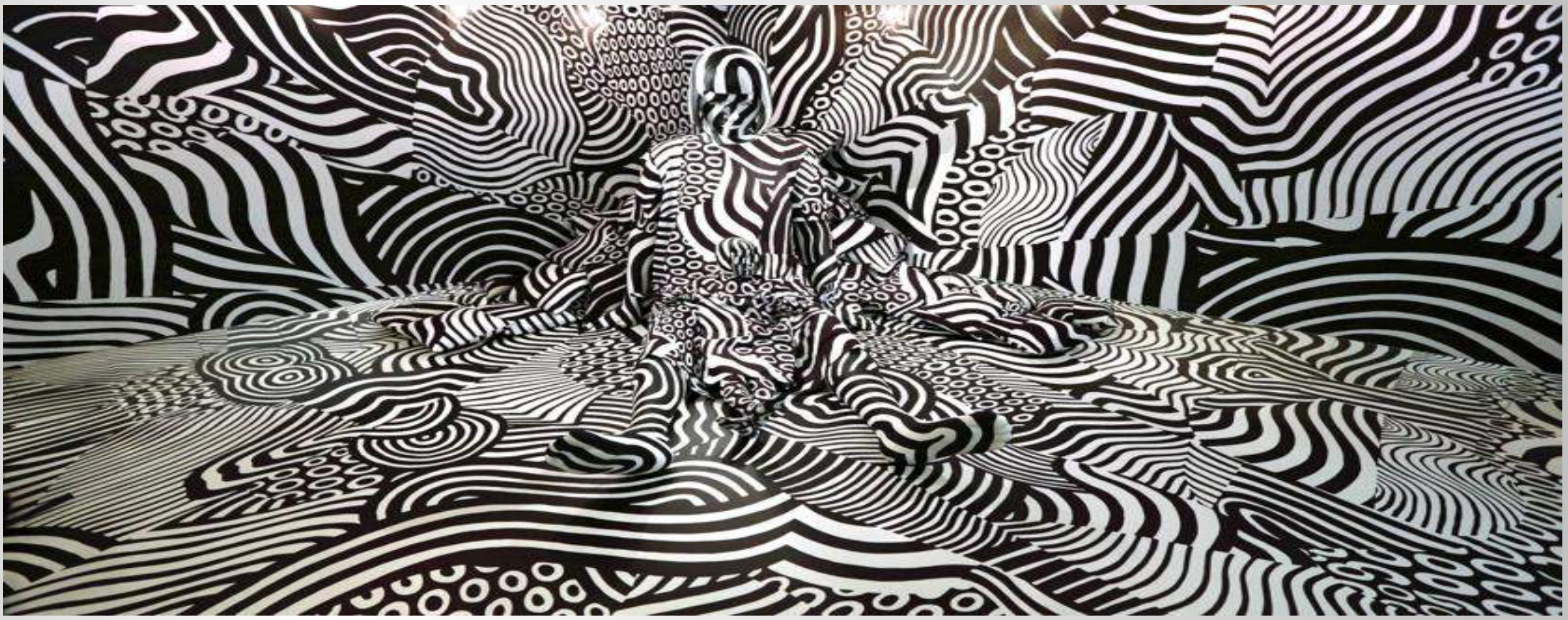
Next NGS approaches to the unsolved: Telethon Undiagnosed Program



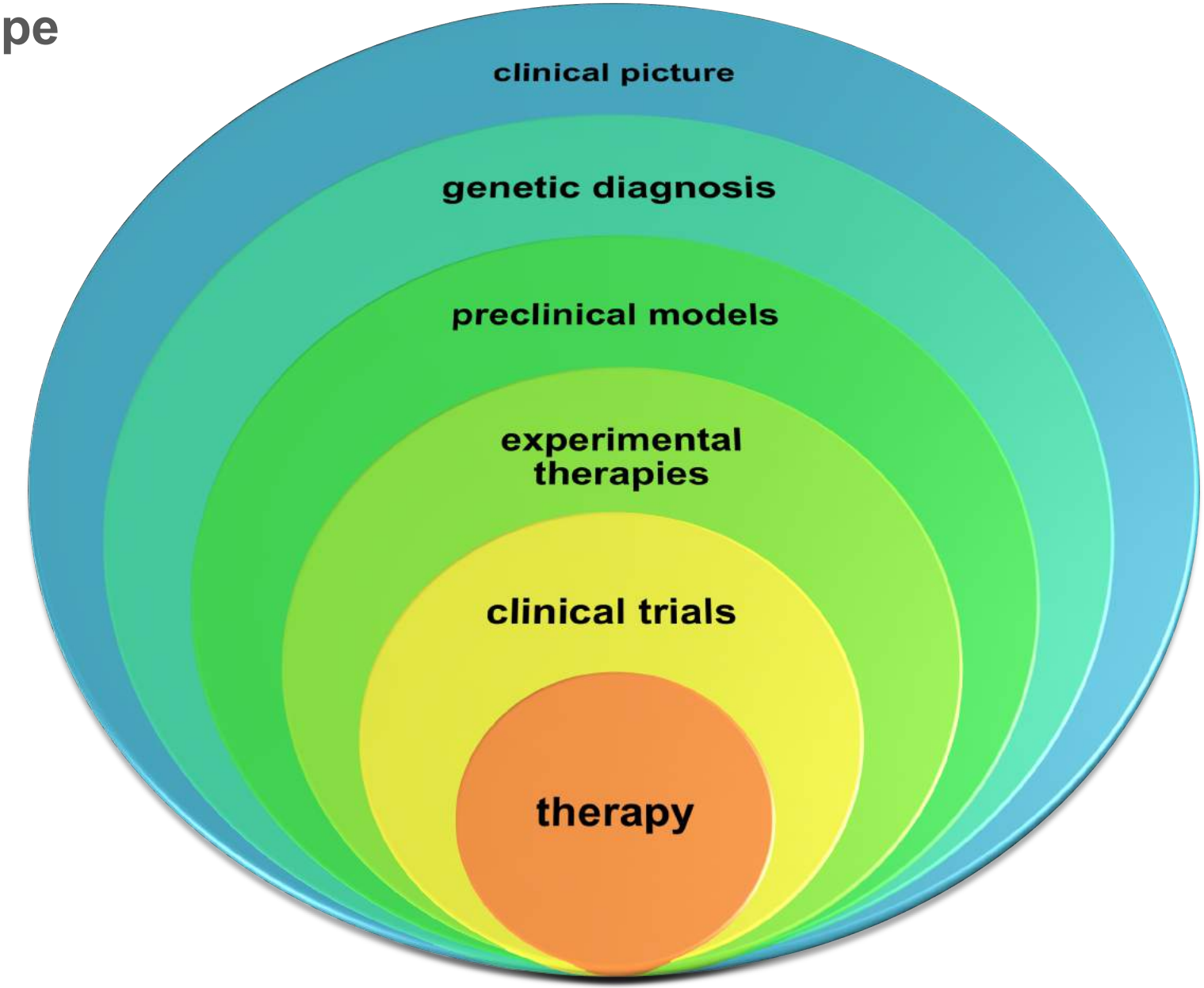
vincenzonigro

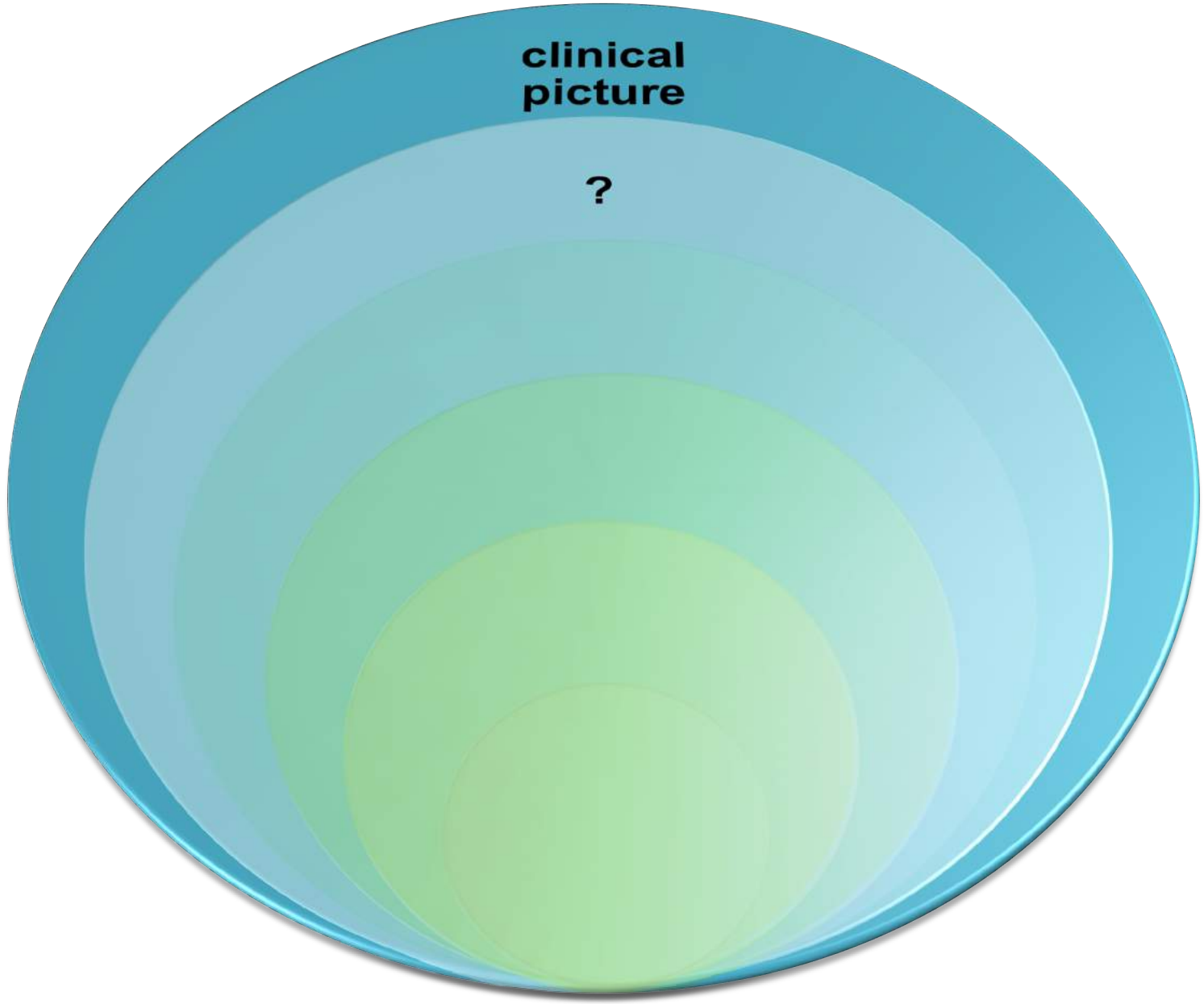
Prof medical genetics

Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy

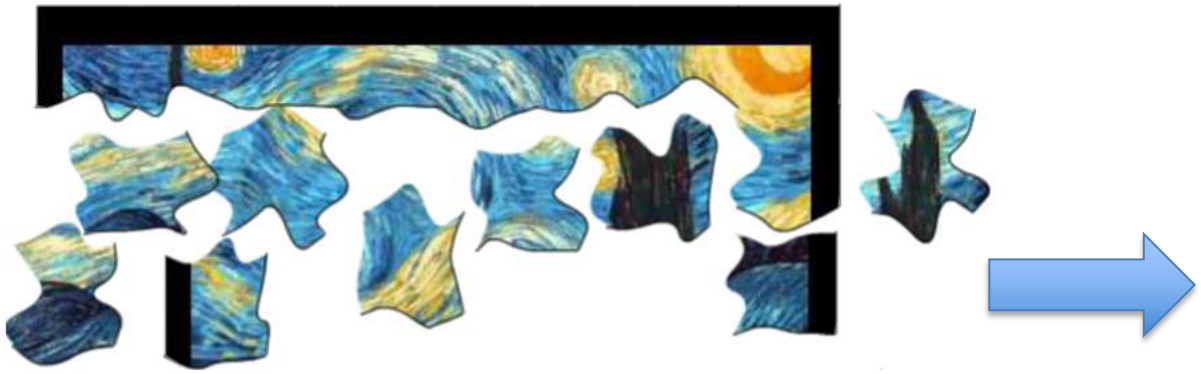
Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli, Italy

funnel of hope




clinical
picture
?

recognize the disease?

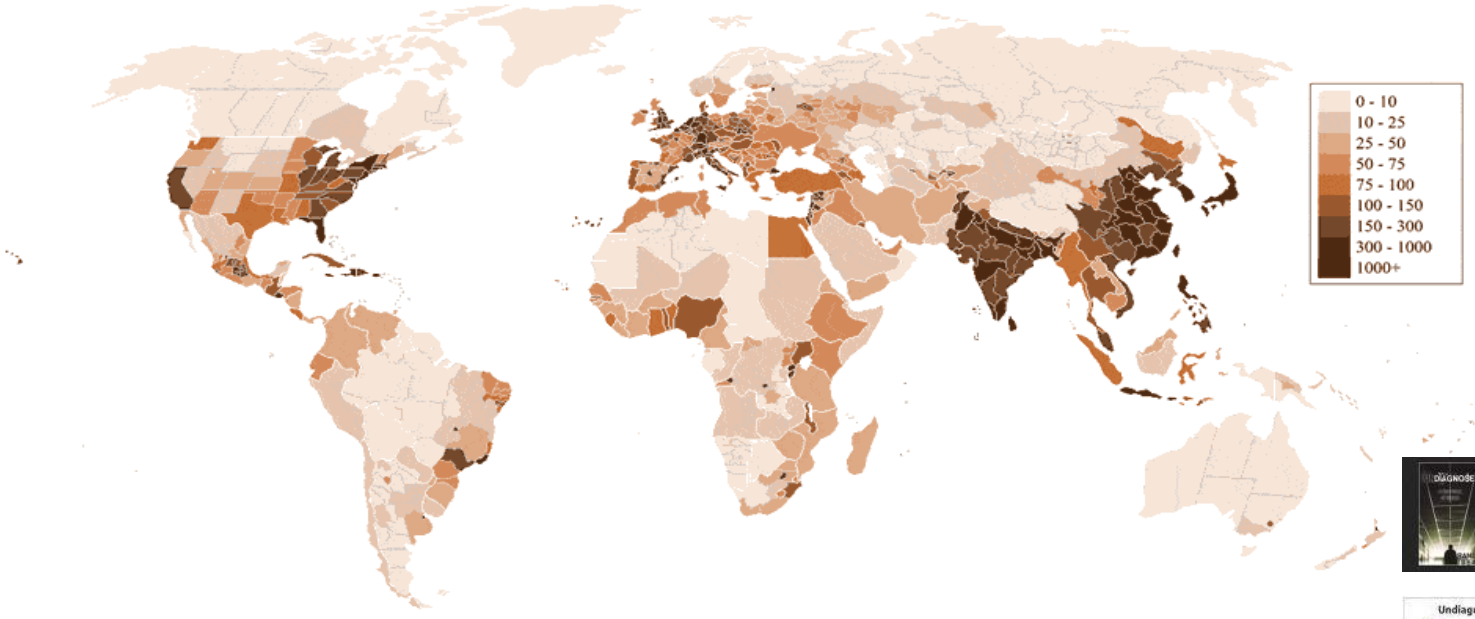


The Starry Night, 1889
Vincent van Gogh

no idea

UNDIAGNOSED DISEASES PROGRAM

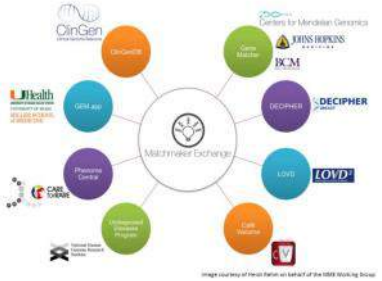
telethon



thousands of unknown genetic disorders

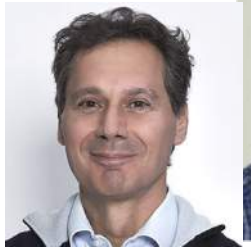
- Without name
- Without diagnosis
- Without genetic testing
- Without prognosis
- Without scientific research
- Without targeted therapy

international initiatives for undiagnosed diseases



The pediatrics and clinical genetics TUDP network

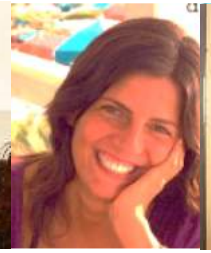
TUDP collaborators


Giorgio Casari


Sandro Banfi


Vincenzo Nigro


Lele Castello


Annalaura Torella


Francesco Musacchia


Margherita Mutarelli


Manuela Dionisi


Gaia Esposito


Mariateresa Pizzo


N. Brunetti-Pierri


G. Cappuccio


M.Pinelli


G. Parenti


S. Fecarotta


A. Selicorni


F. Grilli

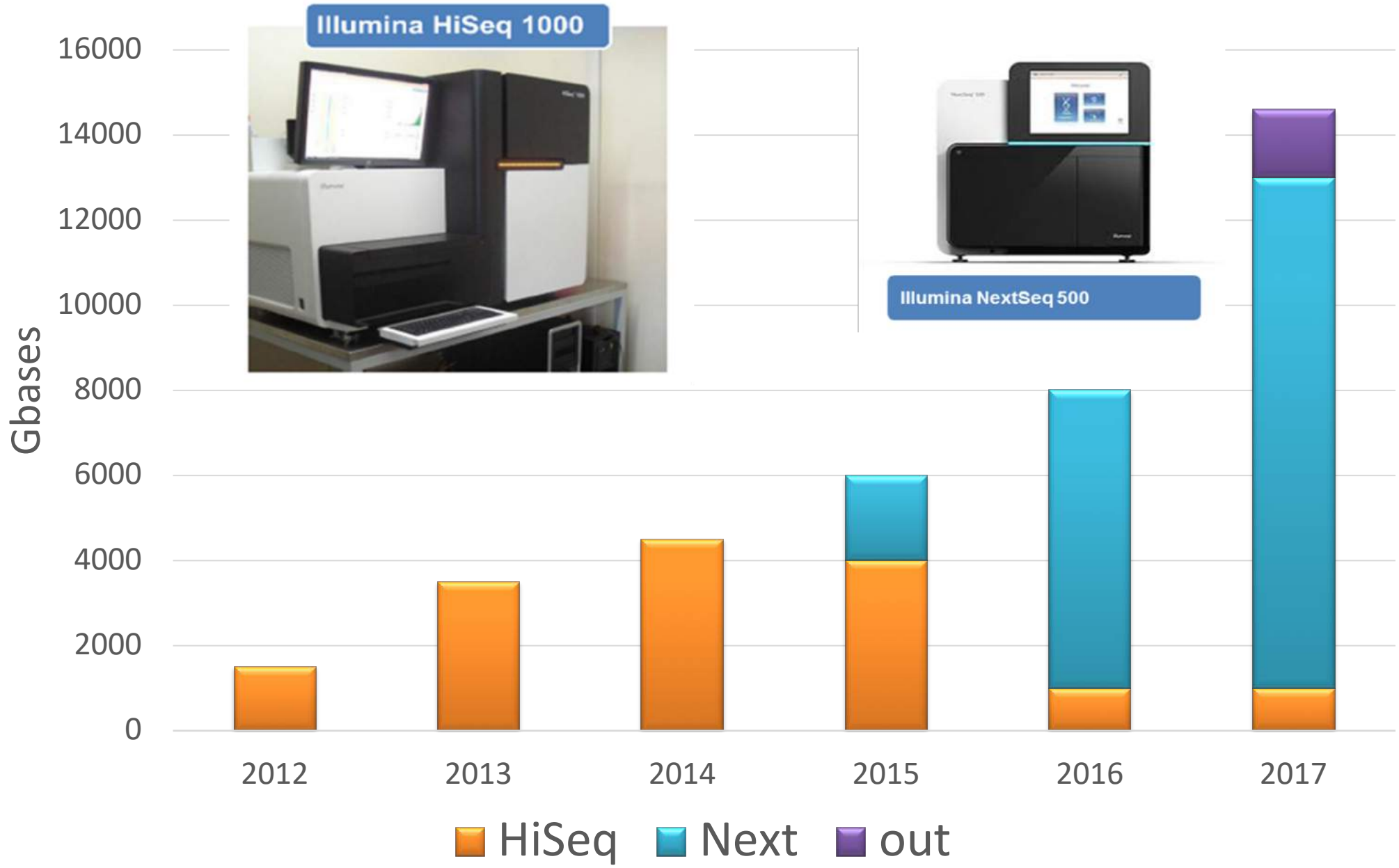

G. Sgroi


S.Maitz


V. Capra

Vincenzo Leuzzi, Policlinico Umberto I, Rome
Marcella Zollino, Policlinico Gemelli, Rome
Renzo Guerrini, A.O.Uni. Meyer, Florence
Sabrina Giglio, A.O.Uni. Meyer, Florence
Maria Donati, A.O.Uni. Meyer, Florence
Corrado Romano, Oasi Maria SS., Troina
Teresa Mattina, Policlinico V. Emanuele, Catania
Giovanni Chillemi, CINECA, Bologna, Chiara Pantaleoni, Istituto Neurologico Besta, Milano

**Bruno Dalla Piccola, Marco Tartaglia, Ospedale Bambino Gesù, Rome


Illumina HiSeq 1000
Illumina NextSeq 500
16000
14000
12000
10000
8000
6000
4000
2000
0
Gbases
2012
2013
2014
2015
2016
2017
HiSeq
Next
out

At Tigem

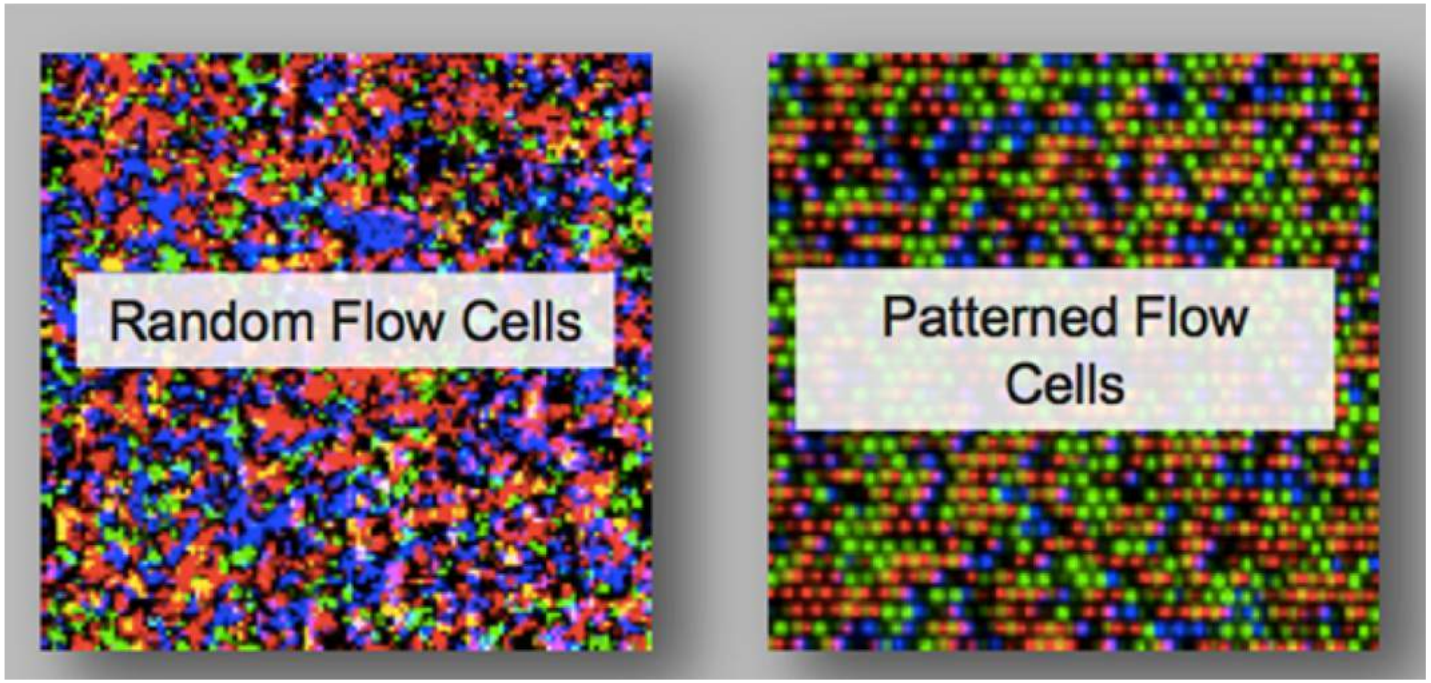
NovaSeq6000

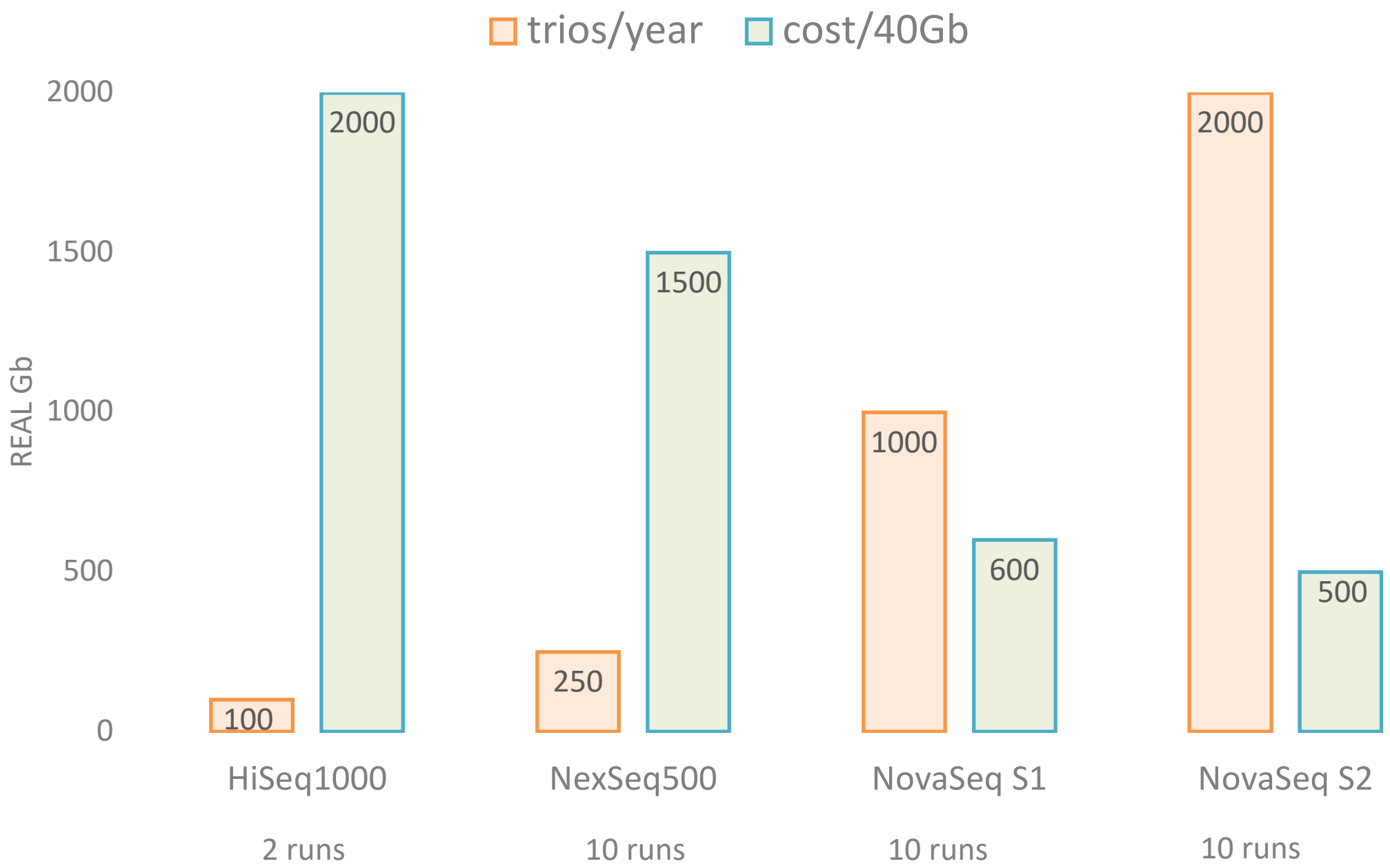
6,000,000,000,000 bp/40 hours

= 40 seconds/ billion DNA bp

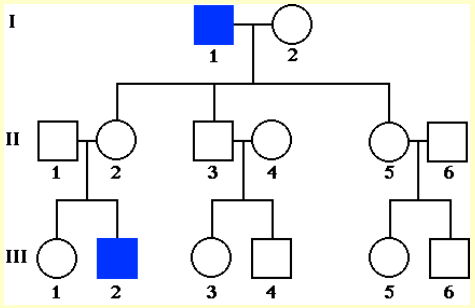
7$/ billion DNA bp

Four different flow cells S1-S4




trios/year
cost/40Gb
REAL Gb
2000
1500
1000
500
0
100
2000
250
1500
1000
600
2000
500
HiSeq1000
NexSeq500
NovaSeq S1
NovaSeq S2
2 runs
10 runs
10 runs
10 runs

Patient expectations: accessibility, diagnosis, sharing, communication



may be a new genetic disease?

clinical check up

sequencing and matching

data sharing validation

genetic disease is well known and patients receive diagnosis

genetic disease can be diagnosed in specific centers

diagnosis of a mutation in a disease gene

return of results and counselling

Informed consent

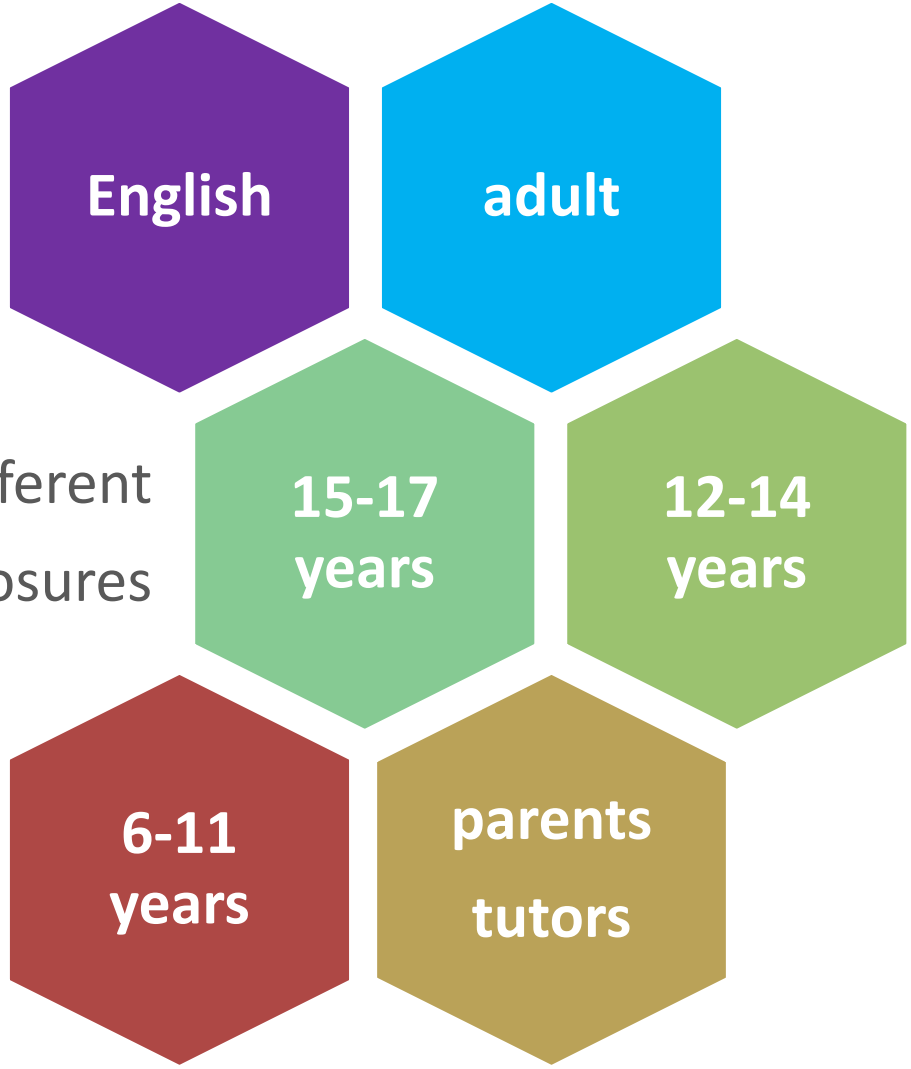
for analyzing NGS data and for sharing results

Informed consent *for analyzing whole exome/genome sequence data from all family members and for sharing* ***deidentified*** *results with other Undiagnosed Diseases networks*

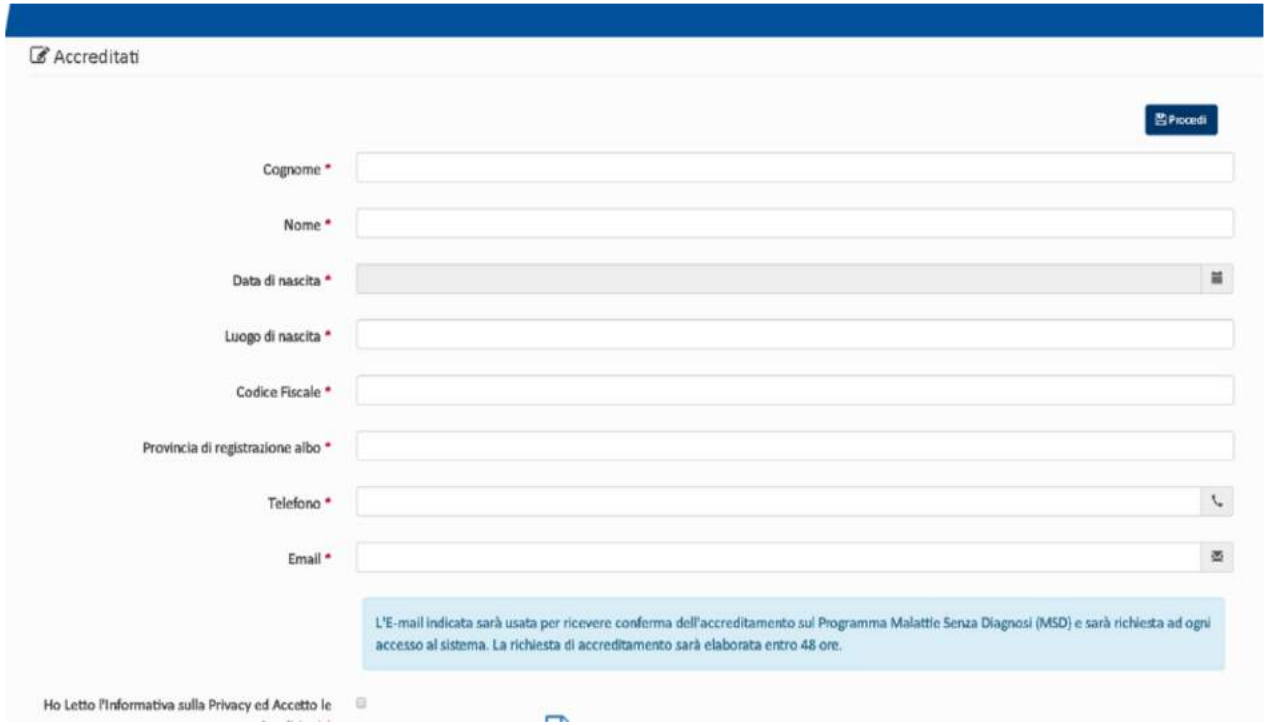
Incidental findings (known, validated actionable

genetic counseling

6 different disclosures

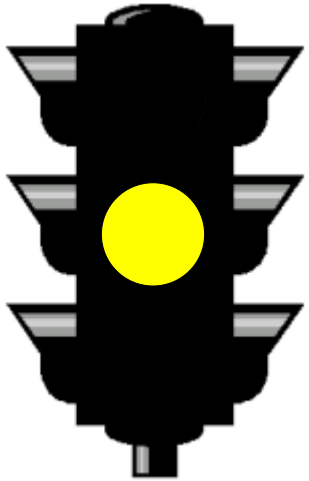


cases recruitment using a web form

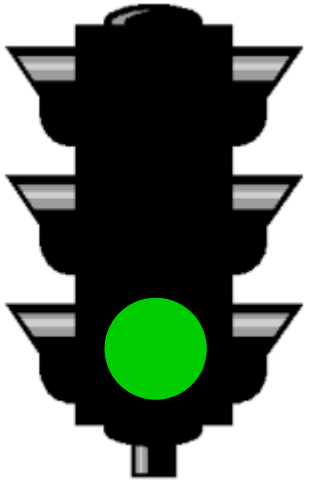


Which responses?

Disease is known or not genetic, an indication for a referral center is provided



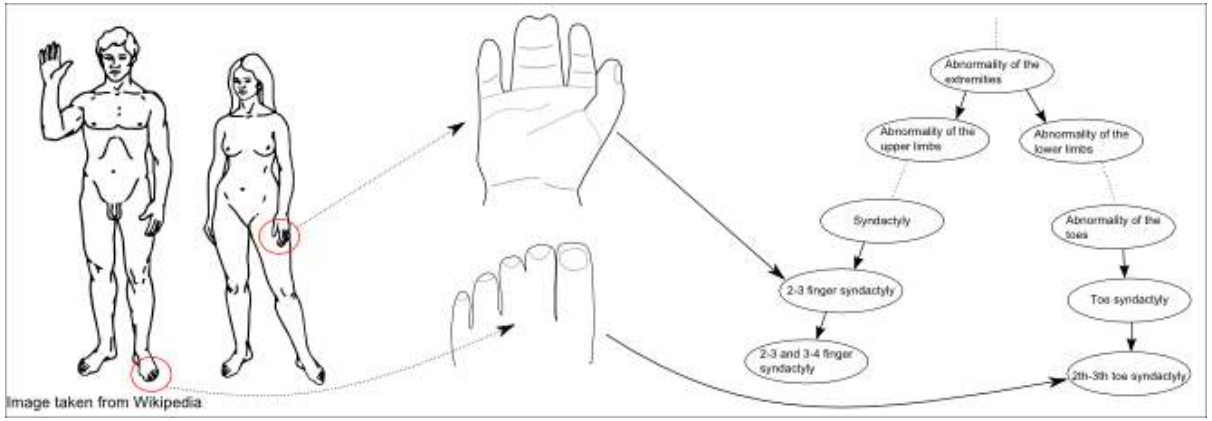
Additional information required



Patient is recalled for deep phenotyping and priority scoring at clinical plenary meeting

standardization of patients

phenotypic data capture and storage using the standardized vocabulary defined by the **Human Phenotype Ontology** (HPO)



Clinical fellows meetings (14 days)

- Aim: monitor the flow of cases submitted to triage
- Attendance: clinical geneticists hired for the projects, Project Manager

Clinical plenary meetings (30 days)

- Aim: final selection of cases to enter the project
- Attendance: mandatory for clinical geneticists hired for the project and their supervisors, Project Coordinator, Project Manager, members of a Board of Independent Clinicians from the three participating Centers.The Board of Independent Clinicians can be expanded to include clinical investigators with key expertise in the cases to be discussed (selections to be made beforehand by the three clinical centers).

Clinical Plenary meeting prioritization criteria

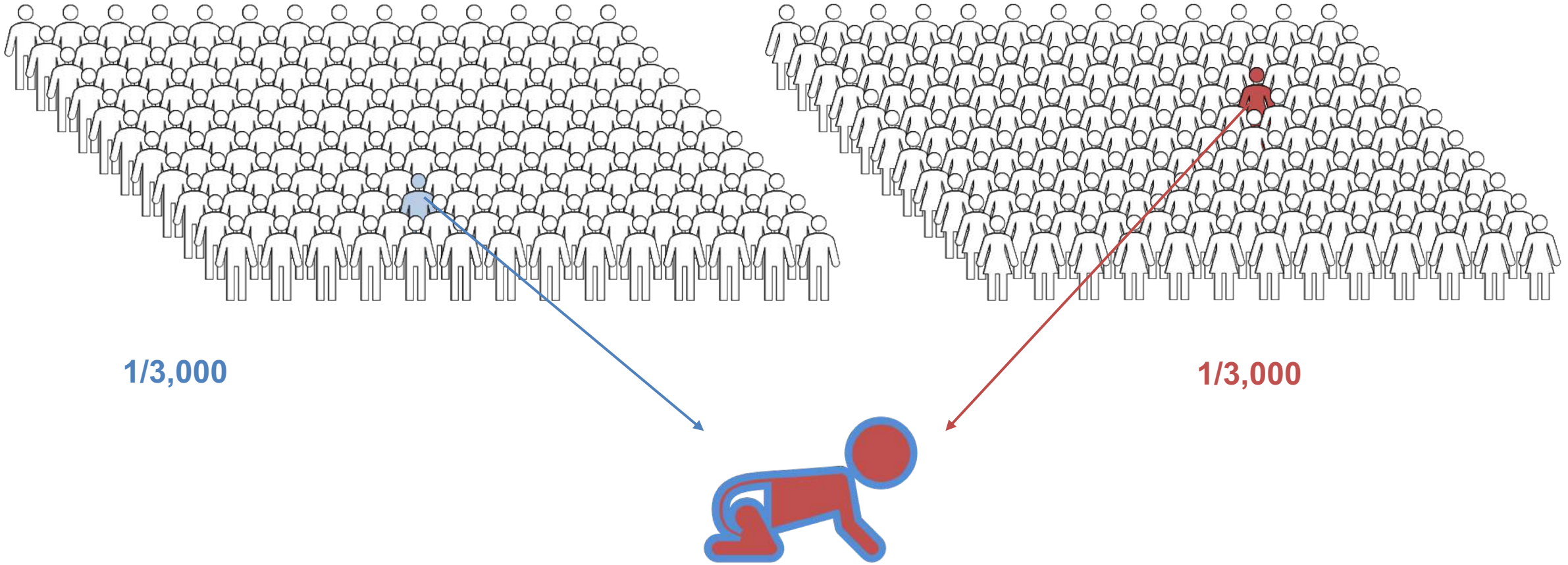
priority is higher

- severity and complexity
- pediatric age
- accurate negative testing
- large pedigree
- new peculiar phenotype

priority is lower

- array-CGH uncertain
- incomplete testing
- nonspecific phenotype
- mild disease

very rare heterozygous carriers, ultra-rare patients



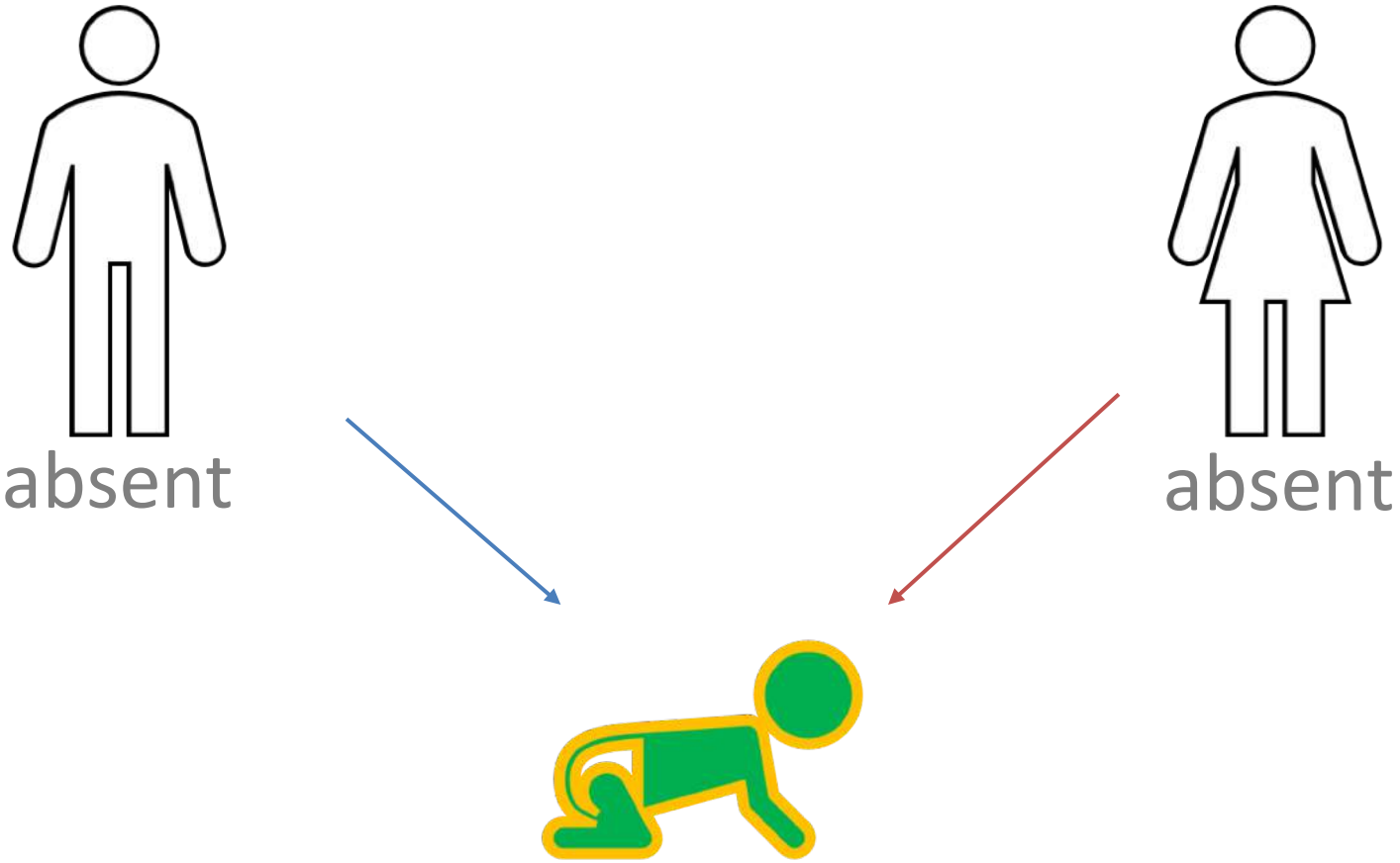
1/3,000

1/3,000

two mutations in the same gene !!

1/36,000,000 = 1-2 patients in Italy

general population, new patients

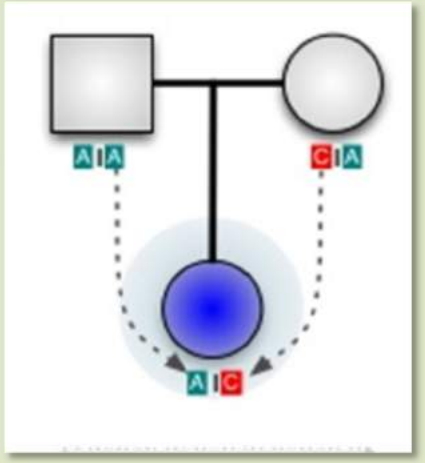


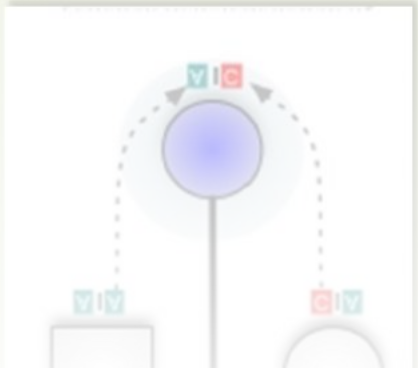
one crucial *de novo* mutation

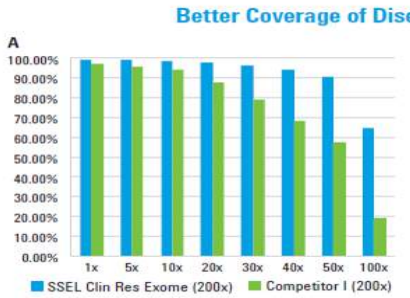
family WES

Trio analysis will be useful

- to improve variant calling and correct errors
- to discover *de novo* variants
- to get phase and haplotype







B

	SSEL Clinical Research Exome	Competitor I
Target Size	54 Mb	12 Mb
Databases Covered		
CCDS	98%	31%
Gencode	98%	30%
UCSC	97%	29%
RefSeq	98%	31%
HGMD_cds	99%	74%
OMIM_cds	99%	41%
ClinVar	98%	82%
Customization	Yes	No

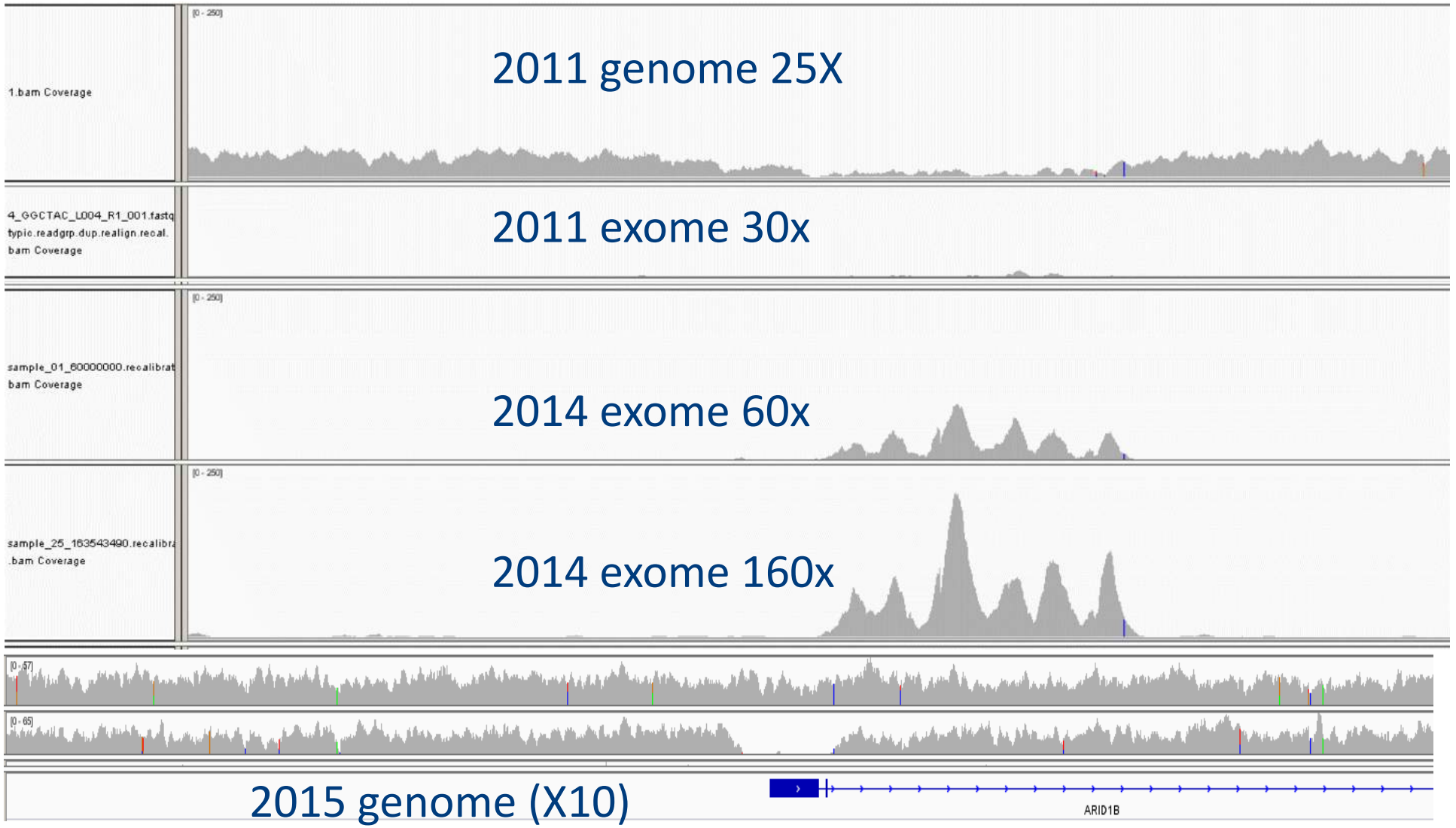
Whole exome target enrichment performed by **SureSelect Clinical Research** Exome 54Mb

sequencing 150x2 nt, av coverage 250x, 20x >95%

Proband has a **double coverage, parents are run separately**

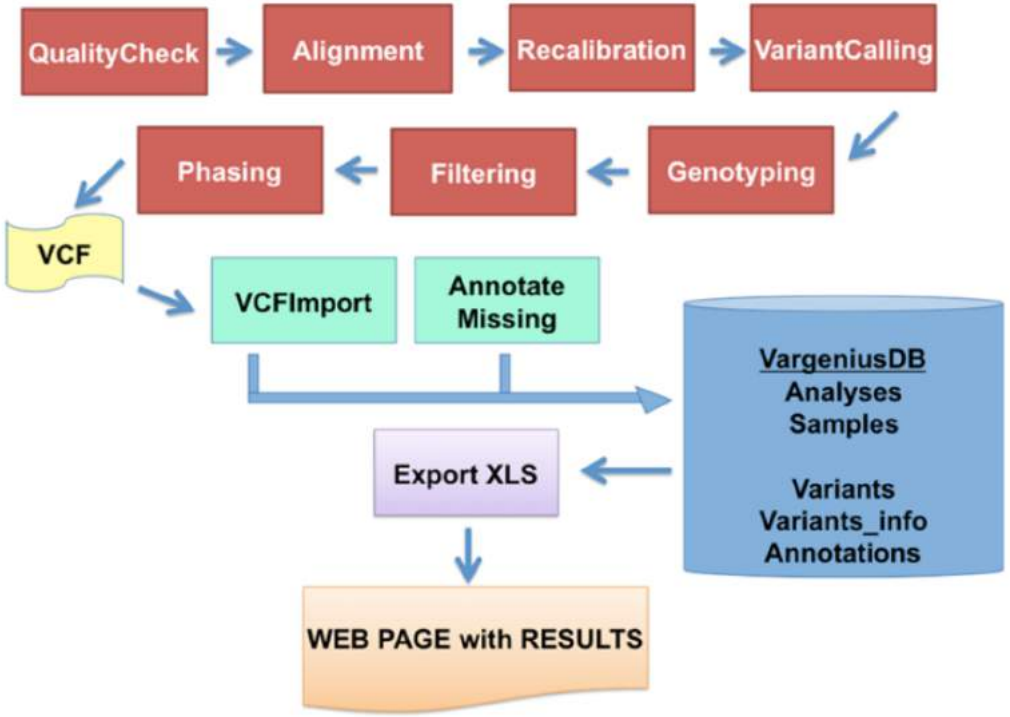
a WES pipeline has been optimized and shared between OPBG (Rome) and TIGEM

Progress of WES and WGS quality (from GWE Santen)

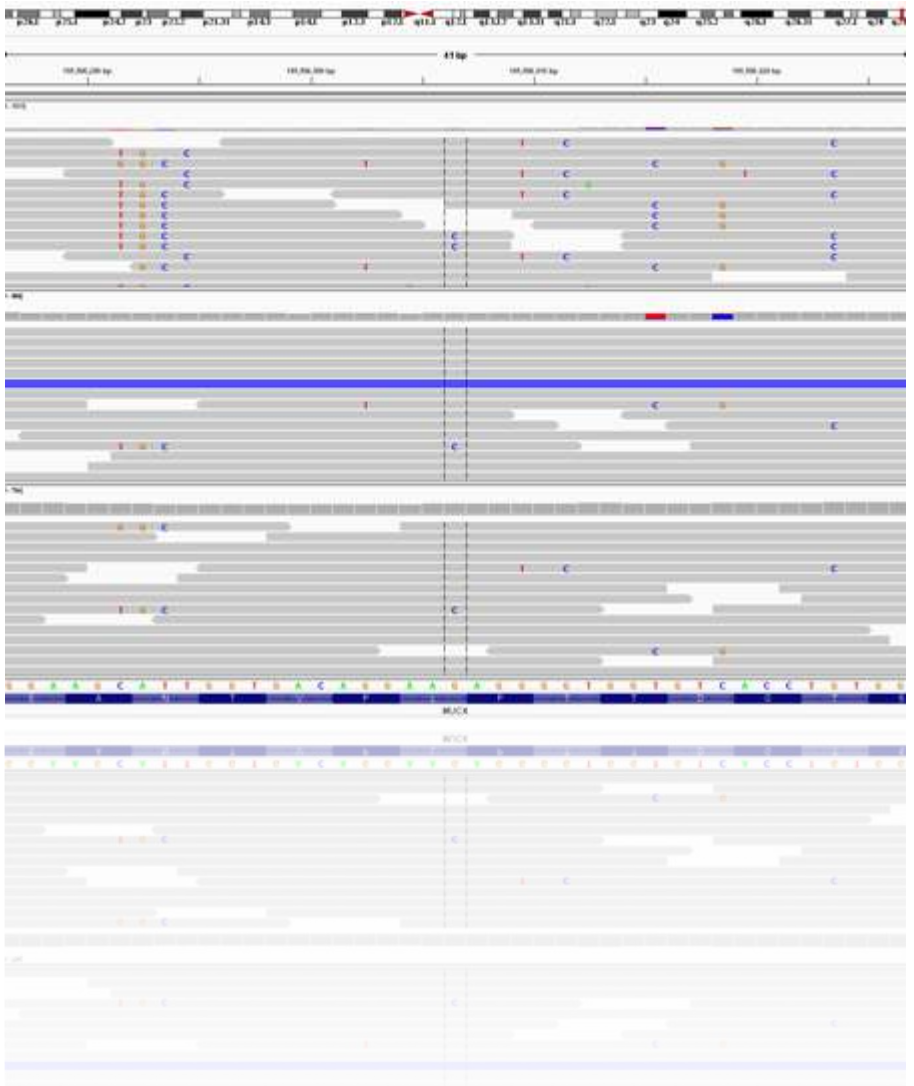


WES CRE Agilent (>20x) in 84 subjects
bases covered

COL6A1	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	99.7	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
COL6A2	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	99.6	99.6	100	100	100	99.9	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	99.6	100
COL6A3	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100
	100	100	100	100	100	100	100	100	100	100	100	100



Standardized pipeline run on CINECA cluster (20min)



NGS meetings (30 days)

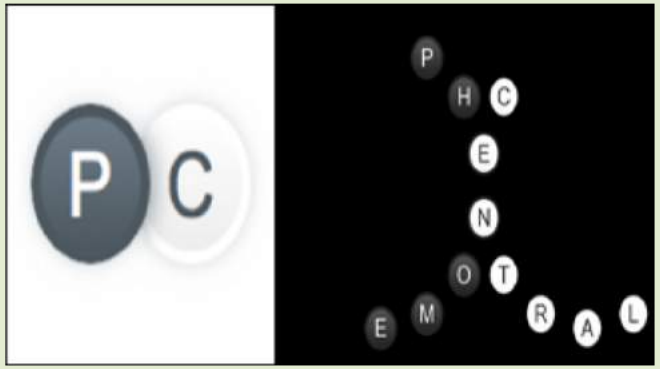
- Aims: comparative NGS analyses. Discussion of genetic data.
- Attendance: mandatory for all those involved in the NGS pipelines and their supervisors, Project Coordinator.

sharing sharing sharing

Data will be mainly shared through **PhenomeCentral** (http://phenomecentral.org)

This has great potential for identifying **additional cases** of phenotypically similar patients required to validate the identified putative disease causative variant(s)

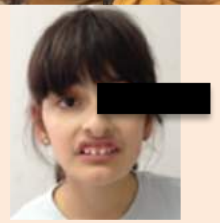
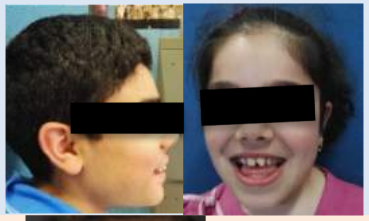
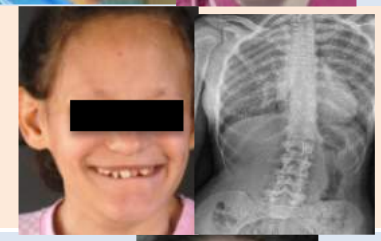
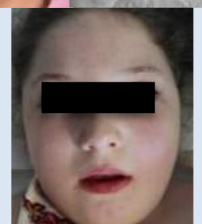
>350 users worldwide, such as the Canadian (**Care for Rare**), US (**Undiagnosed Diseases Network**) and European (**Neuromics**, **AnDDI-rare**) rare disease sequencing programs



- PhenomeCentral, a repository for **secure data sharing** targeted at clinicians and scientists working in the rare disorder community.
- The PhenomeCentral collaboration model allows to **learn about the existence of similar cases** world-wide, which helps to improve understanding of disorder manifestations and confirm underlying causes.
- The **matching** algorithms -the semantic model- are **sensitive to atypical phenotypic manifestations** of disorders

https://www.phenomecentral.org/

sequenced**patients**

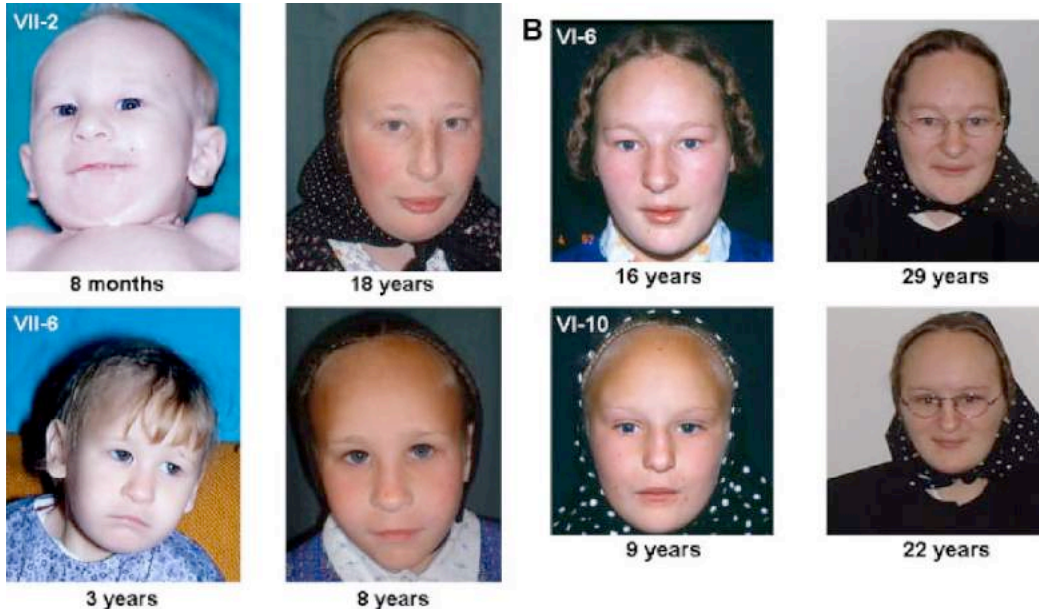
1		17 years ID glaucoma corneal opacity polycystic kidney, spleen, skin and ovarian cysts aracnoid cysts corpus callosum agenesis anosmia macrocephaly	***de novo PLAG1*** ***de novo PPP6R1*** ***comp het MAP4K2*** NA14
2		12 years intellectual disability obsessive compulsive behaviour hypotonia prognathia primary teeth decreased body weight	***de novo SH3BP4*** ***de novo BUB1B*** NA04
3		13, 11 years ID Leber congenital amaurosis microcephaly ataxia bone dysplasia femoral head and lumbar vertebral dysplasia cerebral hypotrophy	***No shared variants*** ***Shared haplotype*** NA11
4		10 years microcephaly, short stature cerebellar atrophy mesencephalon-synapsis aqueductal stenosis C4-C5 and C6-C7 defects brother deceased	***comp het PRG4*** ***comp het THOC6 (LoF)*** GE03
5		8 years severe hypotonia l.limb hypertonia neuro-axonal dystrophy epilepsy optical nerves and chiasma atrophy obesity microcephaly	***de novo KIF1A C92R*** NA13

NEW SYNDROME

AMERICAN JOURNAL
medical genetics

A Novel Autosomal Recessive Malformation Syndrome Associated With Developmental Delay and Distinctive Facies Maps to 16ptel in the Hutterite Population

Kym M. Boycott,[1]* Chandree Beaulieu,[2] Erik G. Puffenberger,[3,4] D. Ross McLeod,[2] Jillian S. Parboosingh,[2] and A. Micheil Innes[2†]



Beaulieu et al. Orphanet Journal of Rare Diseases 2013, 8:62
http://www.ojrd.com/content/8/1/62

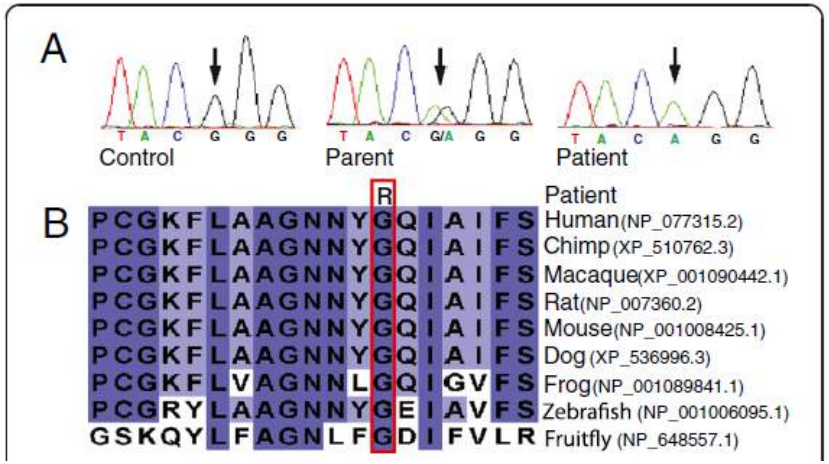
ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Intellectual disability associated with a homozygous missense mutation in *THOC6*

Chandree L Beaulieu[1†], Lijia Huang[1†], A Micheil Innes[2,3], Marie-Andree Akimenko[4], Erik G Puffenberger[5], Charles Schwartz[6], Paul Jerry[7], Carole Ober[8], Robert A Hegele[9], D Ross McLeod[2,3], Jeremy Schwartzentruber[10], FORGE Canada Consortium, Jacek Majewski[10], Dennis E Bulman[1], Jillian S Parboosingh[2,3†] and Kym M Boycott[1*†]

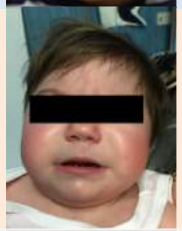
Homozygous p.Gly46Arg, in *THOC6*



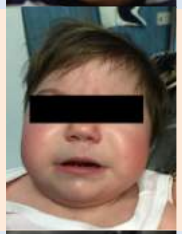
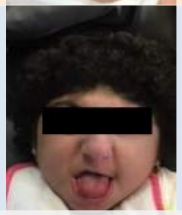
diagnosed**patients**

6		6 years severe cognitive impairment deafness hypotonia anomaly of globus pallidus vomiting	*de novo* ***GRIN2B*** S555N
7		6 years tetralogy of Fallot corectopia esotropia microcephaly short stature	*de novo* ***SMAD4*** I550V
8		15 years blindness spastic tetraparesis seizures lissencephaly ocular proptosis macroglossia accessory spleen conical teeth intestinal malrotation	*autosomal recessive* ***WDR81*** W28X + R619X
9		20-30 years ataxia hypotonia seizures severe ID speech impairment strabismus	*autosomal recessive* ***GAMT*** A22T + A22T
10		5 years microcephaly pontocerebellar atrophy severe ID speech absence epileptic encephalopathy	*autosomal recessive* ***RARS2*** fshift + -2A>G

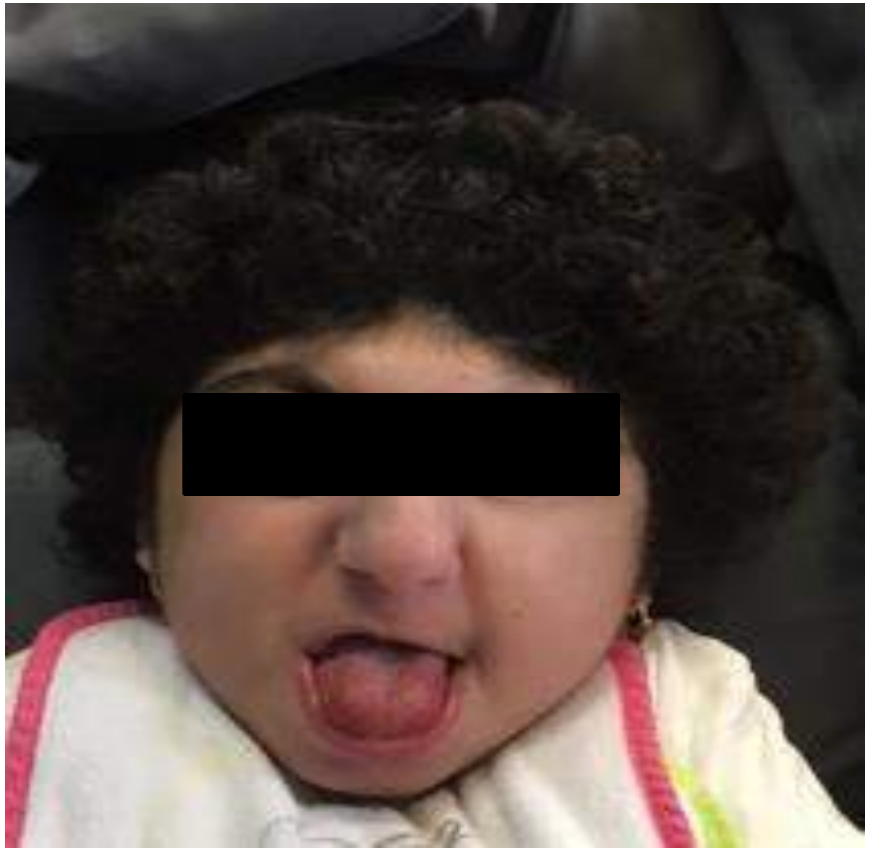
diagnosed**patients**

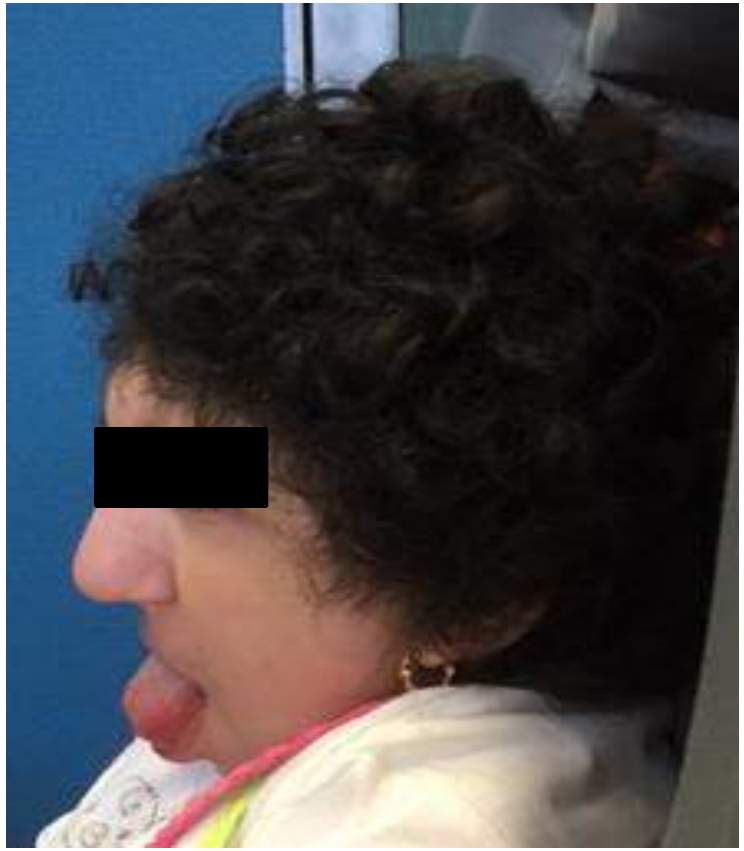
6		6 years severe cognitive impairment deafness hypotonia anomaly of globus pallidus vomiting	*de novo* ***GRIN2B*** S555N
7		6 years tetralogy of Fallot corectopia esotropia microcephaly short stature	*de novo* ***SMAD4*** I550V
8		15 years blindness spastic tetraparesis seizures lissencephaly ocular proptosis macroglossia accessory spleen conical teeth intestinal malrotation	*autosomal recessive* ***WDR81*** W28X + R619X
9		20-30 years ataxia hypotonia seizures severe ID speech impairment strabismus	*autosomal recessive* ***GAMT*** A22T + A22T
10		5 years microcephaly pontocerebellar atrophy severe ID speech absence epileptic encephalopathy	*autosomal recessive* ***RARS2*** fshift + -2A>G

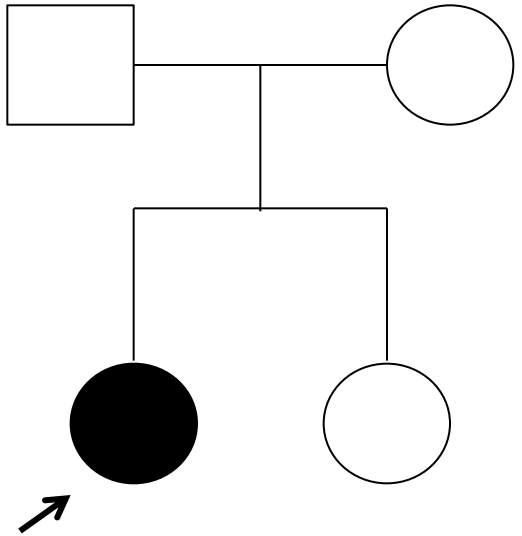
diagnosed**patients**

6		6 years severe cognitive impairment deafness hypotonia anomaly of globus pallidus vomiting	*de novo* ***GRIN2B*** S555N
7		6 years tetralogy of Fallot corectopia esotropia microcephaly short stature	*de novo* ***SMAD4*** I550V
8		15 years blindness spastic tetraparesis seizures lissencephaly ocular proptosis macroglossia accessory spleen conical teeth intestinal malrotation	*autosomal recessive* ***WDR81*** W28X + R619X
9		20-30 years ataxia hypotonia seizures severe ID speech impairment strabismus	*autosomal recessive* ***GAMT*** A22T + A22T
10		5 years microcephaly pontocerebellar atrophy severe ID speech absence epileptic encephalopathy	*autosomal recessive* ***RARS2*** fshift + -2A>G

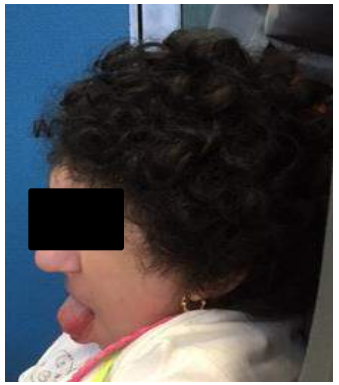
15 years

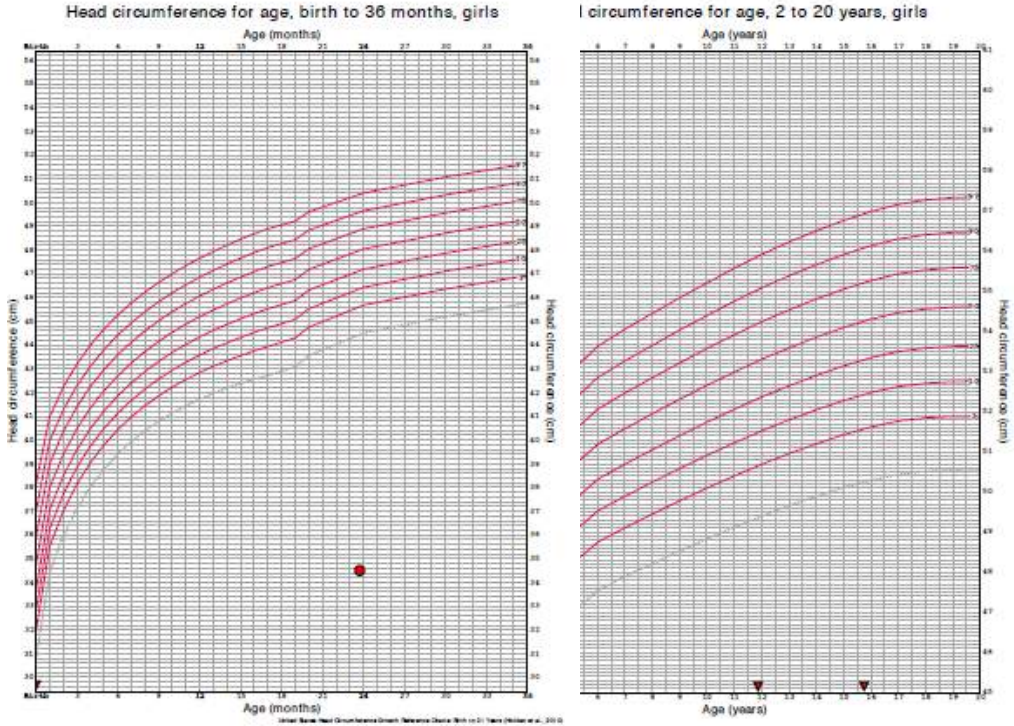




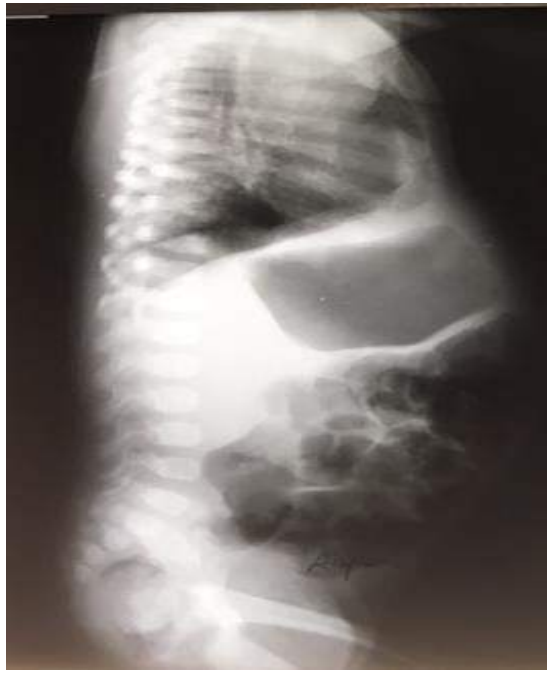


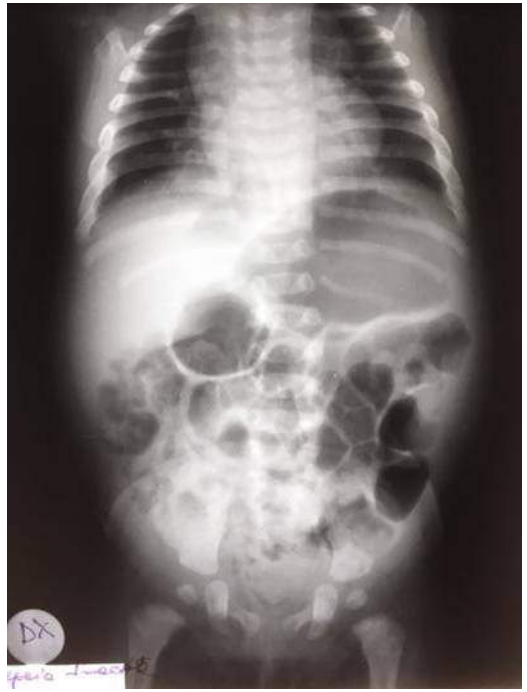
- Born at term by dystocic delivery (facial presentation) after uncomplicated pregnancy
- Healthy non-consanguineous parents
- At birth: weigth 2.9 kg (34°pc), length 46 cm (8° pc), head circumference 28 cm (<3°pc)
- Microcephaly and facial dysmorphisms, (prominence of coronal ridge, ocular proptosis; bulbous nose, macroglossia, crowded and conical teeth)
- Generalized seizures (tonic-clonic) with neonatal onset
- Bilateral glaucoma, blindness
- Recurrent pneumonia
- Feeding problems
- Cyclic vomiting
- Spastic tetraparesis
- Profound ID, no milestone acquisition

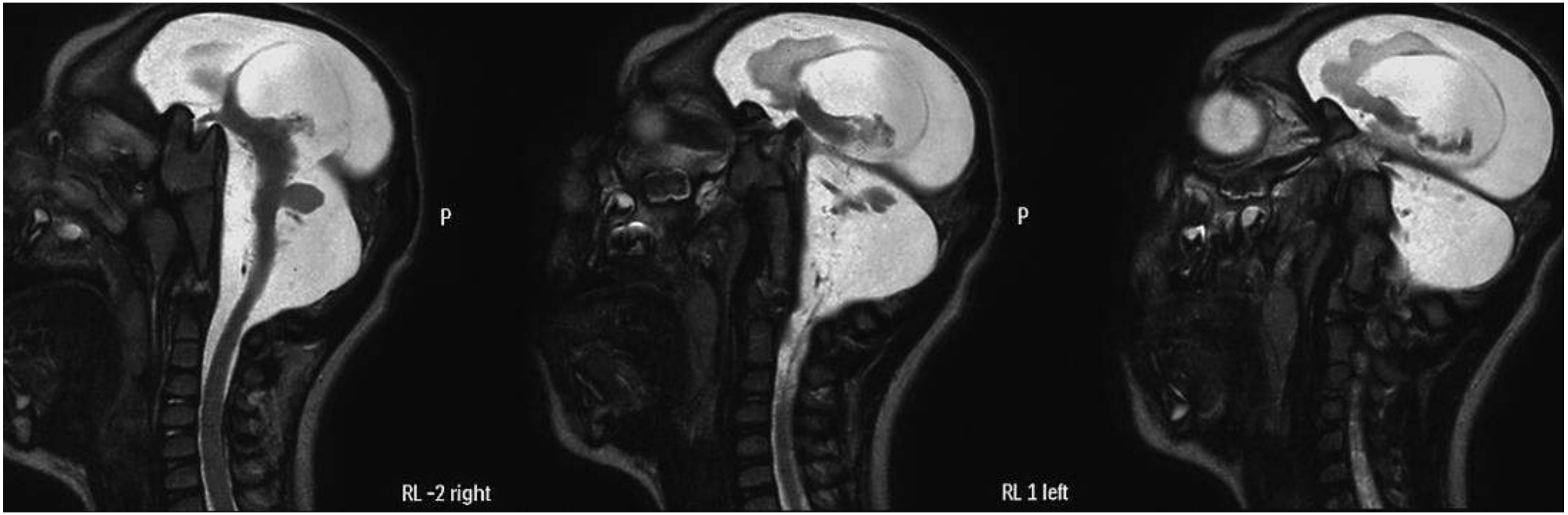




- Abdominal US and Rx study: intestinal malrotation, accessory spleen
- Blood tests: hypercholesterolemia, ALT, AST, GGT, CPK, amilase and lipase mildy elevated
- RX skeletal at 5yrs: bowing radius, congenital hip dysplasia, coccix agenesis
- Karyotype: 46,XX
- Array CGH: negative
- *PTCN, CASK, ARX* genes: no mutations
- Cerebellar and brainstem malformation NGS panel: negative







- EEG: slow ea, undifferentiated nor reactive
- Brain MRI : Lyssencephaly, corpus callosum agenesis, cerebellar and brainstem hypoplasia
- ABR and VEP: absent

New phenotype

WDR81 *chr17:1639471*

Maternal NM_001163673:c.84G>A:p.W28X (exon 2)
Paternal NM_001163673:c.1855C>T:p.R619X (exon 9)

WDR81 encodes a multi-domain transmembrane protein, predominantly expressed in the brain

BBC Home | News | Sport | Radio | TV | Weather | Languages | Search

[an error occurred while processing this directive]

Low graphics | Accessibility help

BBC NEWS

Watch One-Minute World News

News services
Your news when you want it

Last Updated: Tuesday, 7 March 2006, 17:36 GMT

E-mail this to a friend Printable version

Family may provide evolution clue

Five siblings from Turkey who walk on all fours could provide science with an insight into human evolution, researchers have said.

The siblings may have reverted to an ancient form of locomotion (*Image: Passionate Productions/BBC*)

The four sisters and one brother could yield clues to why our ancestors made the transition from four-legged to two-legged animals, says a UK expert.

But Professor Nicholas Humphrey rejects the idea that there is a "gene" for bipedalism, or upright walking.

A BBC documentary about the family will be shown on Friday 17 March.

Professor Humphrey, from the London School of Economics (LSE), says that our own species' transition to walking on two feet must have been a more complex process that involved many changes to the skeleton and to the human genetic make-up.

However, a German group says a genetic abnormality does seem to be involved in the siblings' gait.

Coordination problem

News Front Page
Africa
Americas
Asia-Pacific
Europe
Middle East
South Asia
UK
Business
Health
Science & Environment
Technology
Entertainment
Also in the news
Video and Audio
Programmes
Have Your Say
In Pictures
Country Profiles
Special Reports
RELATED BBC SITES
SPORT

BBC NEWS: VIDEO AND AUDIO
See the siblings walking on their hands and feet
VIDEO

SEE ALSO:
Scientists unearth early skeleton
07 Mar 05 | Science/Nature

RELATED INTERNET LINKS:
London School of Economics
The BBC is not responsible for the content of external internet sites

TOP SCIENCE & ENVIRONMENT STORIES
Night-sky image is biggest ever
Phantom Eye 'spy plane' unveiled
Higgs discovery rumour is denied
News feeds

Passionate PRODUCTIONS

HOME | WHO WE ARE | OUR FILMS | REVIEWS | DVDS | CONTACT US

PEDIGREE DOGS EXPOSED | PEDIGREE DOGS EXPOSED - 3 YEARS ON

THE FAMILY THAT WALKS ON ALL FOURS | CAN DOGS SMELL CANCER? | JERRY LOVE

THE FAMILY THAT WALKS ON ALL FOURS

A family of adult human quadrupeds found living in a remote part of Turkey sparks a fierce scientific debate. A Turkish neuroscientist believes they are evolutionary throwbacks. A German geneticist believes they could hold vital clues about how man became bipeds. But are they right?

Guided by Professor Nick Humphrey and other top experts, the film weaves the scientific evidence with an intimate portrait of the family's life.

The Family That Walks On All Fours first aired in the UK on BBC2 in March 2006. The NOVA version of the film appeared on PBS in the US in November. The film has also been broadcast in 30 other countries. See the NOVA website for the US trailer

autosomal recessive cerebellar ataxia, mental retardation, and dysequilibrium syndrome-2 with homozygous **p.P856L**

Research

Homozygosity mapping and targeted genomic sequencing reveal the gene responsible for cerebellar hypoplasia and quadrupedal locomotion in a consanguineous kindred

Suleyman Gulsuner,[1] Ayse Begum Tekinay,[2] Katja Doerschner,[3,4] Huseyin Boyaci,[3,4] Kaya Bilguvar,[5,6,7] Hilal Unal,[2] Aslihan Ors,[4] O. Emre Onat,[1] Ergin Atalar,[4,8] A. Nazli Basak,[9] Haluk Topaloglu,[10] Tulay Kansu,[11] Meliha Tan,[12] Uner Tan,[13] Murat Gunel,[5,6,7] and Tayfun Ozcelik[1,2,14]

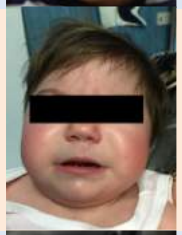
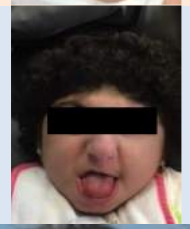
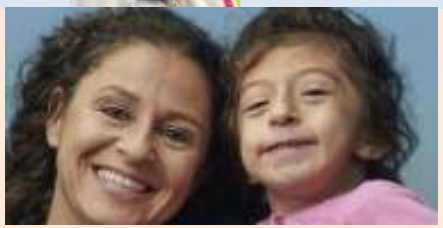
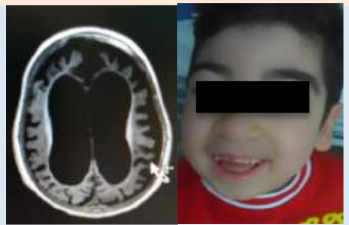
[1]*Department of Molecular Biology and Genetics, Faculty of Science, Bilkent University, Ankara 06800, Turkey;* [2]*Institute of Materials Science and Nanotechnology, Bilkent University, Ankara 06800, Turkey;* [3]*Department of Psychology, Faculty of Economics, Administrative and Social Sciences, Bilkent University, Ankara 06800, Turkey;* [4]*National Research Center for Magnetic Resonance, Bilkent University, Ankara 06800 Turkey;* [5]*Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut 06510, USA;* [6]*Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut 06510, USA;* [7]*Department of Genetics, Center for Human Genetics and Genomics and Program on Neurogenetics, Yale University School of Medicine, New Haven, Connecticut 06510, USA;* [8]*Department of Electrical and Electronics Engineering, Faculty of Engineering, Bilkent University, Ankara 06800, Turkey;* [9]*NDAL Laboratory, School of Arts and Sciences, Bogazici University, Istanbul 34342, Turkey;* [10]*Department of Pediatric Neurology, Ihsan Dogramaci Children's Hospital, Ankara 06100, Turkey;* [11]*Department of Neurology, Hacettepe University Faculty of Medicine, Ankara 06100, Turkey;* [12]*Department of Neurology, Baskent University Faculty of Medicine, Ankara 06490, Turkey;* [13]*Department of Physiology, Cukurova University Faculty of Medicine, Adana 01330, Turkey*

The biological basis for the development of the cerebro-cerebellar structures required for posture and gait in humans is poorly understood. We investigated a large consanguineous family from Turkey exhibiting an extremely rare phenotype associated with quadrupedal locomotion, mental retardation, and cerebro-cerebellar hypoplasia, linked to a 7.1-Mb region of homozygosity on chromosome 17p13.1–13.3. Diffusion weighted imaging and fiber tractography of the patients' brains revealed morphological abnormalities in the cerebellum and corpus callosum, in particular atrophy of superior, middle, and inferior peduncles of the cerebellum. Structural magnetic resonance imaging showed additional morphometric abnormalities in several cortical areas, including the corpus callosum, precentral gyrus, and Brodmann areas BA6, BA44, and BA45. Targeted sequencing of the entire homozygous region in three affected individuals and two obligate carriers uncovered a private missense mutation, WDR81 p.P856L, which cosegregated with the condition in the extended family. The mutation lies in a highly conserved region of WDR81, flanked by an N-terminal BEACH domain and C-terminal WD40 beta-propeller domains. WDR81 is predicted to be a transmembrane protein. It is highly expressed in the cerebellum and corpus callosum, in particular in the Purkinje cell layer of the cerebellum. *WDR81* represents the third gene, after *VLDLR* and *CA8*, implicated in quadrupedal locomotion in humans.

[Supplemental material is available for this article.]

Uner Tan Syndrome : reverse evolution

diagnosed patients

6		6 years severe cognitive impairment deafness hypotonia anomaly of globus pallidus vomiting	*de novo* ***GRIN2B*** S555N
7		6 years tetralogy of Fallot corectopia esotropia microcephaly short stature	*de novo* ***SMAD4*** I550V
8		15 years blindness spastic tetraparesis seizures lissencephaly ocular proptosis macroglossia accessory spleen conical teeth intestinal malrotation	*autosomal recessive* ***WDR81*** W28X + R619X
9		6 years cerebral atrophy skeletal anomalies hearing loss mild ID dysphagia	*de novo* ***NOTCH3*** L2137fs (ex 33) NA22
10		5 years microcephaly pontocerebellar atrophy severe ID speech absence epileptic encephalopathy	*autosomal recessive* ***RARS2*** fshift + -2A>G NA13

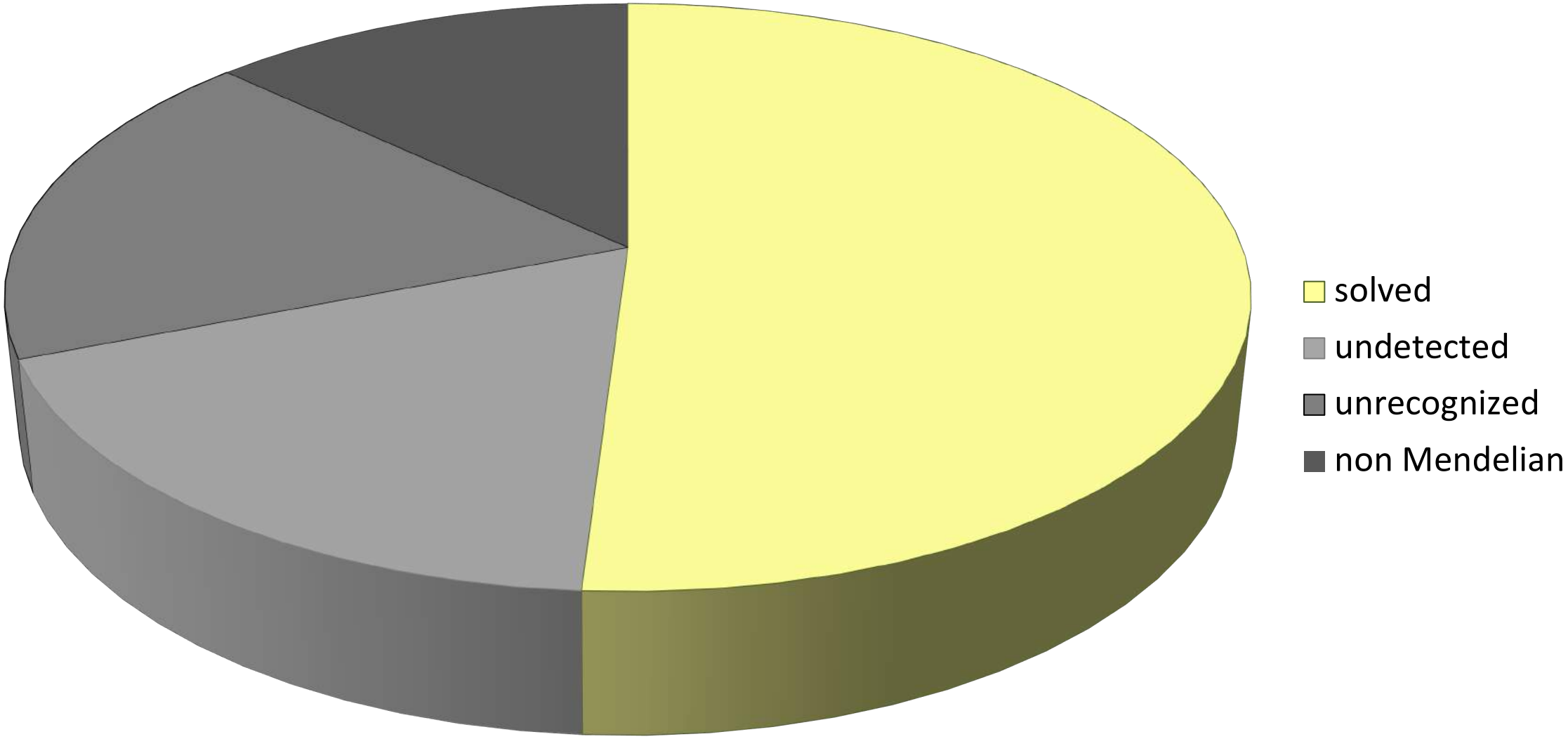
de novo

NOTCH3

L2137fs (exon 33)

TUDP, an update

The goal: 350 undiagnosed families in 3 years	
High priority cases discussed at plenary meeting	263
Ongoing/complete WES analysis	156
Diagnosis success rate	**51 %**
Among solved cases, *de novo* mutations	65 %
Recessive mutations (homozygous + compound het.)	35 %


solved
undetected
unrecognized
non Mendelian

If >90% of genetic cause is known, **why is the NGS diagnostic yield below 50%?**

Undetected mutations

- in regions with low coverage
- **insertions/deletions >20-50nt**
- long repeat expansions
- **copy number variations**
- **translocations**
- **inversions**

Increase NGS diagnostic yield

Unrecognized effects of mutations

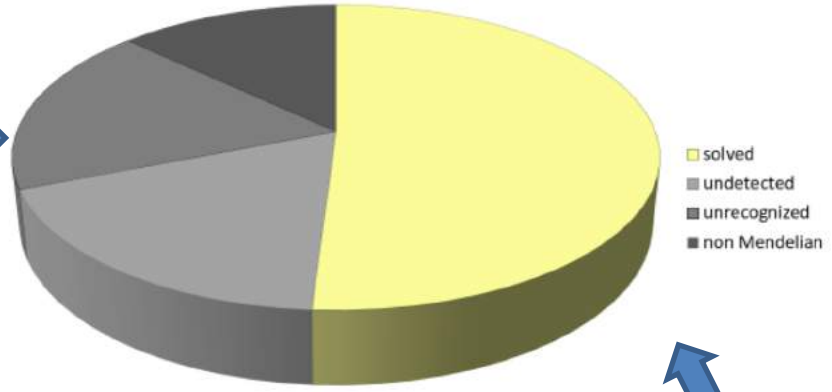
- deep intronic or elusive splicing defects
- in enhancers and promotors
- in genes with unknown function
- **in regions with duplicated sequences**
- in long genes that are variable in the population
- **disease gene has one/more pseudogenes**

Nonmendelian disorders

- Digenic/polygenic
- Immune-related diseases
- environmental

patient selection worsens:
poor clinical studies
isolated cases
mild/late onset

knowledge improves:
number of new disease genes
data sharing
RNA studies
functional studies
WGS of large populations



detection rate improves:
improved coverage/uniformity
pipeline of analysis
WGS
new technologies for nonsubstitutions

To find information everywhere in many newspapers…

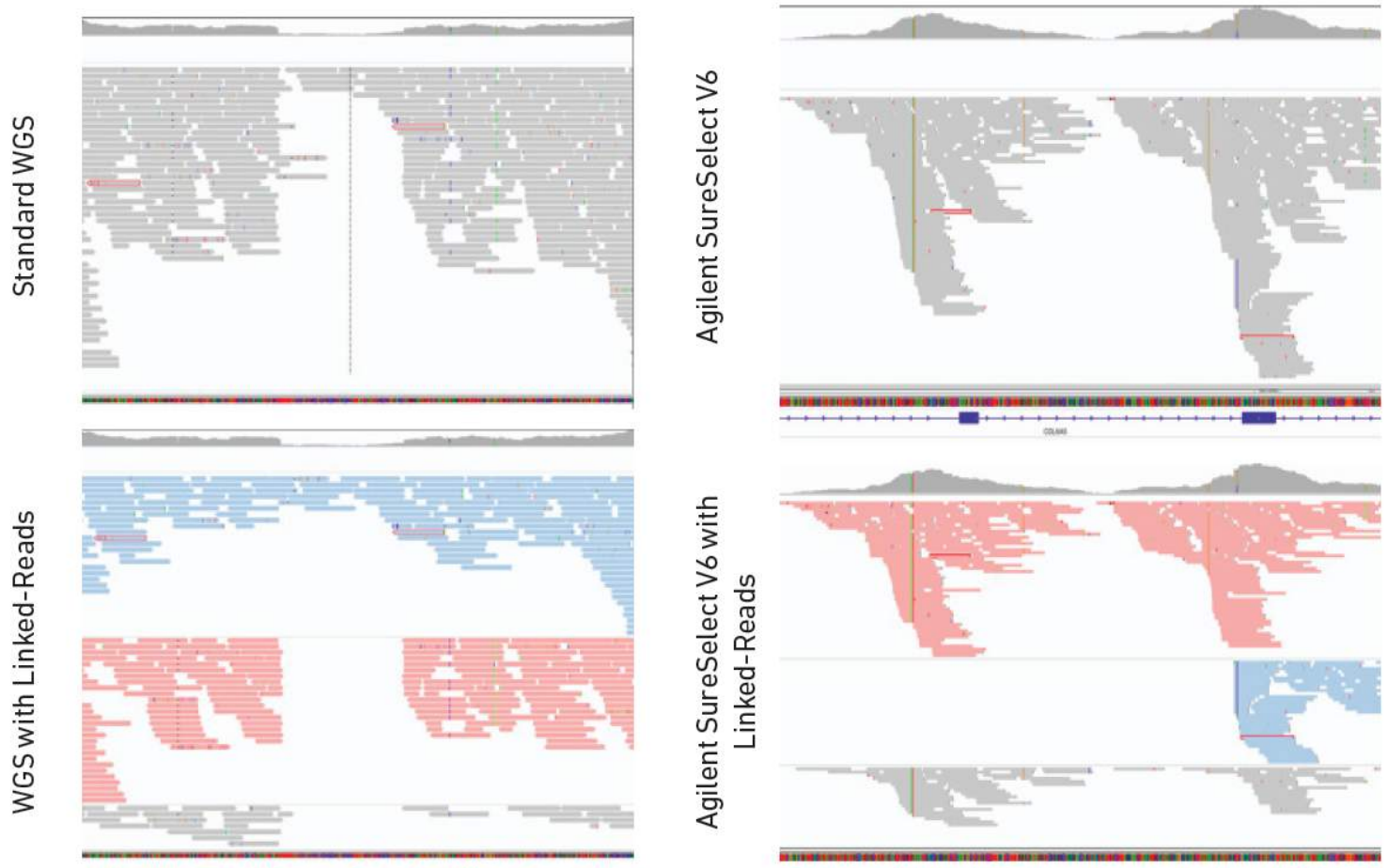
but you have paper strips to be read..

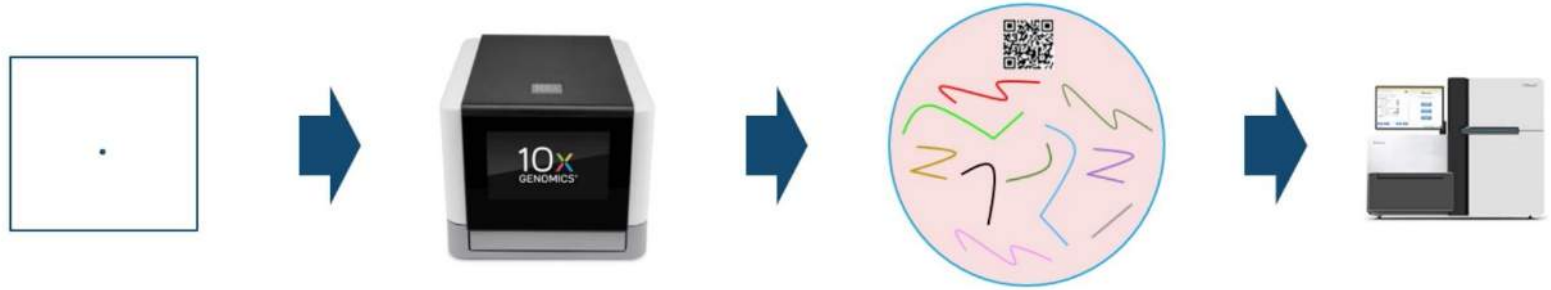
Phased sequencing (10x Genomics)

Standard sequence

hap 1 (mother allele)

hap 2 (father allele)



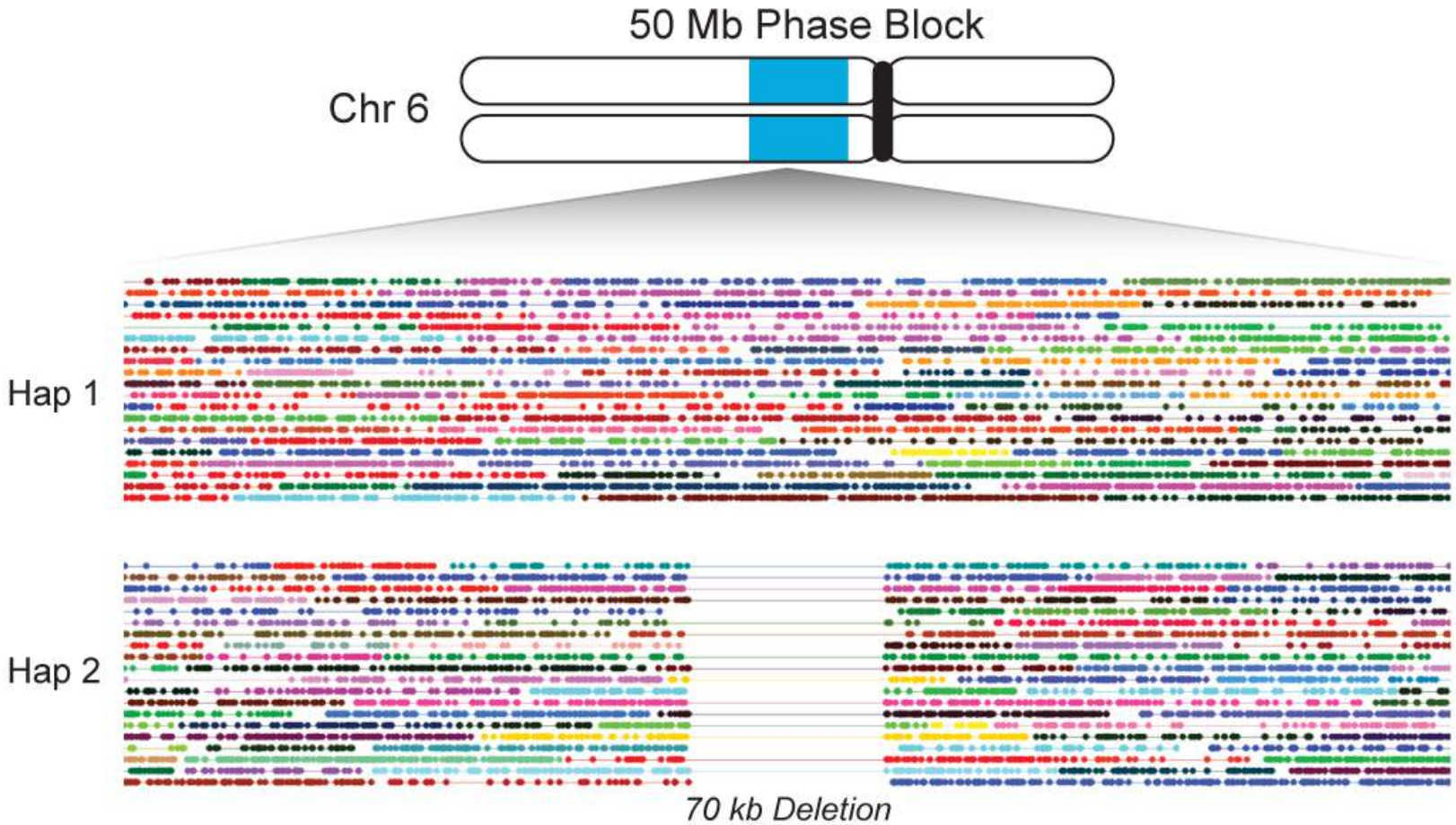


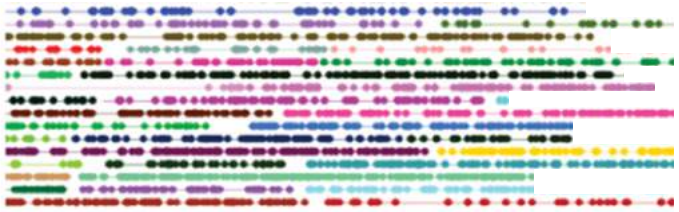
1 ng long DNA

one easy library

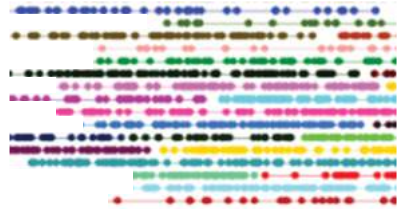
10^6 droplets
10 molecules

HiSeq X



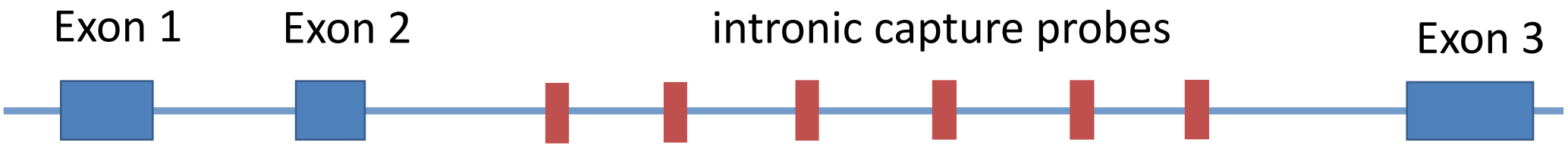


….≠……



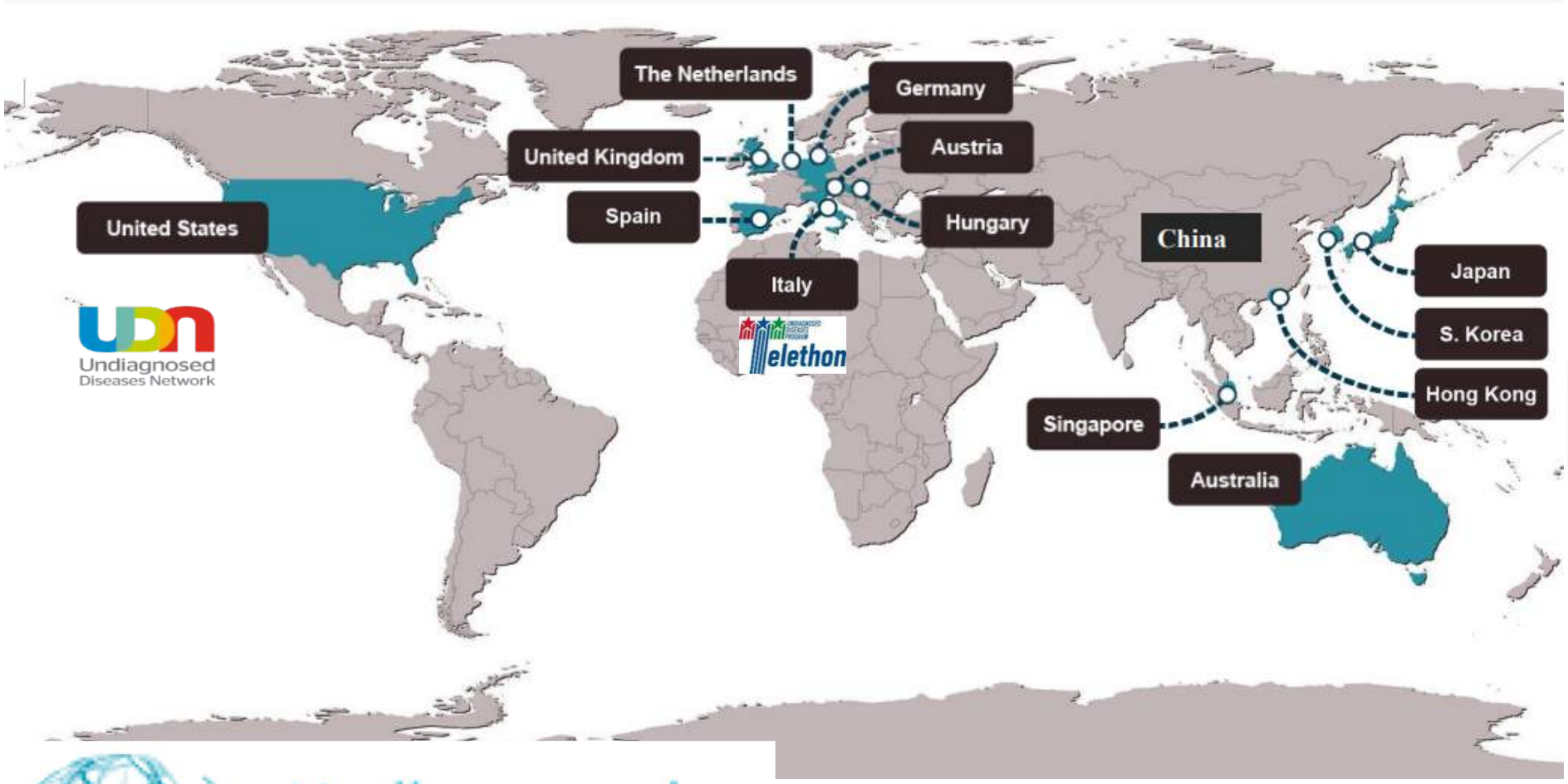
no connection

no phase information



ultra-exome= capture of polymorphic sequences within long introns (>30kb)

The Undiagnosed Diseases Network International (UDNI)

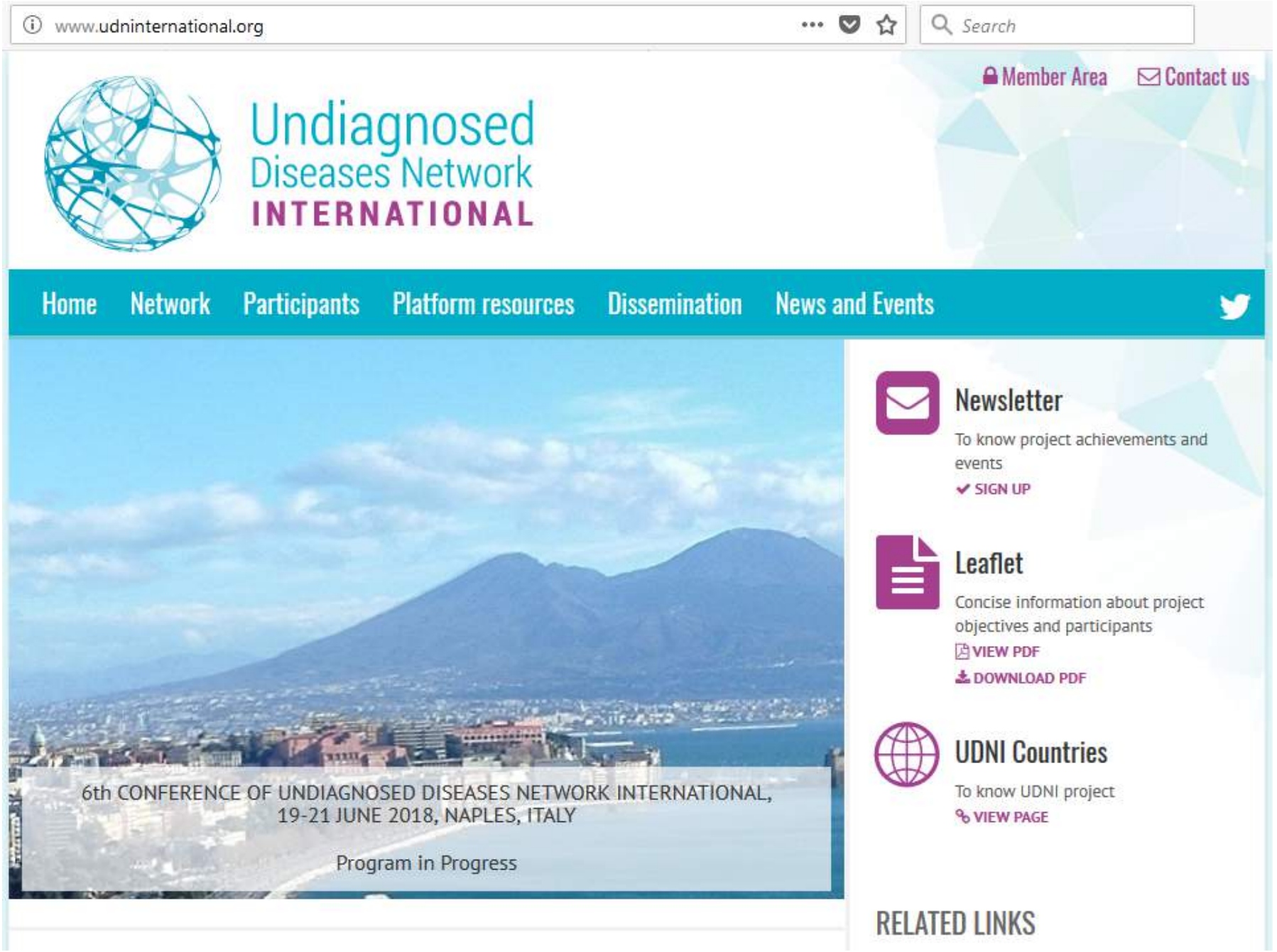


IRUD

2017 entries:
- Sweden
- South Africa

Undiagnosed Diseases Network INTERNATIONAL

UDNI
2018 Meeting
Naples
19-21 June



TELETHON INSTITUTE OF GENETICS AND MEDICINE
igem