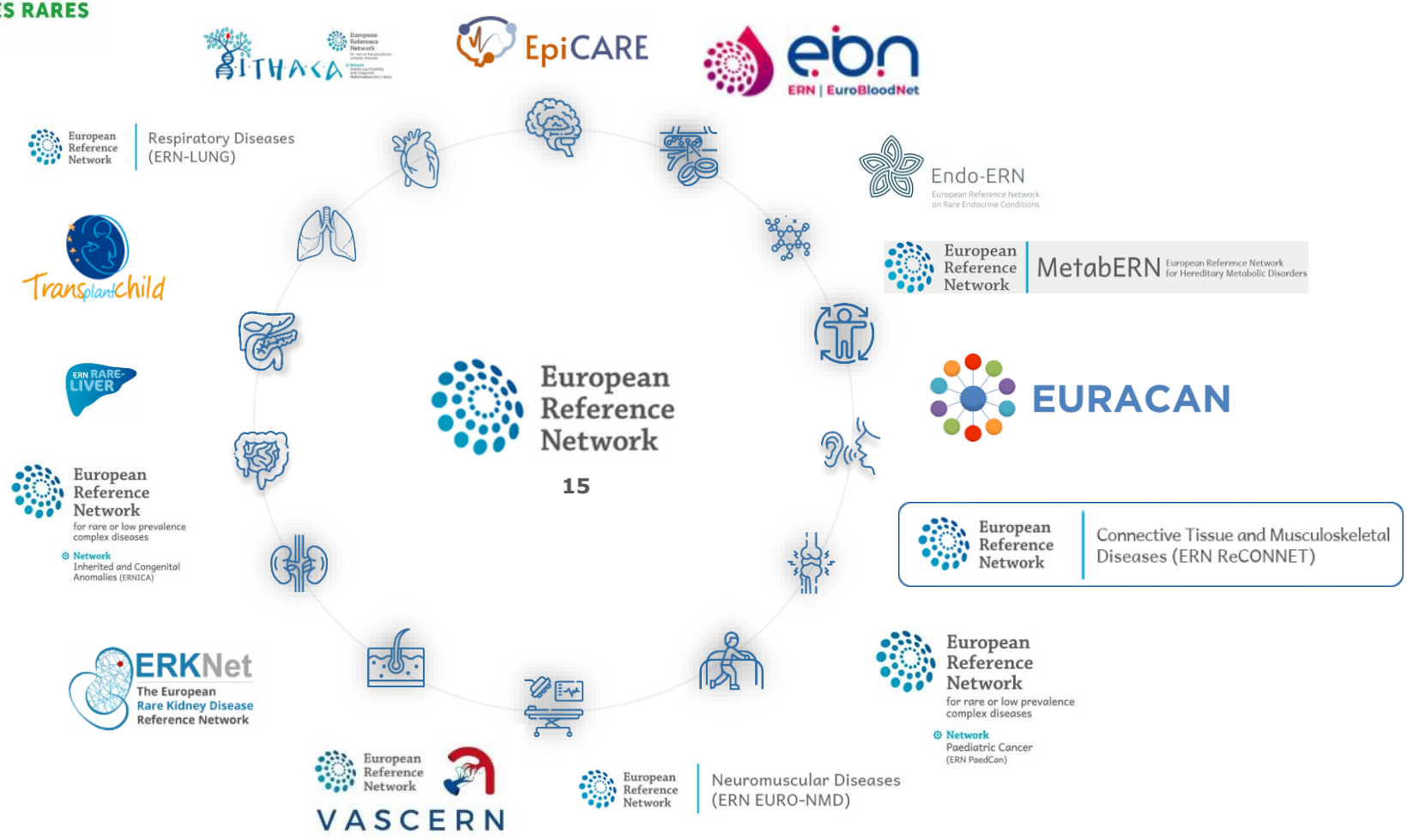


EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW-PREVALENCE AND COMPLEX DISEASES
Share. Care. Cure.

European Reference Networks

European Commission | Health

INSTITUT DES MALADIES RARES
Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

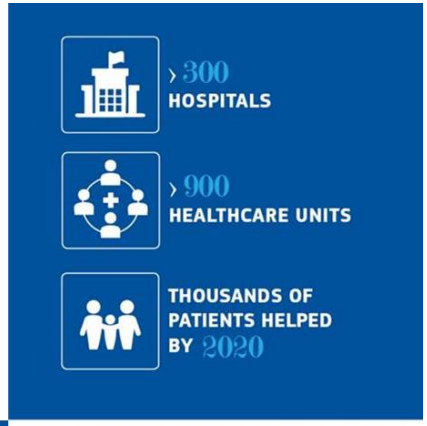


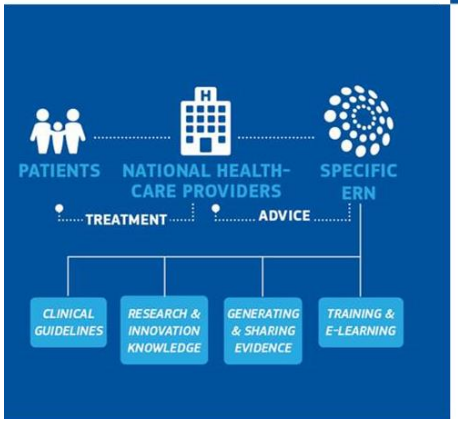
European Reference Networks

Evolutionary

ERN RARE-LIVER Réseau européen de référence dédié aux maladies hépatiques	2017 **9 ERNs**
ERN TRANSPLANT-CHILD Réseau européen de référence dédié à la transplantation chez l'enfant	
Endo-ERN Réseau européen de référence dédié aux maladies endocriniennes	
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 ReCONNET 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	2022 **+ 6 ERNs**
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)	

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

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

Share. Care. Cure.

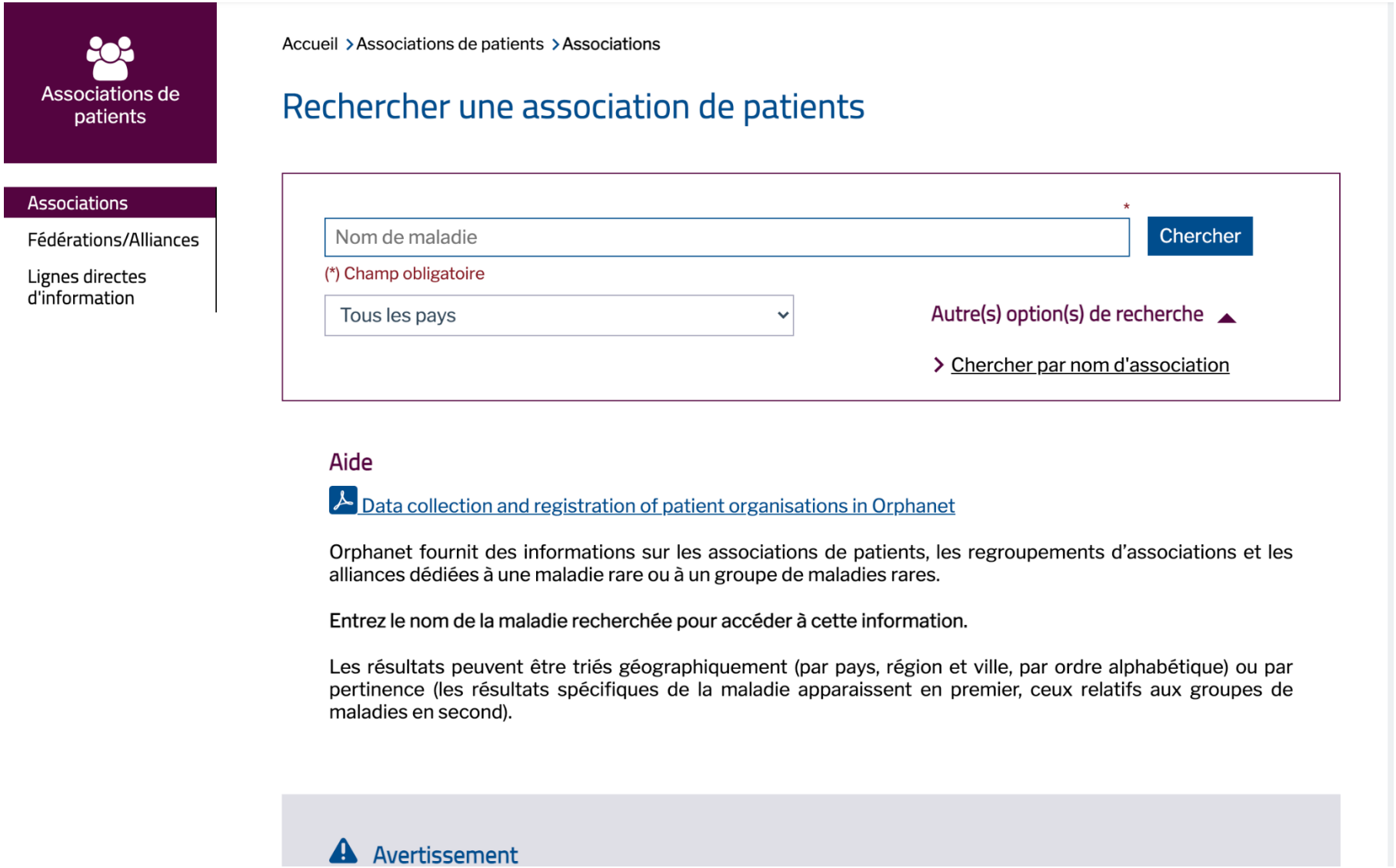
European Reference Networks

European Commission | Health

Rare diseases : information sources

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

…informations



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/NEJMe1102290

RaDiOrg.be
Rare Diseases Organisation

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

orphanhealthcare
Foundation for Rare Diseases

BLACKSWAN FOUNDATION

Fondation Roi Baudouin
Agir ensemble pour une société meilleure

ABMM
Maladies neuromusculaires

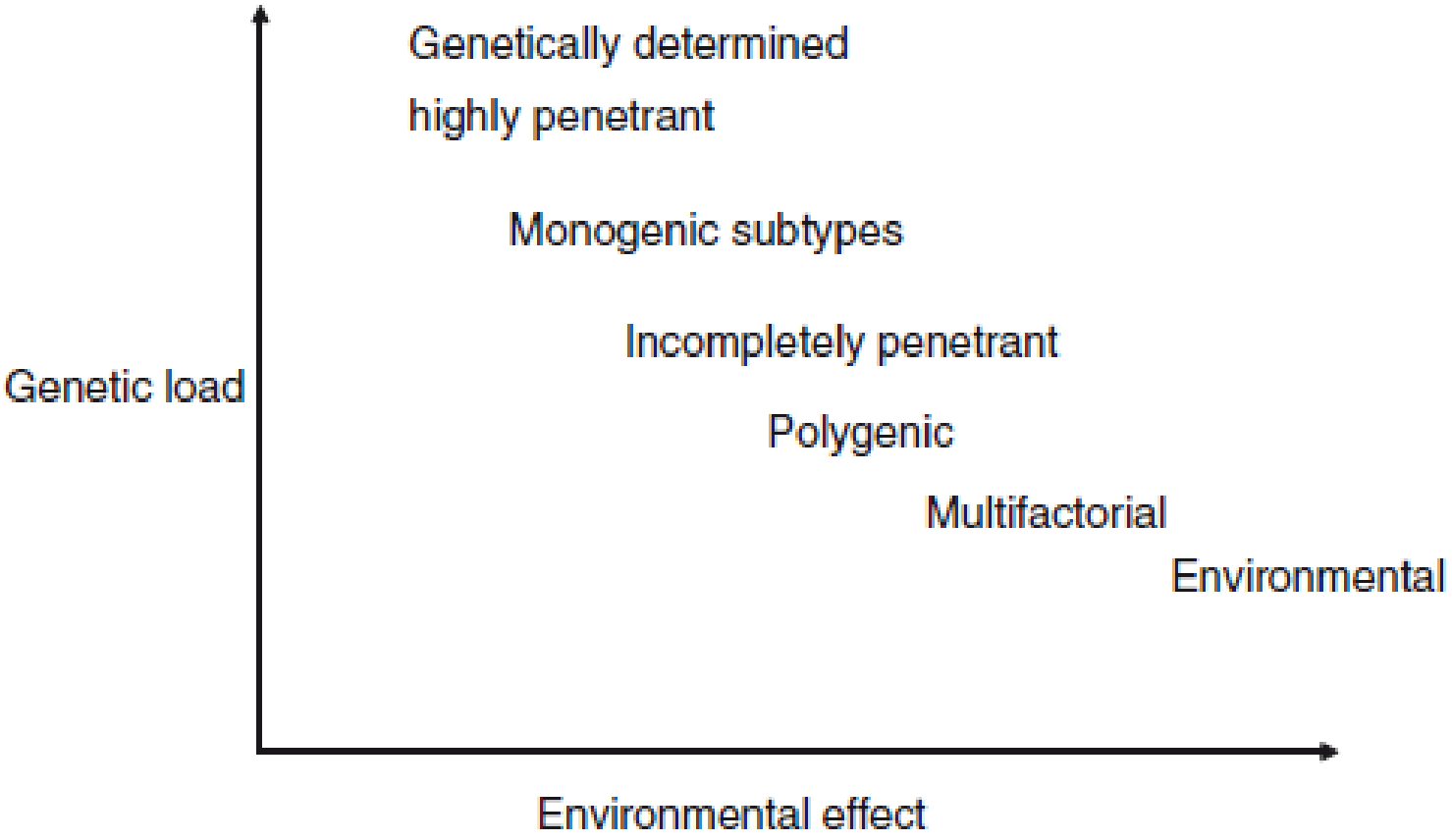
RARE DISORDERS
Maladies Rares
Belgium
Alliance d'associations et de patients concernés par les Maladies Rares

Rare Disorders Belgium

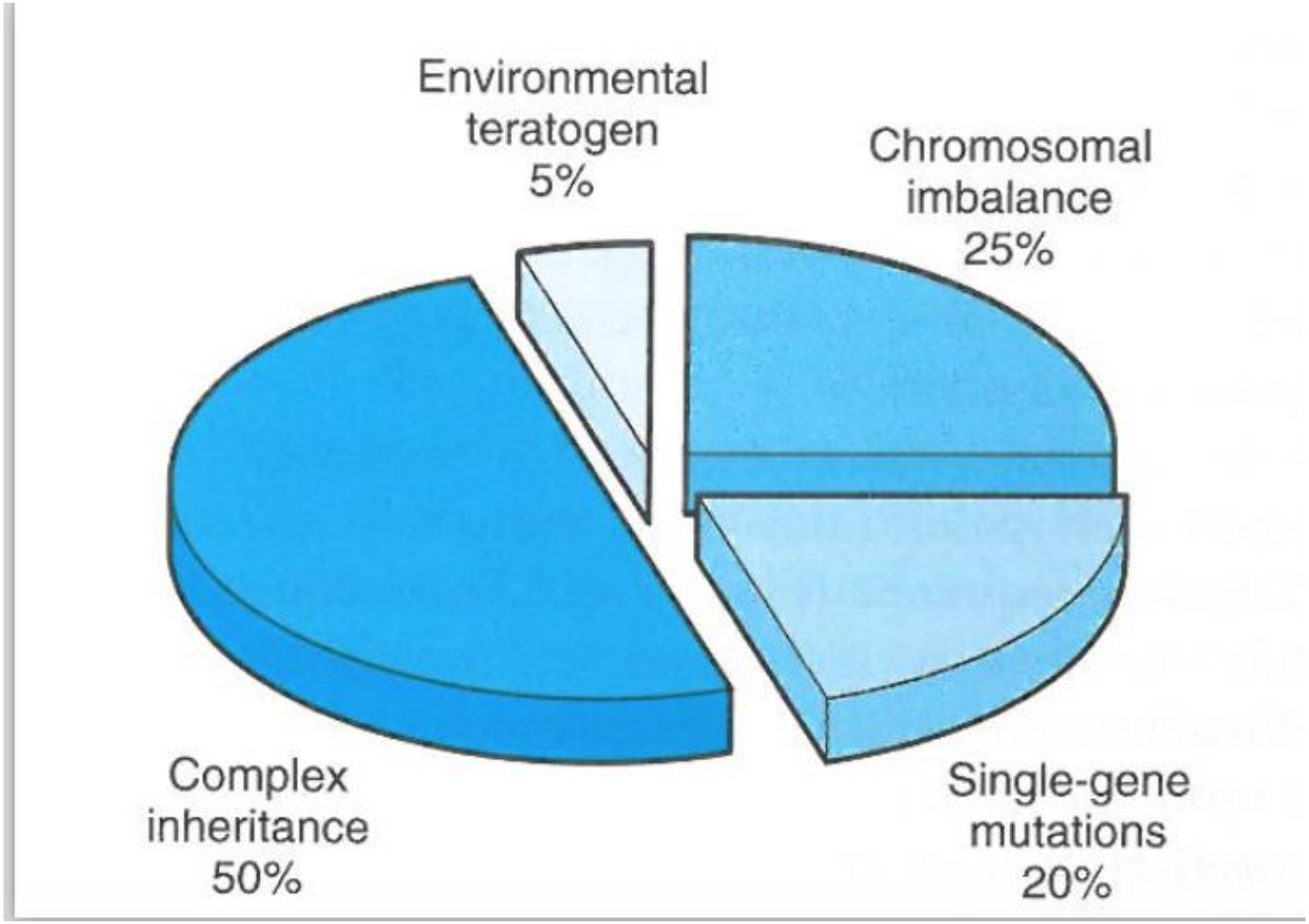
Member of EURORDIS
Rare Diseases Europe

Birth defect - congenital anomaly

- **Prevalence – 3%**



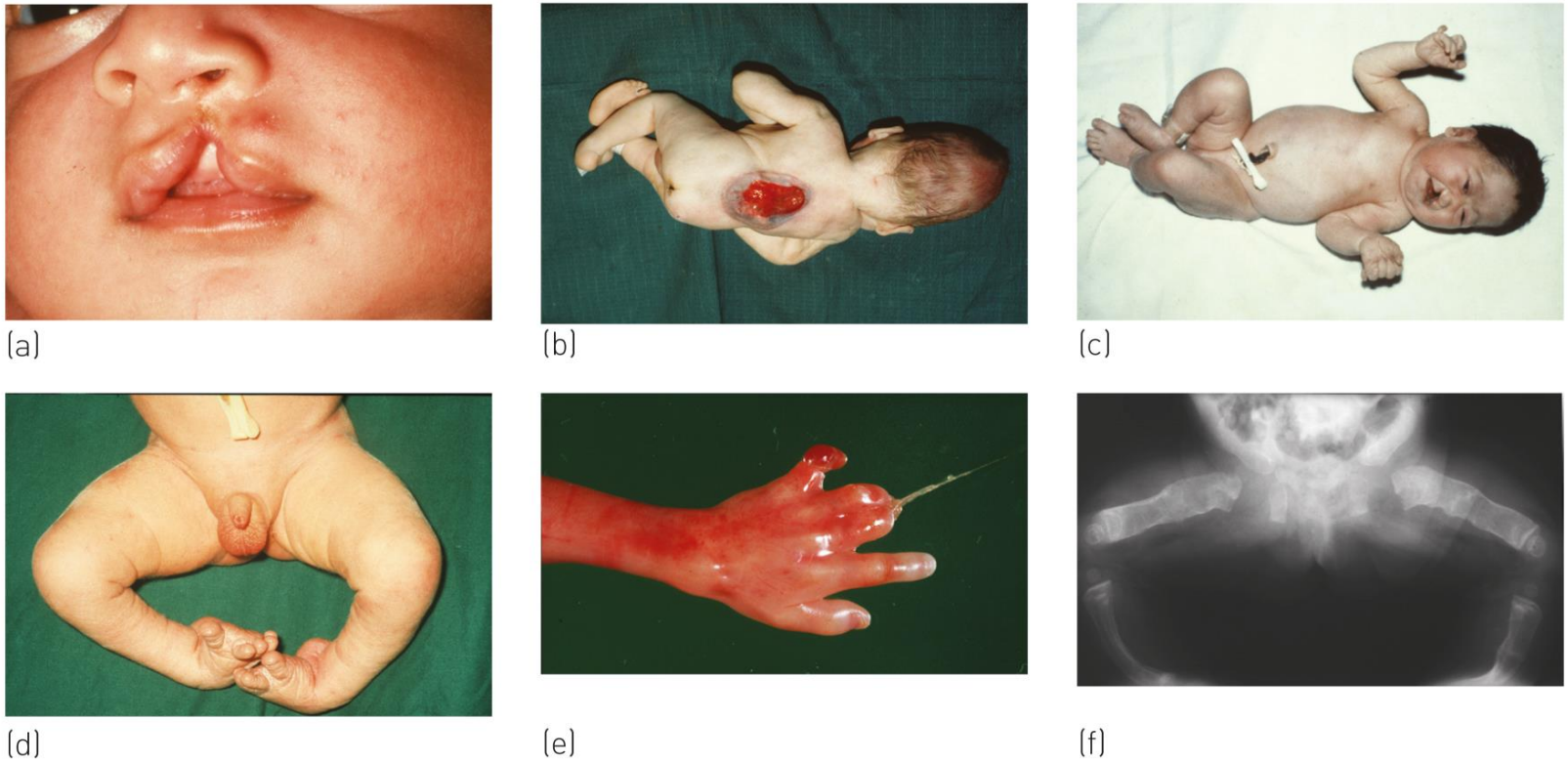
Birth defect – 'main categories'



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/skelettal
- **Malformation** — result from intrinsic abnormalities in one or more genetic program operating during development (e.a polydactyly)

Illustration



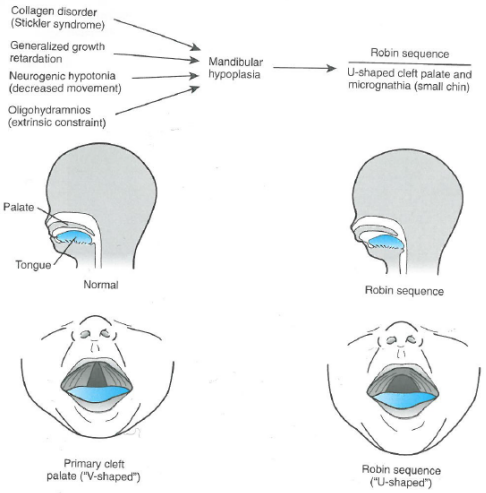
Box figure 14.1 – Clinical photographs of the main types of dysmorphic features.
(a) Cleft lip, a **malformation** representing failure of fusion of components of upper lip. (b) Meningomyelocele, talipes and hydrocephalus, a **malformation sequence** due to failure of closure of the neural tube and consequent 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**.

Reproduced from: **New Clinical Genetics, 3rd edition**
Andrew Read and Dian Donnai ISBN 9781907904677

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'

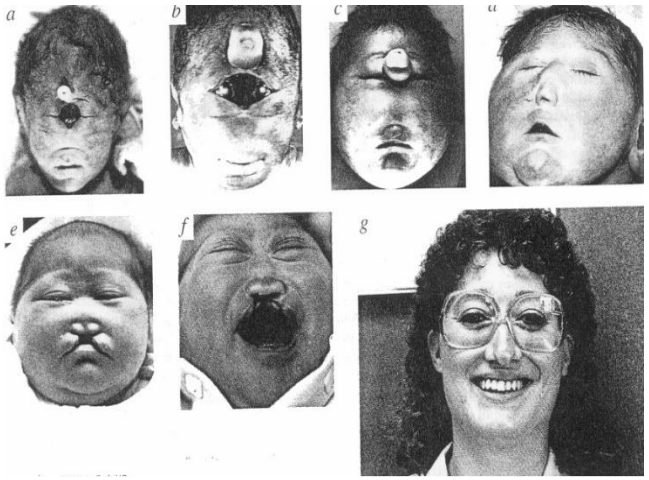
- **Sequence** — **phenotype description** of alteration of structures inside an embryonic field during development - *pleiotropic: effect on a single organ/system* - precise moment
  NOT a diagnosis 'Pierre Robin', Potter'

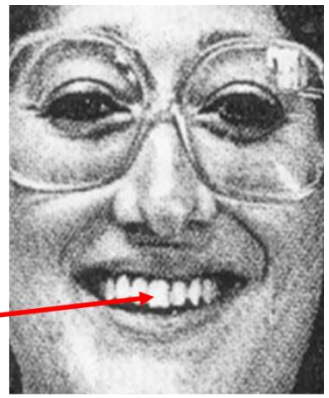


Nosology (ct'd)

- **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





Unique Incisor

Holoprosencephaly Sonic Hedgehoc 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

AMERICAN JOURNAL OF medical genetics PART A 2009;149A(1):1-127

Standard Terminology

- For Head and Face: pg 1- 23

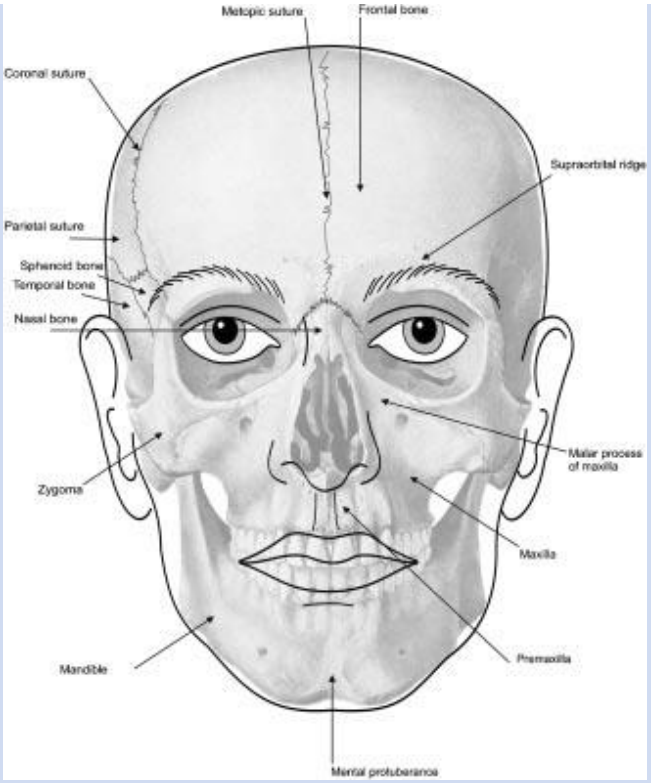


FIG. 1. An antero-posterior view of the cranium and face shows bony landmarks.

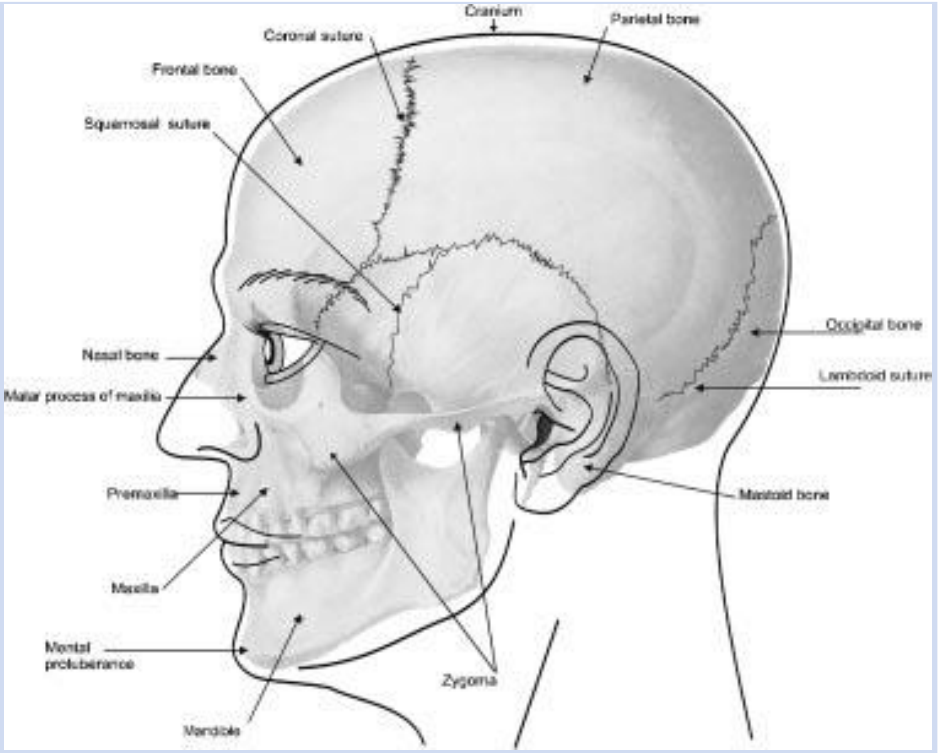


FIG. 2. A lateral view of the cranium and face shows bony landmarks.

AMERICAN JOURNAL OF medical genetics PART A 2009;149A(1):1-23

Standard Terminology

- For Head and Face

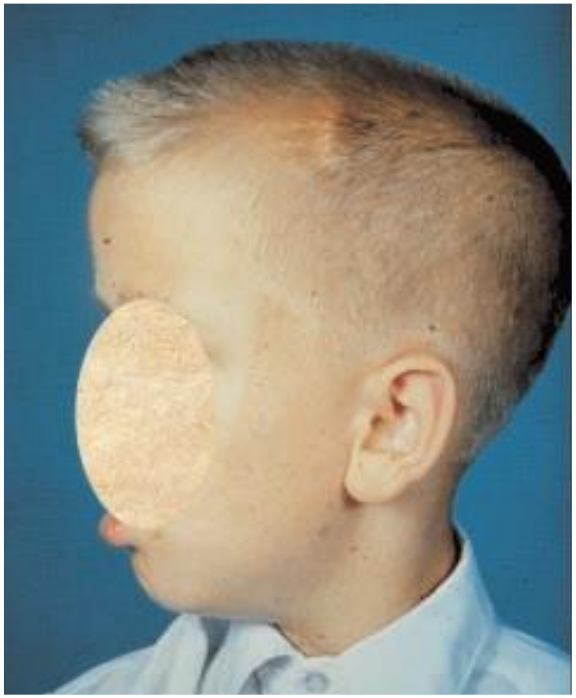


FIG. 7. *Macrocephaly*. Note the increased size of the cranium. Differences in size are difficult to appreciate but increased head size in this child is notable because of comparison with the smaller face.

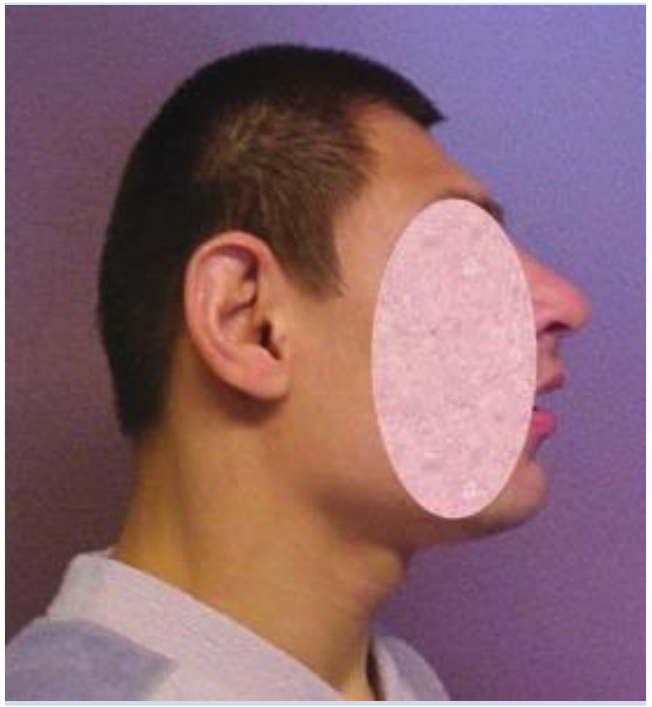
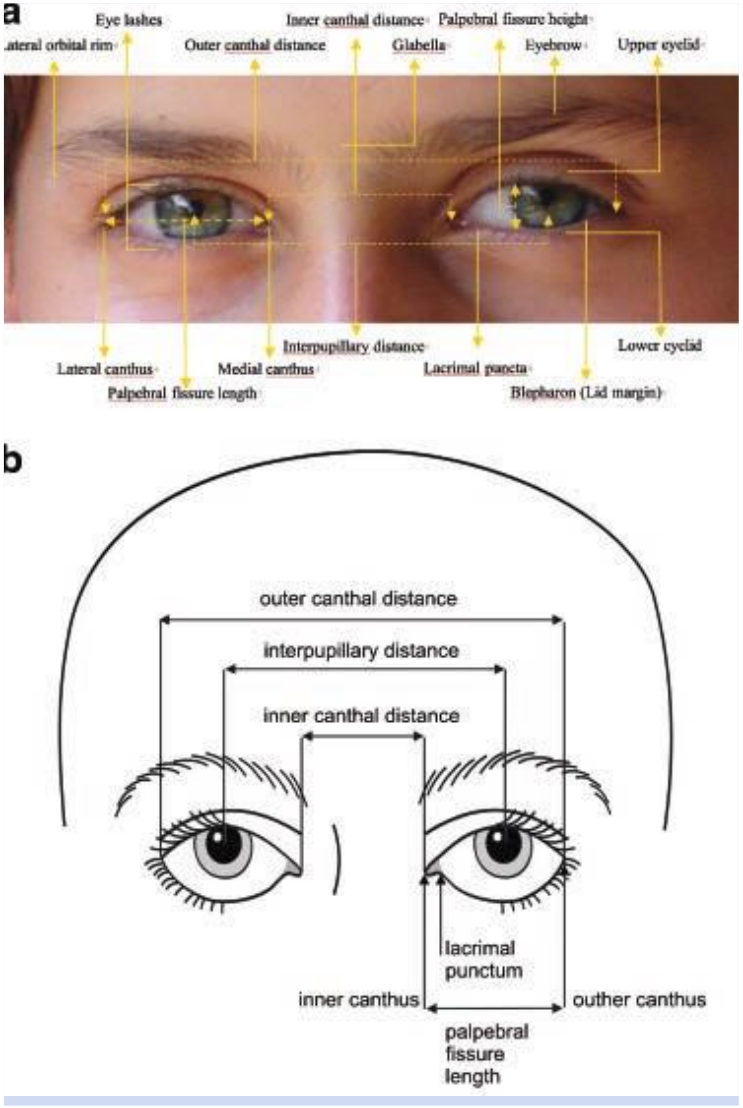


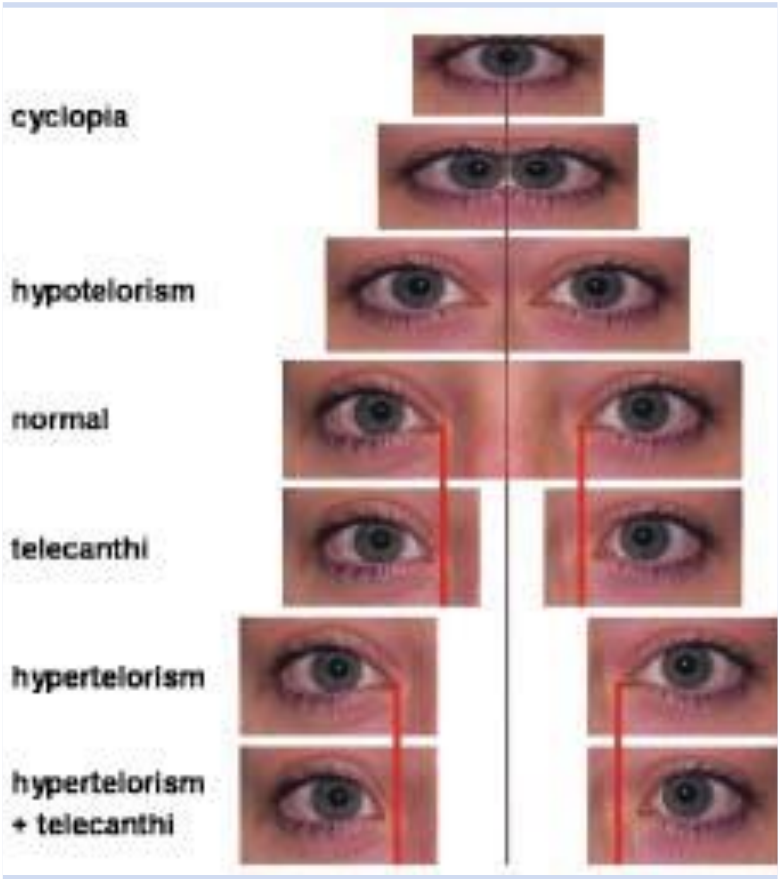
FIG. 8. *Microcephaly*. Decreased size of the cranium is accompanied by marked posterior sloping of the forehead.

AMERICAN JOURNAL OF medical genetics PART A
2009;149A(1):1-127

Standard Terminology

- For Peri orbital Region – pg 29-39

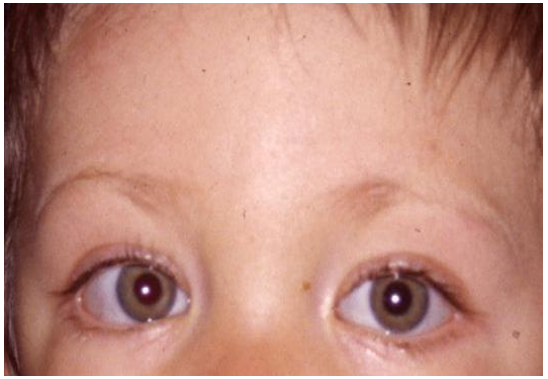




Eyebrows

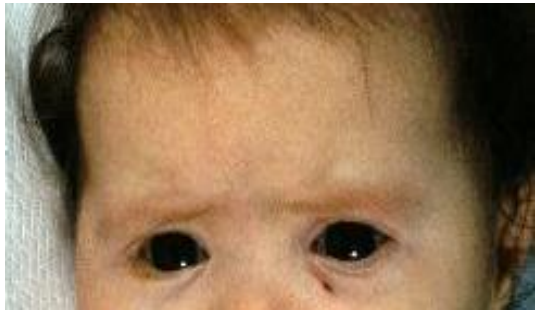
Orientation

- high
- horizontal



Shape

- arched
- heavy

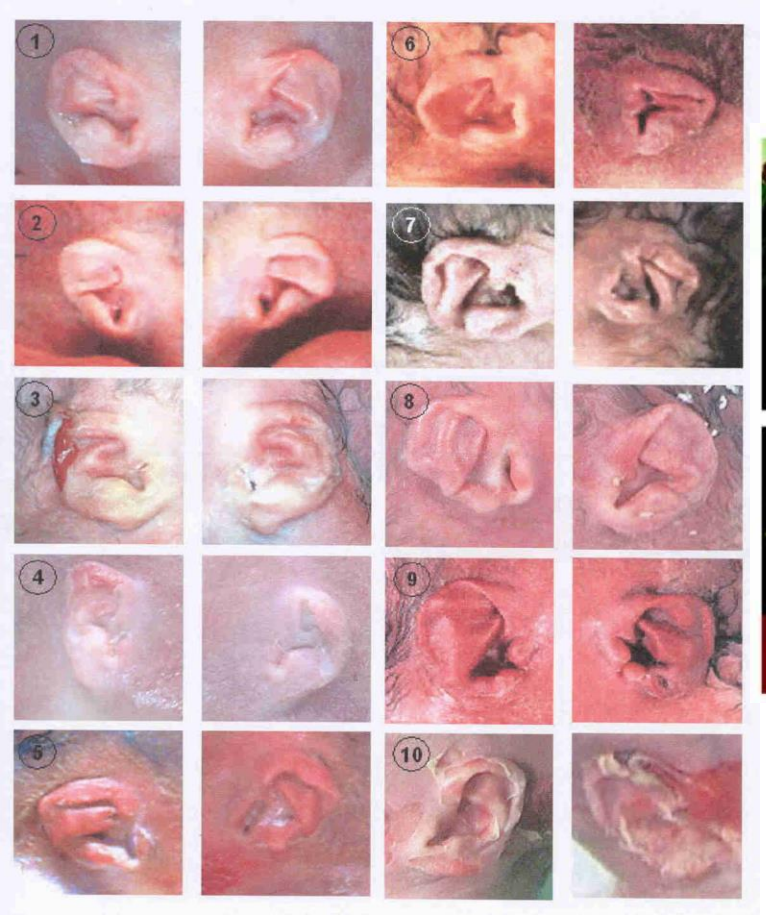


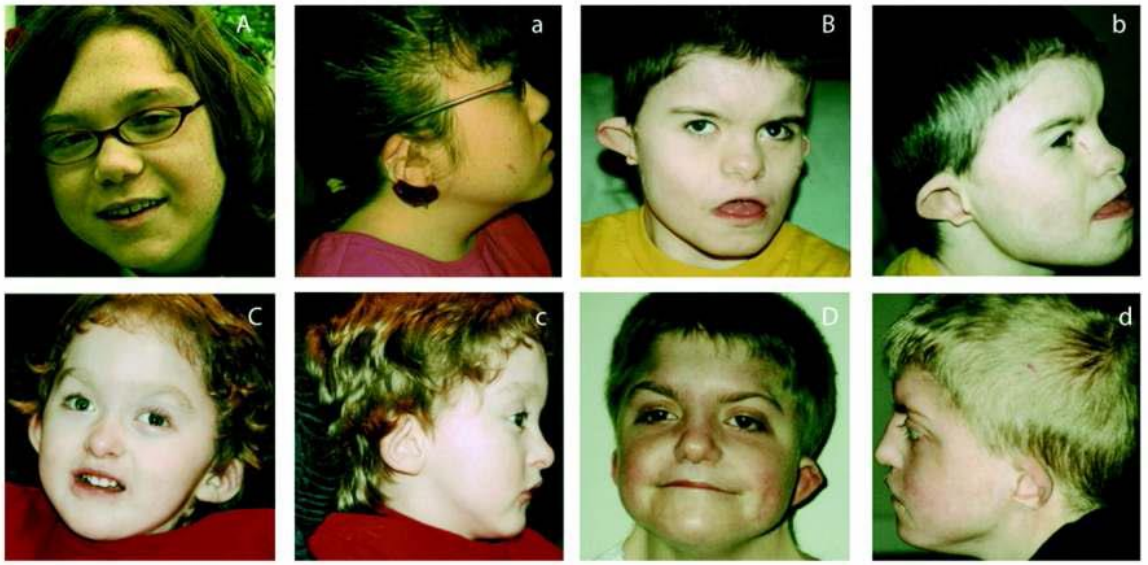
Distinctive

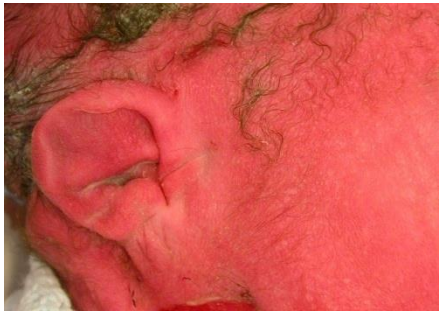
- Synophris (+ deafness,…)

External ears

…pathognomonic for a syndrome







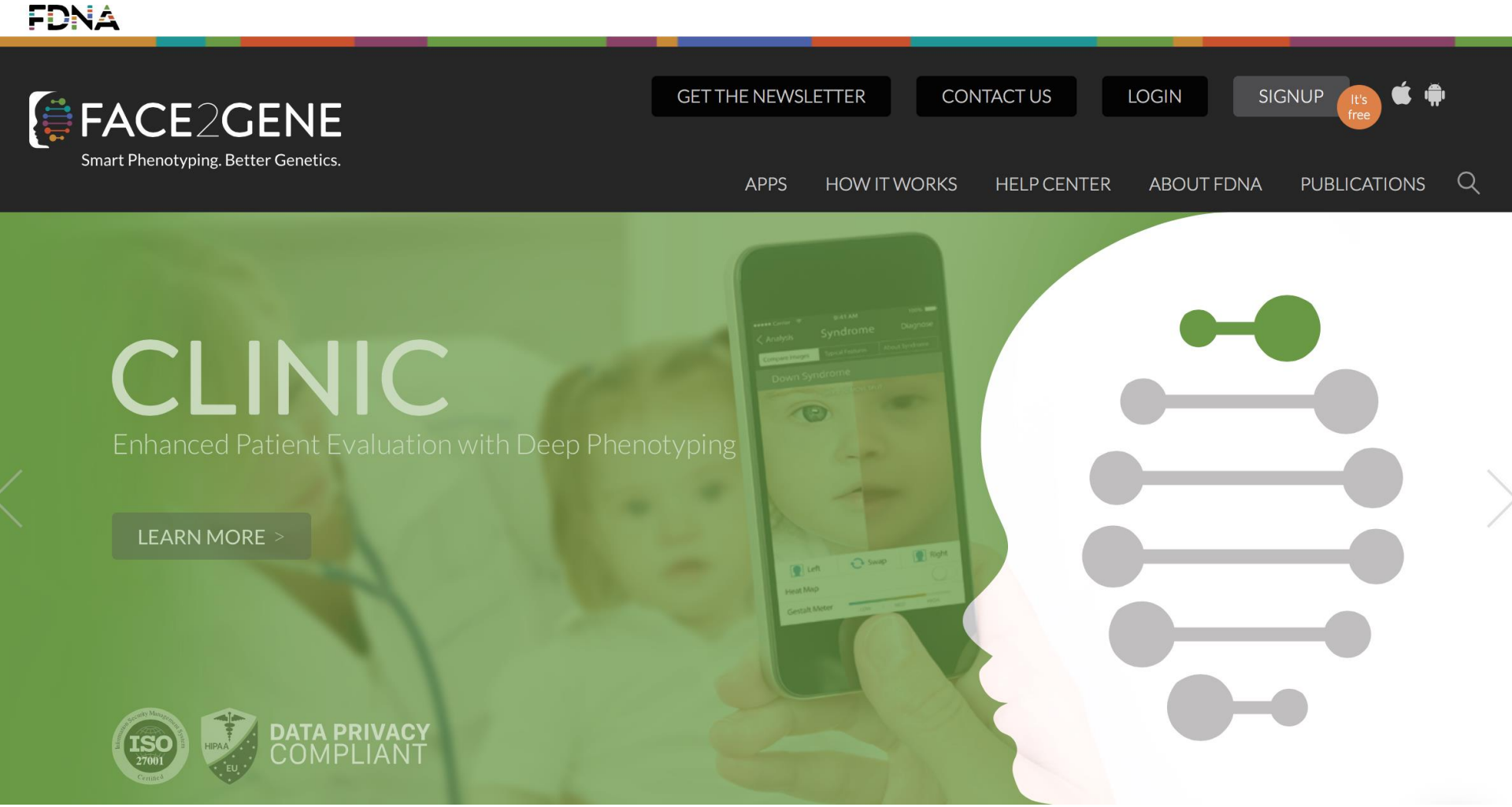
From

‘Face’

To

Gene’…

From Face to Gene ?…



http://www.face2gene.com

Enhanced patient evaluation with Next-Generation Phenotyping

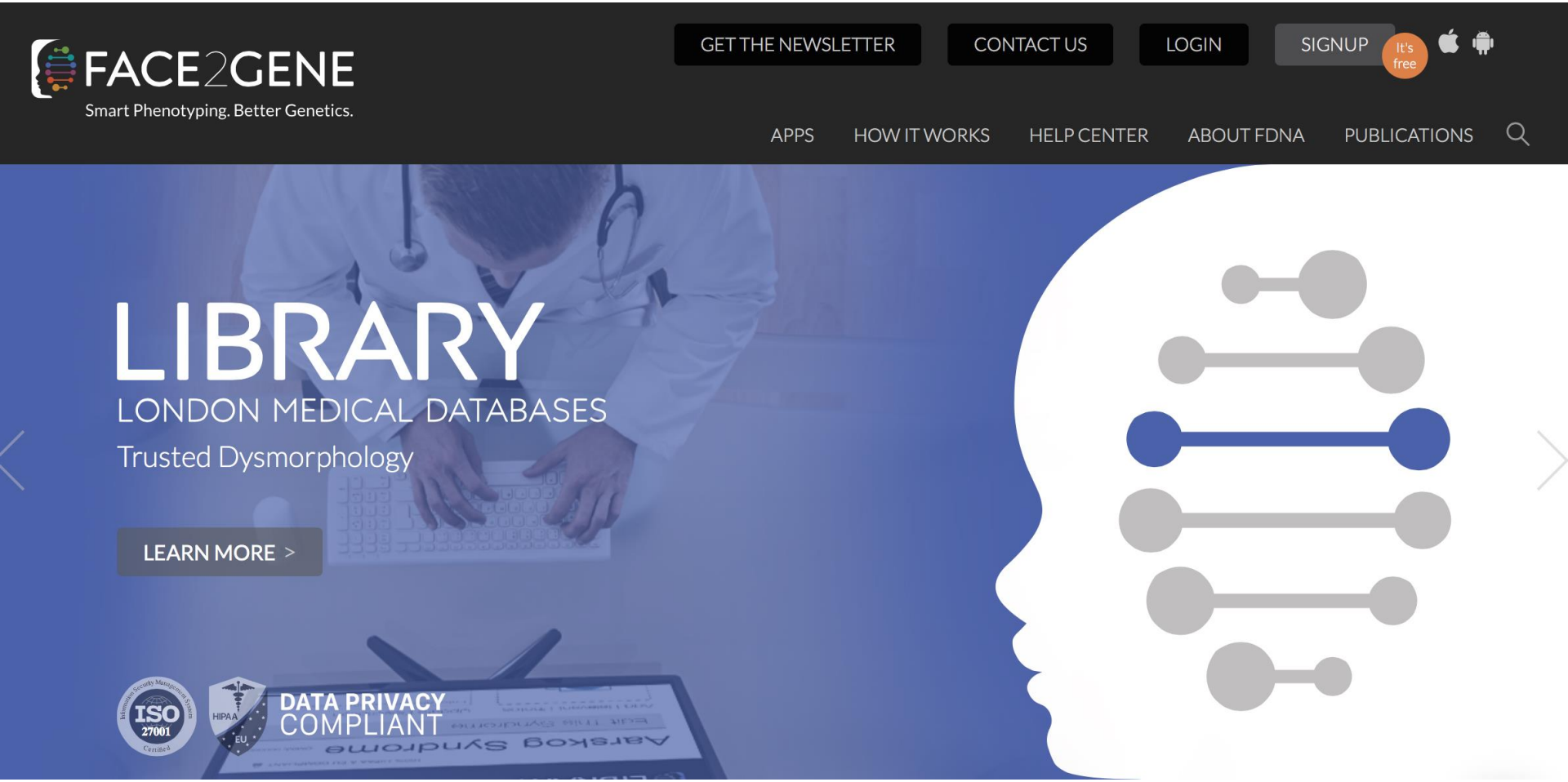
The Genetics Resource

Search for Syndromes

Review Photos & Features

Up-to-date Content through Genetics Community Curation

Ct’d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Collaborative Case Review for Diagnostic Dilemmas

START USING FACE2GENE (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

A second database tool

Human Phenotype Ontology

Home | About | Downloads | Tools | Documentation | Users | History

FAQ | License | Citation | Contact

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 phenome. 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

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HPO Browser

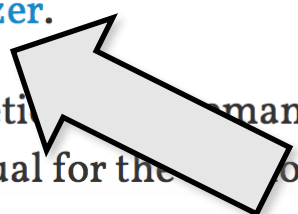
The HPO Browser has a separate page for every term in the HPO. The following page, for instance, is for the root term: http://www.human-phenotype-ontology.org/hpoweb?id=HP:0000118.

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:

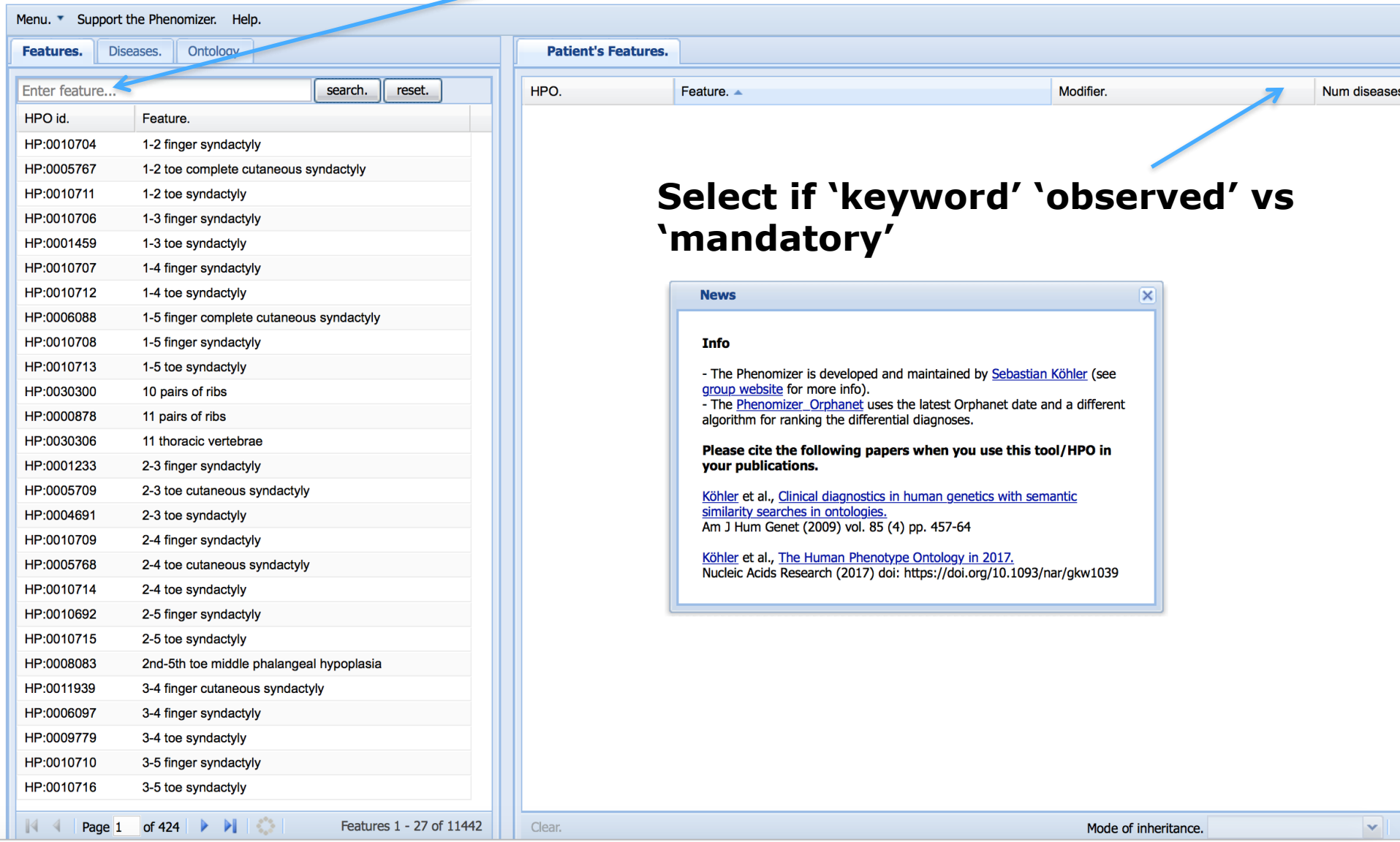
The Phenomizer is available at http://compbio.charite.de/phenomizer.



It is a web-based application for clinical diagnostics in human geneti mantic similarity searches in ontologies Köhler et al., AJHG, October 2009. The Manual for the omizer can be

Catalog – Features on keywords

Insert/select keywords based on features



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

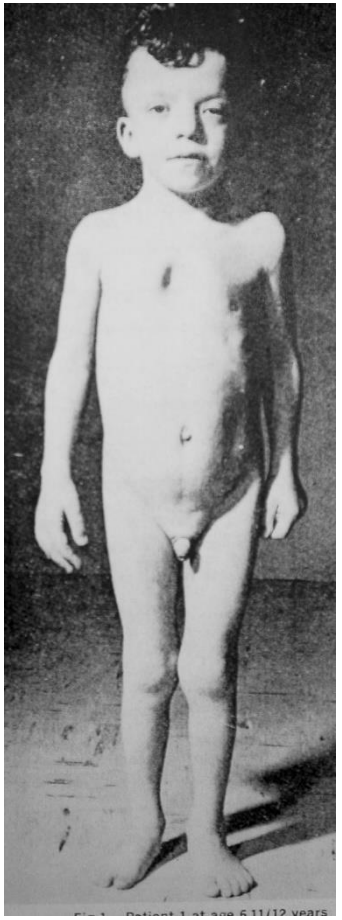
Tool IV - 'Syndromology' derived from syndrome: clinical approach to occurrence multiple congenital anomalies

Ped Cardiology clinic

First description

9 patients with pulmonary valve stenosis, short stature

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

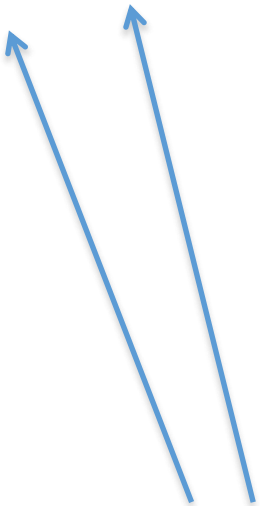


Noonan J and Ehmke D. J Pediatr 1963;63:468-470

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

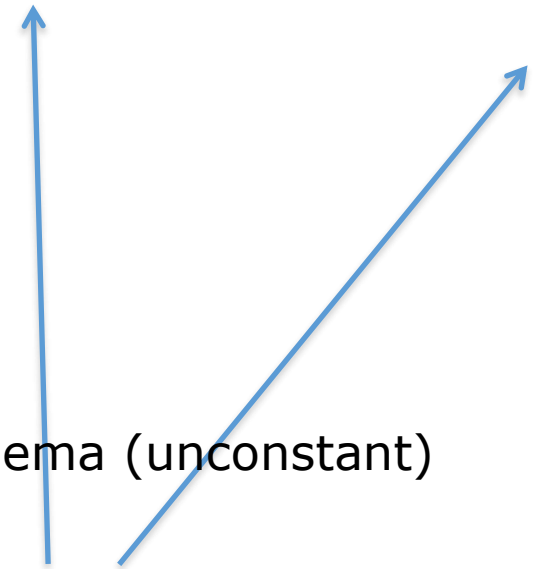


pectus carinatum

Remnant of prenatal nuchal translucency and hygroma

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

...

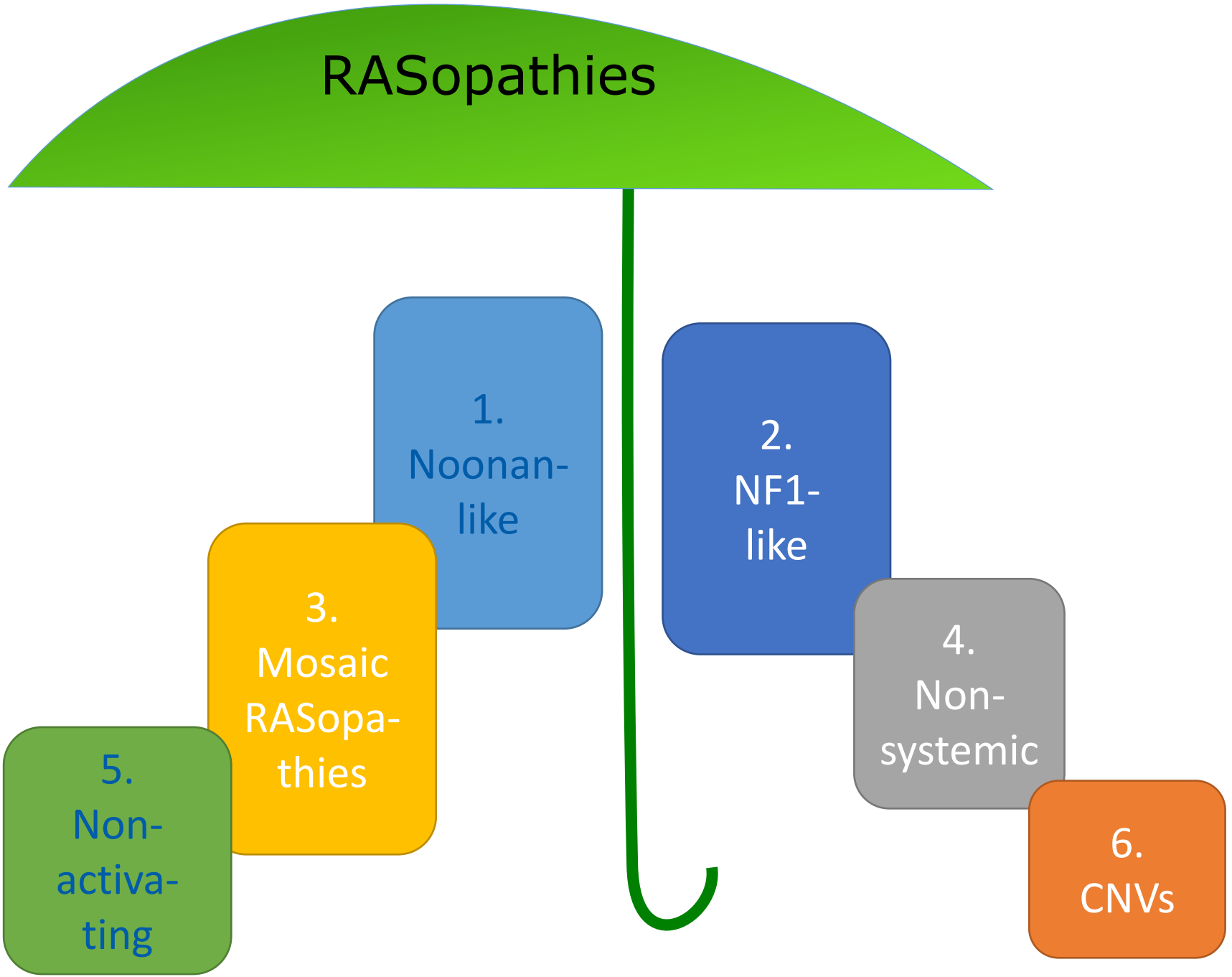
Evolving phenotype with age

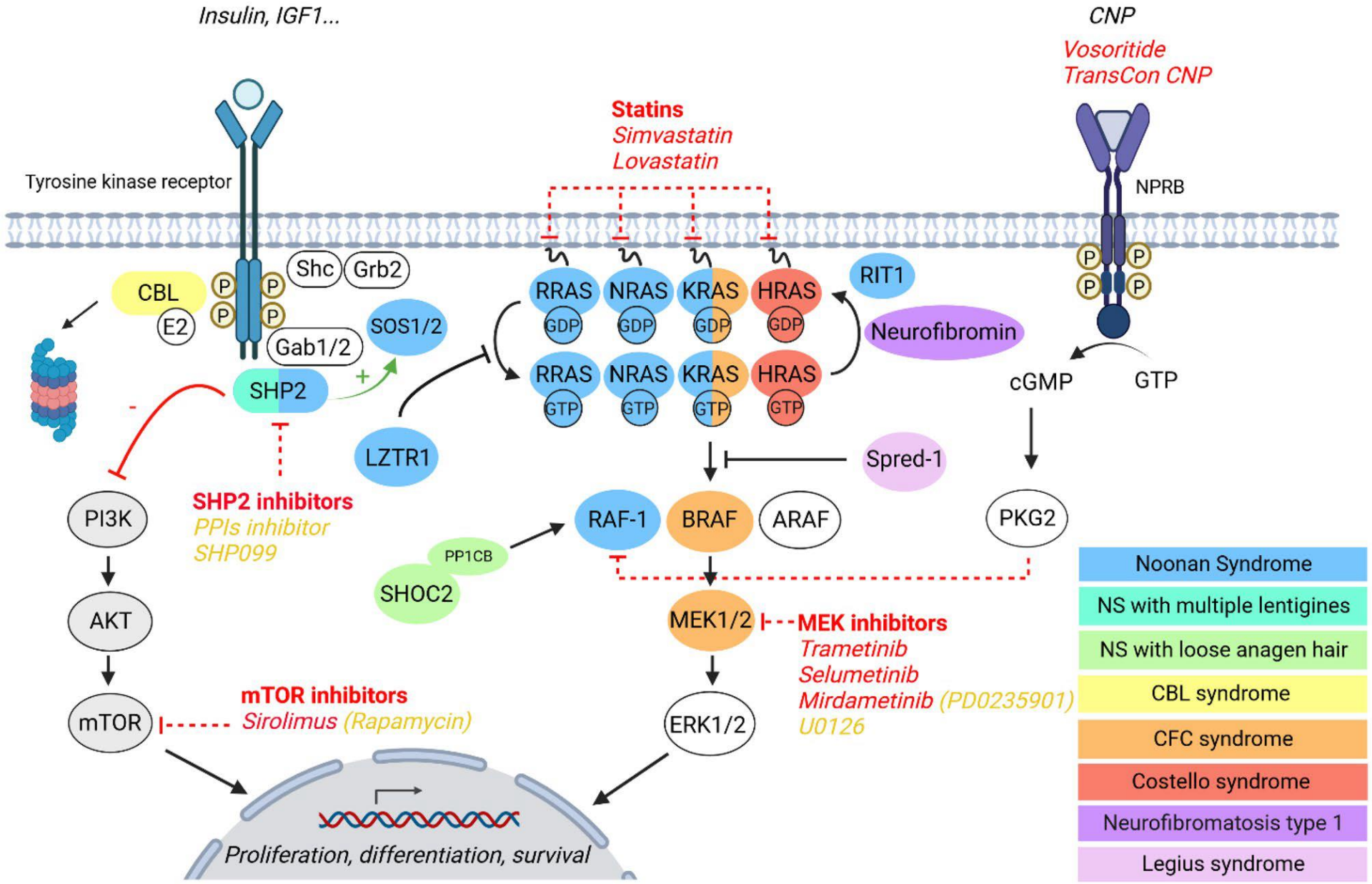
...Knowledge on natural history

…to adulthood

…to adulthood

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


RASopathies
1. Noonan-like
2. NF1-like
3. Mosaic RASopa-thies
4. Non-systemic
5. Non-activa-ting
6. CNVs



PMID: 37863846

Gene	Highest RASopathy Association Achieved	Specific Conditions				
		Noonan	CFC	Costello	NSML	NS/LAH
BRAF	Definitive	Moderate (10.5)	Definitive (13.5)	Disputed	Limited (5.5)	-
HRAS	Definitive	-	-	Definitive (14.5)	-	-
KRAS	Definitive	Definitive (14)	Strong (12.5)	Disputed	-	-
MAP2K1	Definitive	Limited (3.5)	Definitive (12.5)	Disputed	Limited (2.5)	-
MAP2K2	Definitive	Limited (1)	Definitive (12.5)	-	-	-
NRAS	Definitive	Definitive (13.5)	Limited (0.5)	Limited (1)	Limited (3.5)	-
PTPN11	Definitive	Definitive (13.5)	Disputed	Disputed	Definitive (15)	-
RAF1	Definitive	Definitive (13.5)	Disputed	Disputed	Limited (4.5)	-
RIT1	Definitive	Definitive (13.5)	-	-	-	-
SHOC2	Definitive	Disputed	Disputed	Disputed	-	Definitive (12.75)
SOS1	Definitive	Definitive (12.5)	Limited (1.5)	Disputed	-	-
LZTR1†	Strong	Strong (12)	-	-	-	-
PPP1CB	Strong	Strong (12.5)	-	-	-	Strong (12)
SOS2†	Moderate	Moderate (9.5)	-	-	-	-
LZTR1 (AR)	Limited	Limited (8.75)	-	-	-	-
MRAS	Limited	Limited (4.5)	-	-	-	-
RRAS	Limited	Limited (3.25)	-	-	-	-
RASA2	Limited	Limited (1.5)	-	-	-	-
A2ML1	Disputed	Disputed	-	-	-	-
RASA1	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)	
Congenital heart defects (e.g. pulmonary stenosis, hypertrophic cardiomyopathy, atrial septal defect)	Full cardiac evaluation at diagnosis.
Failure to thrive/slow growth rate/feeding problems	Monitor and plot growth on appropriate NS and age-based growth chart.
Short stature	
Developmental delay and neuropsychological/behavioural issues	Refer patient in second half of first year or at diagnosis for formal developmental assessment. Baseline neuropsychological assessment at primary school entry.
Minor renal anomalies	Refer for renal ultrasound at diagnosis.
Bleeding disorders	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.)
Visual problems (e.g. posterior segment ocular changes and anterior segment ocular abnormalities)	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 ?

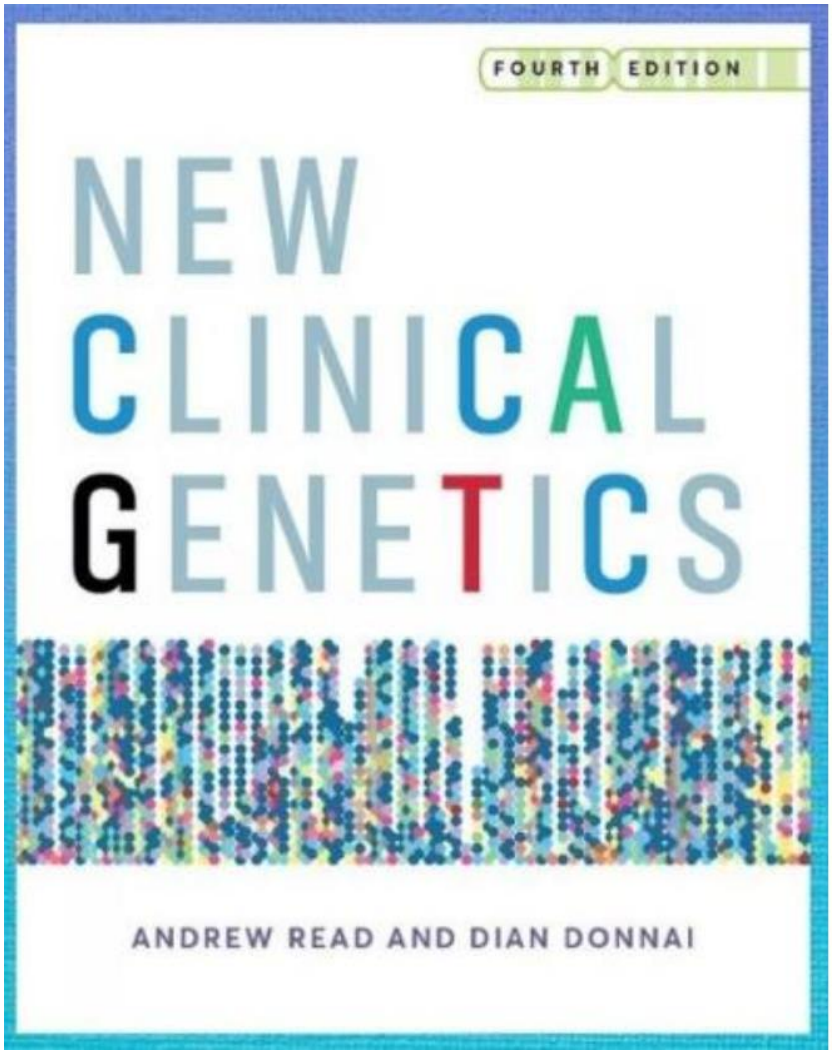
Clinical Geneticists are far less pertinent then thought
Human Hardware/brain memory on 4.000 mendelian disorders and phenotypes ?

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