The rarest among rares:

Clinical and genomic approach to undiagnosed patients

Bruno Dallapiccola
Trento, CIBIO & FBK
November 8th, 2018

Bambino Gesù
OSPEDALE PEDIATRICO

“By definition, diseases without a name and, thus, undiagnosed clinical conditions, are rare diseases”

Ségolène Aymé, Founder of Orphanet

Rare diseases' definitions

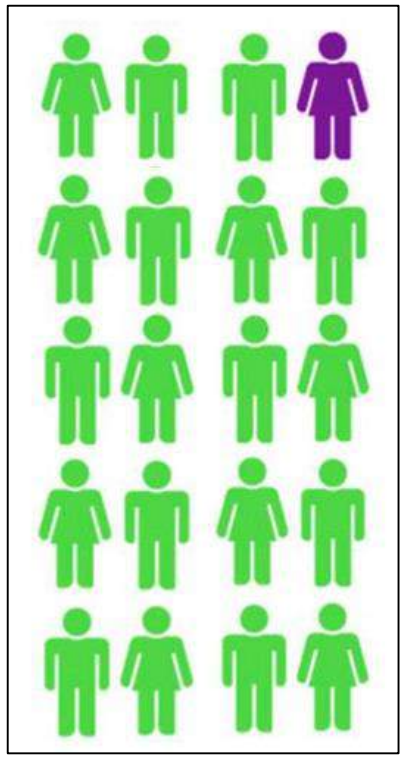
- Affect <200 000 individuals (< 1:1.500)

- Affect <50 000 individuals (<1:2.500)

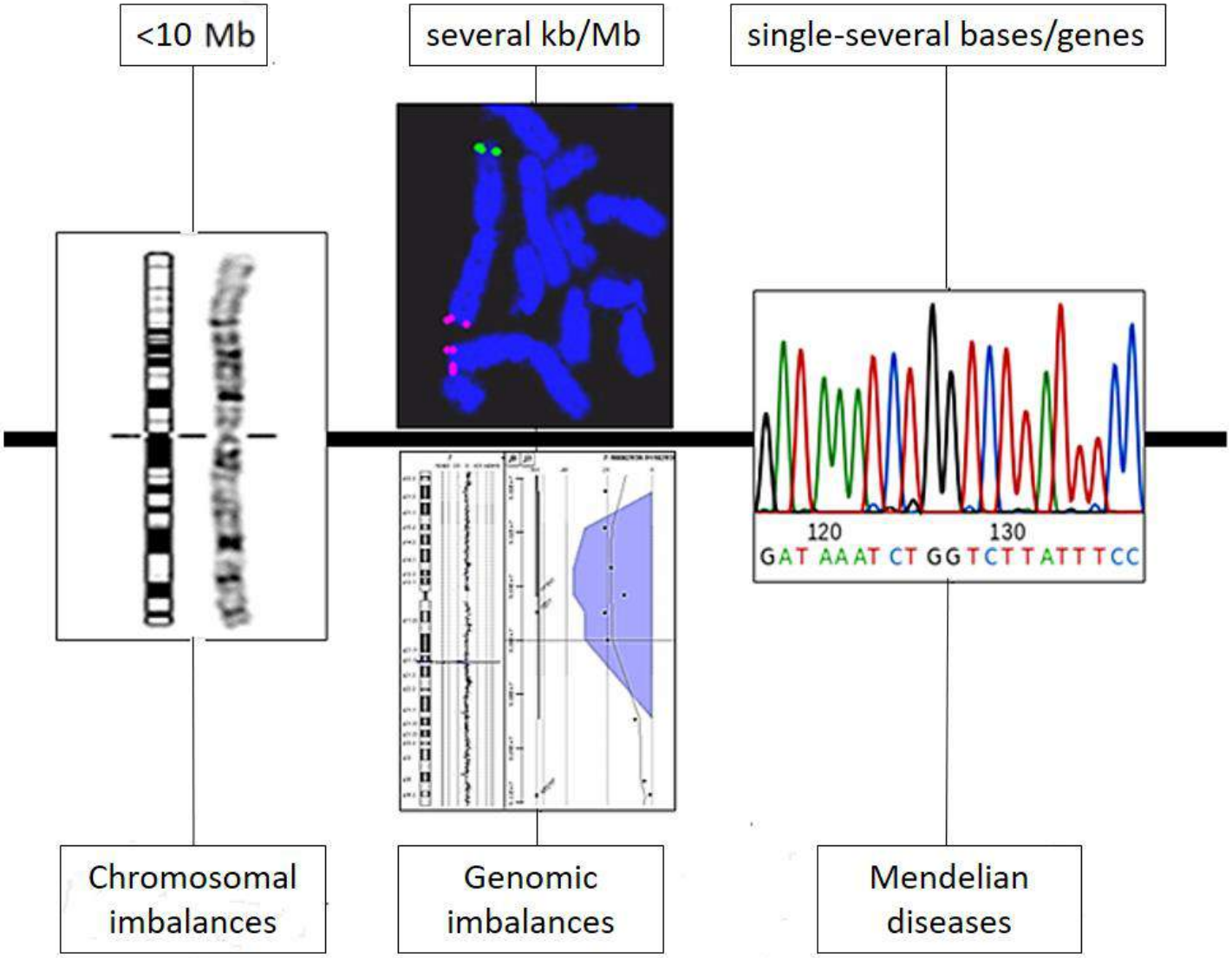
- Affect <5:10 000 individuals (<1:2.000)

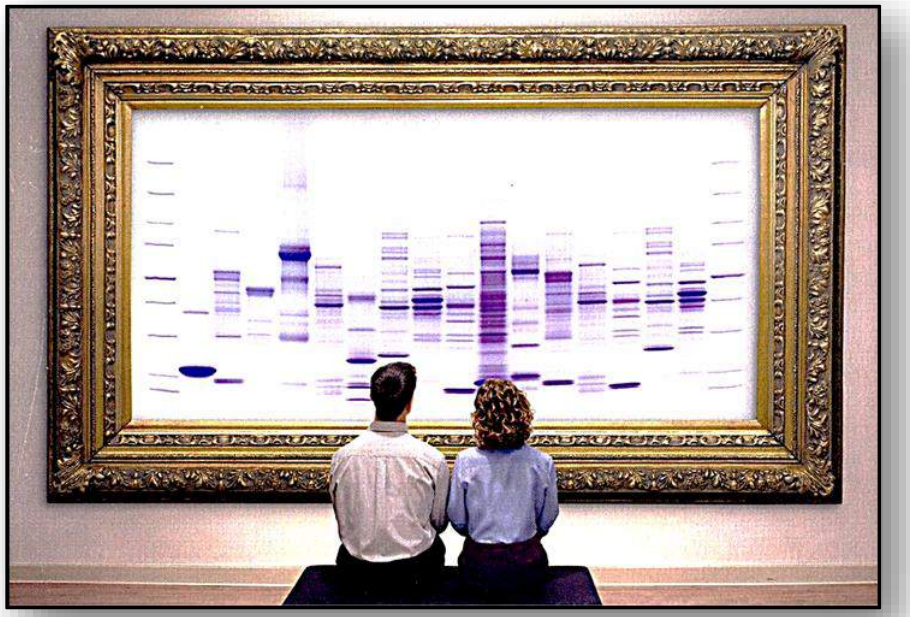
The rare diseases' figures

- There are >7 000 RDs (and ~300 rare tumors).
- >1:20 people affected.
- 1-2 million people affected in Italy?
- ~30 million people affected in Europe.
- ~350 million people worldwide.
- >50% of patients are children.
- 30% of patients has a life expectancy of <5 years.
- 90% are genetic diseases.



Traditional genetic approaches to rare diseases





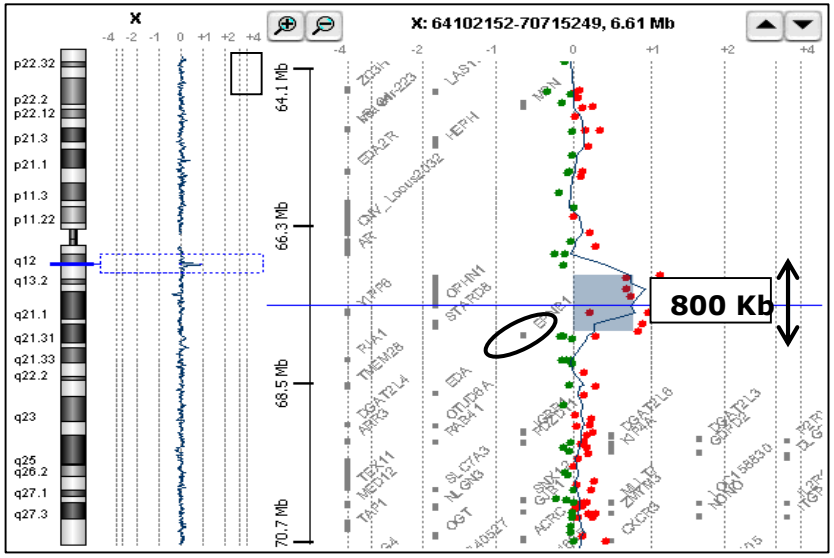
“Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder”.

National Institute of Health, 2018

Impact of genetic testing

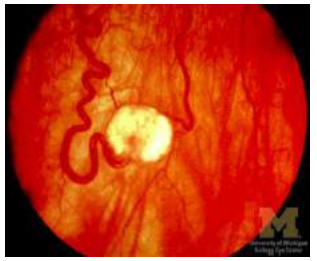
To make the diagnosis

- Intellectual disability
- Hypotonia, muscles hypotrophy
- Microcephaly
- Convulsions
- Scoliosis
- MRI cerebral/cerebellar hypotrophy

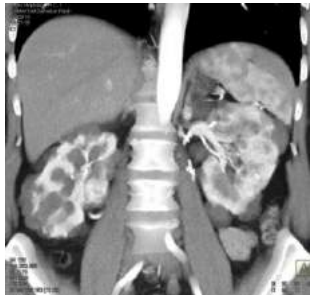


dupXq12q13 - *OPHN1* gene

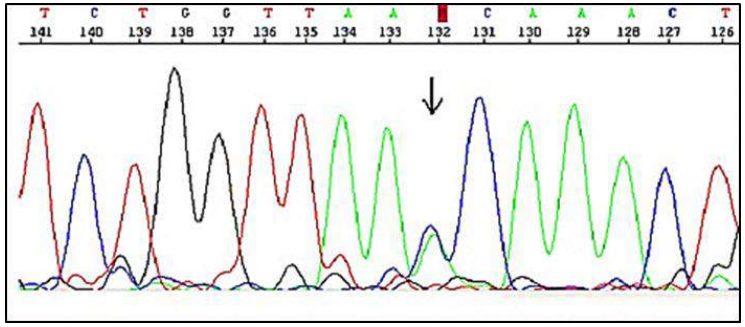
To confirm a clinical diagnosis



- Retinal capillary hemangiomas



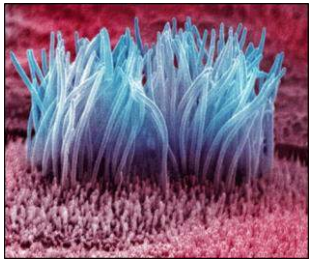
- multiple bilateral renal cell carcinomas
- cystic pancreatic lesions

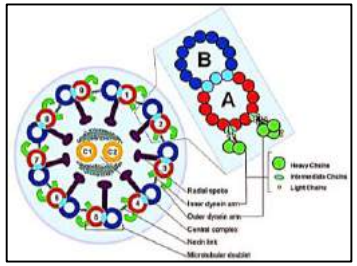


Von Hippel Lindau diseaase – *VHL* gene mutation

Impact of genetic testing

To address genetic heterogeneity

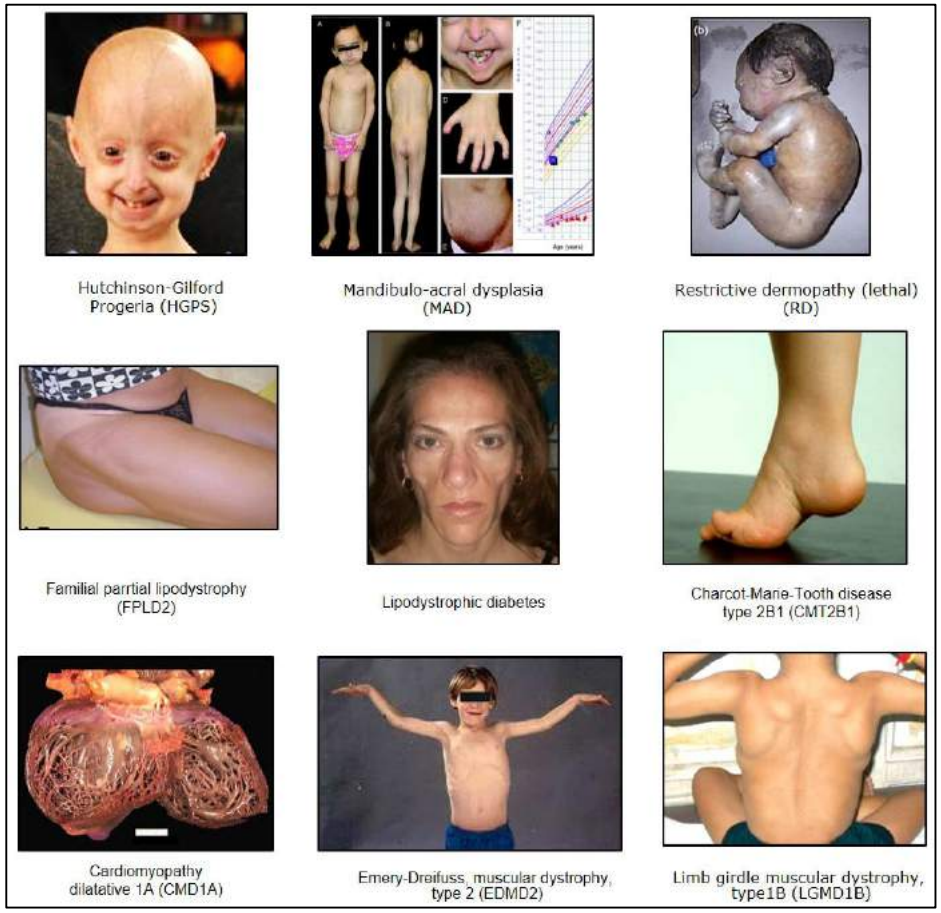




Location	Phenotype	Gene/Locus
2p23.3	Ciliary dyskinesia, primary, 21	DRC1
3p21.31	Ciliary dyskinesia, primary, 22	ZMYND10
3p21.1	?Ciliary dyskinesia, primary, 37	DNAH1
3q26.33	Ciliary dyskinesia, primary, 14	CCDC39
5p15.2	Ciliary dyskinesia, primary, 3, with or without situs inversus	DNAH5
5q11.2	Ciliary dyskinesia, primary, 29	CCNO
6p21.1	Ciliary dyskinesia, primary, 12	RSPH9
6q22.1	Ciliary dyskinesia, primary, 11	RSPH4A
6q25.3	Ciliary dyskinesia, primary, 32	RSPH3
7p22.3	Ciliary dyskinesia, primary, 18	DNAAF5
7p15.3	Ciliary dyskinesia, primary, 7, with or without situs inversus	DNAH11
7p14.1	Ciliary dyskinesia, primary, 6	NME8
8q22.2	Ciliary dyskinesia, primary, 28	SPAG1
8q24.22	Ciliary dyskinesia, primary, 19	LRRC6
9p13.3	Ciliary dyskinesia, primary, 1, with or without situs inversus	DNAI1
10p12.1	Ciliary dyskinesia, primary, 23	ARMC4
11q13.4	Ciliary dyskinesia, primary, 34	DNAJB13
12q13.12	Ciliary dyskinesia, primary, 27	CCDC65
14q21.3	Ciliary dyskinesia, primary, 10	KTU
14q24.3	Ciliary dyskinesia, primary, 16	DNAL1
15q13.1-q15.1	Ciliary dyskinesia, primary, 4	CILD4
15q21.3	Ciliary dyskinesia, primary, 25	DNAAF4
15q24-q25	Ciliary dyskinesia, primary, 8	CILD8
16q22.2	Ciliary dyskinesia, primary, 5	HYDIN
16q24.1	Ciliary dyskinesia, primary, 13	DNAAF1
16q24.3	Ciliary dyskinesia, primary, 33	GAS8
17q21.2	Ciliary dyskinesia, primary, 35	TTC25
17q21.31	Ciliary dyskinesia, primary, 17	CCDC103
17q25.1	Ciliary dyskinesia, primary, 9, with or without situs inversus	DNAI2
17q25.3	Ciliary dyskinesia, primary, 15	CCDC40
19p13.2	Ciliary dyskinesia, primary, 30	CCDC151
19q13.33	Ciliary dyskinesia, primary, 20	CCDC114
19q13.42	Ciliary dyskinesia, primary, 2	DNAAF3
21q22.11	Ciliary dyskinesia, primary, 26	C21orf59
21q22.3	Ciliary dyskinesia, primary, 24	RSPH1
Xq22.3	Ciliary dyskinesia, primary, 36, X-linked	PIH1D3

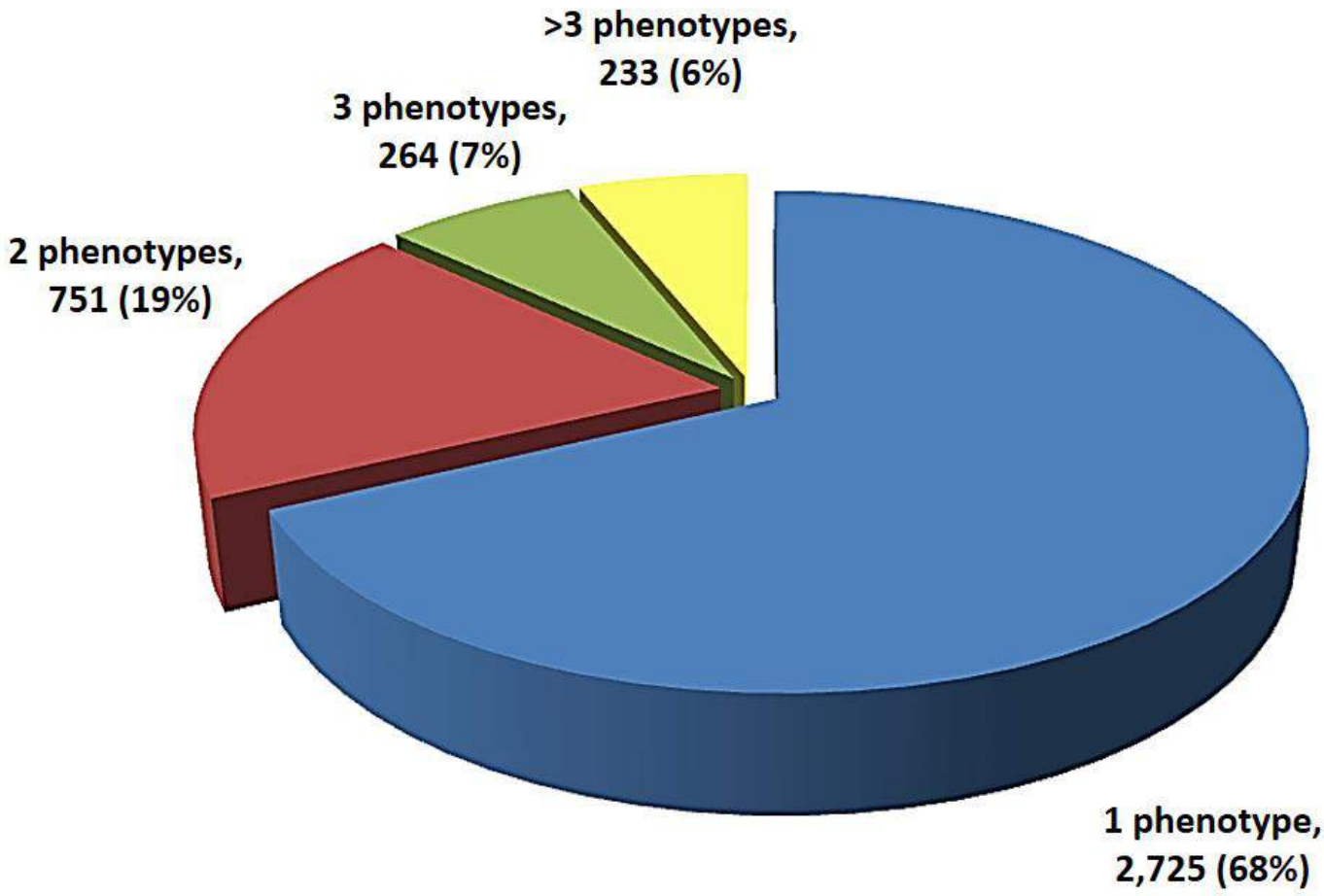
Primary ciliary dyskinesia

To address genotype-phenotype correlations



LMNA/C gene mutations

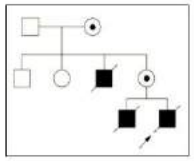
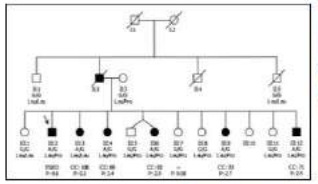
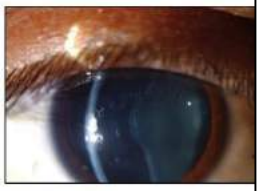
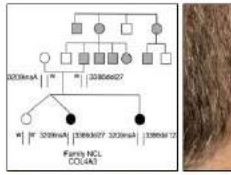
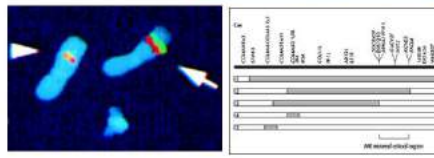
Phenotype distribution in 3,973 annotated genes
(OMIM updated October 22nd, 2018)



Impact of genetic testing

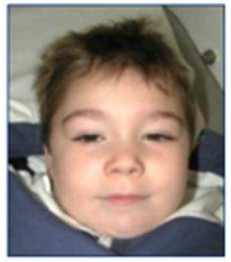
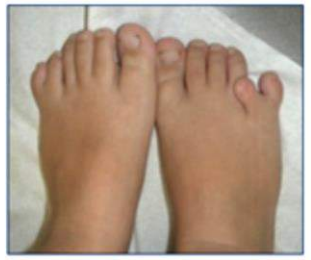
To address heterogeneity of inheritance models

- X-linked *(COL4A5)* 70-80%
- Autosomal dominant *(COL4A3)* 15-20%
- Autosomal recessive *(COL4A3, COL4A4)* rare
- Syndromic, contiguous genes – rare - AMME: Alport syndrome, Mental retardation, Medio-facial hypoplasia, Elissocytosis

Alport syndrome

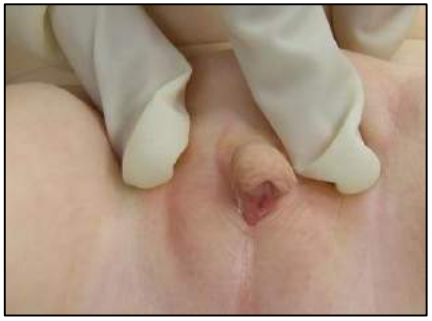
To uncover the mechanisms of atypical inheritance

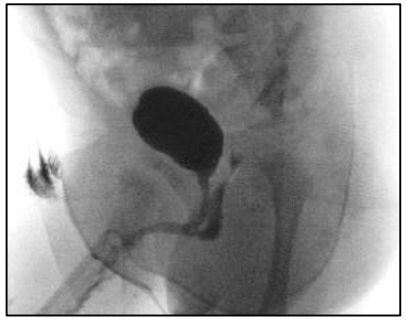



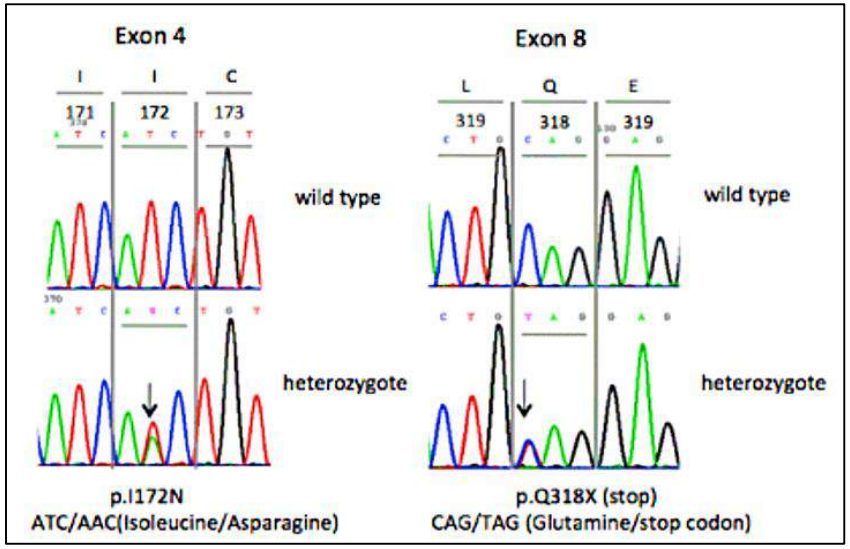
Triallelic Bardet Biedl syndrome

Impact of genetic testing

To chose the more appropriate therapy

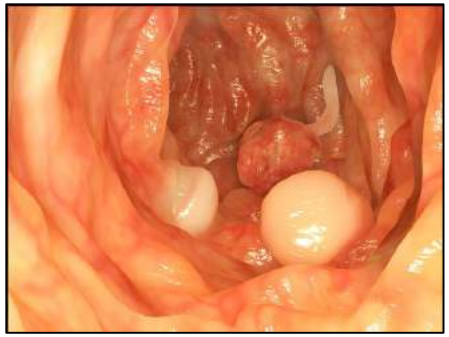


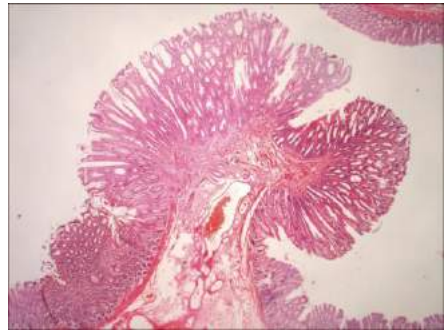


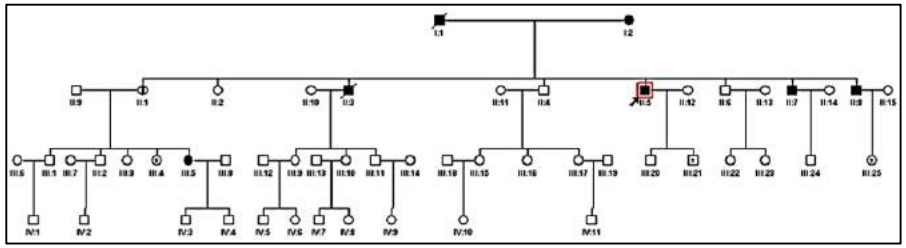


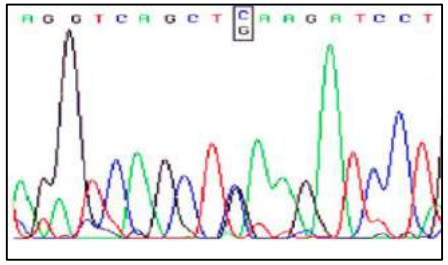
Adrenogenital syndrome – 21-hydroxilase deficiency

Presymptomatic testing to avoid inappropriate procedures





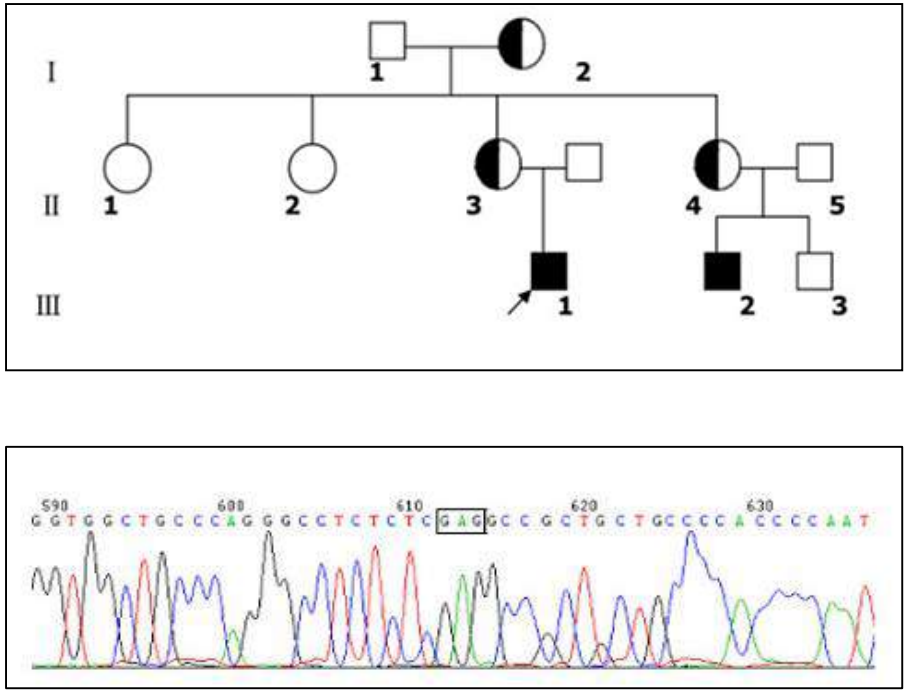




Familial adenomatous polyposis

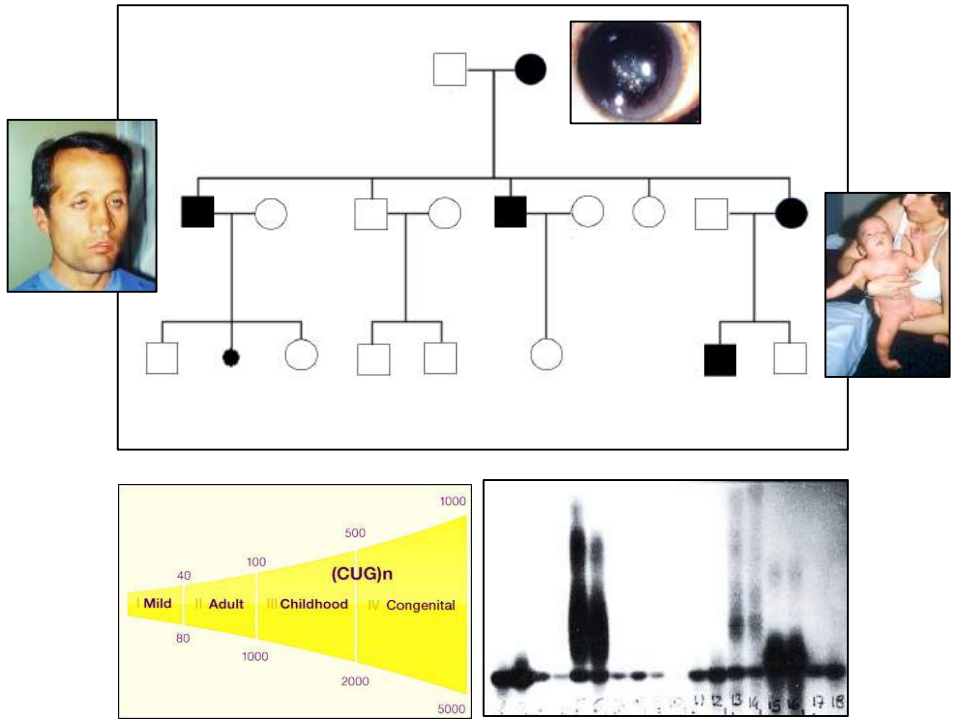
Impact of genetic testing

To provide accurate genetic counselling



X-linked nephrogenic diabetes insipidus (*AVPR2* gene)

To predict the disease's severity

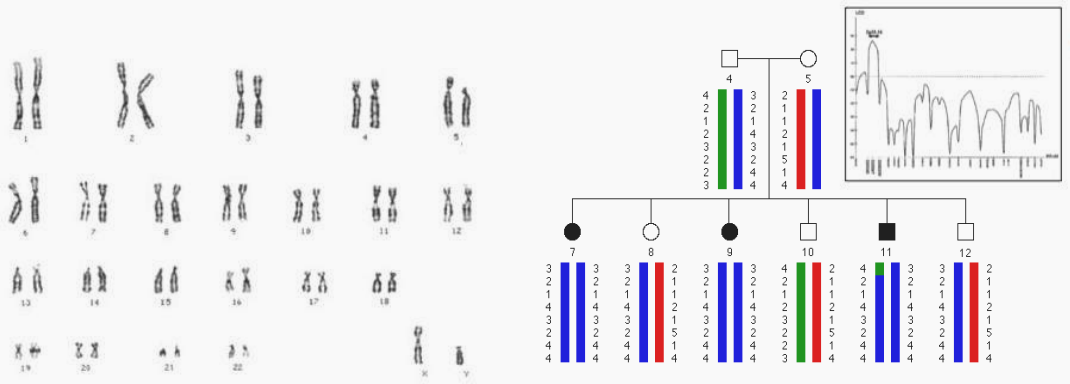


Myotonic dystrophy 1 (*DMPK* gene)

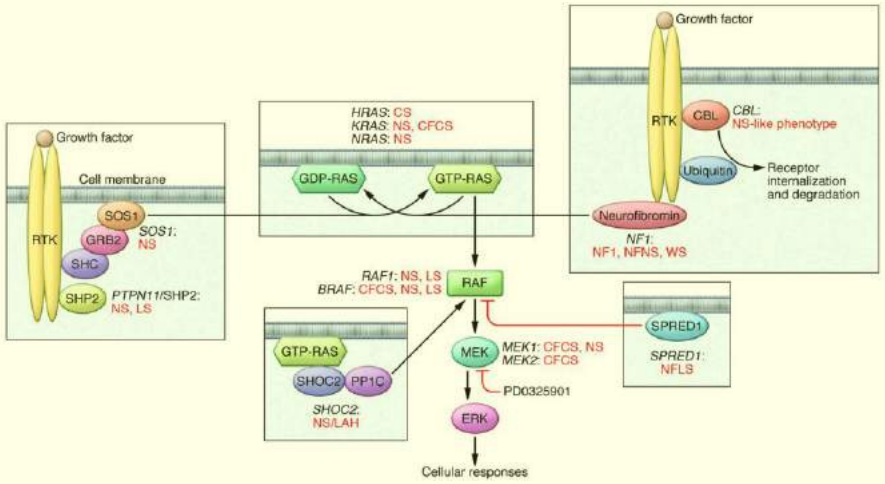
Positional Cloning

↓

Positional Candidacy

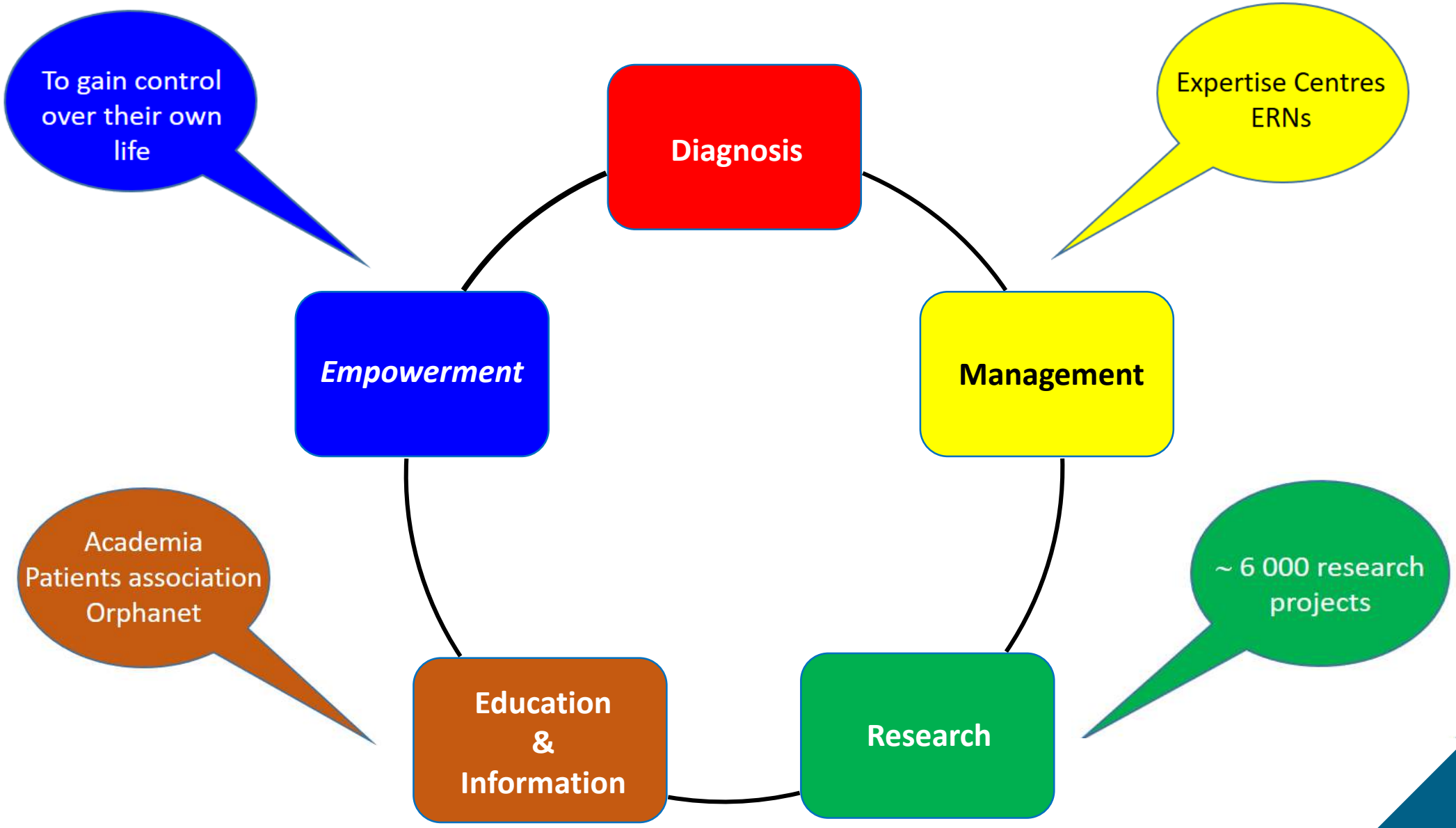


Functional Candidacy

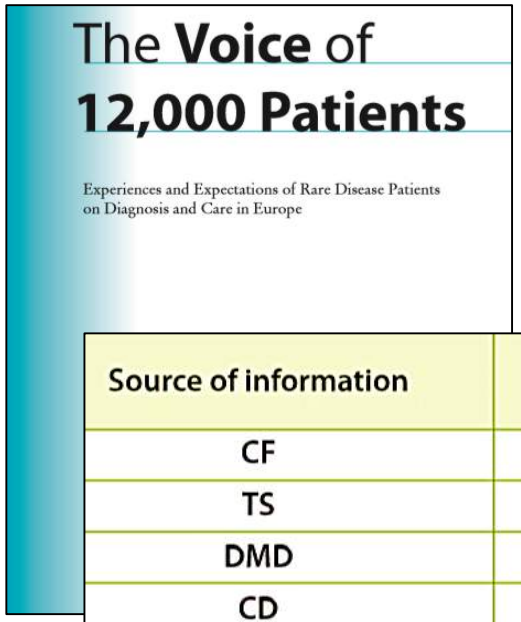


The traditional approaches to genetic diseases have uncovered the molecular defect underlying a few thousands Mendelian disorders. The progress has been relatively slow because of the small number of informative families and limited information on the diseases' mechanisms.

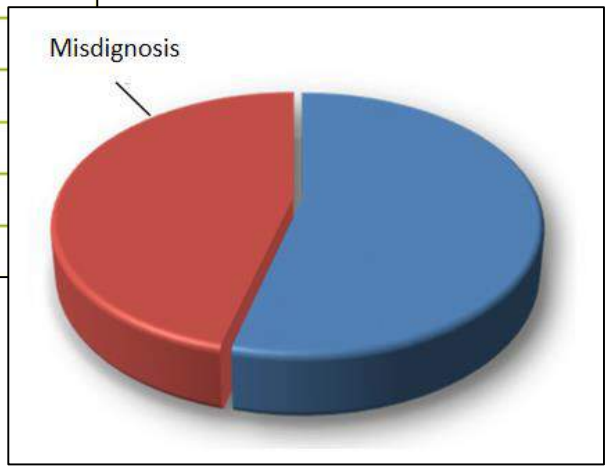
The rare diseases cornerstones



Diagnostic delays and misdiagnosis



Source of information	Delay in diagnosis for 50% of patients	Delay in diagnosis for 75% of patients
CF	1.5 months	15 months
TS	4 months	3 years
DMD	12 months	3 years
CD	12 months	5.8 years
PWS	18 months	6.1 years
MFS	18 months	11.1 years
FRX	2.8 years	5.3 years
EDS	14 years	28 years



- Average diagnostic delay: 7.6 years in USA; 5.6 years in UK
- 40% of patients are originally misdiagnosed.

Undiagnosed patients

- 6% of RD patients remains undiagnosed *(National Institute of Health).*
- 40% of disabled children does not have a diagnosis *(Roxby P, BBC News, UK, February 2nd, 2014).*

Patients organisations (SWAN - Syndrome Without A Name)

USA

Australia

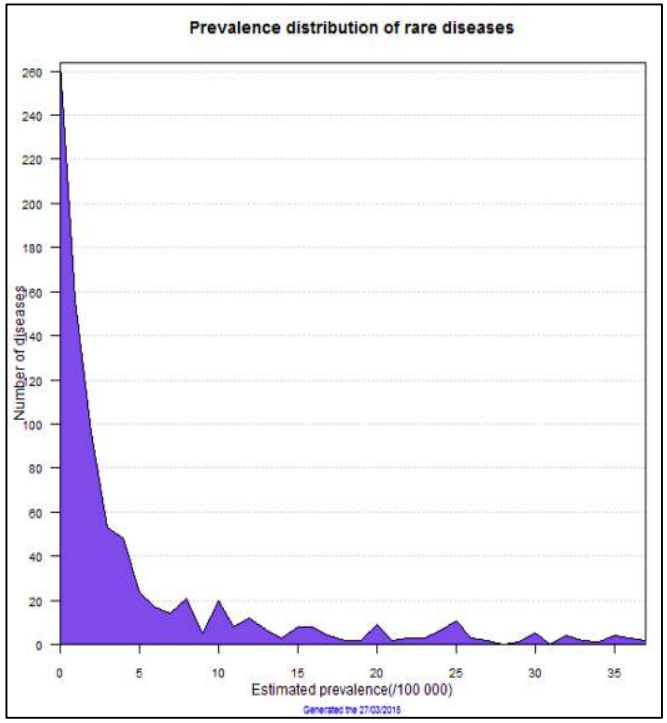
New Zeland

UK

Italy

Why so many undiagnosed patients?

- The “rarity’s” figures *(according to Orphanet)*:
  - ~ 100 RDs: prevalence between 5 to 1 in 10 000;
  - ~ 250 RDs: prevalence between 1 in 10 000 to 1 in 100 000;
  - ~1 000 RDs: prevalence between 1in 100 000 to 1 in 1 million;
  - >5 000: a few patients worldwide.
- Absence of diagnostic “handles”.
- Unusual presentation of a known disorder.
- Casual associations of two RDs.
- New diseases.

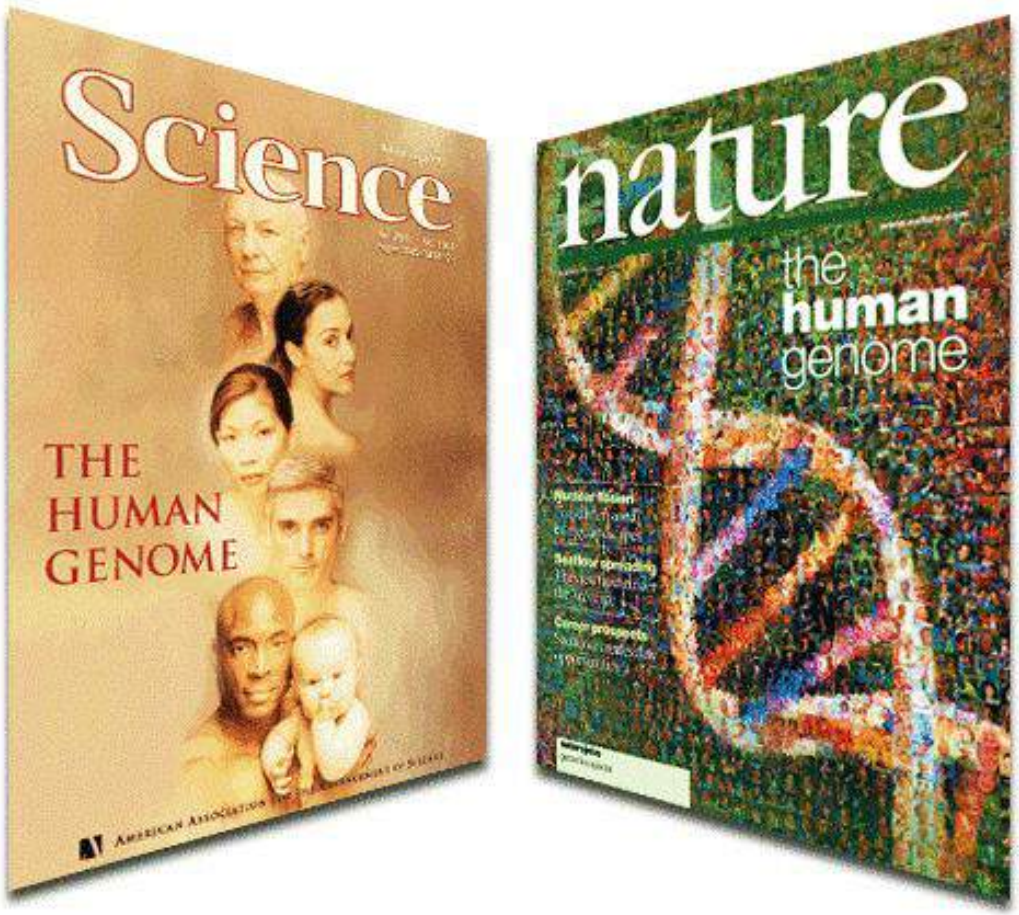


The Human Genome Project

First draft June 26th, 2000

Human Genome Project

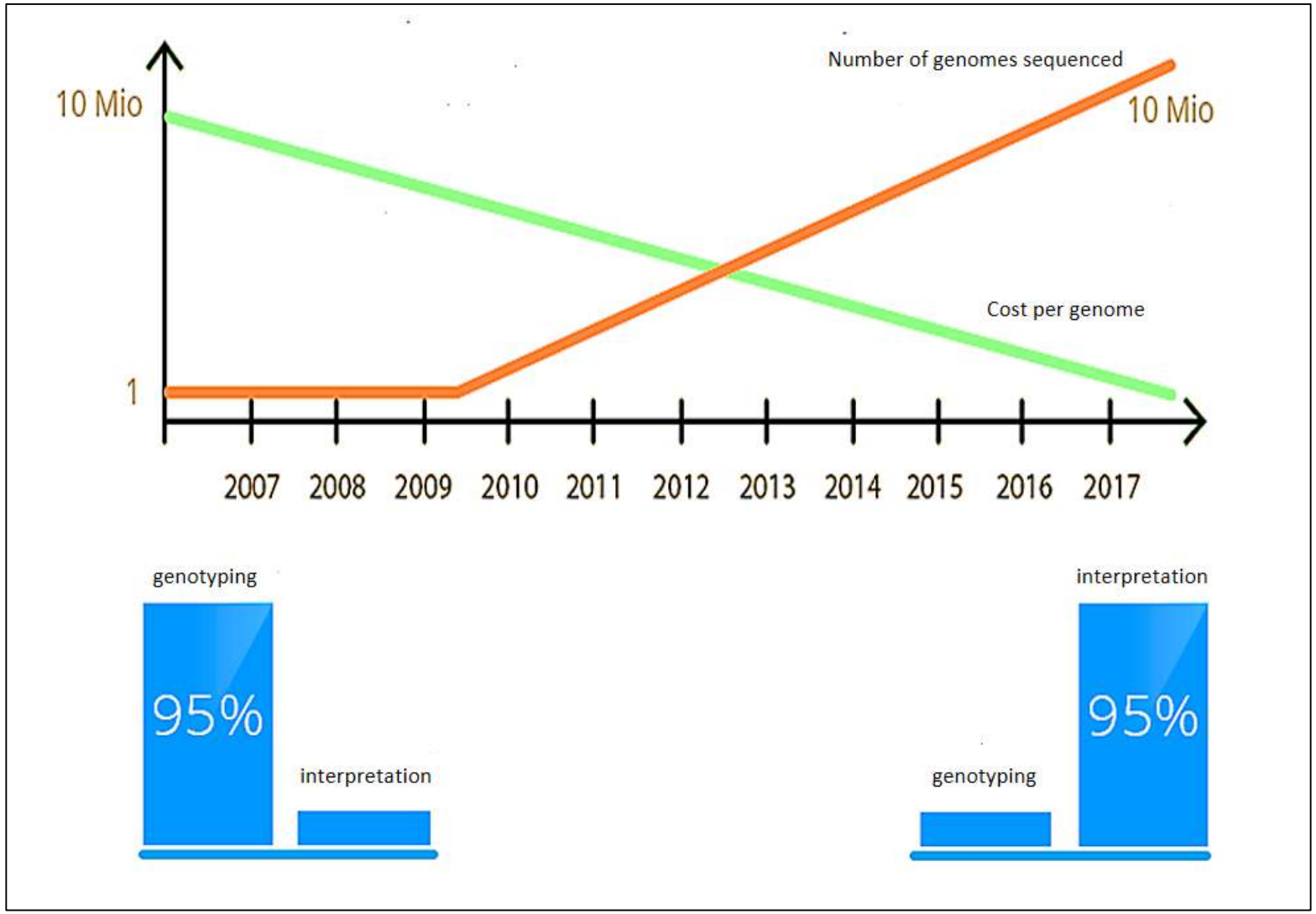
February 15-16, 2001



"… The complete human genome sequence will facilitate the identification of all genes that contribute to disease."

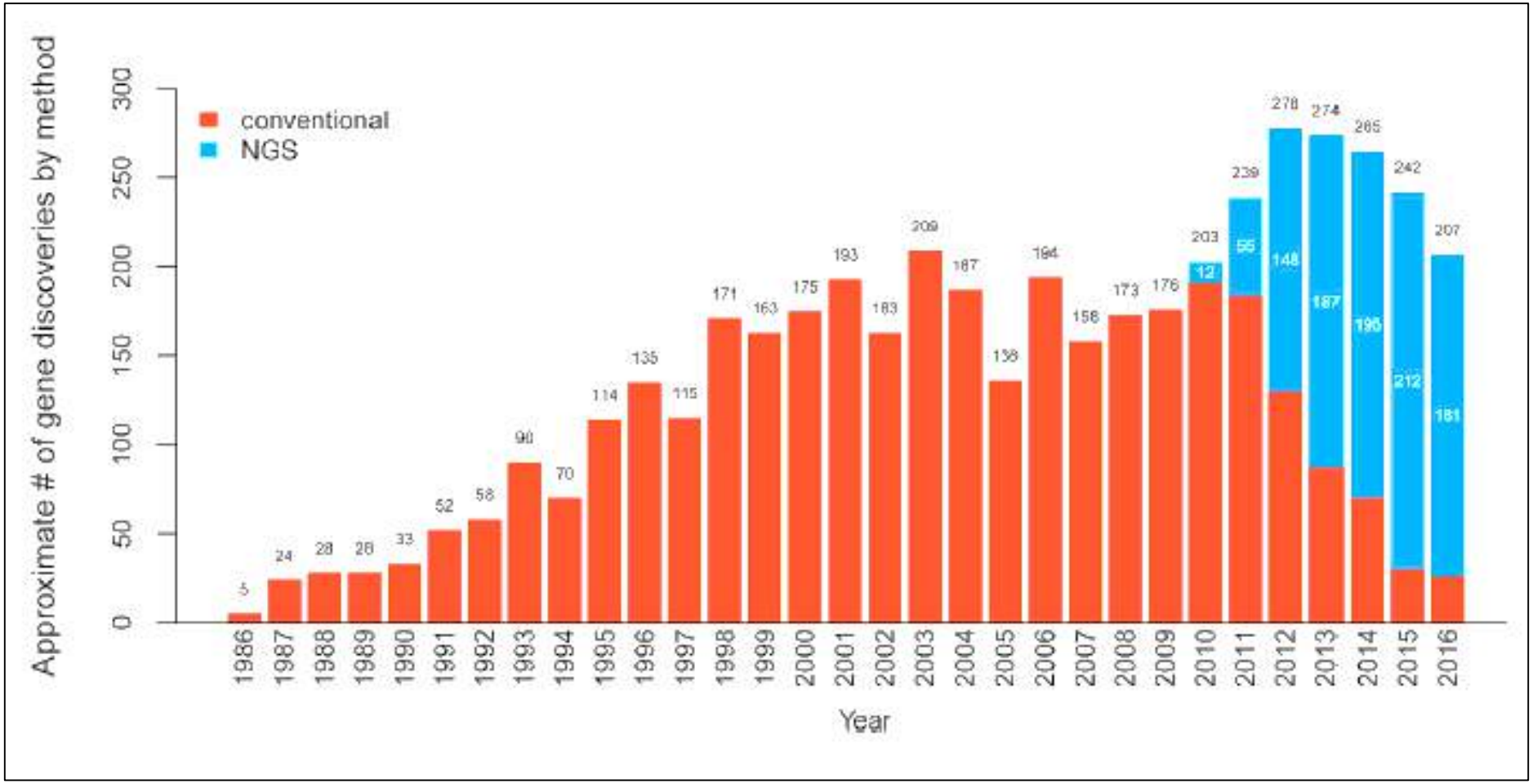
The genetic (technological) revolution

During the last 18 years, the genetic revolution has cut down by a figure of about 250 000 times, the *duration* and *costs* of genomic analyses



The NGS impact onto gene discovery

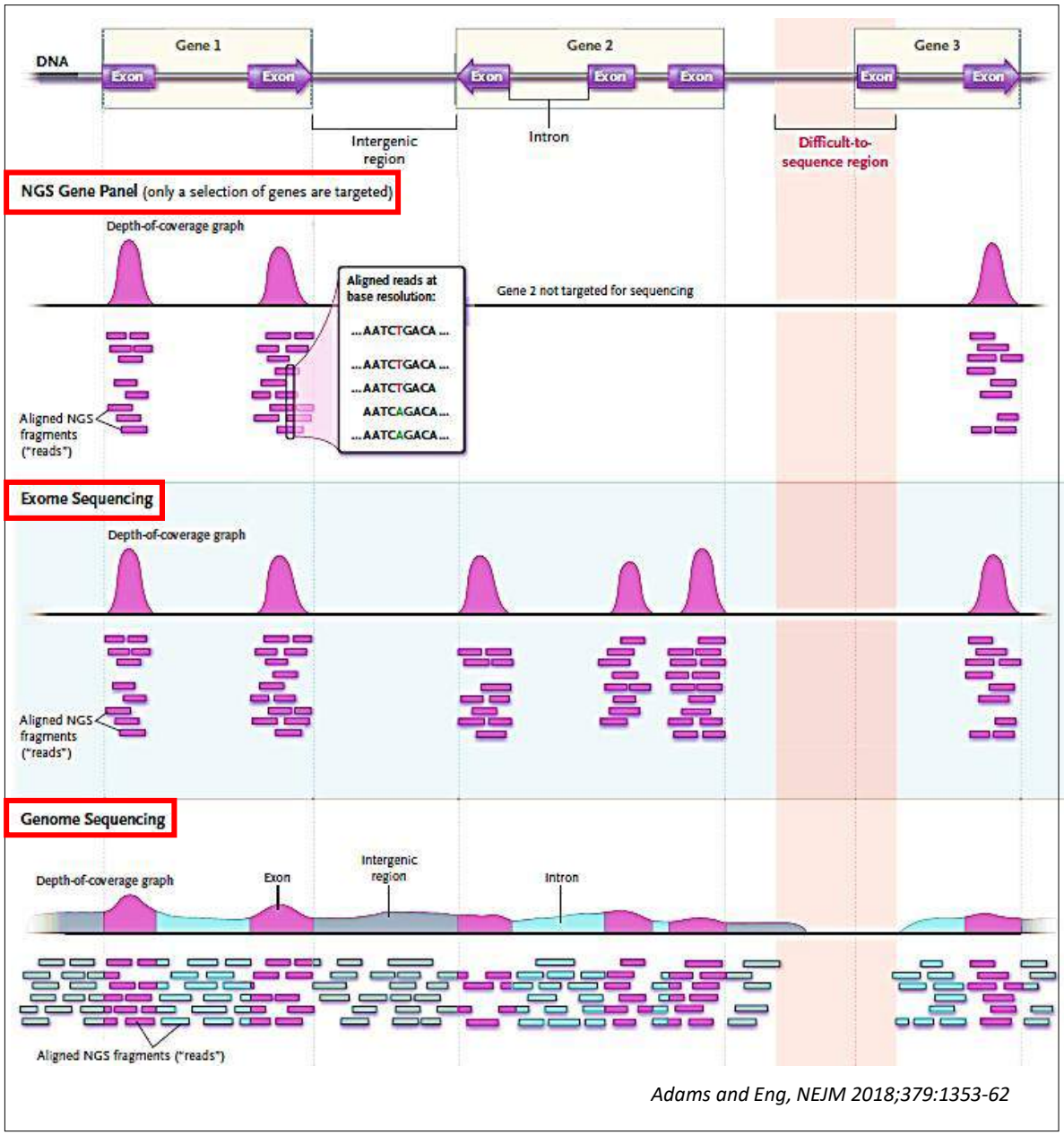
Boycott et al, Am J Hum Genet, 2017; 100:695-705



Genes, diseases and disease-genes

Number of Entries in OMIM (Updated November 6th, 2018)					
MIM Number Prefix	**Autosomal**	**X-Linked**	**Y-Linked**	**Mitochondrial**	**Totals**
Gene description	15,174	731	49	35	15,989
Phenotype description, molecular basis known	4,999	327	4	31	5,361
Phenotype description or locus, molecular basis unknown	1,447	124	4	0	1,575
Other, mainly phenotypes with suspected Mendelian basis	1,653	105	3	0	1,761

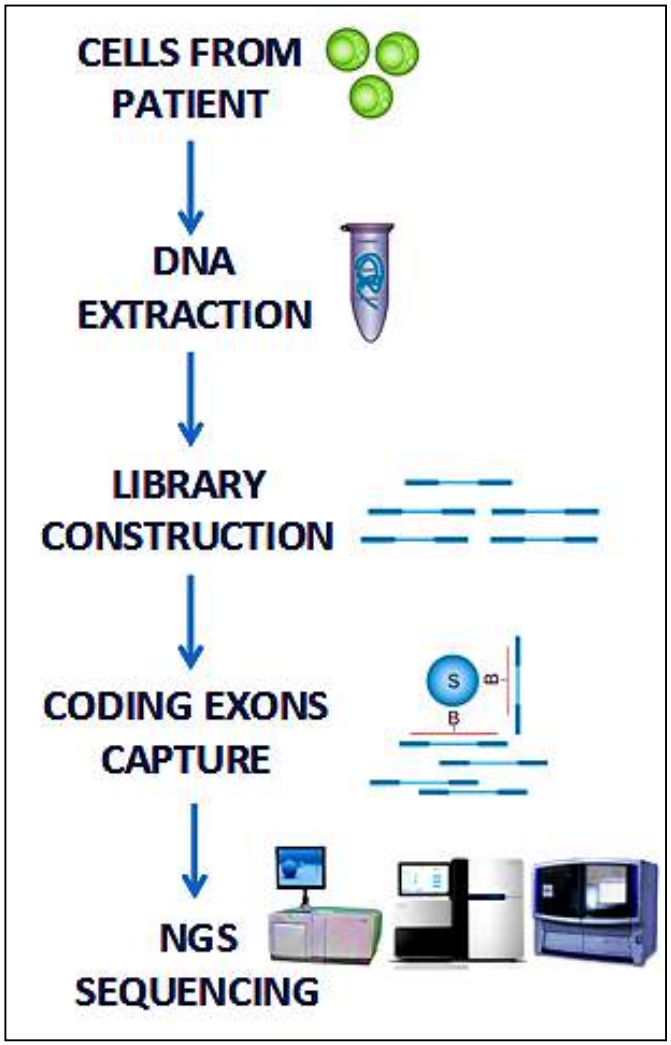
NGS approaches to disease-gene discovery and diagnostics

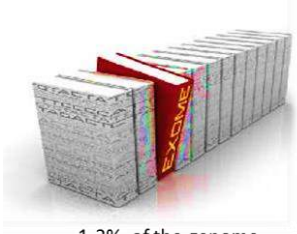


Adams and Eng, NEJM 2018;379:1353-62

Whole exome sequencing (WES) workflow

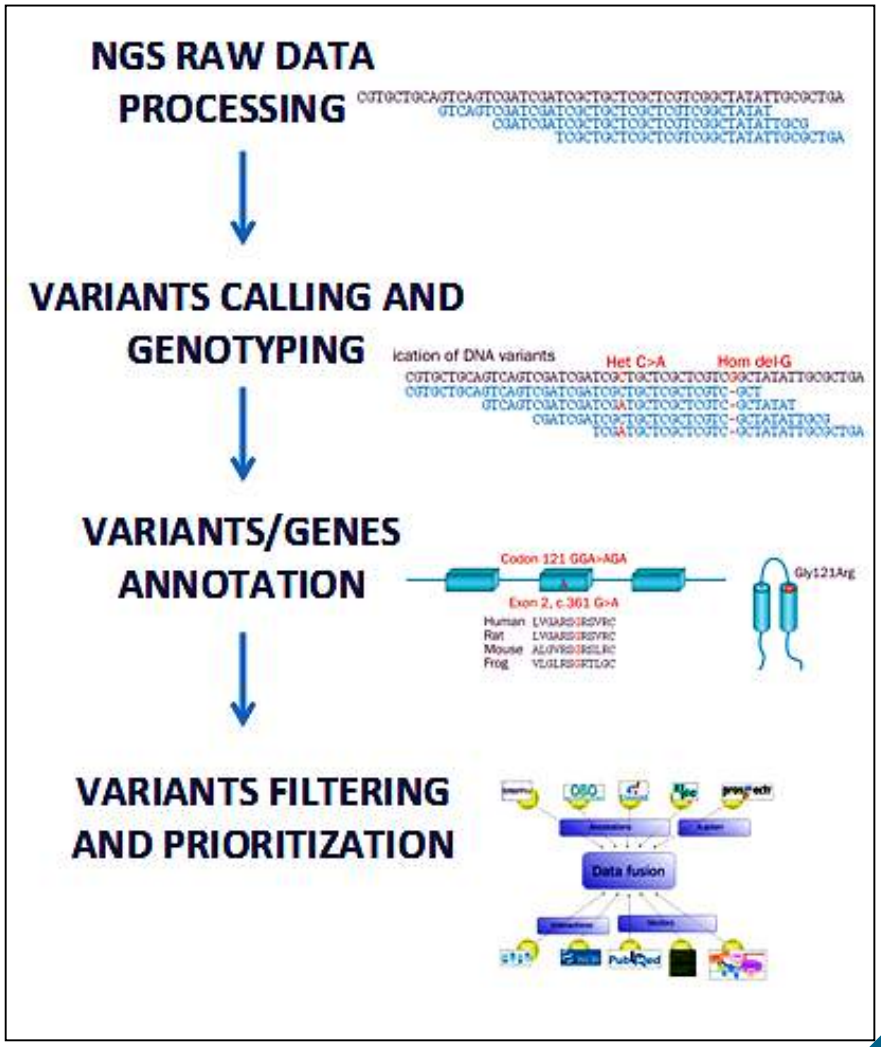
Experimental workflow (3 days)





1-2% of the genome
>70% disease-causing variants

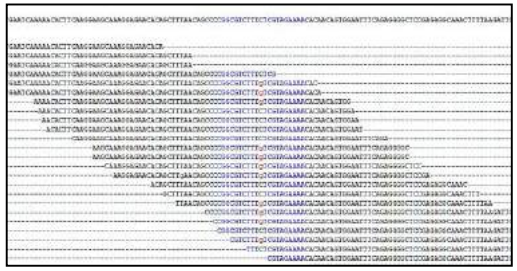
Bioinformatic workflow (5 hours)



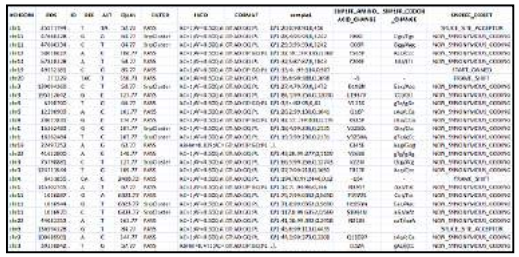
WES data analysis

WES data processing, reads alignment, and variants call lead to thousands of variants

Alignment



~ 40-100,000 variants



Functional annotation

- Recurrence
- Functional impact
- Associated clinical data
- Pathways and processes
- Expression
- Data from animal model

Assumptions

- Mutations affect CDS.
- Mutations are rare, likely private.
- Mutations are expected to have functional impact.

Analysis

- Focused on known disease genes.
- Extended to all annotated genes.

FILTERING BASED ON EFFECT

↓

FILTERING FOR PRIVATE VARIANTS

↓

RANKING VARIANTS BY CONSERVATION AND RELEVANCE TO PATIENT'S SYMPTOMS

↓

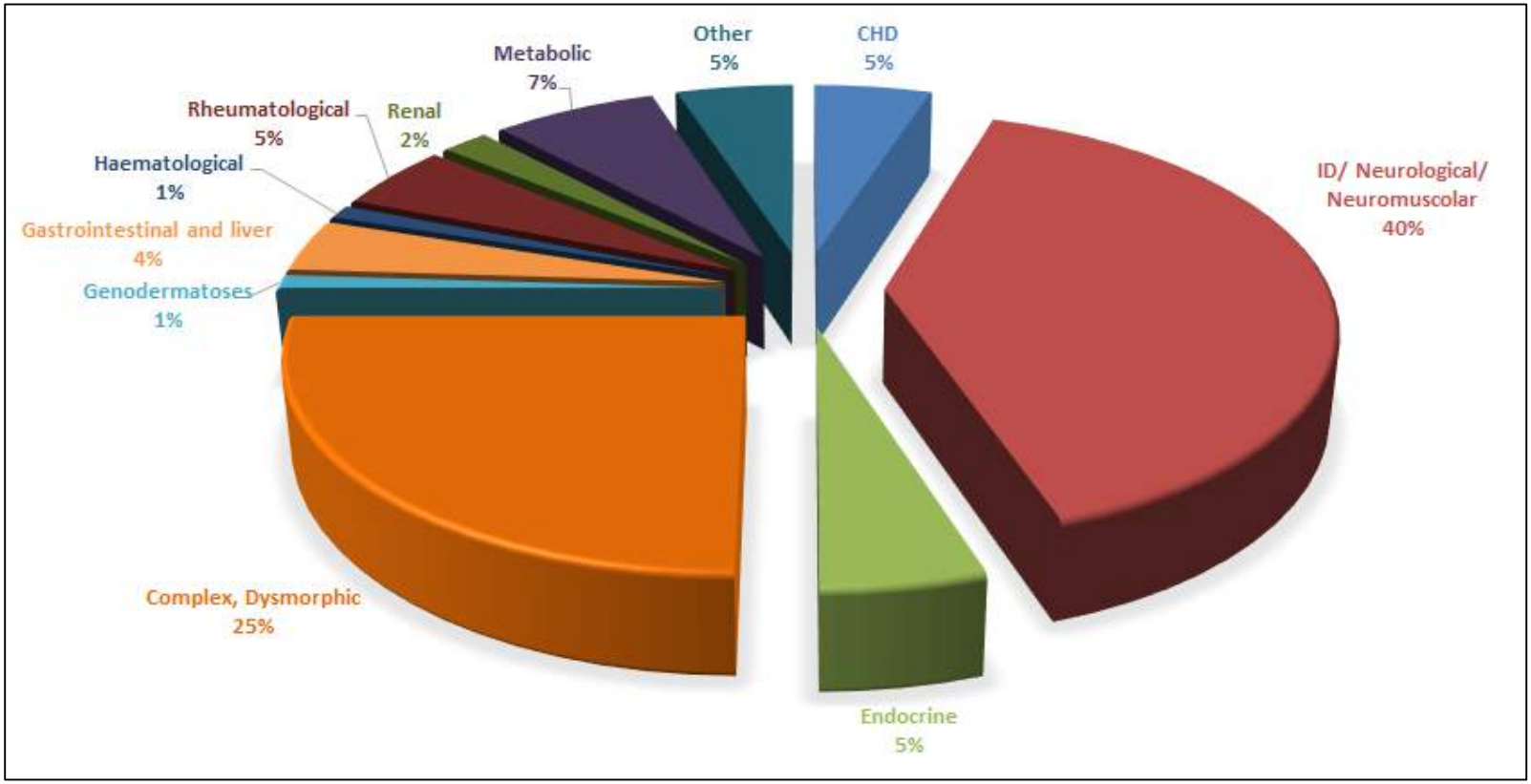
VARIANT VALIDATION

Models

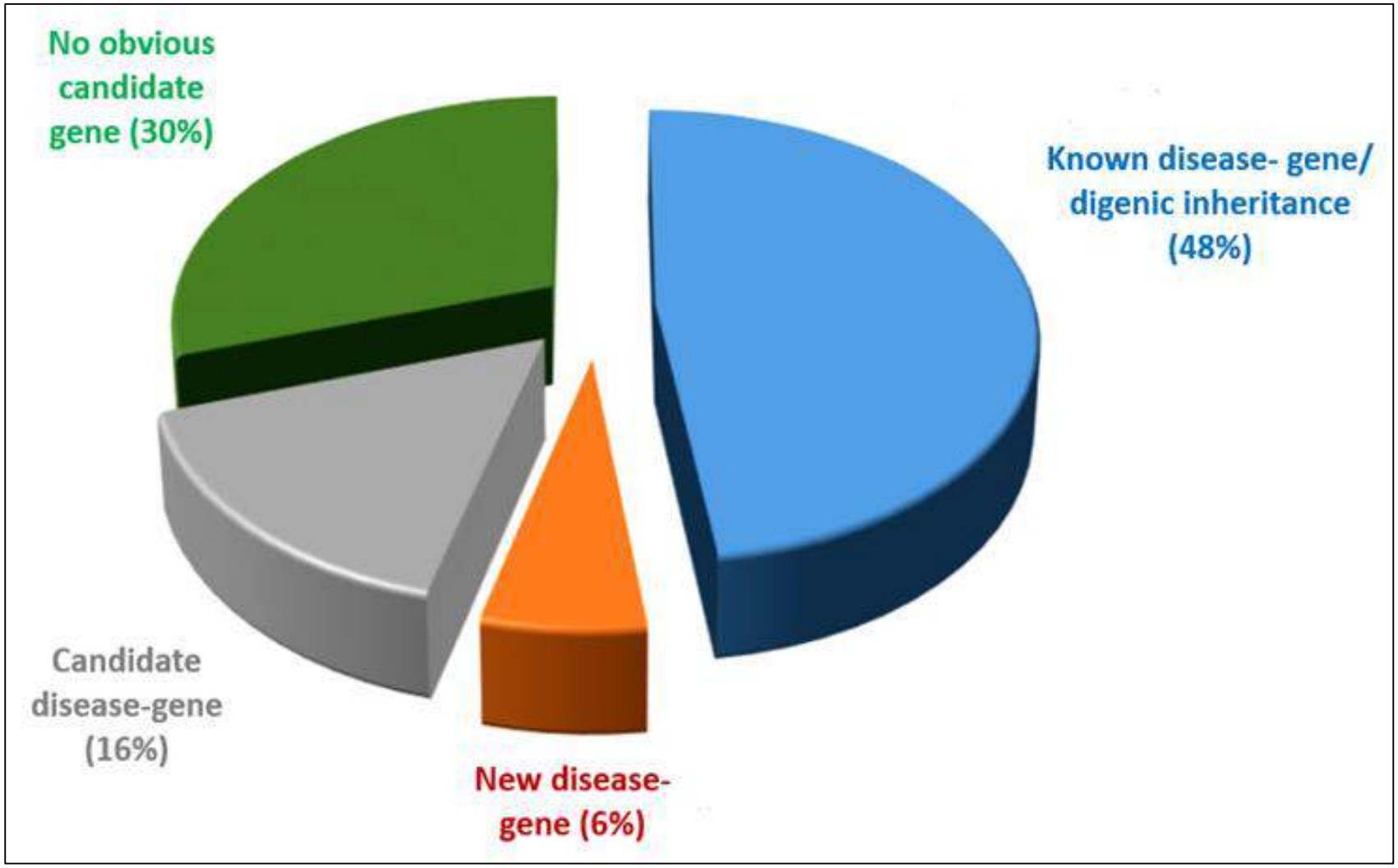
- Autosomal dominant
- Autosomal recessive
- X-linked dominant
- X-linked recessive
- Postzygotic
- Structural
- Digenic
- Imprinted
- Mitochondrial

The OPBG pilot research-project on undiagnosed patients
(years 2013-2015)

- 123 probands/trios
- undiagnosed diseases/complex phenotypes
- Unsolved by high resolution array-CGH & targeted gene analyses
- Average diagnostic delay: 7 years



Results of the OPBG pilot UND study



Impact of the pilot UND study onto the OPBG *Genetic Diagnostic Laboratory*

- *Up to year 2015*

  - 150 disease-genes routinely available for diagnosis

- *From 2016 onwards*

  - 2 436 genes routinely analysed
  - Panels available for analysing 41 diseases' groups

  - Clinical exome (mendeliome):
    > 6 800 genetic diseases

The OPBG 2016-2018 «UND patients program»

Major goals and concepts

- Al clinical level:

  To validate WES/WGS/WTS as first-pass diagnostic tools and transfer them to clinical practice.

- At research level:

  To understand the molecular background of rare and newly recognized Mendelian disease.

Nasce il primo ambulatorio in Italia dedicato alle malattie rare senza diagnosi

Nella sede di San Paolo un nuovo percorso dedicato per ridurre i tempi diagnostici e di presa in carico

Opening of the first Italian outpatient clinic for patients affected by undiagnosed diseases

At the St Paul out-patient clinic an innovative track to shorten the diagnostic and management procedures

12 ottobre 2016

- ~350 patients evaluated each year.
- Average age: 12yr.
- Average time required to conclude a clinical case: 6 mo. from first evaluation.

Online medical advice

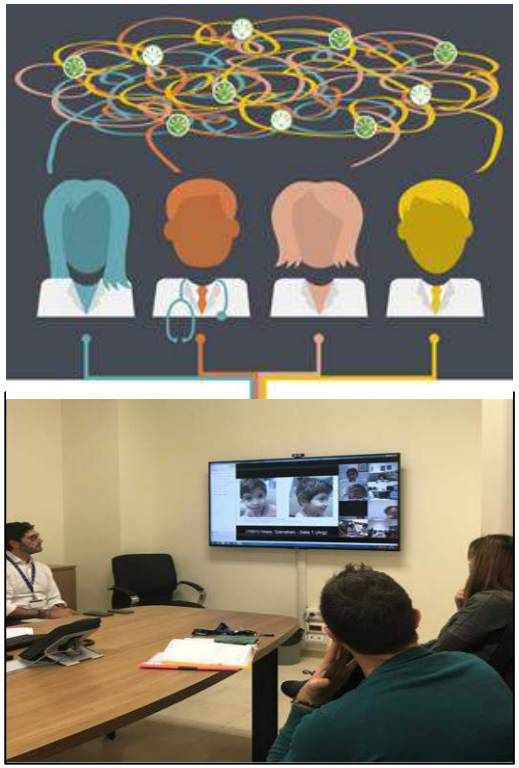
vs

Face-to-face clinical assessment

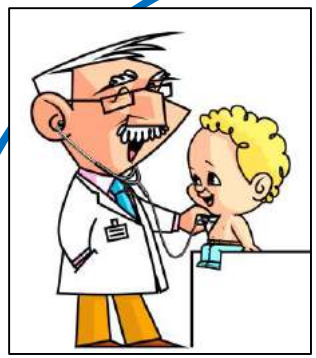
The Italian Clinical genetic experts' teleconsultation network

Partner

Associated



The OPBG flow-chart for UND patients



outpatient

inpatient

clinical evaluation & instrumental/laboratory exams

Diagnosed patient

Care and follow up plan

Diagnostic hypothesis

undiagnosed patient

multidisciplinary team evaluation

undiagnosed patient

WES

Standardized phenotyping

Clinical re-evaluation & laboratory exams based on WES output

diagnosed patient

Novel disorder/condition

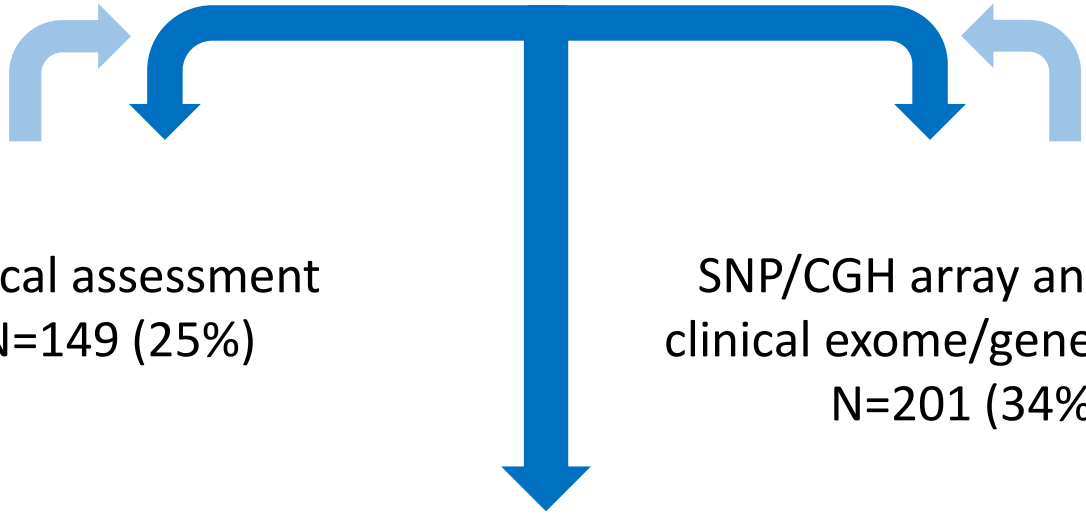
undiagnosed patient

Care and follow up plan

Genetic & *in silico*, *in vitro* and *in vivo* functional validation

The OPBG UND program
Cohort and selection of cases

Study sessions (Oct 2016 - Sept 2018), N=58
Discussed cases, N=652 (591 patients)

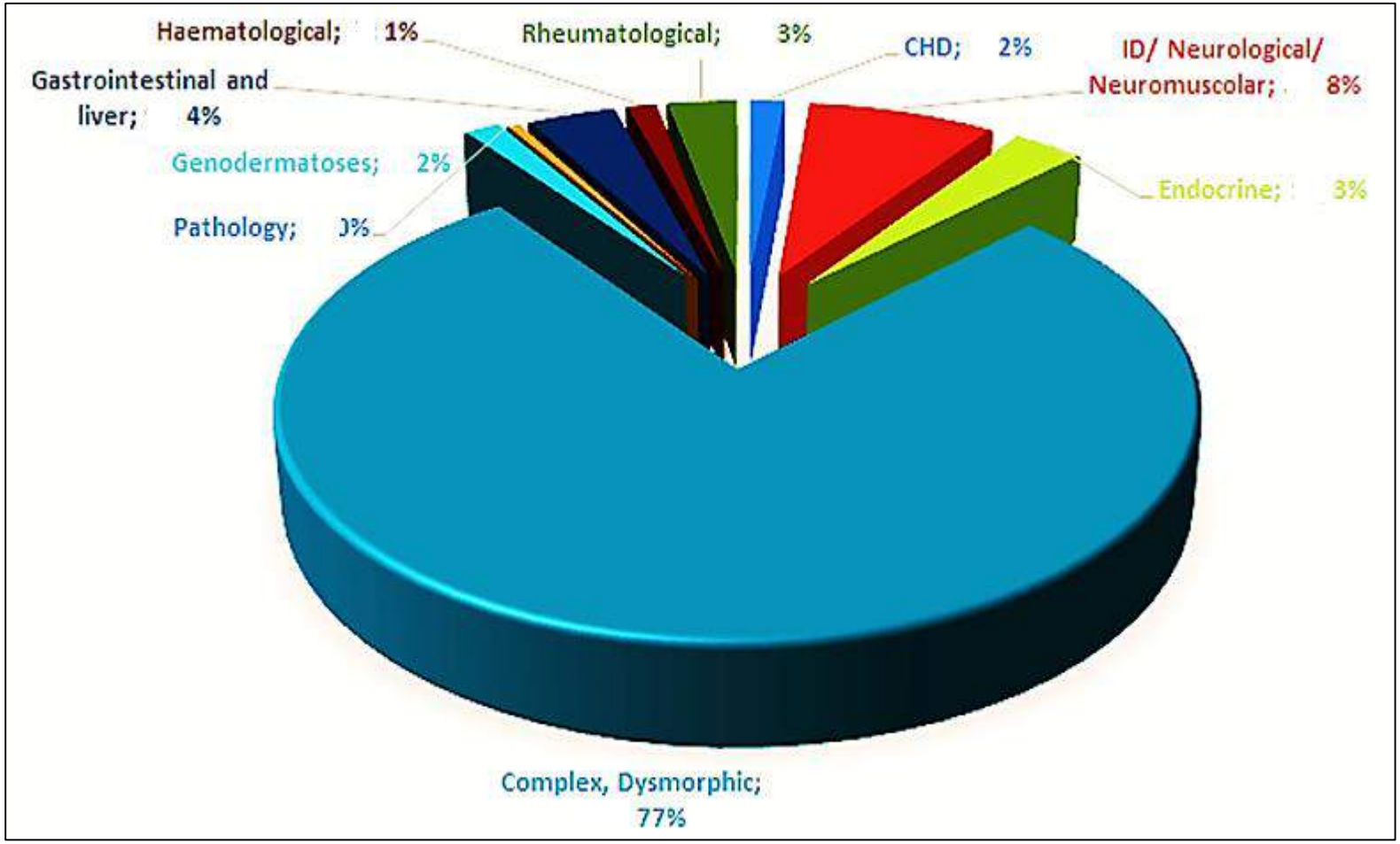


Clinical assessment
N=149 (25%)

SNP/CGH array analysis,
clinical exome/gene panels,
N=201 (34%)

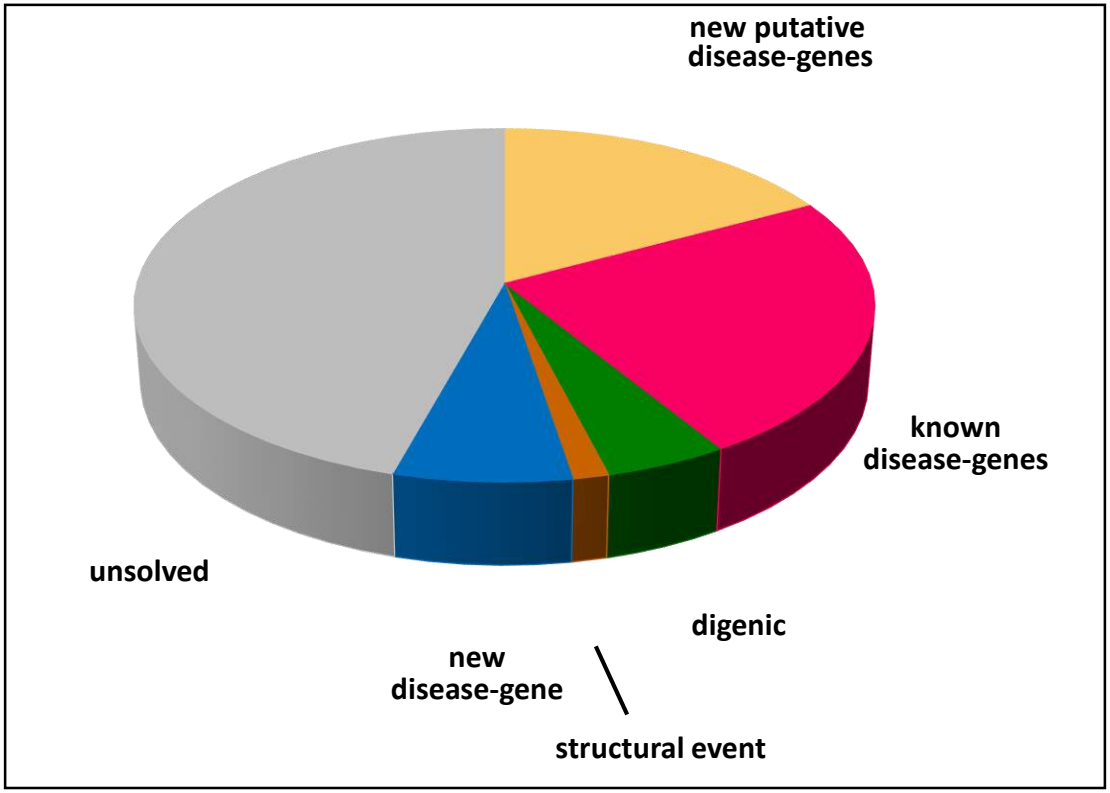
WES, N=241 (41%)

Multidisciplinary teleconsultations (Oct 2016-Sept 2018)



The OPBG UND program
WES results

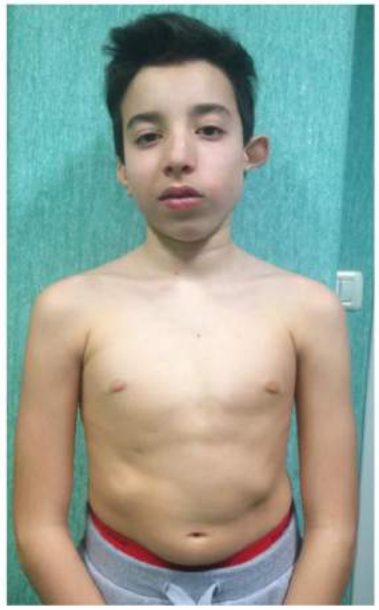
Novel disease genes	**7.0%**
Known disease genes	**33.0%**
phenotypic expansion & allelic disorders	*16.0%*
recently identified disease genes (<3 years)	*26.8%*
false negative	*1.2%*
postzygotic events	*1.2%*
Digenic events	**3.0%**
Structural rearrangements	**0.6%**
Novel candidates	**16.0%**
Unsolved	**40.4%**

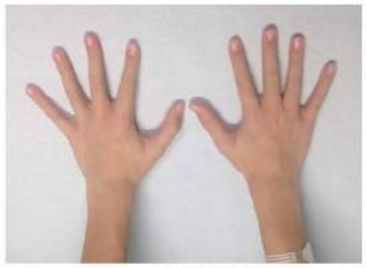


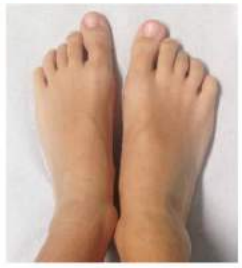
The OPBG UND program: new disease-gene (OMIM 184255)

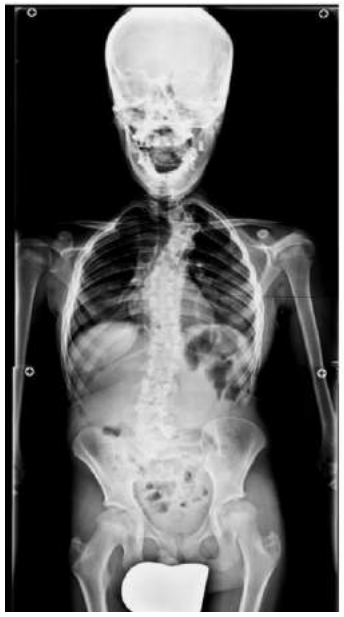
Spondylometaphyseal dysplasia, Sutcliffe type

Fibronectin-1, high molecular weight glycoprotein, present on cell surfaces, in extracellular fluids, connective tissues, and basement membranes

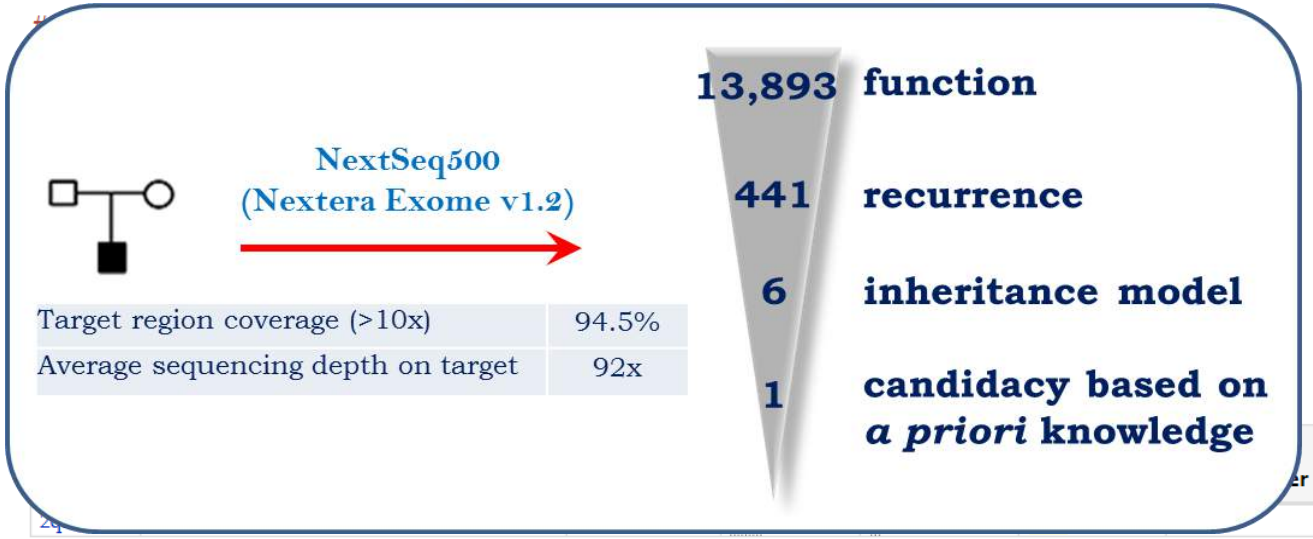






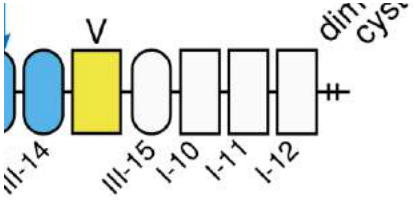


- Skeletal dysplasia
- short stature
- scoliosis
- vertebral anomalies, irregular metaphyses with «corner fractures»
- facial asymmetry
- dysplastic ears.



974Arg
974Pro

FN1 **(MIM #135600)**
(het. c.367T>C, *de novo*,
p.Cys123Arg; NM_212482.2)



OMIM 604934
PEAMO
Progressive Encephalopathy, Amyotrophy, Optic Atrophy

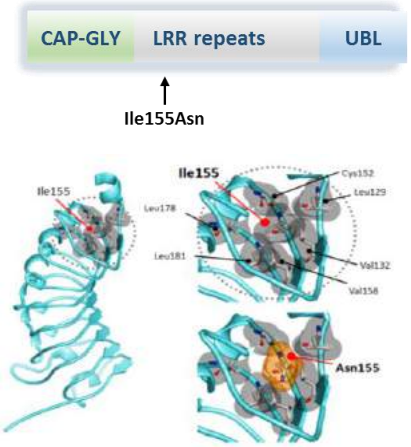
The OPBG UND program: new diseases
Aberrant microtubule dynamics and neurodegeneration

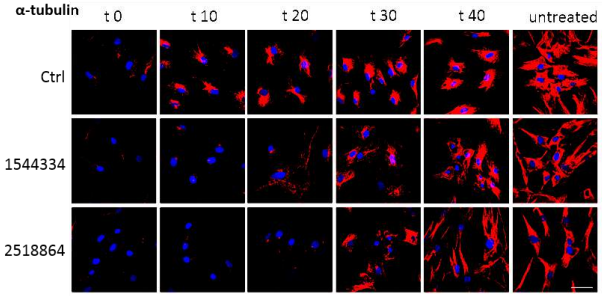
OMIM 617193
PEBAT
Progressive Encephalopathy, Brain Atrophy, Thin Corpus Callosum

The American Journal of Human Genetics *99*, 974–983, October 6, 2016

TBCE Mutations Cause Early-Onset Progressive Encephalopathy with Distal Spinal Muscular Atrophy

Antonella Sferra,[1,11] Gilbert Baillat,[2,11] Teresa Rizza,[1] Sabina Barresi,[1] Elisabetta Flex,[3] Giorgio Adele D'Amico,[1] Emanuele Bellacchio,[1] Andrea Ciolfi,[1,4] Viviana Caputo,[5] Serena Cecchetti,[6] Annalaura Torella,[7,8] Ginevra Zanni,[1] Daria Diodato,[1] Emanuela Piermarini,[1] Marcello Niceta,[1] Antonietta Coppola,[9] Enrico Tedeschi,[10] Diego Martinelli,[1] Carlo Dionisi-Vici,[1] Vincenzo Nigro, Bruno Dallapiccola,[1] Claudia Compagnucci,[1] Marco Tartaglia,[1,12,*] Georg Haase,[2,12] and Enrico Bertini[1,12,*]

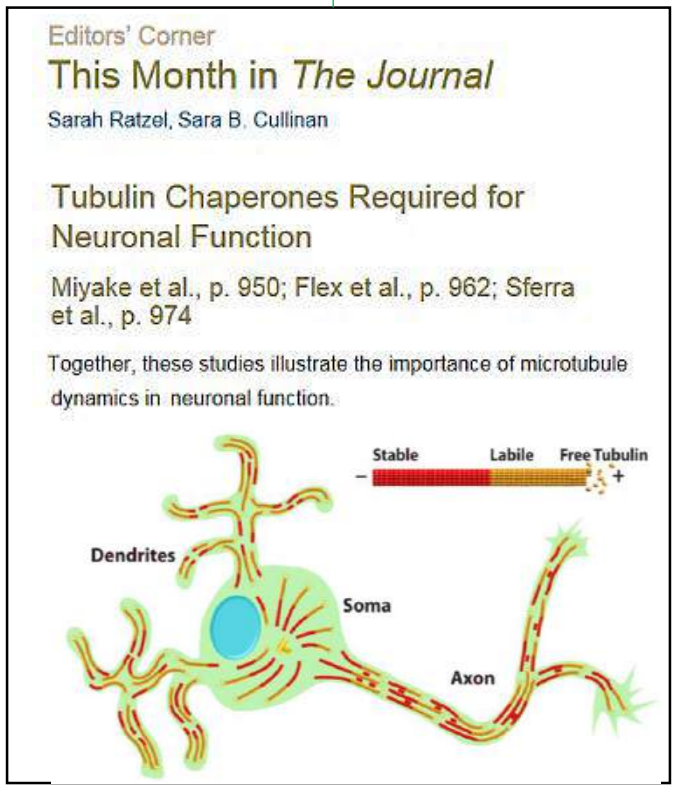


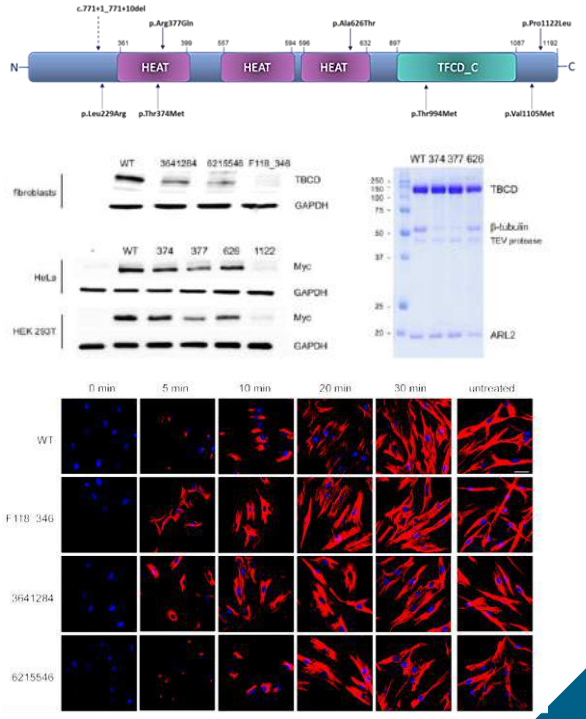


The American Journal of Human Genetics *99*, 962–973, October 6, 2016

Biallelic Mutations in *TBCD*, Encoding the Tubulin Folding Cofactor D, Perturb Microtubule Dynamics and Cause Early-Onset Encephalopathy

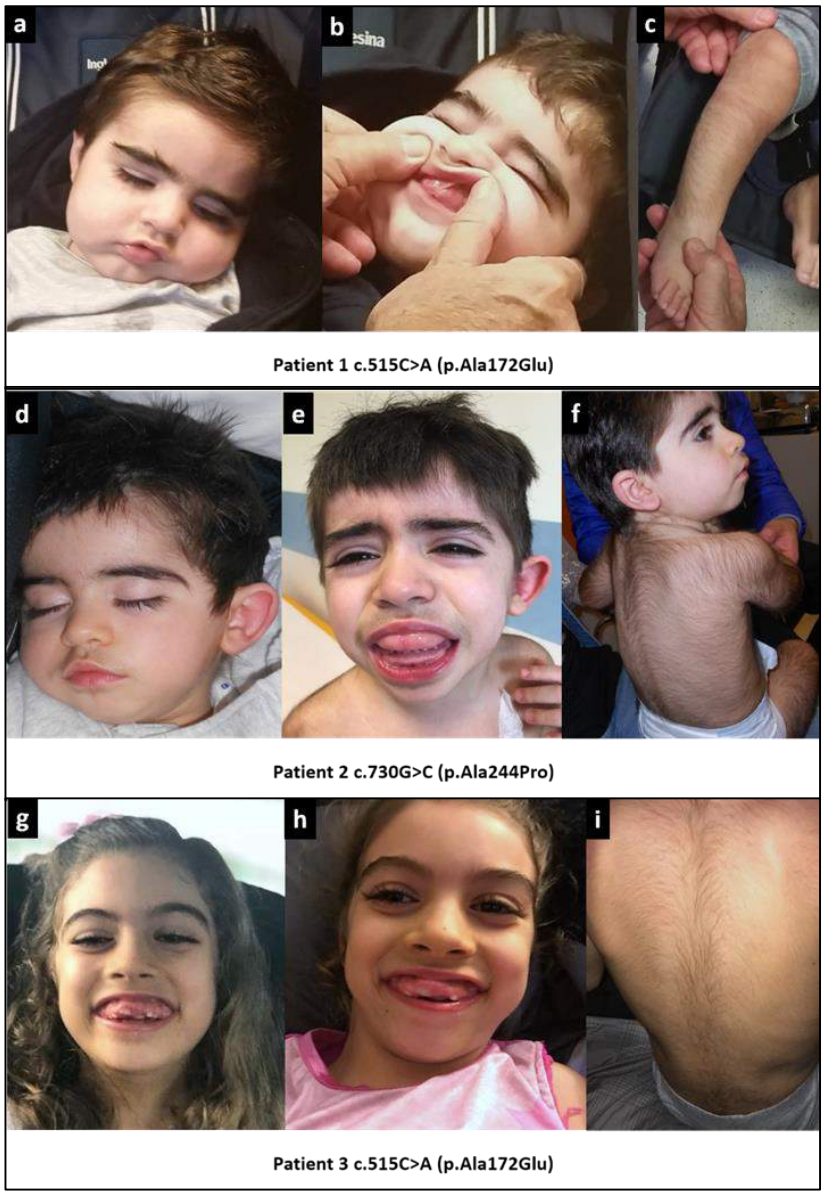
Elisabetta Flex,[1,18] Marcello Niceta,[2,18] Serena Cecchetti,[3] Isabelle Thiffault,[4,5,6] Margaret G. Au,[7] Alessandro Capuano,[2] Emanuela Piermarini,[2] Anna A. Ivanova,[8] Joshua W. Francis,[8] Giovanni Chillemi,[9] Balasubramanian Chandramouli,[10] Giovanna Carpentieri,[1,11] Charlotte A. Haaxma,[12] Andrea Ciolfi,[2,13] Simone Pizzi,[2] Ganka V. Douglas,[14] Kara Levine,[14] Antonella Sferra,[2] Maria Lisa Dentici,[2] Rolph R. Pfundt,[12] Jean-Baptiste Le Pichon,[15] Emily Farrow,[4] Frank Baas,[16] Fiorella Piemonte,[2] Bruno Dallapiccola,[2] John M. Graham, Jr.,[7] Carol J. Saunders,[4,5,6] Enrico Bertini,[2] Richard A. Kahn,[8] David A. Koolen,[17] and Marco Tartaglia[2,*]



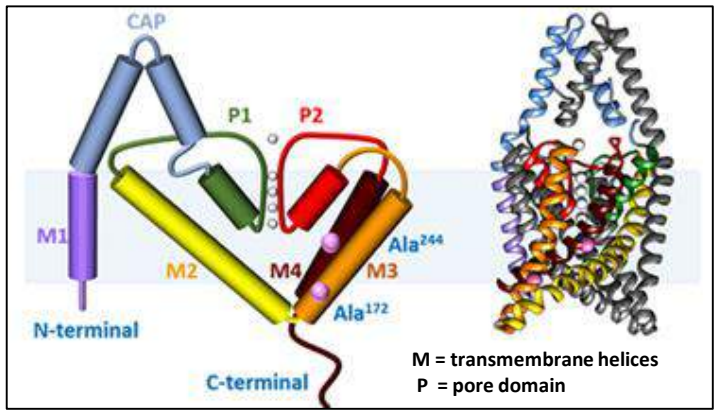


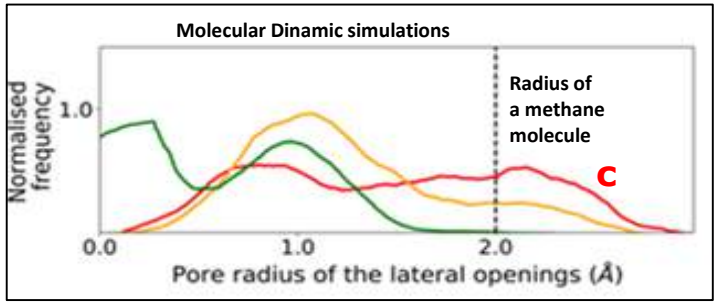
The OPBG UND program: new disease (FEIGH syndrome)

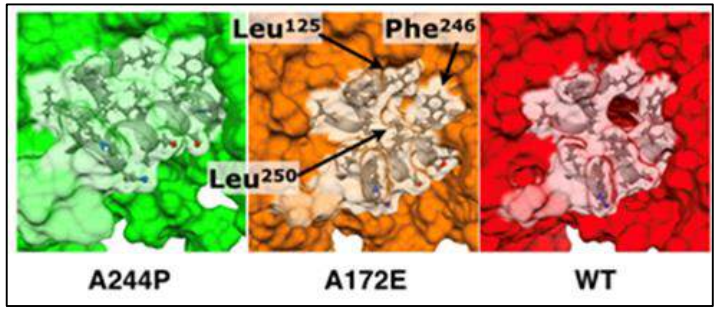
Facial dysmorphism, Epilepsy, Intellectual disability, Gingival hypertrophy, Hypertrichosis



Potassium Channel, Subfamily K, member 4; *KCNK4*







The OPBG UND program
Major research outputs

disease gene	year	inheritance	disease	ref.
KCNH1	2014	AD	Zimmerman-Laband syndrome	Nat Genet, 2015, 47:661-7
KCNJ6	2014	AD	Keppen-Lubinsky syndrome	Am J Hum Genet, 2015, 96:295-300
NKX6-2	2014	AR	hypomyelinating leukodystrophy	Brain, 2017, 140:2550-6
TBCD	2014	AR	early-onset neurodegenerative disorder	Am J Hum Genet, 2016, 99:962-73
RNF220	2014	AR	hypomyelinating leukodystrophy	*Manuscript in preparation*
TBCE	2014	AR	early-onset progressive encephalopathy	Am J Hum Genet, 2016, 99:974-83
TUBB2A	2014	AR	early-onset neurodegenerative disorder	Hum Mol Genet, 2018, 27:1892-904
CDC42	2015	AD	variable syndromic traits	Am J Hum Genet, 2018, 102:309-20
DYNC2LI1	2015	AR	Ellis-van Creveld syndrome	Clin Genet, 2018, 93:632-9
CREBBP	2015	AD	Novel syndromic condition	Am J Med Genet A, 2016, 170:2681-93
SPEN	2015	AD	novel syndromic disorder	*Manuscript in preparation*
TBCK	2015	AR	infantile syndromic encephalopathy.	Am J Hum Genet, 2016, 98:771-81
ATP6V1C1	2016	AD	novel syndromic disorder	*Manuscript in preparation*
FN1	2016	AD	spondylometaphyseal dysplasia	Am J Hum Genet, 2017, 101:815-23
KIF5B	2016	AR	epileptic encephalopathy	*Manuscript in preparation*
SCUBE3	2016	AR	novel syndromic disorder	*Manuscript in preparation*
TET1	2016	AR	novel syndromic disorder	*Manuscript in preparation*
CLTC	2017	AD	epileptic encephalopathy	Am J Hum Genet, 2017, 101:664-85
DHDDS	2017	AD	epileptic encephalopathy	Am J Hum Genet, 2017, 101:664-85
H3F3A,H3F3B	2017	AD	neurologic dysfunction and congenital anomalies	*Nat Commun, under revision*
KCNK4	2017	AD	novel syndromic disorder	Am J Hum Genet, 2018, 103:621-30
PIGK	2017	AR	congenital disorder of glycosylation	*Manuscript in preparation*
SMARCC1	2018	AD	novel syndromic disorder	*Manuscript in preparation*
POU3F3	2018	AR	novel syndromic disorder	*Manuscript in preparation*

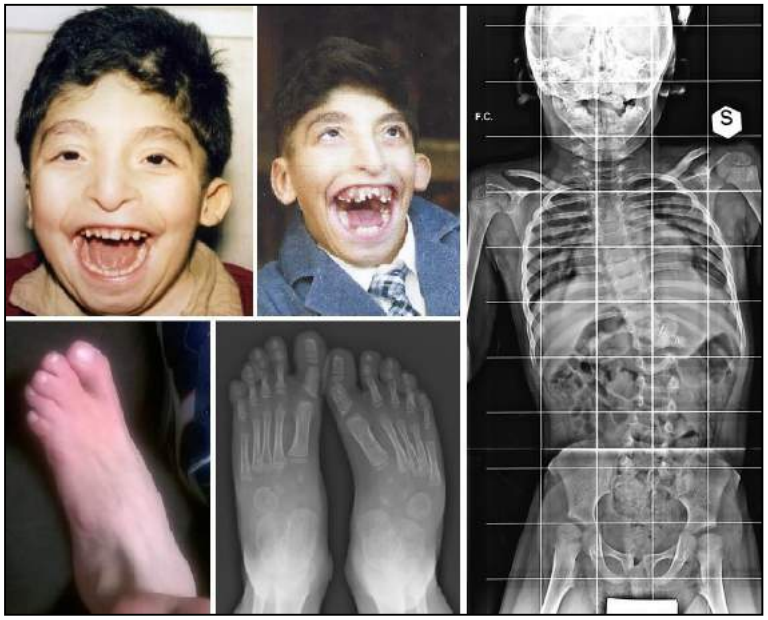
In total: ***20 novel disease-genes***, *14 new diseases*

Clinical exome in the OPBG genetic diagnostic laboratory
(Jan 2016 - Oct 2018)

- Analyzed genes per sample: 6 800
- Analyzed patients (trios): 478
- Solved cases 310 (65%)

Clinical exome

Diagnosis attained in a complex patient



- Male 7 year-old.
- Microcephaly, facial dysmorphism.
- Pectus excavatum, scoliosis.
- Hands' camptodactyly, toes syndactyly, varus-supinatus right forefoot, valgus-pronate left forefoot.
- MRI: hypoplasic corpus callosum and cerebellar vermis, enlarged cerebral ventricles and periencephalic spaces.
- Atrial septal defect, persistent left superior vena cava.
- Bilateral optic and chorio-retinal atrophy.
- Severe mental retardation; unable to walk unsupported, absent speech.

TARP syndrome

311900

TARP SYNDROME; TARPS

Alternative titles; symbols

TALIPES EQUINOVARUS, ATRIAL SEPTAL DEFECT, ROBIN SEQUENCE, AND PERSISTENCE OF LEFT SUPERIOR VENA CAVA
PIERRE ROBIN SYNDROME WITH CONGENITAL HEART MALFORMATION AND CLUBFOOT

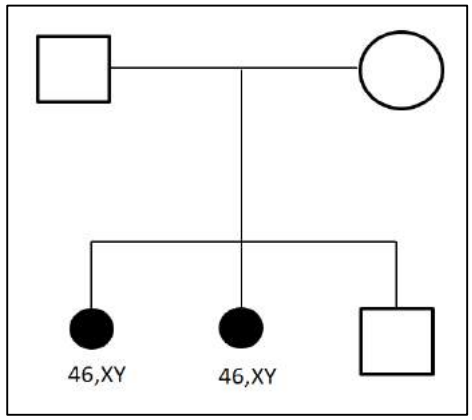
Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
Xp11.3	TARP syndrome	311900	XLR	3	RBM10	300080

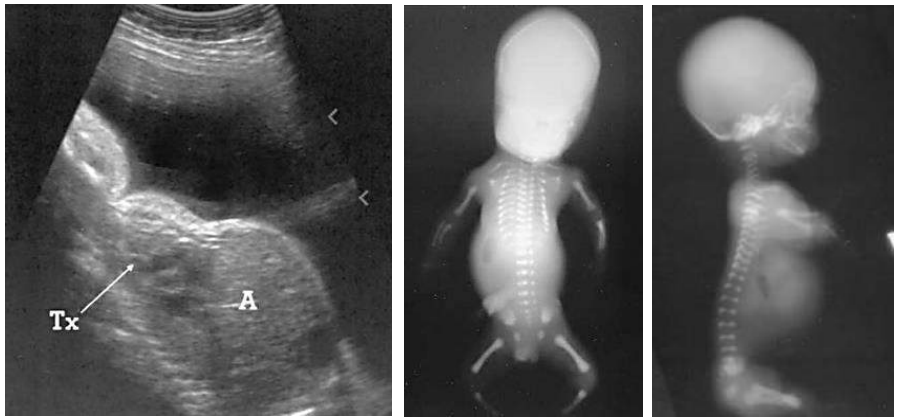
Clinical features	TARPS	Smith-Lemli-Opitz syndrome	Oral-Facial-Digital syndromes	Joubert syndrome and related disorders	Greig syndrome / Pallister-Hall / Hydrolethalus	Ellis-van Creveld and Short-Rib polydactyly syndromes	Bardet-Biedl syndromes
Cardiac defect	+	+	+	+	+	+	+
Atrial septal defect	+	+	+	+	+	+	+
Persistent left superior vena cava	+	+	-	-	-	+	+
Abnormal pulmonary venous drainage	+	+	-	-	-	-	-
Atrioventricular canal defect	-	+	+	-	+	+	+
Common atrium	-	-	+	-	-	+	+
Conotruncal defect	+	-	+	-	-	-	-
Left-sided obstruction	+	-	+	+	-	-	-
Postaxial polydactyly	+	+	+	+	+	+	+
Skeletal anomalies (others than polydactyly)	+	-	-	-	+	+	-
Oral hamartoma	+	+	+	-	-	+	-
Cerebellar anomaly	+	-	+	+	-	-	-
Ocular anomalies	+	+	-	+	-	-	+
Pulmonary anomalies	+	+	-	-	-	+	-
Inheritance	**XL**	**AR**	**XLD, AR**	**AR**	**AD**	**AR, AD**	**AR**
Causative genes	*RBM10*	*DHCR7*	*OFD1, WDPCP, TTCTN3*	*INPPSE, TMEM216, TMEM138, CEP290, CEP104, NPHP1, TMEM237, ARL13B, CC2D2A, CEP120, TMEM67, KIF7, TMEM107, TMEM231*	*GLI3, KIF7*	*EVC, EVC3, WDR35*	*BBS1-BBS12, CCDC28B, SDCCAG8, ARL6, TMEM67, C8orf37, MKS1, MKKS*

Clinical exome

Diagnosis reconsidered



- Two foetus with IUGR
- Hypoplasic thorax and lungs, short ribs, hypoplasic long bones, slightly bowed humeri and femurs
- Intestinal dilatation in the 1st foetus
- Abnormal right kidney with cystic tubular dysplasia in the 2nd foetus.

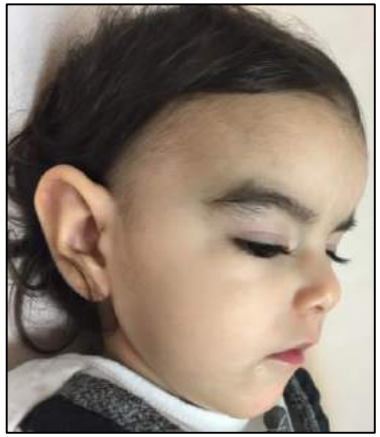


NGS analysis of foetal DNA performed in Germany.
The panel included 17 genes related to short ribs skeletal dysplasias:
NEK1, TTC21B, IFT1T2, IFT80, DYNC2H1, DYNC2D1, KIAA0586, WDR19, WDR35, IFT140, WDR80, WDR34, CEP120, EVC, EVC2, IFT122, IFT43.

No pathogenic variant detected.

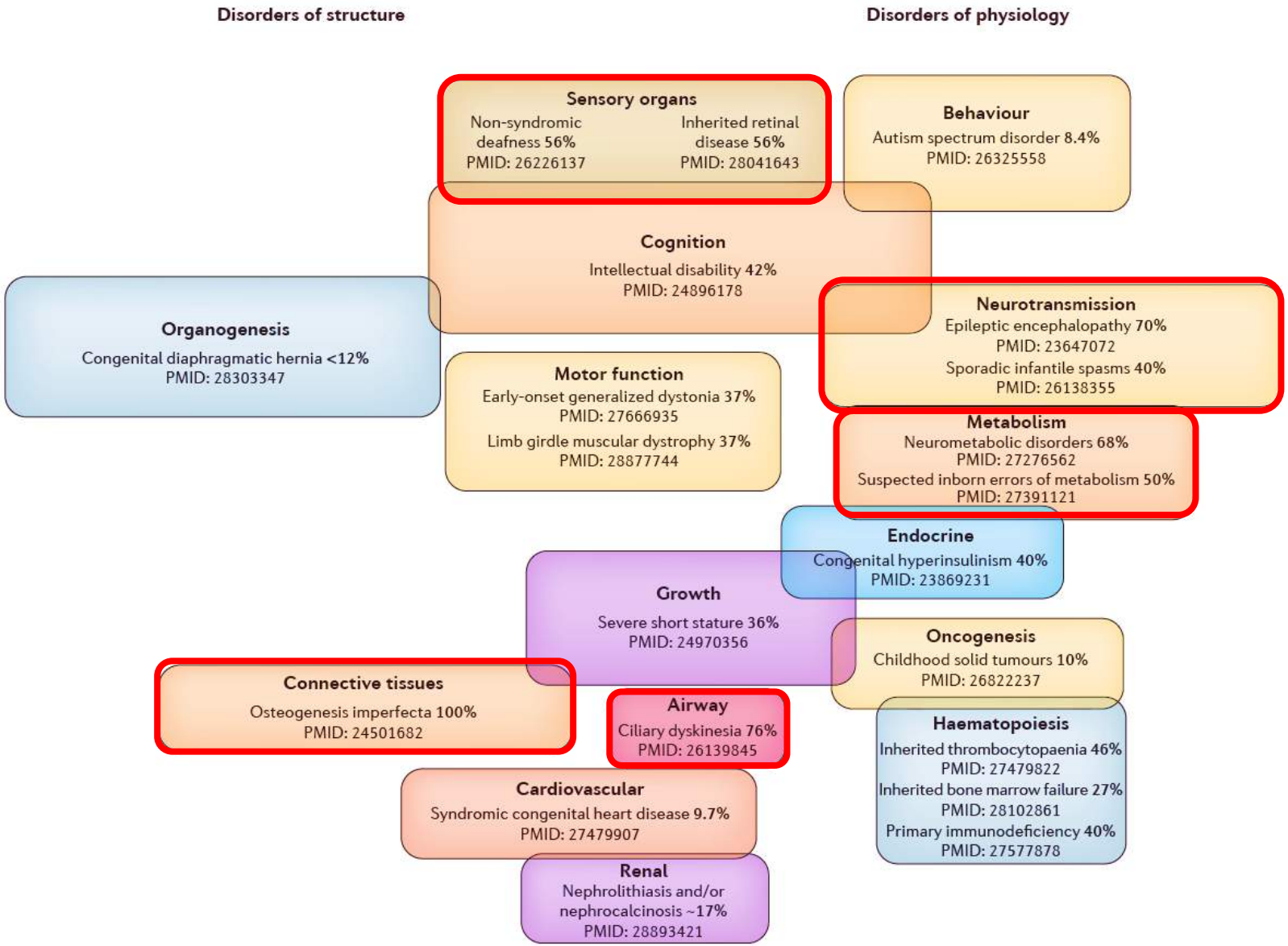
Clinical exome

Identification of a new genotype-phenotype correlation



- Growth retardation prenatal onset
- Delayed psychomotor development
- Facial dysmorphism (Kabuki-like syndrome)
- Hypoplasic adenohypophysis, absent neurohypophysis

Diagnostic rates based on WES in classes of paediatric genomic diseases



Wright CF et al, Nature Reviews Genetics, 2018;19:253-268

A new paradigm for patients affected by undiagnosed rare diseases

The decreasing cost of genotyping information

Lu JT et al, NEJM, 2014;371:593-6

Ministero della Salute

Consiglio Superiore di Sanità

Sessione L (2014-2017)

Presidente: Prof.ssa Roberta Siliquini

Segretario Generale: Dott.ssa Daniela Rodorigo

Sezione I

Presidente: Prof. Rocco Bellantone

Segretario tecnico: Dr. Stefano Moriconi

Gruppo di Lavoro

"Impatto socio-economico sul sistema sanitario delle tecniche di sequenziamento di seconda generazione (NGS) nell'inquadramento dei pazienti senza diagnosi"

Coordinatore: Prof. Bruno Dallapiccola

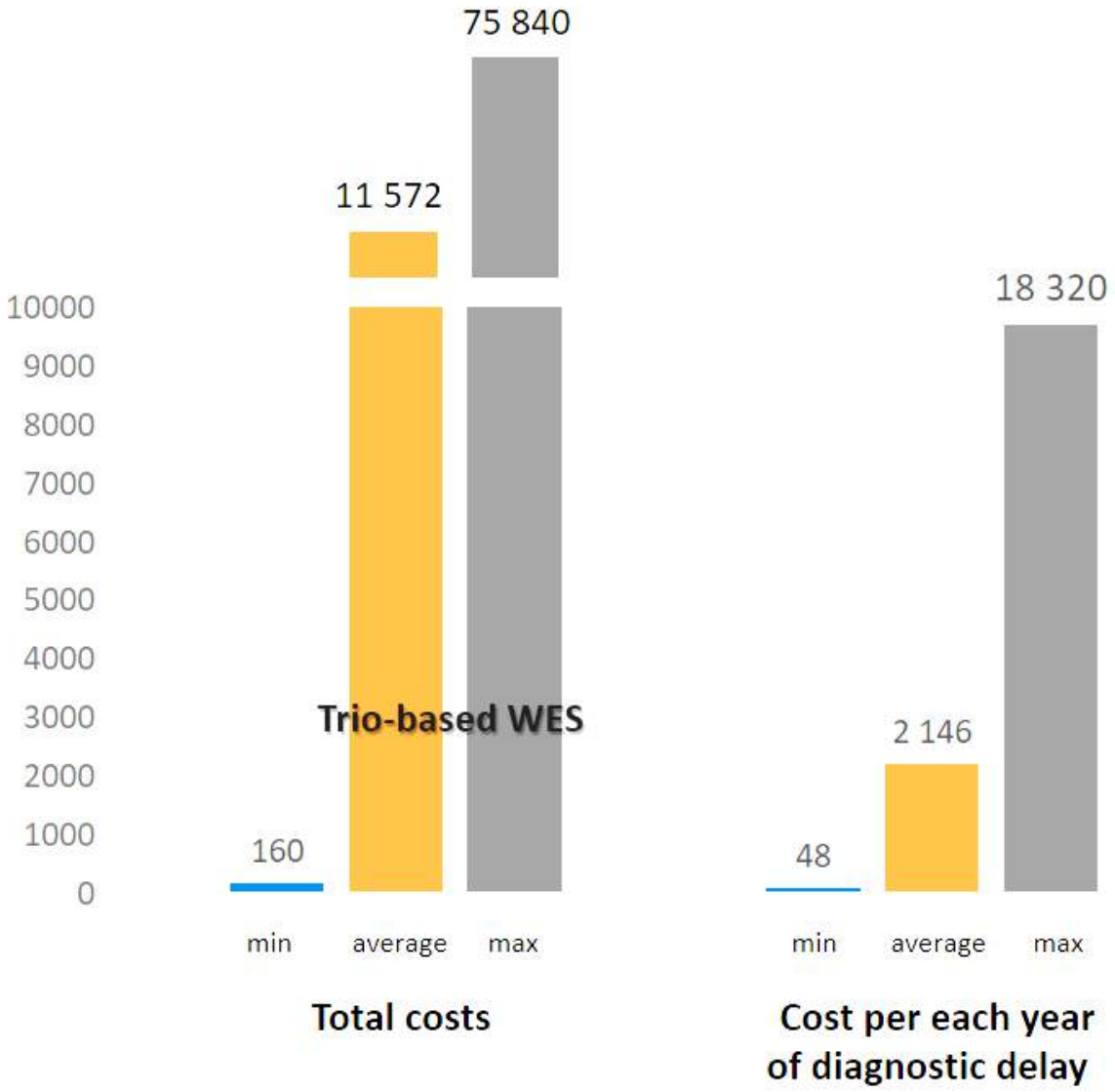
Raccomandazioni

WES cost-effectiveness analysis

- Sub-cohort: 211 patients (1mo – 43ys).
- All investigations, procedures and inpatient/outpatient assessments collected retrospectively by using the informative system of the Bambino Gesù Children's Hospital.

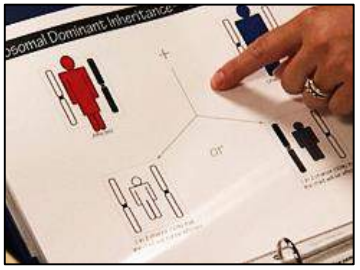
- Costs of diagnostic procedures calculated based on the Italian NHS tabs: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=3662&area=programmazioneSanitariaLea&menu=vuoto.
- Assessed parameters: total costs; minimum, maximum and average costs for each indicator; costs of each year of diagnostic delay.

Cost-effectiveness analysis (€)



The diagnosis's impact

- To not feel alone, and, thus, to be part of a community.
- To obtain targeted genetic counselling.
- To access tools available for the genetic monitoring of pregnancies at risk.
- Improvement of the disease's management.
- Availability of personalised/precision medicine (in some cases).



Take-home messages

- NGS offers unique opportunities in translational medicine.
- WES has a high diagnostic yield when applied to undiagnosed patients (> 50% in our UND OPBG).
- A significant proportion of cases carries mutations in novel disease-genes, but this is highly dependent on patients' enrollment criteria.
- Among cases with mutations in known disease-genes, a large fraction (>55% in UND OPBG) manifests either an atypical presentation, or an allelic disorder, or has mutation(s) in a recently identified disease-gene.
- Functional validation efforts (*in vitro* and *in vivo*) are mandatory to support the causative role of mutation(s).

The OPBG team

Clinical Geneticists
Maria Cristina Digilio
Maria Lisa Dentici
Clementina Radio

-omic Research Lab
Marco Tartaglia
Marcello Niceta
Sabina Barresi
Francesca Pantaleoni

Bioinformaticians
Andrea Ciolfi
Simone Pizzi

Diagnostic Genetic Lab
Antonio Novelli
Emanuele Agolini
Francesca Terracciano
Francesca Lepri

Clinicians

Andrea Bartuli	*rare diseases*
Enrico Silvio Bertini	*neuromuscular diseases*
Carlo Dionisi Vici	*metabolic diseases*
Francesco Vigevano	*neurological disorders*
Marco Cappa	*endocrine diseases*
Fabrizio De Benedetti	*rheumatic disease*
Franco Locatelli	*oncological-haematological disorders*
Pietro Bagolan	*paediatric surgery*
Renato Cutrera	*lung diseases*
Francesco Emma	*kidney diseases*
May El Hachem	*skin diseases*
Giuliano Torre	*gastrointestinal diseases*

Structural Biology
Emanuele Bellacchio

Cell Biology
Maria Letizia Motta
Valentina Muto
Claudia Compagnucci
Antonella Sferra
Martina Venditti

Computational Infrastructure

CINECA