ADULT-ONSET NEUROLOGICAL DISORDERS

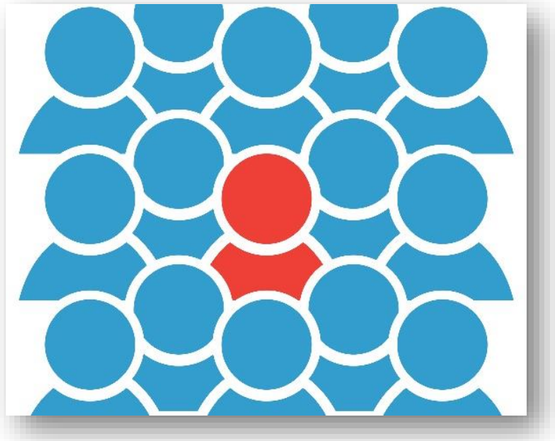
Bart DERMAUT

I. INTRODUCTION: RARE (NEUROLOGICAL) DISORDERS

II. UD-PROZA

III. NEUROGENETICS DIAGNOSTICS

rare diseases



- Rare disease: < 1:2000 (EU), <1:1250 (US)
- Rare diseases = frequent: globally, **3.5-5.6%** have a rare disease
- 80% genetic
  - >6000 rare diseases
  - **> 1400 monogenic brain diseases**
  - 50% unexplained

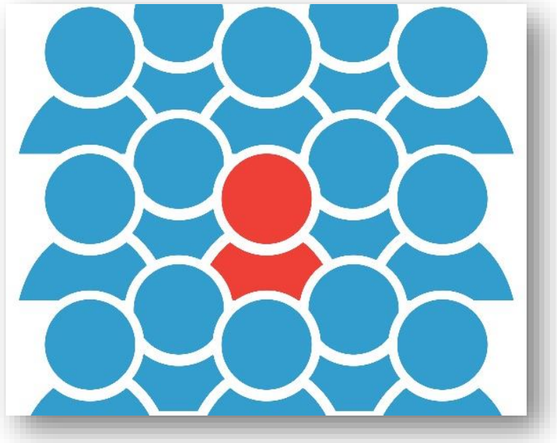
precision medicine

- individual patient characteristics (genetics, biomarkers, imaging, ...)

↓

- Psychosocial consequences for patient and family
- Treatment and prevention tailored to the individual patient (~20%)

rare diseases



Belgium: around 660,000 to 880,000 cases

Europe: about 27 to 36 million cases

Worldwide: about 350 million cases

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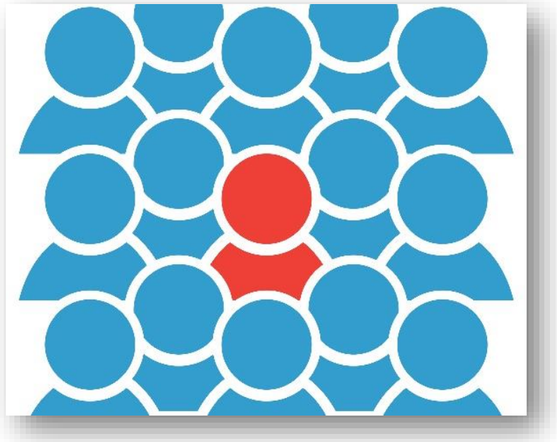

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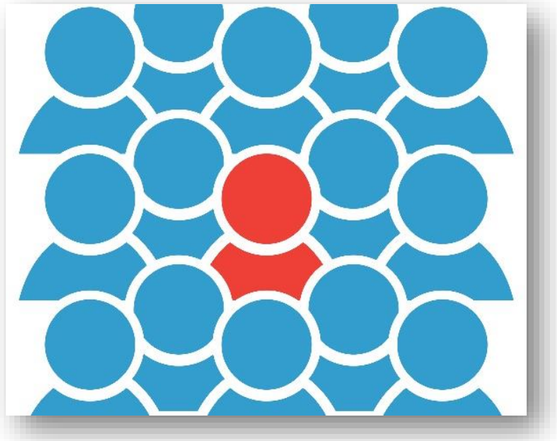
international networks

- IRDiRC
- Matchmaker Exchange
- ERNs (ERN-RND)
- SolveRD, UDNI

NGS

- Diagnostic yield NGS: 3-70 %
- Cost-efficient in pediatric cohorts
- Multiple pathogenic variants in 1 patient
- Missing heritability (WGS, epigenomics)

rare diseases



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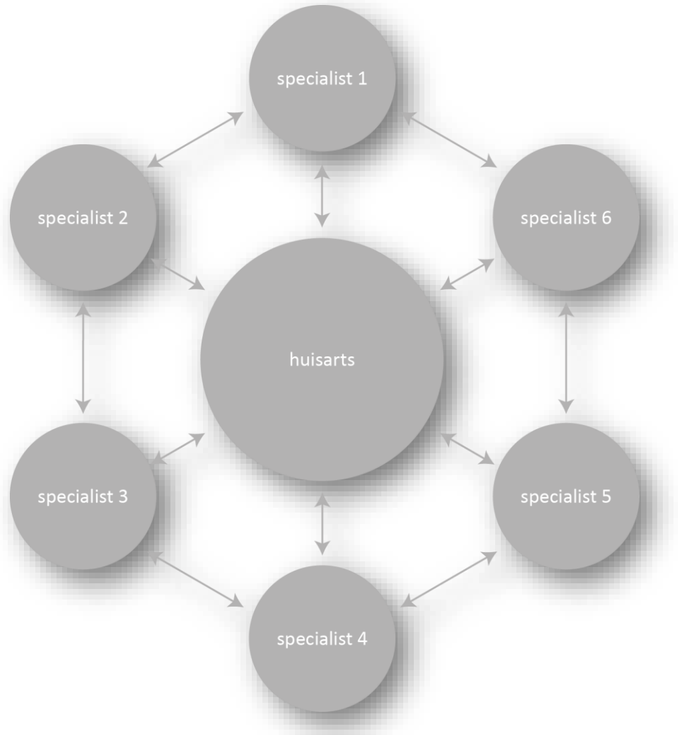
diagnostics difficult



- Diagnostic Odyssey
- In numbers:
- 44% are misdiagnosed
- 75% receive wrong treatment
- 22% consulted >5 doctors
- 7% consulted >10 doctors

II. UD-PROZA

PrOZA

2015: Programma voor Ongediagnosticeerde Zeldzame Aandoeningen (**PrOZA**); Eng. **UD-Proza**

Bruce Poppe, Dimitri Hemelsoet, Steven Callens, **Wim Terryn**

Multidisciplinary: genetics, neurology, general internal medicine, infectiology

De Morgen
vrijdag 22/05/2015
SND World's Best Designed Newspaper
www.demorgen.be

Na eerste titel is alles mogelijk voor Gantoise, zegt Hans Vandeweghe

'DE GENTSE VOETBALBEER IS LOS'

Geen diagnose?

Team van topdokters schiet collega's te hulp

'Bewapen rebellen om IS te stoppen'

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UD-PrOZA

2015: Programma voor Ongediagnosticeerde Zeldzame Aandoeningen (**PrOZA; Eng. UD-PrOZA**)

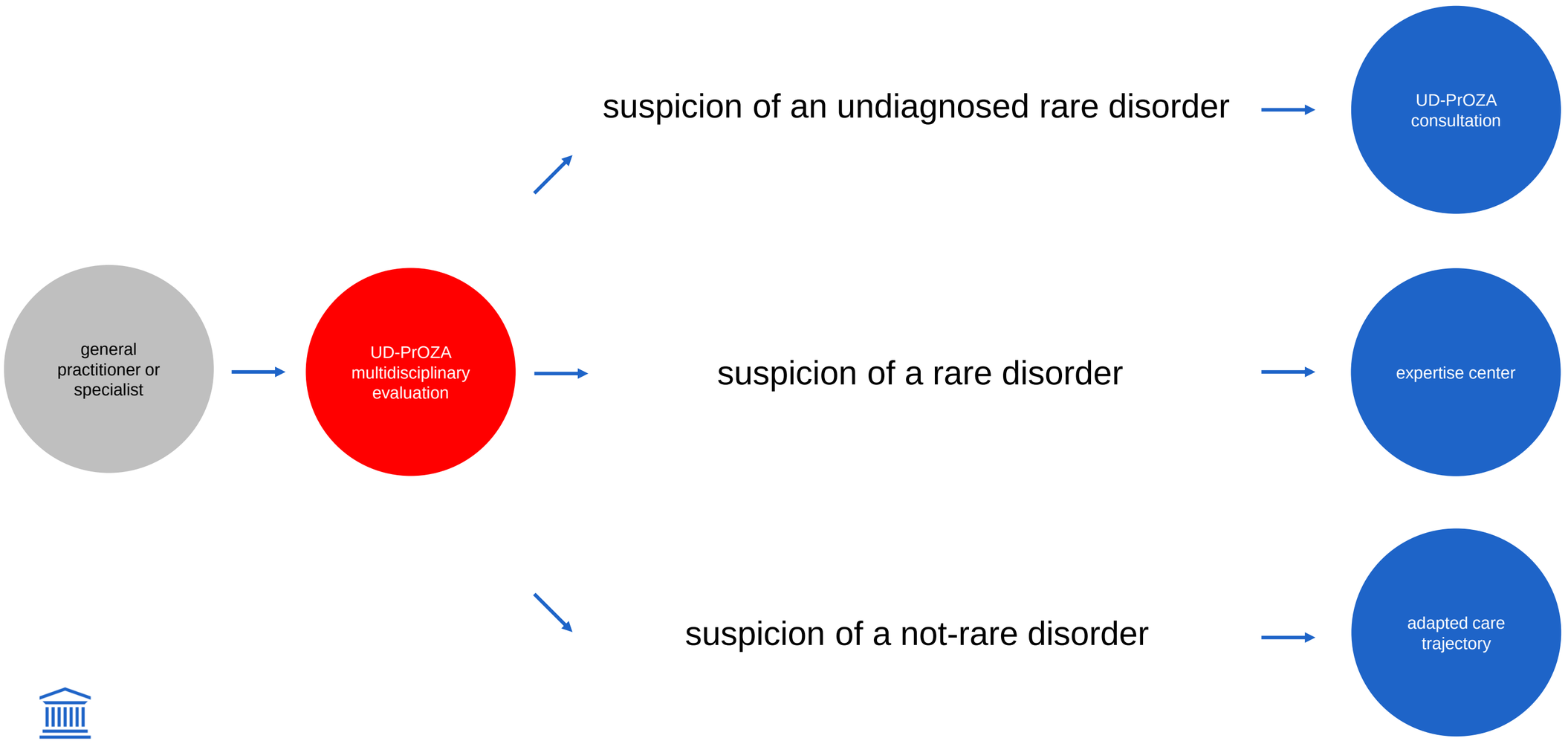
Bruce Poppe, Dimitri Hemelsoet, Steven Callens, Wim Terryn, Bart Dermaut

Nika Schuermans, Sanne Steyaert, Filomeen Haerynck, Patrick Verloo, Arnaud Vanlander

Multidisciplinary: **genetics, neurology, general internal medicine, infectiology, pediatrics, immunology**

Internationally connected: Solve-RD, ERDERA

the UD-PrOZA algorithm



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UD-PrOZA: results July 2015 – June 2020

Schuermans *et al.*
Orphanet Journal of Rare Diseases (2022) 17:210
https://doi.org/10.1186/s13023-022-02365-y

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Shortcutting the diagnostic odyssey: the multidisciplinary Program for Undiagnosed Rare Diseases in adults (UD-PrOZA)

Nika Schuermans[1,2*†], Dimitri Hemelsoet[3†], Wim Terryn[4], Sanne Steyaert[5], Rudy Van Coster[6], Paul J. Coucke[1,2], Wouter Steyaert[7], Bert Callewaert[1,2], Elke Bogaert[1,2], Patrick Verloo[6], Arnaud V. Vanlander[6], Elke Debackere[1,2], Jody Ghijsels[1,2], Pontus LeBlanc[1,2], Hannah Verdin[1,2], Leslie Naesens[8,9], Filomeen Haerynck[8], Steven Callens[5], Bart Dermaut[1,2†], Bruce Poppe[1,2†]for UD-PrOZA

Nika

Dimitri

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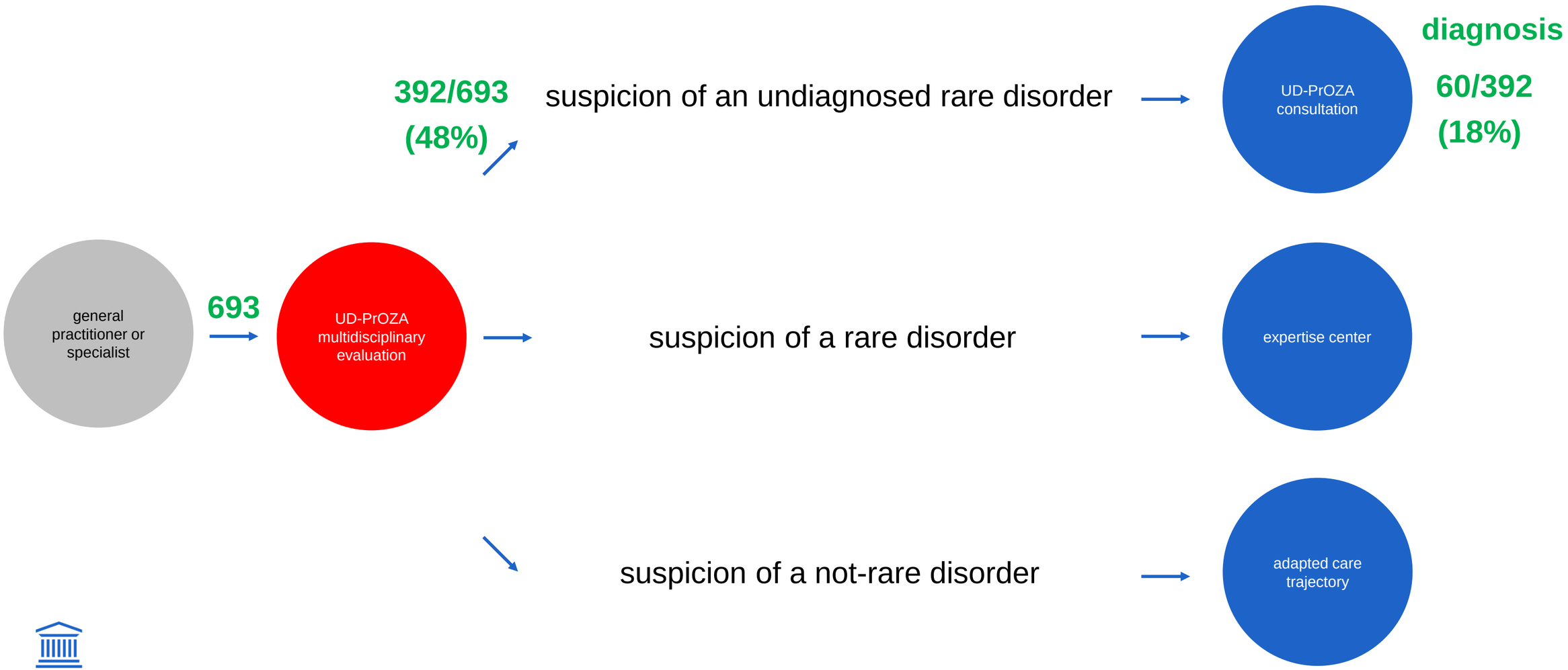

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UD-PrOZA: results July 2015 – June 2020

Table 1 Patient information of all referrals, of the accepted referrals and of the patients that have been diagnosed by UD-PrOZA

	All referrals (n = 692)	Accepted referrals (n = 329)	Diagnosed patients (n = 60)
Mean age (years ± SD)	42 ± 16	40.5 ± 16	39 ± 14
Sex (%)			
Male	277 (41)	144 (44)	30 (50)
Female	400 (59)	183 (56)	30 (50)
Referred by (%)			
General practitioner	292 (46)	67 (21)	7 (12)
Specialist	348 (54)	249 (79)	51 (88)
Complaint (%)			
Objectifiable	386 (60)	285 (87)	60 (100)
Not objectifiable	259 (40)	44 (13)	0 (0)

average diagnostic odyssey: 19 years!

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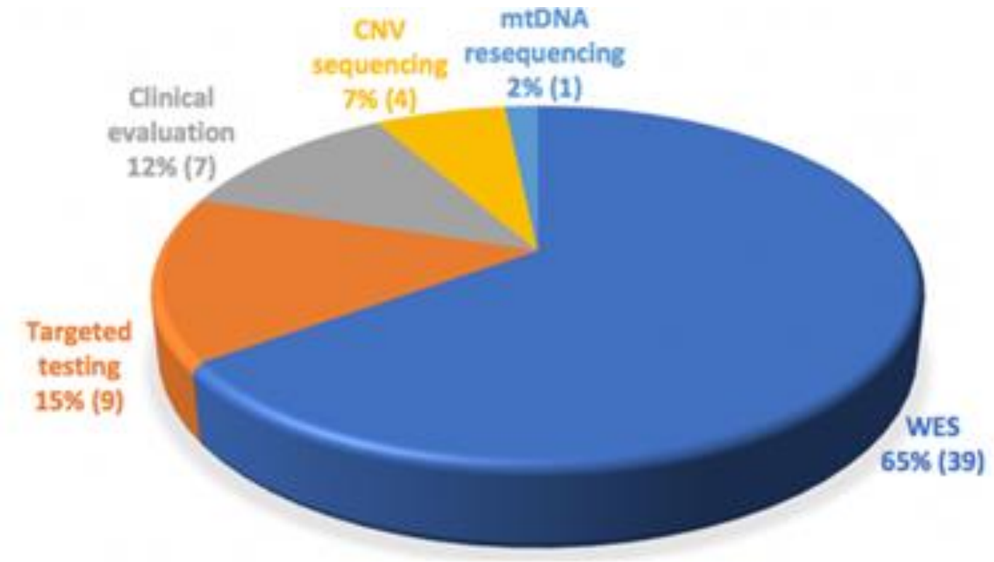
UD-PrOZA: results July 2015 – June 2020

60 diagnoses

53 genetic Dx (88%)

7 clinical Dx (12%)



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94% >18j

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Primary symptoms (%)			
Neurologic	270 (42)	177 (54)	35 (58)
Immunologic/infectious	133 (21)	63 (19)	8 (14)
Musculoskeletal	107 (17)	20 (6)	2 (3)
Rheumatologic	25 (4)	15 (5)	0 (0)
Cardiac/vascular	19 (3)	13 (4)	2 (3)
Gastrointestinal	18 (3)	5 (2)	1 (2)
Other	74 (11)	36 (11)	12 (20)

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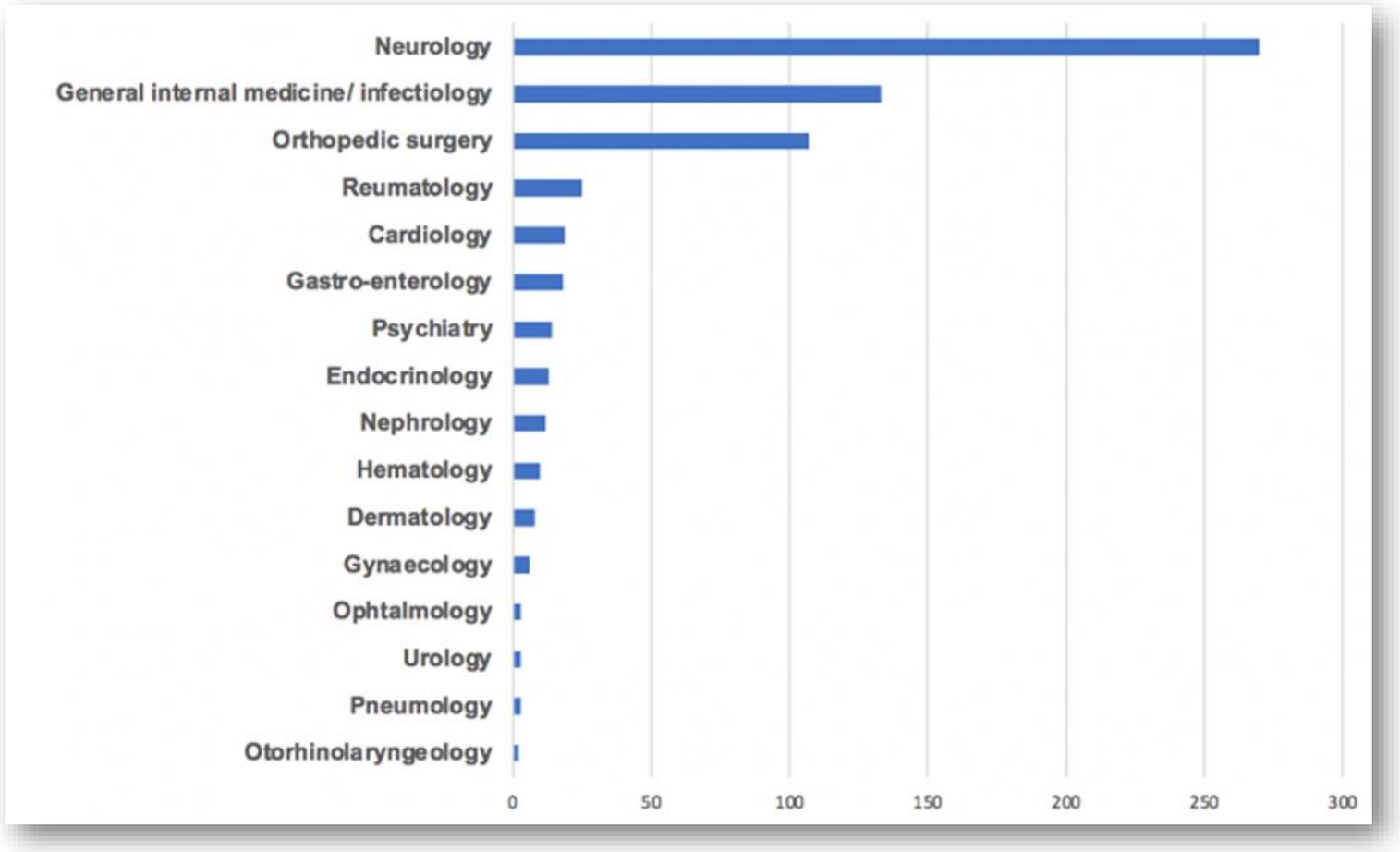

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UD-PrOZA: results July 2015 – June 2020

7 clinical diagnoses

ID	Sex	Phenotype/Medical history	Additional testing	Diagnosis
54	M	Aortic valve stenosis, third-degree atrioventricular block, neurosensorial deafness, axonal polyneuropathy, episodic vertigo, multinodular goiter	Ophthalmological examination: salt and pepper pigmentary retinopathy, lens opacities	**Congenital rubella syndrome**
55	M	Syrian origin, developmental delay, severe intellectual disability, small stature, facial dysmorphism	Blood analysis: TSH, FT3, FT4, conventional karyotyping: trisomy 21	**Congenital hypothyroidism secondary to trisomy 21**
56	F	Fever, skin rash, polyarthritis, myalgia, pharyngitis, pericarditis, pleuritis, splenomegaly, elevated ESR, CRP and serum ferritin, granulocytosis	Blood analysis: neutrophils, ferritin, CRP	**Adult Still's disease**
57	M	Dyspnea, cough, wheezing, allergic rhinitis, eczema, erythroderma, axonal peripheral polyneuropathy, eosinophilia (58% lab test 2016)	46XY; FIP1L1-PDGFRA fusion absent	**Primary hypereosinophilic syndrome**
58	M	Arthritis, myalgia, urticaria, anemia, abdominal pain, nausea, vomiting, scleritis	Blood analysis: C1q, C1q auto antibodies	**McDuffie syndrome (hypocomplementemic urticarial vasculitis)**
59	M	Progressive muscle weakness and atrophy right hand (predominantly affecting C8-T1 musculature), absence of sensory deficits	MRI cervical spine, mtDNA sequencing/WES negative	**Hirayama disease (monomelic amyotrophy)**
60	F	Diffuse musculoskeletal pain, episodic fever, urticarial skin rash, and malabsorption after bariatric surgery	Hereditary fever gene panel analysis negative, favorable response to corticoid and antibiotic treatment	**BADAS (Bowel Associated Dermatosis Arthritis Syndrome)/ Blind loop syndrome**

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‘Actionable secondary findings’ in **7%** of the exomes

Secondary finding	OMIM phenotype (MIM number)
PALB2 c.2834+1G>T	Breast cancer, susceptibility to, AD (114480)
LDLR p.Gly343Cys	Hypercholesterolemia, familial, 1, AD/AR (143890)
BRCA1 p.Glu733ThrfsTer5	Breast cancer, susceptibility to, AD (114480)
MUTYH p.Tyr152Cys	Adenomas, multiple colorectal, AR (608456)
BRCA2 p.His2090GlnfsTer9	Breast cancer, susceptibility to, AD (114480)
CHEK2 c.444+1G>A	Breast cancer, susceptibility to, AD (114480)
CHEK2 c.1100del	Breast cancer, susceptibility to, AD (114480)
MYBPC3 p.Gly235SerfsTer74	Left ventricular noncompaction 10, AD (615396) Cardiomyopathy, hypertrophic, 4, AD/AR (115197)
HOXB13 p.Gly84Glu	Prostate cancer, hereditary, 9 (610997)
ATM p.Glu522IlefsTer43	Breast cancer, susceptibility to, AD (114480) Ataxia-telangiectasia, AR (208900)
HOXB13 p.Gly84Glu	Prostate cancer, hereditary, 9 (610997)
ATM p.Asp841IlefsTer6	Breast cancer, susceptibility to, AD (114480) Ataxia-telangiectasia, AR (208900)

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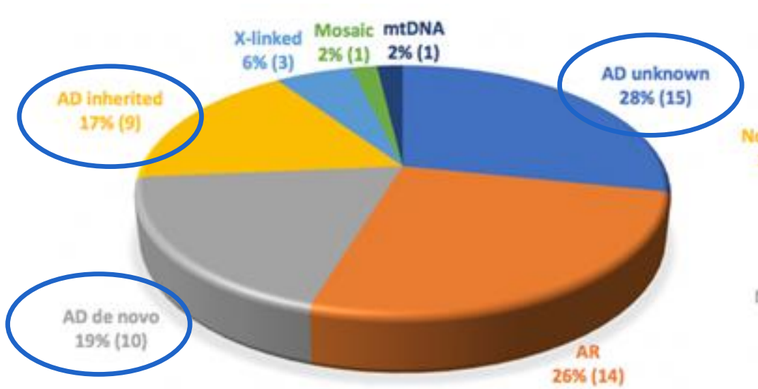

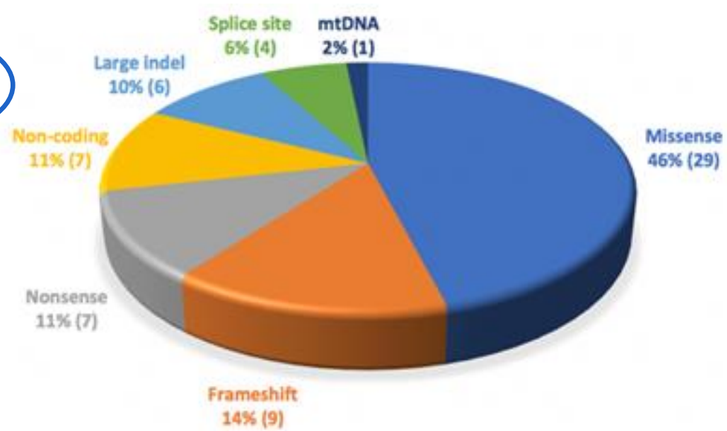

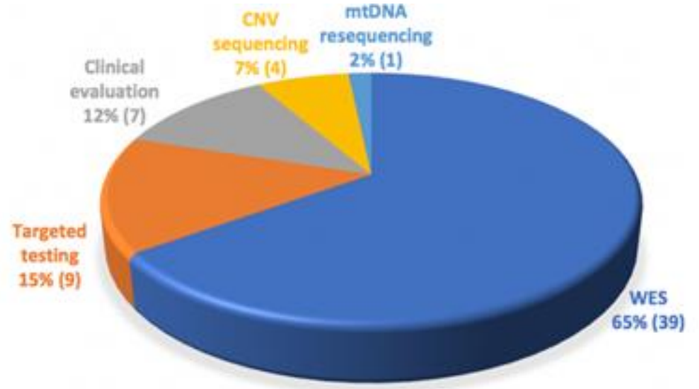

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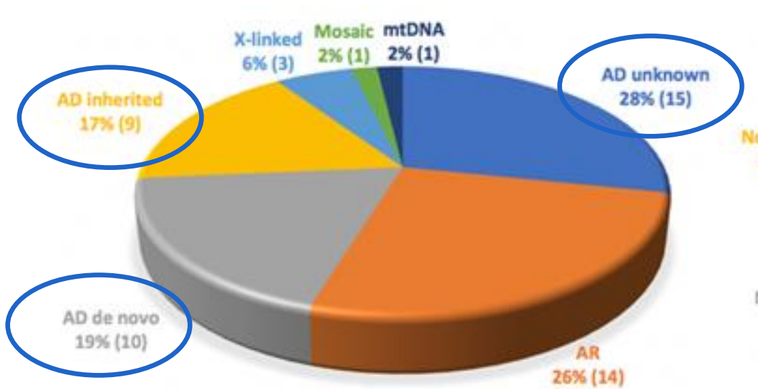

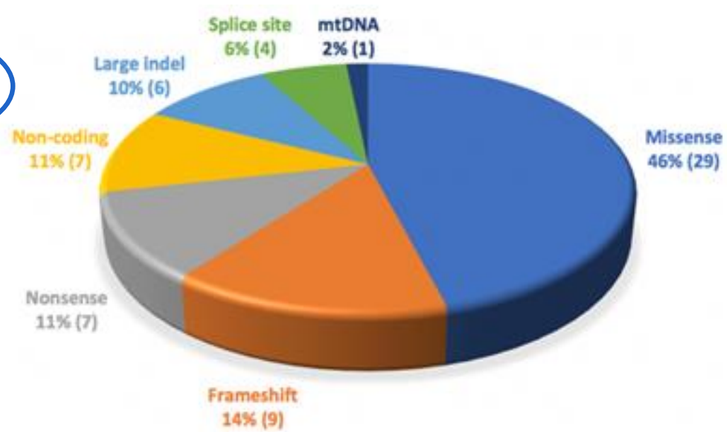

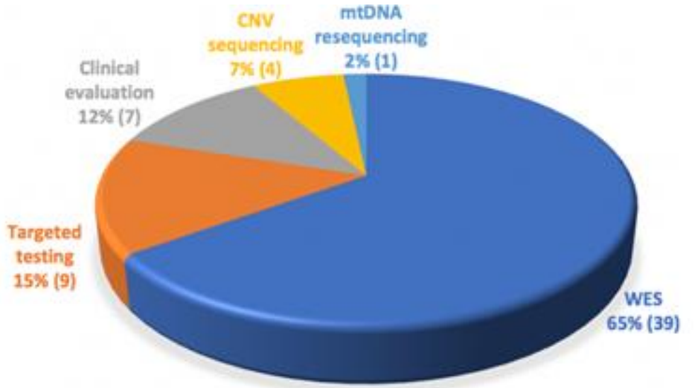

! 56% **negative family history**

! Time between first symptoms and Dx **19 years (1-52 years)**

! 3 patients with **>1 rare disease** (*TP53+NF1* / *PKD1+COL4A1* / *PKD1+TTN*)

! **Therapeutic implications** for 7 patients

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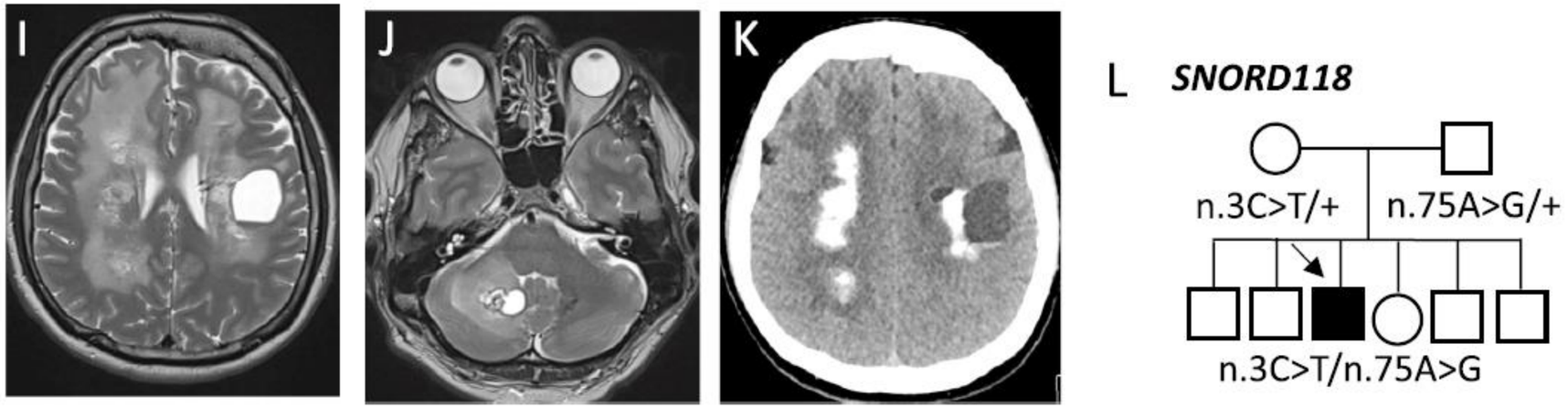
7/60 (12%) diagnoses with therapeutic implications

Example 1



ID	Sex	Patient phenotype	Onset	Delay (y)	Family History	Tool	Gene(s)	RefSeq	Variant(s)	ACMG criteria	Segregation	OMIM phenotype	Prevalence (Orphanet)
4	M	Hypokinetic dysarthria, brain cysts and calcifications	Adulthood	6	No	Targeted testing	***SNORD118***	NR_033294.1	n.3C>T; n.75A>G	PM2, PM3, PP4, PP5 PM2, PM3, PP4, PP5	Compound heterozygous	Leukoencephalopathy, brain calcifications, and cysts; autosomal recessive (614561)	<1/1.000.000

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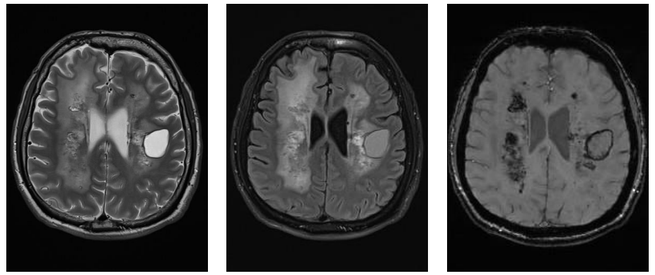
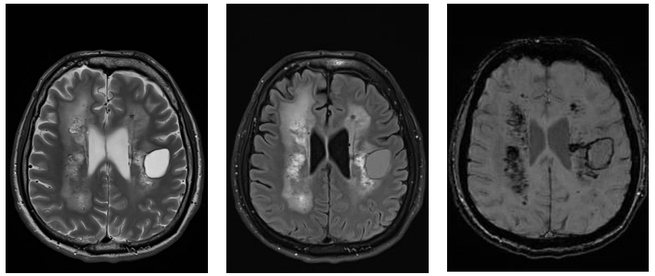
Example 1

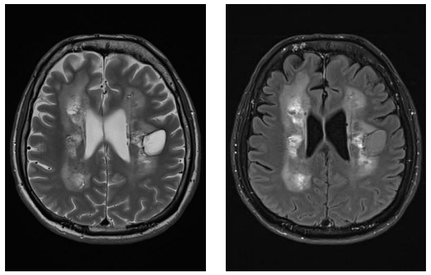
6m



12m



6m following stop



***SNORD118* patient - anti-VEGF treatment with bevacizumab: reduction of the cyst**

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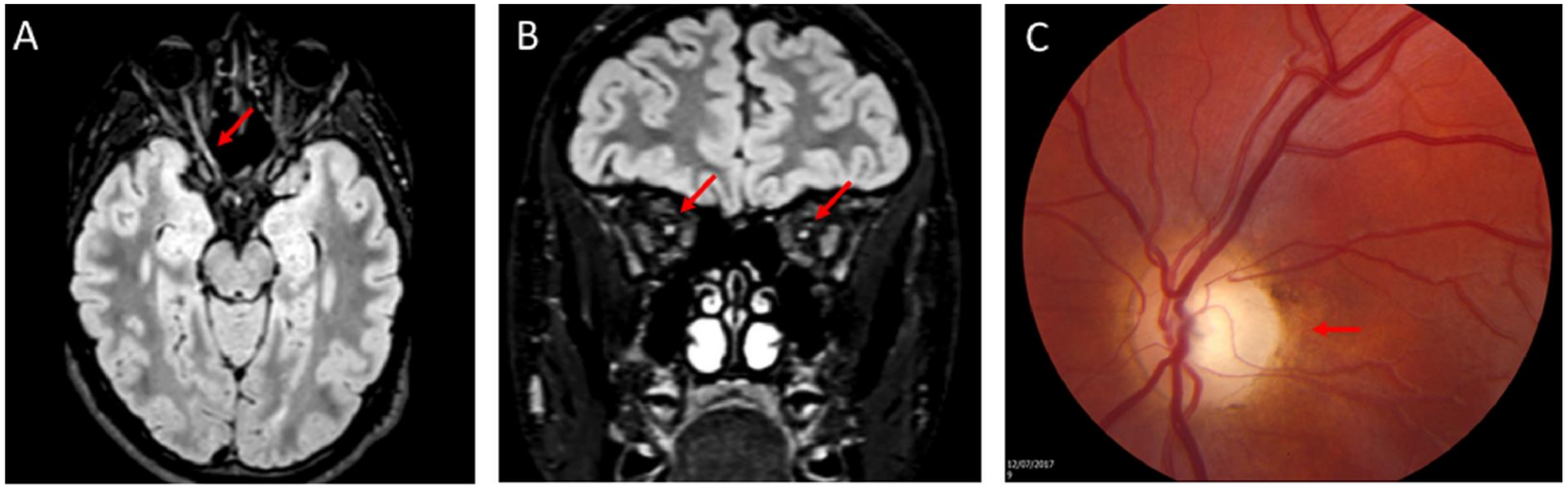
7/60 (12%) diagnoses with therapeutic implications

Example 2



ID	Sex	Patient phenotype	Onset	Delay (y)	Family History	Tool	Gene(s)	RefSeq	Variant(s)	ACMG criteria	Segregation	OMIM phenotype	Prevalence (Orphanet)
10	M	Motor delay, autism, bilateral optic neuritis	Childhood	15	Yes	WES singleton	***BTD***	NM_001281723.1	c.106G>A, p.Gly36Ser[(a)]; c.1273T>C, p.Cys425Arg[(a)]	PM1, PM2, PP2, BP4, PM3, PP4 PM1, PM2, PM5, PP2, PP3, PP4	Compound heterozygous	Biotidinase deficiency; autosomal recessive (253260)	1-9/100.000

Treatment with biotin supplements: improvement of vision and motor function!

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Van Iseghem et al, 2019

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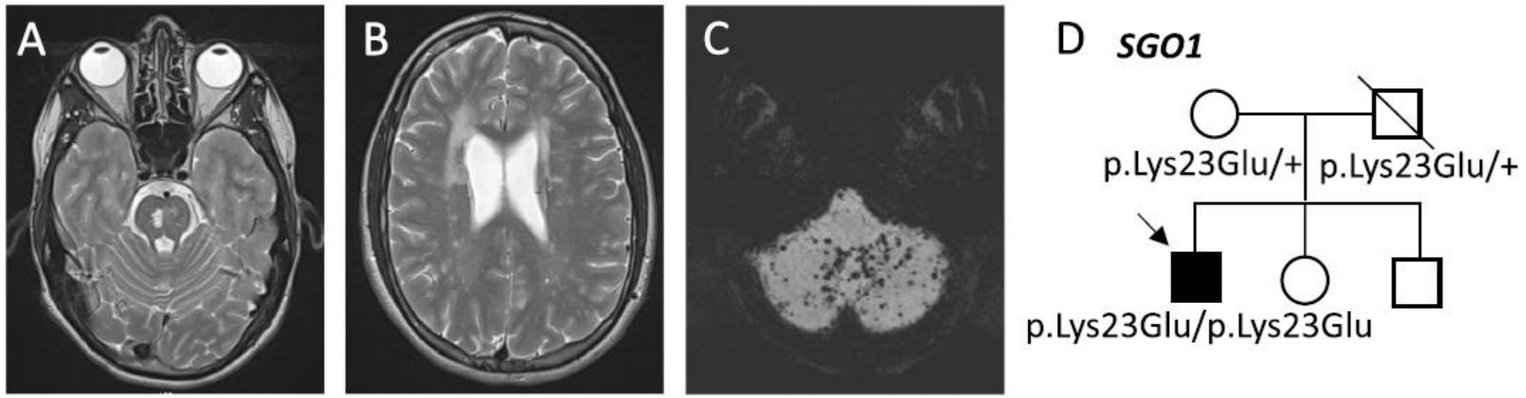
4/60 (4%) diagnoses with expansion of the phenotype

Example



ID	Sex	Patient phenotype	Onset	Delay (y)	Family History	Tool	Gene(s)	RefSeq	Variant(s)	ACMG criteria	Segregation	OMIM phenotype	Prevalence (Orphanet)
8	M	Intracerebral hemorrhages, paralytic ileus, skin lesions	Neonatal	19	No	WES singleton	*SGO1*	NM_001012413.3	c.67A>G, p.Lys23Glu	PP1, PP3, PP4, PP5, PM1	Homozygous	Chronic atrial and intestinal dysrhythmia; autosomal recessive (616201)	<1/1.000.000

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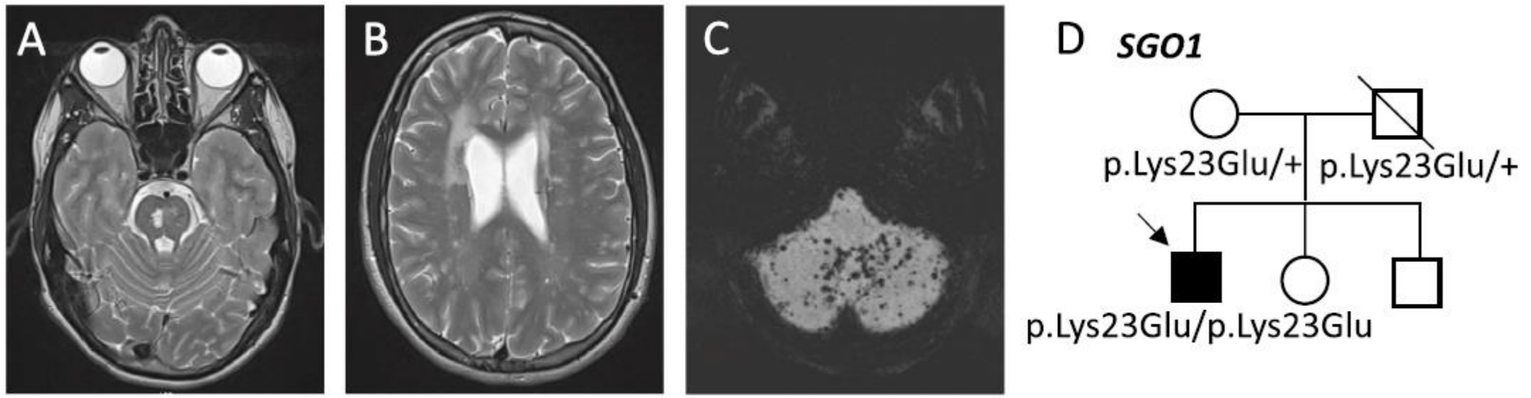

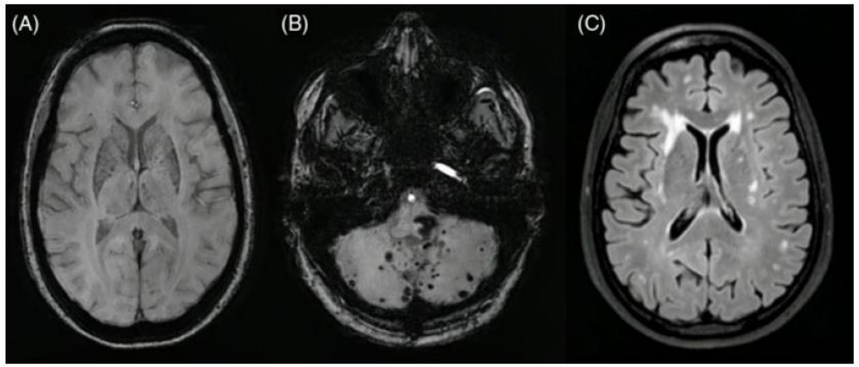

Nehme et al, 2020

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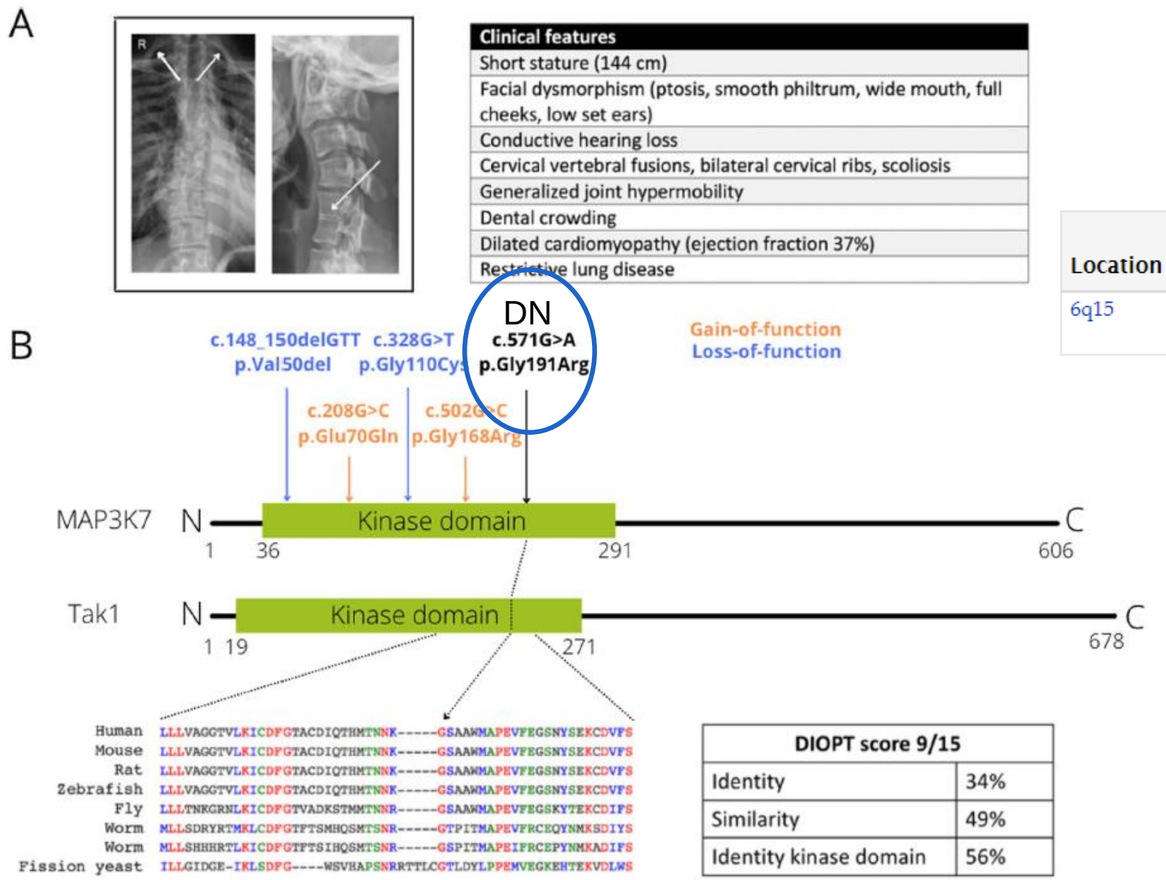
Fast variant modeling in *Drosophila*

Example



Clinical features
Short stature (144 cm)
Facial dysmorphism (ptosis, smooth philtrum, wide mouth, full cheeks, low set ears)
Conductive hearing loss
Cervical vertebral fusions, bilateral cervical ribs, scoliosis
Generalized joint hypermobility
Dental crowding
Dilated cardiomyopathy (ejection fraction 37%)
Restrictive lung disease

Location	Phenotype (View Clinical Synopses)	Phenotype MIM number	Inheritance
6q15	Cardiospondylocarpofacial syndrome LoF	157800	AD
	Frontometaphyseal dysplasia 2 GoF	617137	AD

DIOPT score 9/15	
Identity	34%
Similarity	49%
Identity kinase domain	56%

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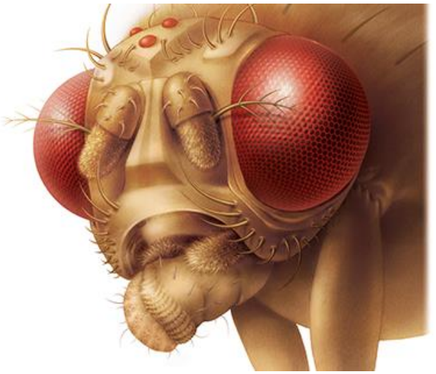

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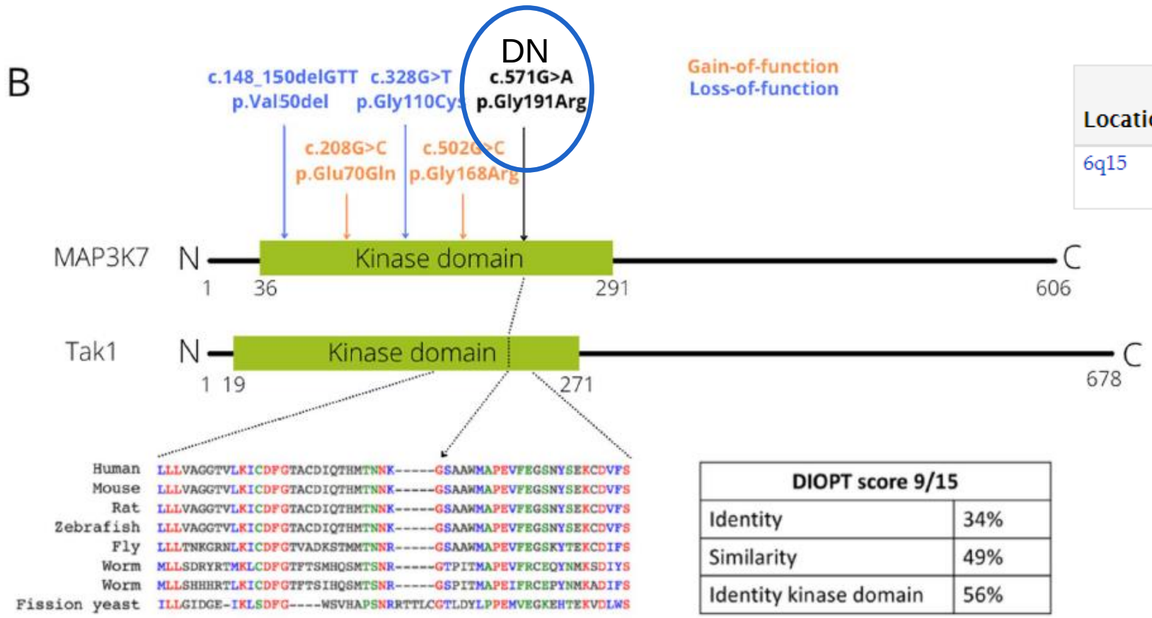

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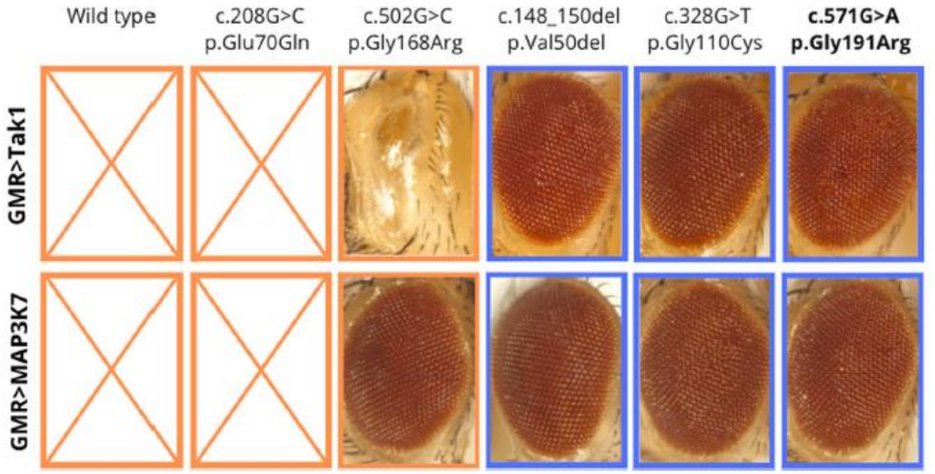

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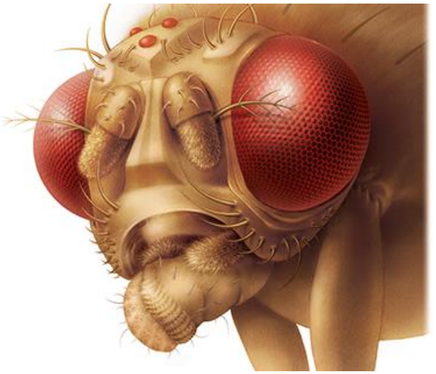
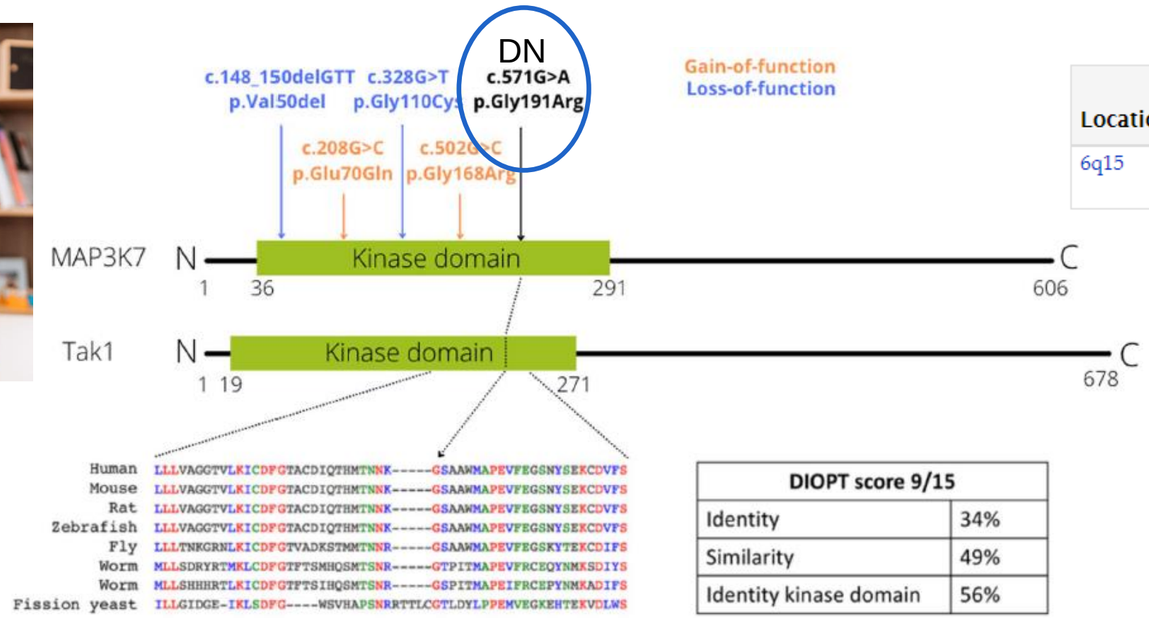
UD-PrOZA: results July 2015 – June 2020

Fast variant modeling in *Drosophila*

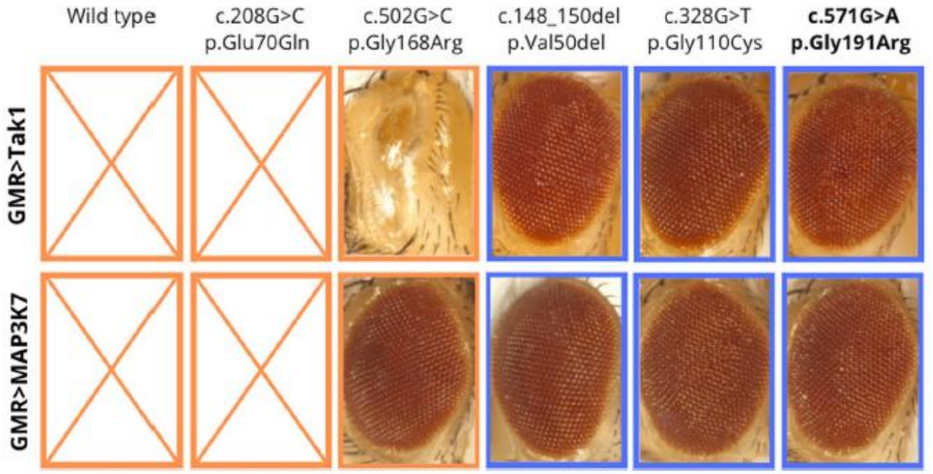


Dr. Elke Bogaert



DIOPT score 9/15	
Identity	34%
Similarity	49%
Identity kinase domain	56%

Location	Phenotype (View Clinical Synopses)	Phenotype MIM number	Inheritance
6q15	Cardiospondylocarpofacial syndrome LoF	157800	AD
	Frontometaphyseal dysplasia 2 GoF	617137	AD



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UD-PrOZA: results July 2015 – June 2020

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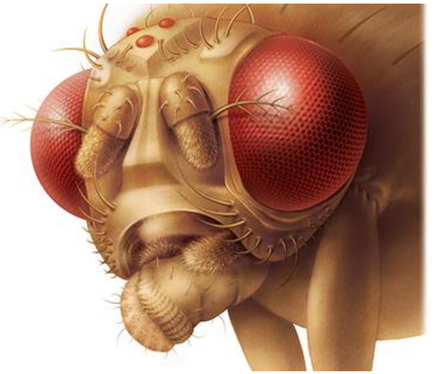

Dr. Elke Bogaert

ARTICLE

SRSF1 haploinsufficiency is responsible for a syndromic developmental disorder associated with intellectual disability

Elke Bogaert,[1,2,46] Aurore Garde,[3,4,46] Thierry Gautier,[5,46] Kathleen Rooney,[6,7,46] Yannis Duffourd,[3,8] Pontus LeBlanc,[1,2] Emma van Reempts,[1,2] Frederic Tran Mau-Them,[3,8] Ingrid M. Wentzensen,[9] Kit Sing Au,[10,11] Kate Richardson,[10,11] Hope Northrup,[10,11] Vincent Gatinois,[12] David Geneviève,[13,14] Raymond J. Louie,[15] Michael J. Lyons,[15] Lone Walentin Laulund,[16] Charlotte Brasch-Andersen,[17,18] Trine Maxel Juul,[17] Fatima El It,[3] Nathalie Marle,[19] Patrick Callier,[3,19] Raissa Relator,[7] Sadegheh Haghshenas,[7] Haley McConkey,[6,7] Jennifer Kerkhof,[7] Claudia Cesario,[20] Antonio Novelli,[20]

(Author list continued on next page)

Bogaert et al., 2023, The American Journal of Human Genetics *110*, 790–808
May 4, 2023 © **2023 The Authors.**
https://doi.org/10.1016/j.ajhg.2023.03.016

SolveRD
Solving the Unsolved Rare Diseases

UNIVERSITEIT GENT

Schuermans, Hemelsoet et al, 2022

UD-PrOZA: results July 2015 – June 2020

3 novel monogenic disease genes

1.

The American Journal of Human Genetics *103*, 245–260, August 2, 2018 **245**

ARTICLE

IRF2BPL Is Associated with Neurological Phenotypes

Paul C. Marcogliese,[1,25] Vandana Shashi,[2,25] Rebecca C. Spillmann,[2] Nicholas Stong,[3] Jill A. Rosenfeld,[1] Mary Kay Koenig,[4] Julián A. Martínez-Agosto,[5,6,7] Matthew Herzog,[5] Agnes H. Chen,[8] Patricia I. Dickson,[8] Henry J. Lin,[8] Moin U. Vera,[8] Noriko Salamon,[9] John M. Graham, Jr.,[6] Damara Ortiz,[10] Elena Infante,[10] Wouter Steyaert,[11] Bart Dermaut,[11] Bruce Poppe,[11] Hyung-Lok Chung,[1] Zhongyuan Zuo,[1] Pei-Tseng Lee,[1] Oguz Kanca,[1] Fan Xia,[1] Yaping Yang,[1] Edward C. Smith,[12] Joan Jasien,[12] Sujay Kansagra,[12] Gail Spiridigliozzi,[13] Mays El-Dairi,[14] Robert Lark,[15] Kacie Riley,[2] Dwight D. Koeberl,[2] Katie Golden-Grant,[16] Program for Undiagnosed Diseases (UD-PrOZA), Undiagnosed Diseases Network, Shinya Yamamoto,[1,17,18,19] Michael F. Wangler,[1,17,18] Ghayda Mirzaa,[20,21] Dimitri Hemelsoet,[22] Brendan Lee,[1] Stanley F. Nelson,[5] David B. Goldstein,[3] Hugo J. Bellen,[1,17,18,19,23,*] and Loren D.M. Pena[2,24,*]

Interferon regulatory factor 2 binding protein-like (*IRF2BPL*) encodes a member of the IRF2BP family of transcriptional regulators. Currently the biological function of this gene is obscure, and the gene has not been associated with a Mendelian disease. Here we describe seven individuals who carry damaging heterozygous variants in *IRF2BPL* and are affected with neurological symptoms. Five individuals who carry *IRF2BPL* nonsense variants resulting in a premature stop codon display severe neurodevelopmental regression, hypotonia, progressive ataxia, seizures, and a lack of coordination. Two additional individuals, both with missense variants, display global developmental delay and seizures and a relatively milder phenotype than those with nonsense alleles. The *IRF2BPL* bioinformatics signature based on population genomics is consistent with a gene that is intolerant to variation. We show that the fruit-fly *IRF2BPL* ortholog, called *pits* (protein interacting with Ttk69 and Sin3A), is broadly detected, including in the nervous system. Complete loss of *pits* is lethal early in development, whereas partial knockdown with RNA interference in neurons leads to neurodegeneration, revealing a requirement for this gene in proper neuronal function and maintenance. The identified *IRF2BPL* nonsense variants behave as severe loss-of-function alleles in this model organism, and ectopic expression of the missense variants leads to a range of phenotypes. Taken together, our results show that *IRF2BPL* and *pits* are required in the nervous system in humans and flies, and their loss leads to a range of neurological phenotypes in both species.

2.

nature genetics

Article

https://doi.org/10.1038/s41588-023-01535-3

Loss of phospholipase PLAAT3 causes a mixed lipodystrophic and neurological syndrome due to impaired PPARγ signaling

Schuermans, El Chehadeh, Hemelsoet, Gautheron et al, 2023

Received: 22 December 2022

Accepted: 16 September 2023

Published online: 02 November 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Phospholipase A/acyltransferase 3 (PLAAT3) is a phospholipid-modifying enzyme predominantly expressed in neural and white adipose tissue (WAT). It is a potential drug target for metabolic syndrome, as *Plaat3* deficiency in mice protects against diet-induced obesity. We identified seven patients from four unrelated consanguineous families, with homozygous loss-of-function variants in *PLAAT3*, who presented with a lipodystrophy syndrome with loss of fat varying from partial to generalized and associated with metabolic complications, as well as variable neurological features including demyelinating neuropathy and intellectual disability. Multi-omics analysis of mouse *Plaat3*$^{-/-}$ and patient-derived WAT showed enrichment of arachidonic acid-containing membrane phospholipids and a strong decrease in the signaling of peroxisome proliferator-activated receptor gamma (PPARγ), the master regulator of adipocyte differentiation. Accordingly, CRISPR–Cas9-mediated *PLAAT3* inactivation in human adipose stem cells induced insulin resistance, altered adipocyte differentiation with decreased lipid droplet formation and reduced the expression of adipogenic and mature adipocyte markers, including PPARγ. These findings establish PLAAT3 deficiency as a hereditary lipodystrophy syndrome with neurological manifestations, caused by a PPARγ-dependent defect in WAT differentiation and function.

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3. *ACMSD*: A.R. metabole aandoening, in uitwerking

aminocarboxymuconate-semialdehyde-decarboxylase

UD-PrOZA: results July 2015 – June 2020

3 novel monogenic disease genes

1.

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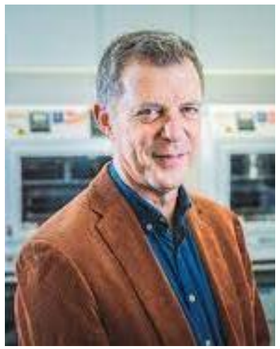
Zebrafish Facility Ghent CORE

Andy Willaert



Paul Coucke

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aminocarboxymuconate-semialdehyde-decarboxylase

UD-PrOZA: results July 2015 – June 2020

3 novel monogenic disease genes

	Name	Referred patients	Monocentric/ multicentric	Accepted patients*	% of patients < 18y	Diagnostic rate	Phenotypes	Reference
1.	Initiative on Rare and Undiagnosed Disease in Japan (IRUD)	5359	Multicentric	4205	*NA*	42.9%	Diverse	Takahashi et al. [15]
2.	Undiagnosed Disease Network (UDN)	1519	Multicentric	601	57%	35%	Diverse	Splinter et al. [14]
3.	Program for undiagnosed rare diseases (UD-PrOZA)	692	Monocentric	329	6.7%	18%	Diverse	*This study*
4.	Singapore Undiagnosed Disease Program	NA	Multicentric	196	90%	37.2%	Global developmental delay/ Congenital malformations	Bhatia et al. [16]
5.	The Korean undiagnosed diseases program (KUDP)	NA	Multicentric	72	94.8%	38.9%	Diverse	Kim et al. [17]
	SpainUDP	NA	Multicentric	30	74.1%	67%	Diverse	López-Martín et al. [18]
6.	The Italian Undiagnosed Rare Diseases Network (IURDN)	110	Multicentric	13	31% (92% onset < 18y)	53.8%	Diverse	Salvatore et al. [19]
7.	Undiagnosed Diseases Program – Western Australia (UDP-WA)	NA	Multicentric	NA	NA	NA	NA	Baynam et al. [46]
8.	National Network to Collaborate on Diagnosis and Treatment of Rare Diseases China	NA	Multicentric	NA	NA	NA	NA	Ren et al. [47]

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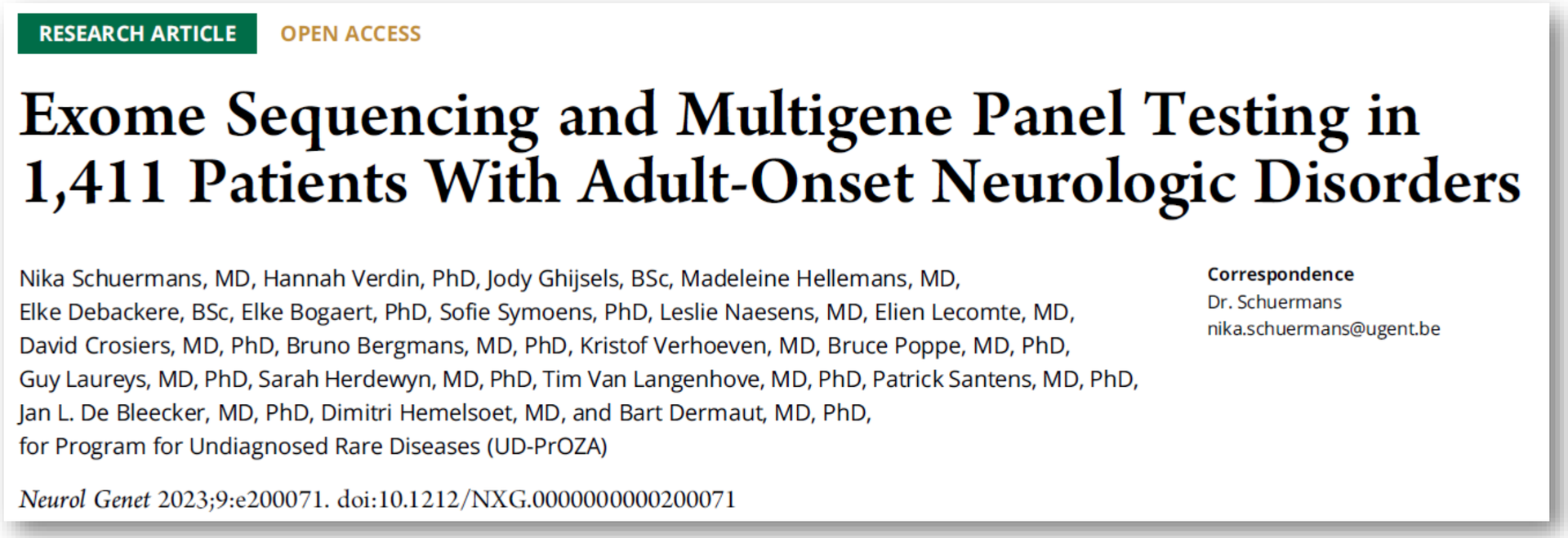
III. NEUROGENETICS DIAGNOSTICS

Neurogenetics diagnostics: results January 2019 – April 2022



RESEARCH ARTICLE OPEN ACCESS

Exome Sequencing and Multigene Panel Testing in 1,411 Patients With Adult-Onset Neurologic Disorders

Nika Schuermans, MD, Hannah Verdin, PhD, Jody Ghijsels, BSc, Madeleine Hellemans, MD, Elke Debackere, BSc, Elke Bogaert, PhD, Sofie Symoens, PhD, Leslie Naesens, MD, Elien Lecomte, MD, David Crosiers, MD, PhD, Bruno Bergmans, MD, PhD, Kristof Verhoeven, MD, Bruce Poppe, MD, PhD, Guy Laureys, MD, PhD, Sarah Herdewyn, MD, PhD, Tim Van Langenhove, MD, PhD, Patrick Santens, MD, PhD, Jan L. De Bleecker, MD, PhD, Dimitri Hemelsoet, MD, and Bart Dermaut, MD, PhD, for Program for Undiagnosed Rare Diseases (UD-PrOZA)

Correspondence
Dr. Schuermans
nika.schuermans@ugent.be

Neurol Genet 2023;9:e200071. doi:10.1212/NXG.0000000000200071

retrospective study: evaluation of all patients for whom one (96%) or more than one (4%) of the 7 ‘neuro gene panels’ were requested between January 2019 and April 2022

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Schuermans et al, 2023

Neurogenetics diagnostics: results January 2019 – April 2022

H9.1-OP2-B26: Genpanel Leukodystrophy, in voege op 24/08/2020

Leukodystrophy panel		
versie	V2 (265 genen)	Centrum voor Medische Genetica Gent

H9.1-OP2-B25: Genpanel Ataxia Spasticity, in voege op 24/08/2020

Ataxia Spasticity panel		
versie	V2 (390 genen)	Centrum voor Medische Genetica Gent

H9.1-OP2-B27: Genpanel Movement Disorders, in voege op 24/08/2020

Movement Disorders panel		
versie	V2 (269 genen)	Centrum voor Medische Genetica Gent

H9.1-OP2-B28: Genpanel Paroxysmal Episodic Disorders, in voege op 24/08/2020

Paroxysmal Episodic Disorders panel		
versie	V2 (53 genen)	Centrum voor Medische Genetica Gent

H9.1-OP2-B29: Genpanel PME, 16-Oct-2018, in voege op 17/10/2018

PME panel		
versie	16-Oct-2018 (34 genen)	Centrum voor Medische Genetica Gent

H9.1-OP2-B30: Genpanel NBIA, 16-Oct-2018, in voege op 17/10/2018

NBIA panel		
versie	16-Oct-2018 (16 genen)	Centrum voor Medische Genetica Gent

H9.1-OP2-B44: Genpanel ALS, v3 in voege op 11/04/2023

ALS panel		
versie	v3 (40 genen)	Centrum voor Medische Genetica Gent

Ataxia Spasticity

Gene panel

Gene panel information

Gene panel	**Ataxia Spasticity**
Version	3
Total genes	508
Activation date	Tuesday 12 december 2023
Publisher	Center for Medical Genetics, Ghent

Panel composition based on Genomics England Panelapp, OMIM, PubMed

! Thnx Dr. Hannah Verdin

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Neurogenetics diagnostics: results January 2019 – April 2022

Table 1 Description of the Patient Cohort

	Total patient cohort (%)
N	1,411
Age (y) (mean ± SD)	51 ± 20
Younger than 18	97 (7)
Aged 18 or older	1,314 (93)
Sex	
Male	669 (47)
Female	742 (53)
Gene panel	
Leukoencephalopathy	535 (38)
Ataxia spasticity	365 (26)
Movement disorders	378 (27)
Paroxysmal episodic disorders	99 (7)
Progressive myoclonic epilepsy (PME)	7 (0)
Neurodegeneration with brain iron accumulation (NBIA)	11 (1)
Amyotrophic lateral sclerosis (ALS)	16 (1)

93% >18 yrs

7 panels: total **725 genes** associated with Mendelian neurological disorders

250 different **requesters** (mainly neurologists)

Not included: peripheral neuropathies, myopathies, neuromuscular diseases

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Schuermans et al, 2023

Neurogenetics diagnostics: results January 2019 – April 2022

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→ Total diagnostic yield 144/1411 = **10%**

Jody Ghijsels

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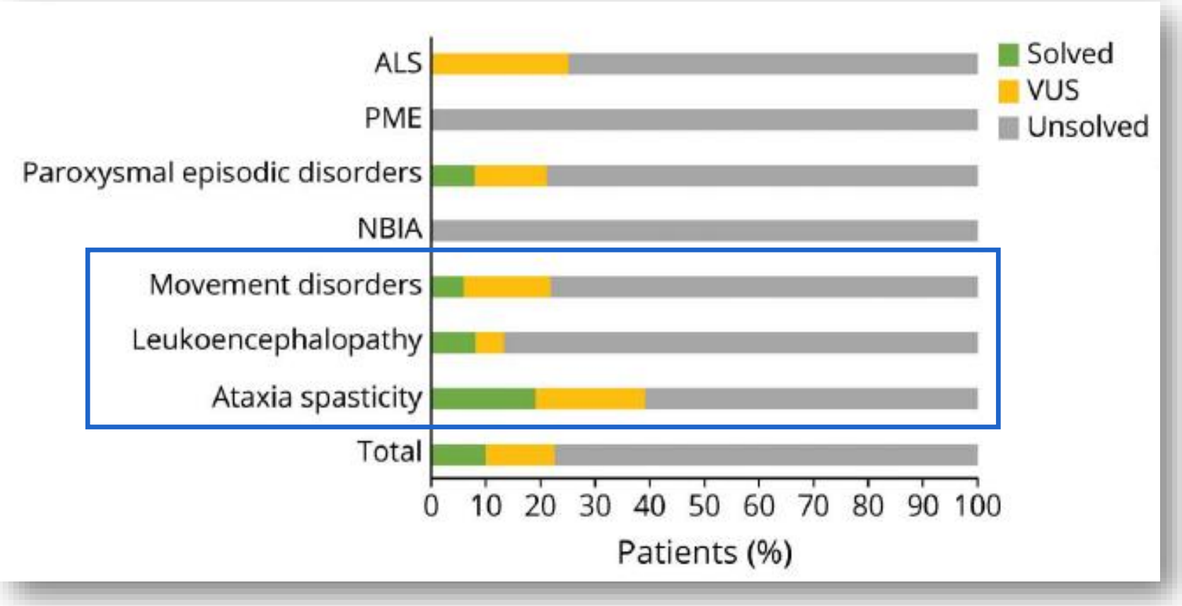

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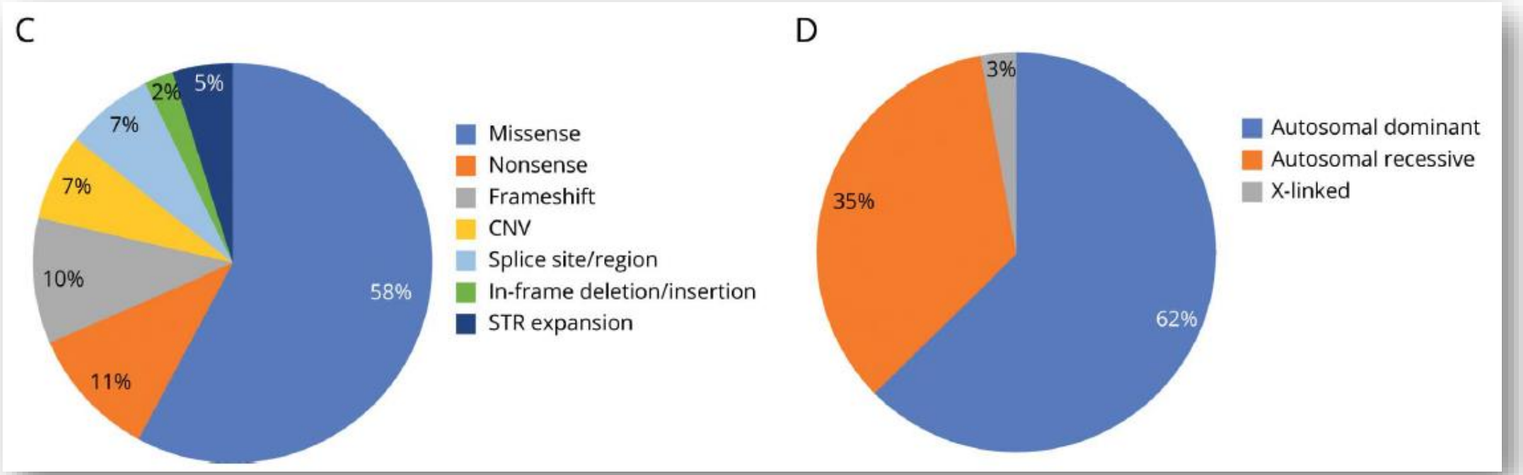

47% positive family history, first symptoms average 37 yeras, average **diagnostic delay 14 years**

Jody Ghijsels

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Schuermans et al, 2023

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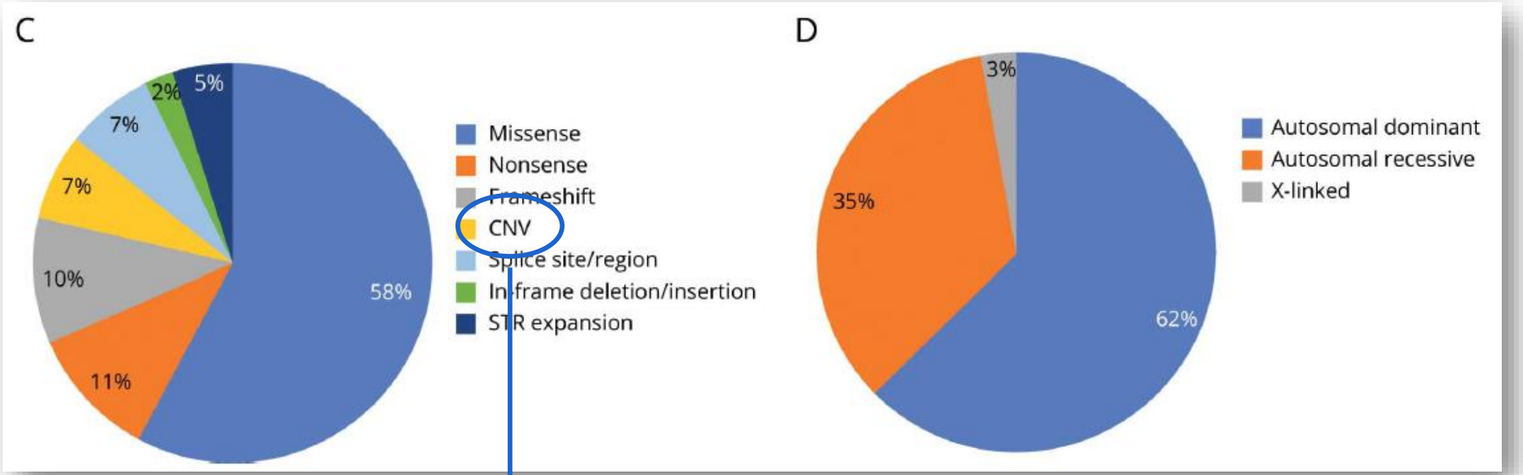

ExomeDepth, 11 patiënten (0,8%)

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Schuermans et al, 2023

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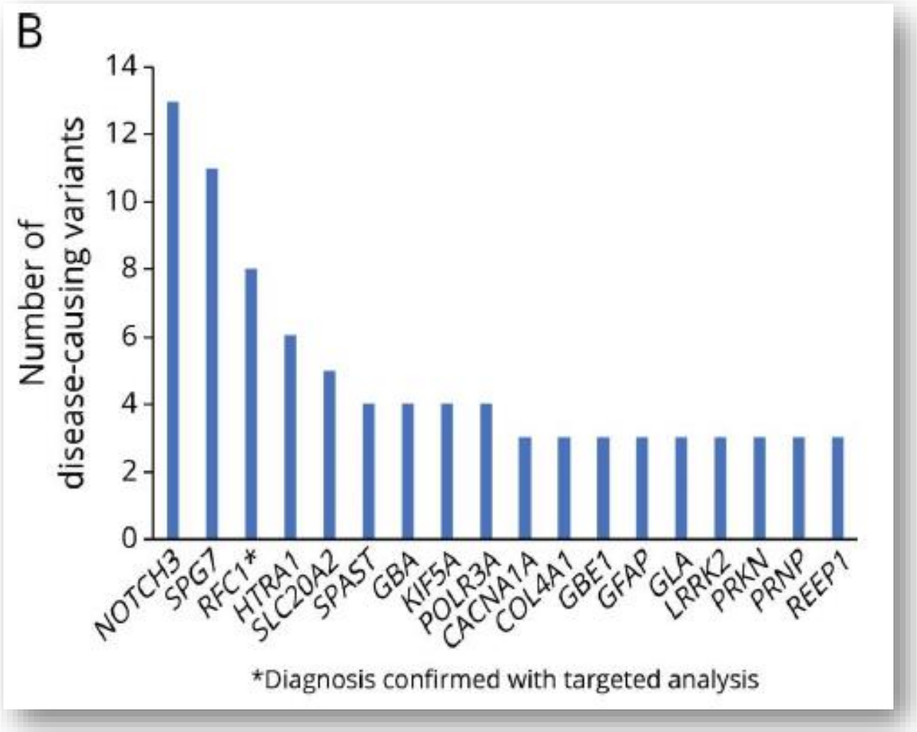

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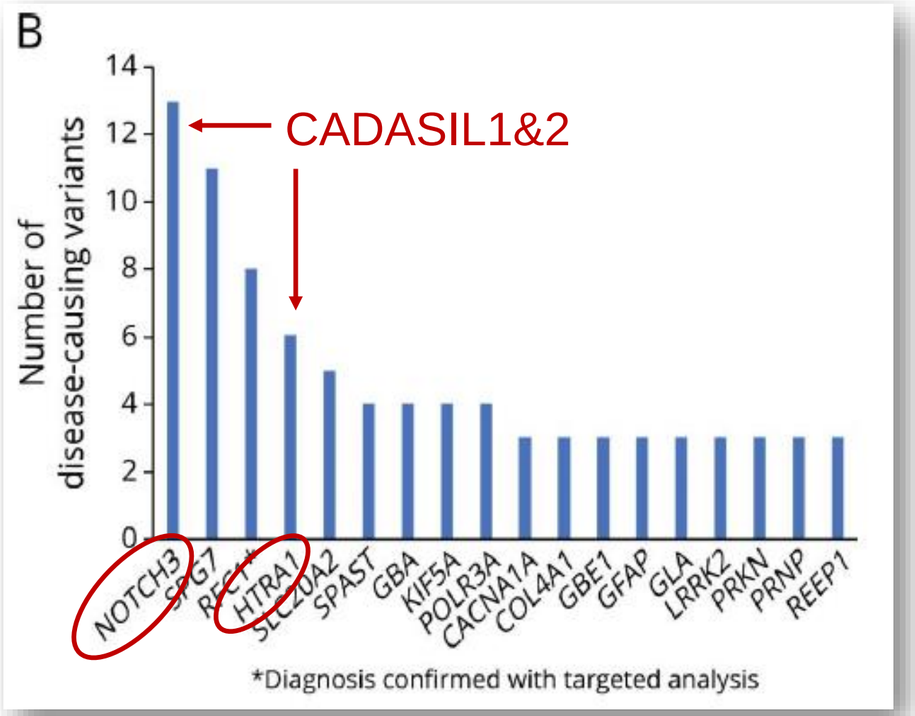

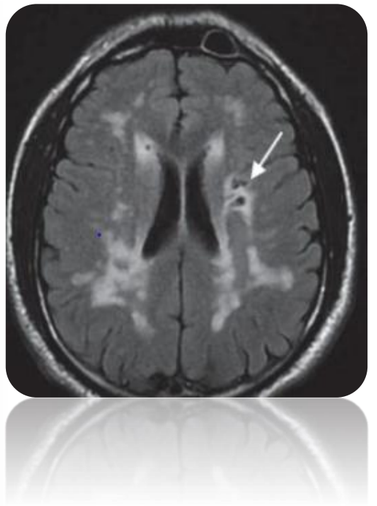

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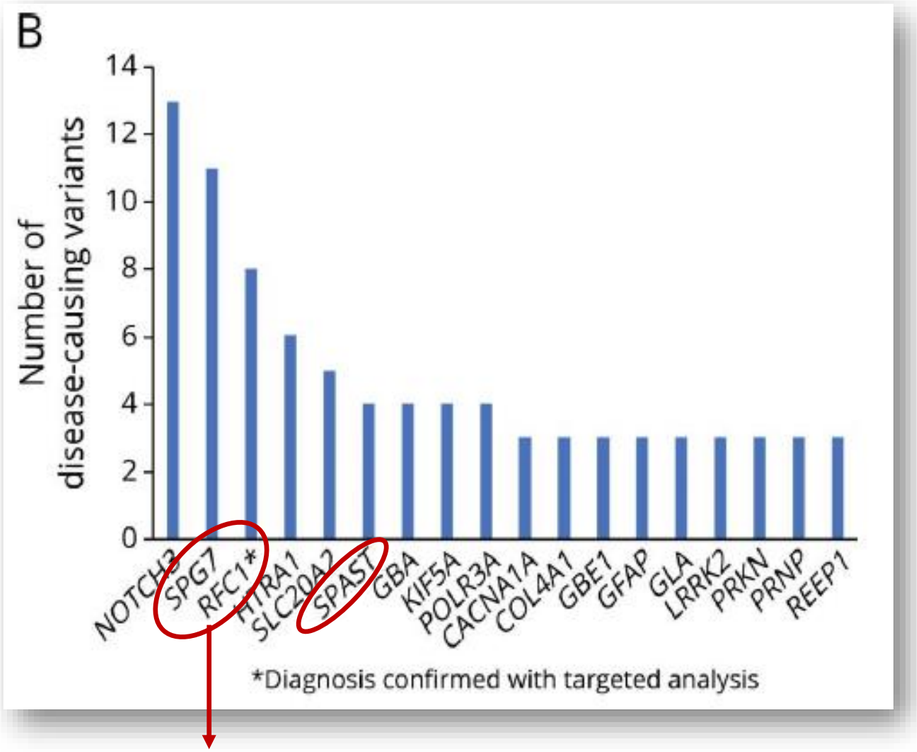
Movement disorders	378 (27)	22 (15)
Paroxysmal episodic disorders	99 (7)	8 (6)
Progressive myoclonic epilepsy (PME)	7 (0)	0 (0)
Neurodegeneration with brain iron accumulation (NBIA)	11 (1)	0 (0)
Amyotrophic lateral sclerosis (ALS)	16 (1)	0 (0)

Total diagnostic yield 144/1411 = **10%**



***c*erebellar *a*taxia, *n*europathy, *v*estibular *a*reflexia syndrome (CANVAS)**: homozygosity for SNP rs2066782, in linkagedisequilibrium with the intronic pathogenic pentanucleotide repeat expansion in *RFC1*,

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Neurogenetics diagnostics: results January 2019 – April 2022

Table 1 Description of the Patient Cohort

	Total patient cohort (%)	Diagnosed patients (%)
N	1,411	144
Age (y) (mean ± SD)	51 ± 20	50 ± 19
Younger than 18	97 (7)	10 (7)
Aged 18 or older	1,314 (93)	134 (93)
Sex		
Male	669 (47)	73 (51)
Female	742 (53)	71 (49)
Gene panel		
Leukoencephalopathy	535 (38)	44 (30)
Ataxia spasticity	365 (26)	70 (49)
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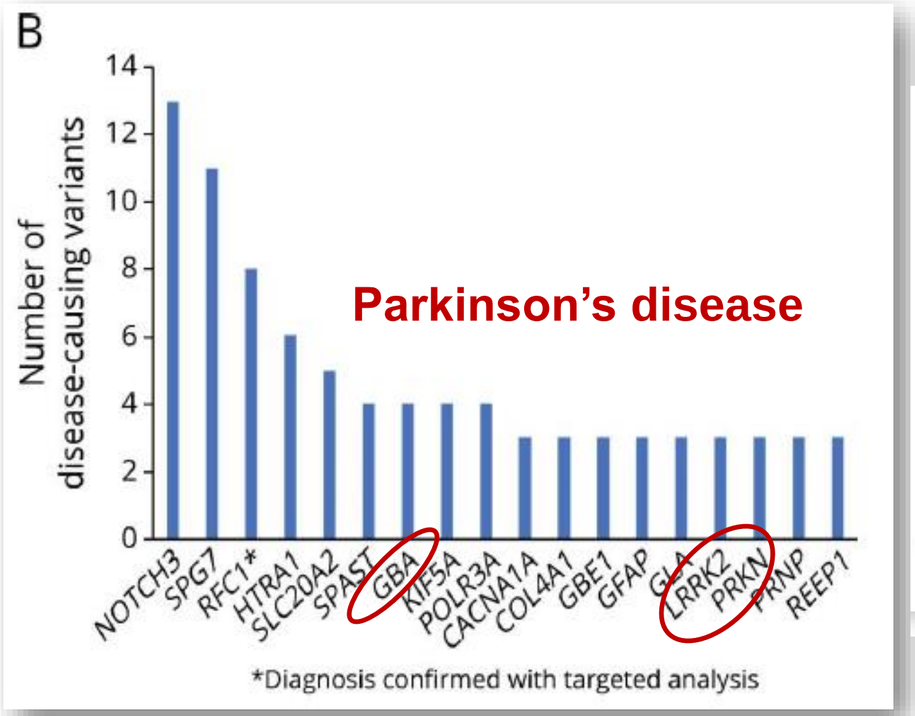

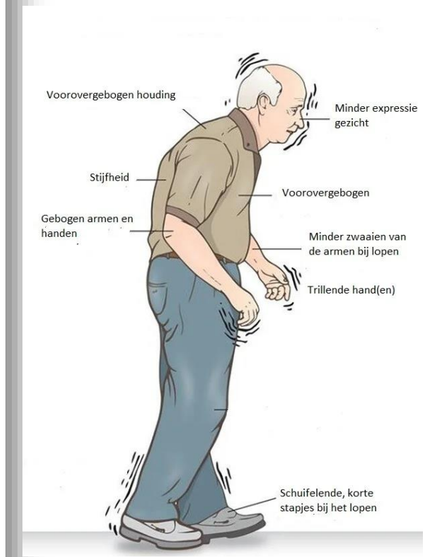

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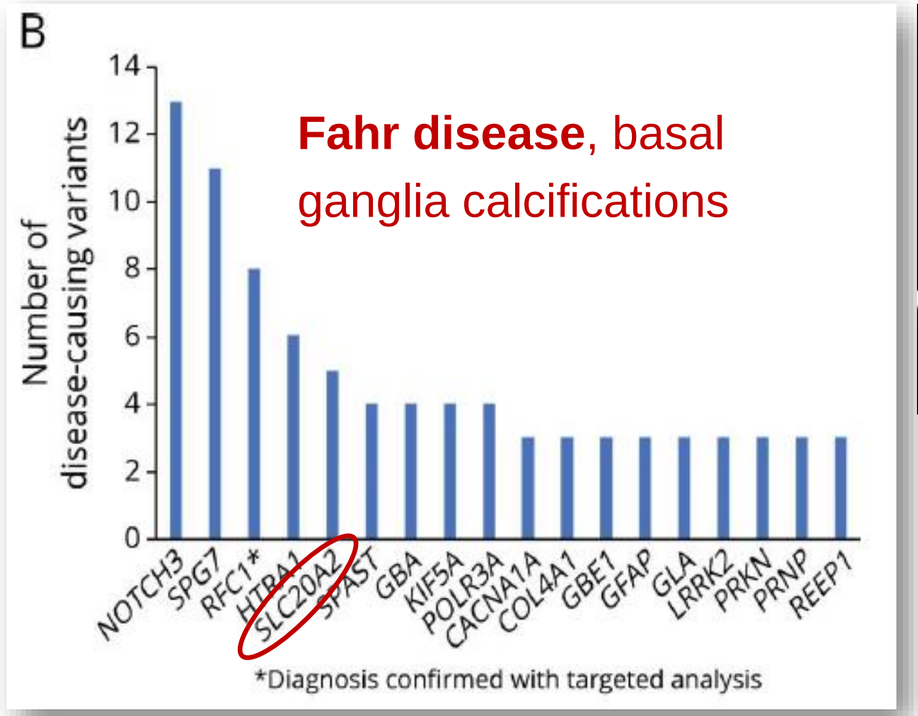
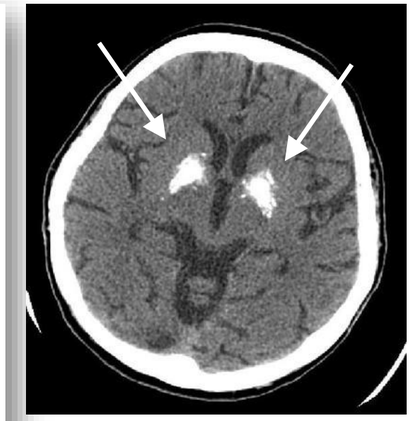


Fahr disease, basal ganglia calcifications



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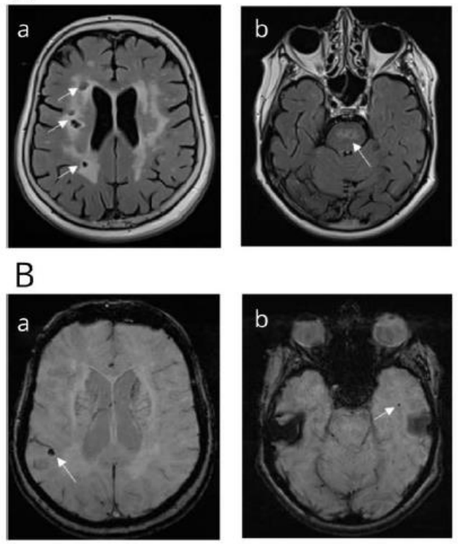
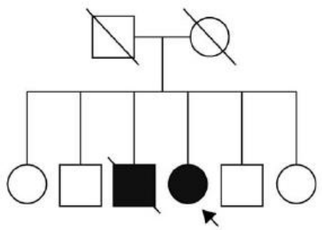
A



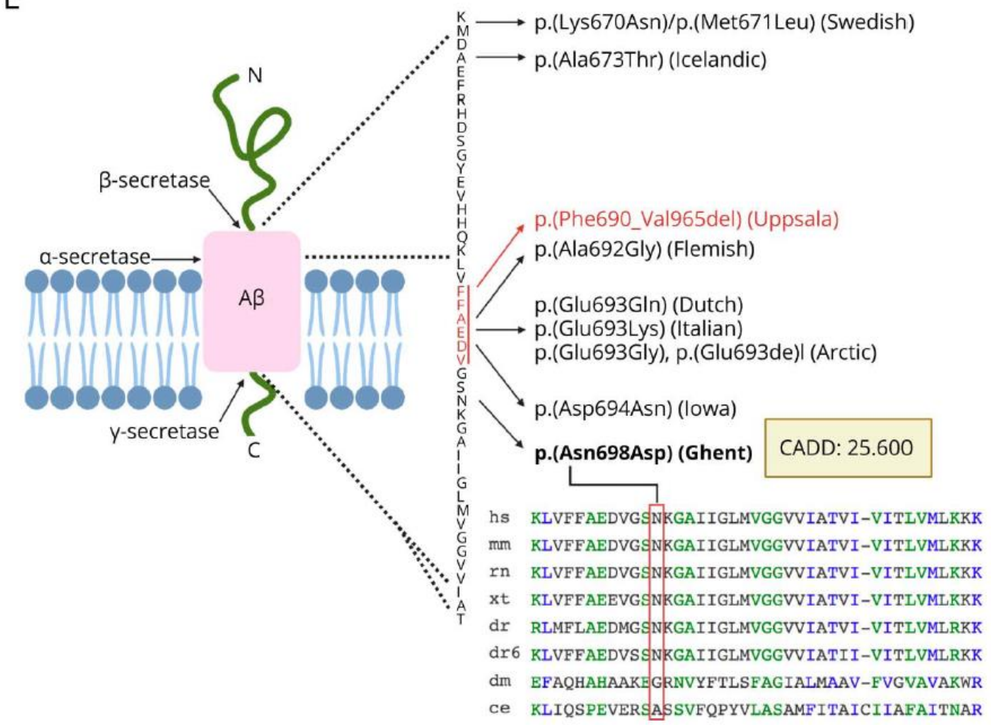
C



D

	Total tau (pg/mL)	*p* tau (pg/mL)	Amyloid β1-42 (pg/mL)	Amyloid β1-42/β1-40
Patient	**428**	47	1,017	0.072
Reference	<403	<50	>722	>0.070

E



75 years, stroke, leukoencefalopathy

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Conclusions:

- First study with **large cohort (n>1000)** on utility of WES in an adult neurological population

- overall **yield 10%**, ataxia/spasticity panel highest yield (19%)

- diagnostics is complex:

1. 60% A.D. vs 46% positieve family history: reduced and age-dependent penetrance, differences in expressivity

2. clinical presentation often the same as in sporadic forms (eg Parkinson, Alzheimer, ALS)

3. Molecular: repeat expansions, mtDNA, non-coding variants (b.v; *POLR3A* c.1909+22G>A)

4. Class 3 variants: often no segregation

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Thanks !

RESEARCH ARTICLE OPEN ACCESS

Exome Sequencing and Multigene Panel Testing in 1,411 Patients With Adult-Onset Neurologic Disorders

Nika Schuermans, MD, Hannah Verdin, PhD, Jody Ghijsels, BSc, Madeleine Hellemans, MD, Elke Debackere, BSc, Elke Bogaert, PhD, Sofie Symoens, PhD, Leslie Naesens, MD, Elien Lecomte, MD, David Crosiers, MD, PhD, Bruno Bergmans, MD, PhD, Kristof Verhoeven, MD, Bruce Poppe, MD, PhD, Guy Laureys, MD, PhD, Sarah Herdewyn, MD, PhD, Tim Van Langenhove, MD, PhD, Patrick Santens, MD, PhD, Jan L. De Bleecker, MD, PhD, Dimitri Hemelsoet, MD, and Bart Dermaut, MD, PhD, for Program for Undiagnosed Rare Diseases (UD-PrOZA)

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Neurol Genet 2023;9:e200071. doi:10.1212/NXG.0000000000200071

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Orphanet Journal of Rare Diseases (2022) 17:210
https://doi.org/10.1186/s13023-022-02365-y

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Shortcutting the diagnostic odyssey: the multidisciplinary Program for Undiagnosed Rare Diseases in adults (UD-PrOZA)

Nika Schuermans[1,2*†], Dimitri Hemelsoet[3†], Wim Terryn[4], Sanne Steyaert[5], Rudy Van Coster[6], Paul J. Coucke[1,2], Wouter Steyaert[7], Bert Callewaert[1,2], Elke Bogaert[1,2], Patrick Verloo[6], Arnaud V. Vanlander[6], Elke Debackere[1,2], Jody Ghijsels[1,2], Pontus LeBlanc[1,2], Hannah Verdin[1,2], Leslie Naesens[8,9], Filomeen Haerynck[8], Steven Callens[5], Bart Dermaut[1,2†], Bruce Poppe[1,2†]for UD-PrOZA

https://www.ugent.be/schenken/nl/hoe-steunen/steun-een-fonds/fonds-alzheimer.htm

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Op deze pagina

- → Een gift aan Fonds Alzheimer en Neurodegeneratieve Aandoeningen?
- → Meer info over het fonds?
- → Meer info over het onderzoek?
- → Wat kan ik nog doen?
- → Contacteer ons

Fonds Alzheimer en Neurodegeneratieve Aandoeningen

Mede door de veroudering van de bevolking zal **het aantal Alzheimer patiënten in de toekomst sterk toenemen**. Niet enkel bij ouderen, maar **ook bij jong volwassenen**. We weten ondertussen dat er een genetische component is, maar ons begrip van de ziekte, het ontstaan en de behandeling ervan zijn nog zeer beperkt.

De **ervaren teams van prof. dr. Bart Dermaut** en dr. Tim Van Langenhove hopen hier verandering in te brengen. Ze specialiseren zich onder meer in de **genetische analyse** en het klinisch-diagnostisch onderzoek van deze ziekte en aanverwante, neurodegeneratieve aandoeningen. Het Fonds stelt hen in staat om snellere en grotere stappen te nemen in hun onderzoek.

Een gift aan Fonds Alzheimer en Neurodegeneratieve Aandoeningen?

Uw gift aan het Fonds Alzheimer draagt bij aan een beter begrip van neurodegeneratieve aandoeningen zoals de ziekte van Alzheimer, zodat we die in de toekomst kunnen genezen.

Een gift van € 100 wordt bijvoorbeeld gebruikt om de toxische eiwitten in cellen van demente patiënten te kleuren of om bepaalde stoffen in het bloed van demente patiënten op te meten. Met een gift van € 500 wordt er een vliegenmodel gemaakt om neurologische ziekten te bestuderen of kan er een nieuwe soort hersenscan bij patiënten worden afgenomen. Met een gift van € 1.000 kan men de genetische fout bepalen die dementie veroorzaakt.

→ Ik doe een online gift

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