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A national diagnostic framework for patients with ultra-rare disorders: molecular genetic findings using phenotypic and sequencing data

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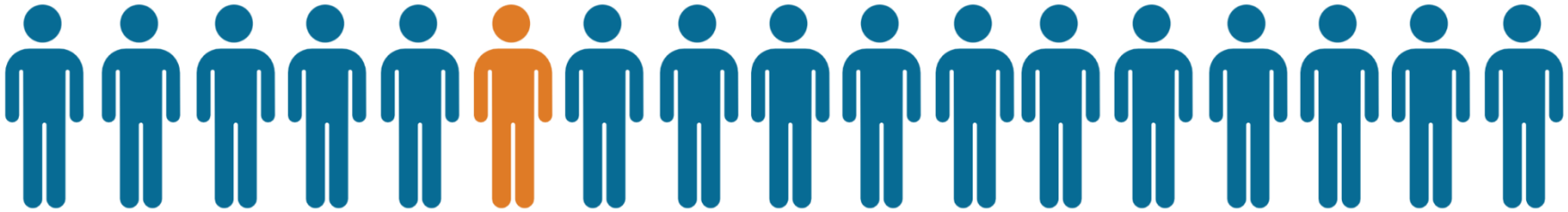
Rare diseases



- Rare diseases affect about 6% of the population
- >30 million people in EU are affected by rare diseases (1:2,000)
- 1:50,000 maximum prevalence for a disease to be considered ultra-rare

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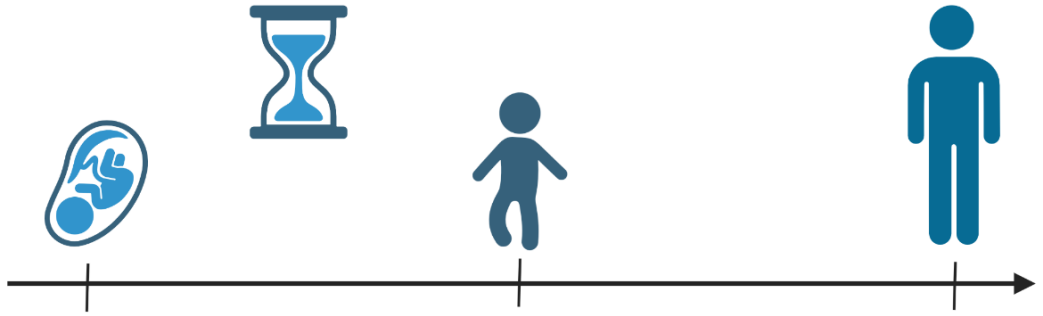
Main challenges adressed in TN project



Severely delayed time to diagnosis

~ 4 years

Multidisciplinary care and comprehensive genetic diagnostics required

Implementation of exome sequencing (ES) in the standard health care of patients with rare diseases

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TRANSLATE-NAMSE Network

- 10 Centers for Rare Diseases (CRD/ZSE)

Berlin, Bochum, Bonn, Dresden, Duisburg/Essen, Hamburg, Heidelberg, Kiel/Lübeck, München, Tübingen

- 4 Institutes of Human Genetics (sequencing):

Berlin, Bonn, München, Tübingen

- Health insurance companies

AOK Nordost und BARMER

- ACHSE

Krude et al., W3-001

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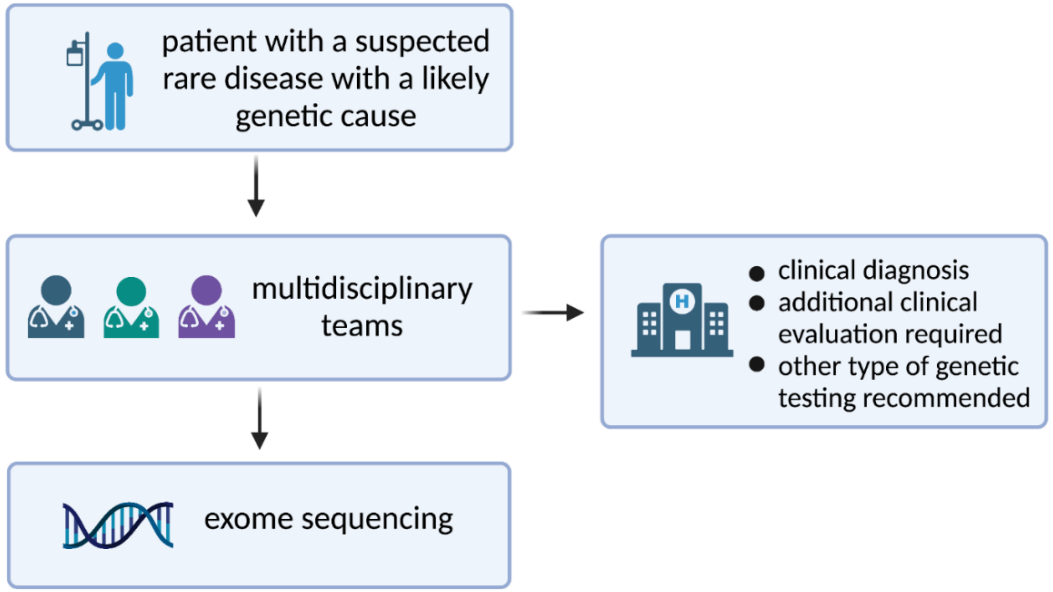
TRANSLATE-NAMSE Workflow and cohort size



January 2018 - December 2020

A **total** number of patients enrolled in the study: **5652**

Exome sequencing was initiated for: **1309** pediatric and **268** adult patients

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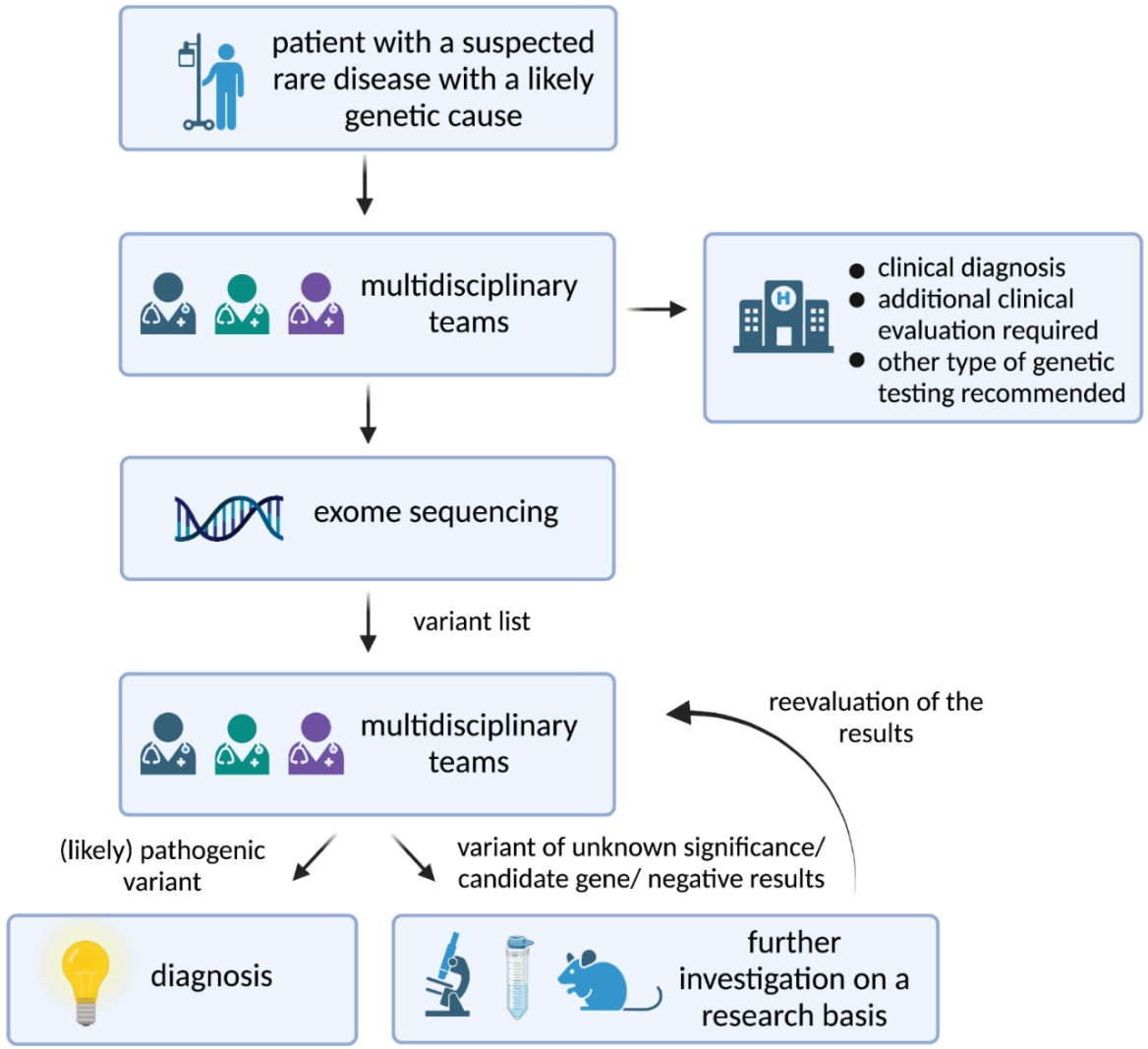
TRANSLATE-NAMSE Workflow and cohort size



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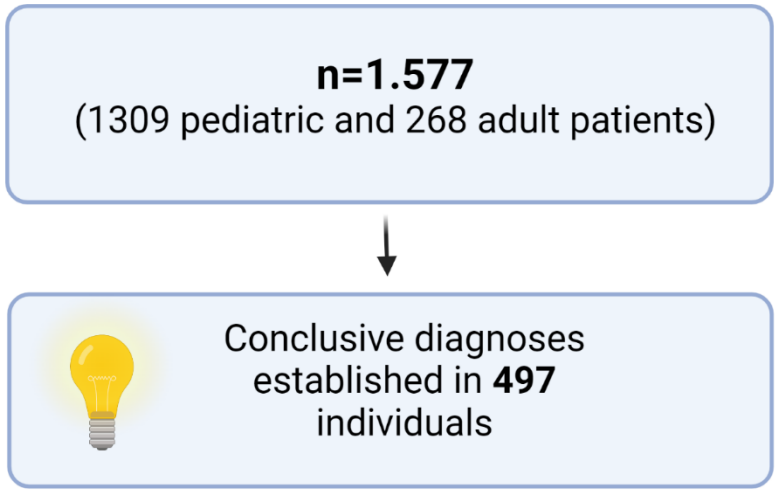
Diagnostic yield



32%

400 unique diagnostic-grade genes (DGG), suggesting that **ultra-rare disorders** were enriched in the TN cohort

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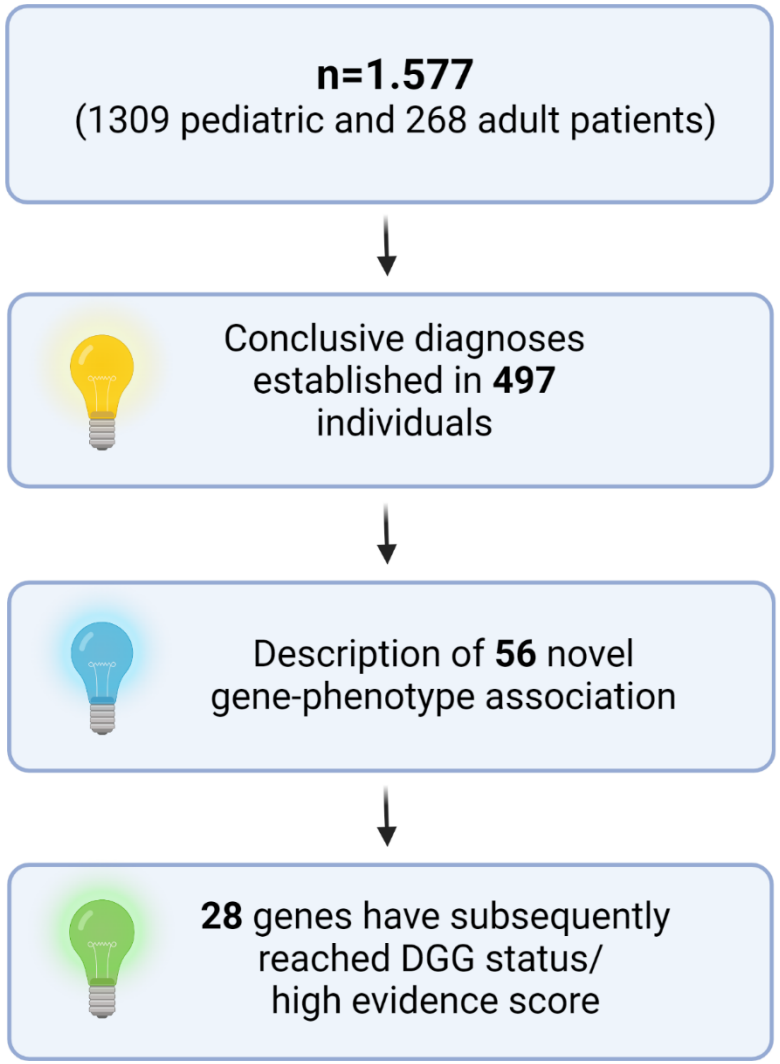
Diagnostic yield



32%

400 unique diagnostic-grade genes (DGG), suggesting that **ultra-rare disorders** were enriched in the TN cohort

Mainly in individuals with **neurodevelopmental delay**

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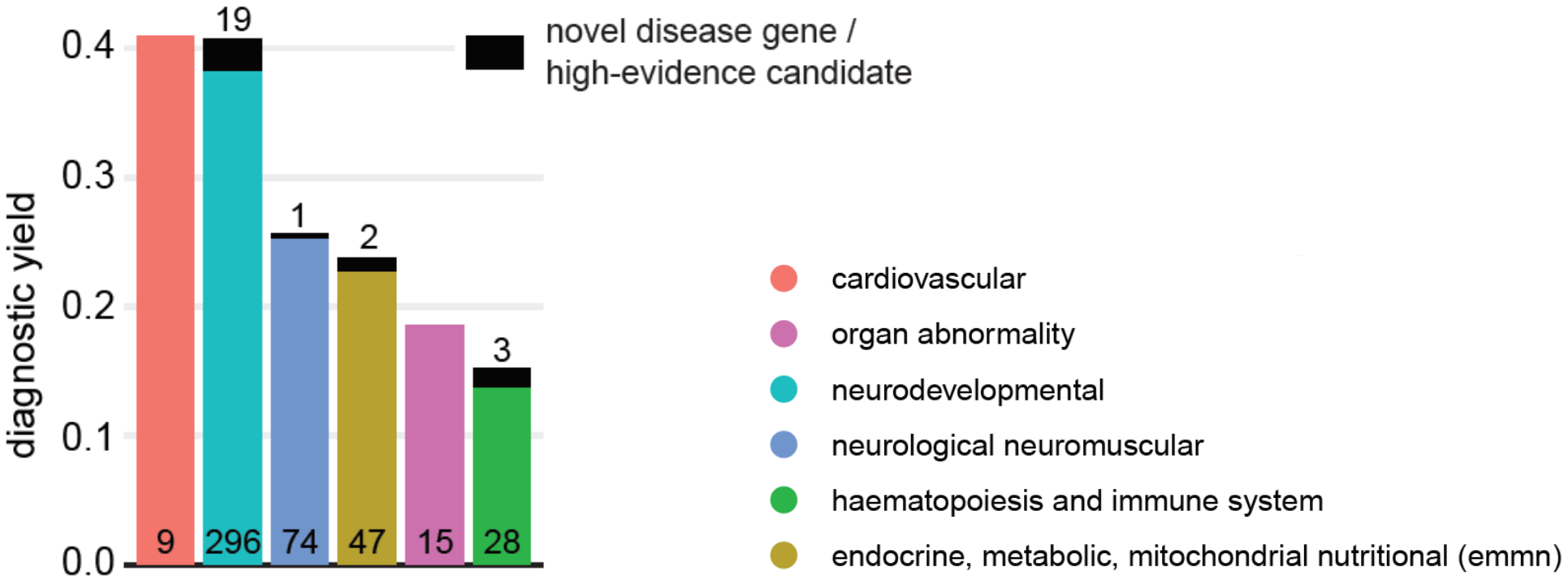
Diagnostic yield according to disease groups



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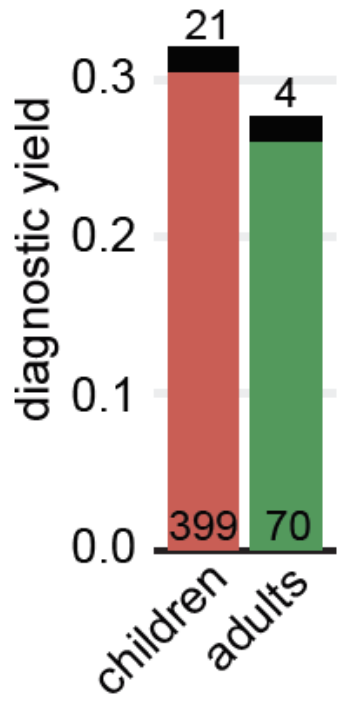
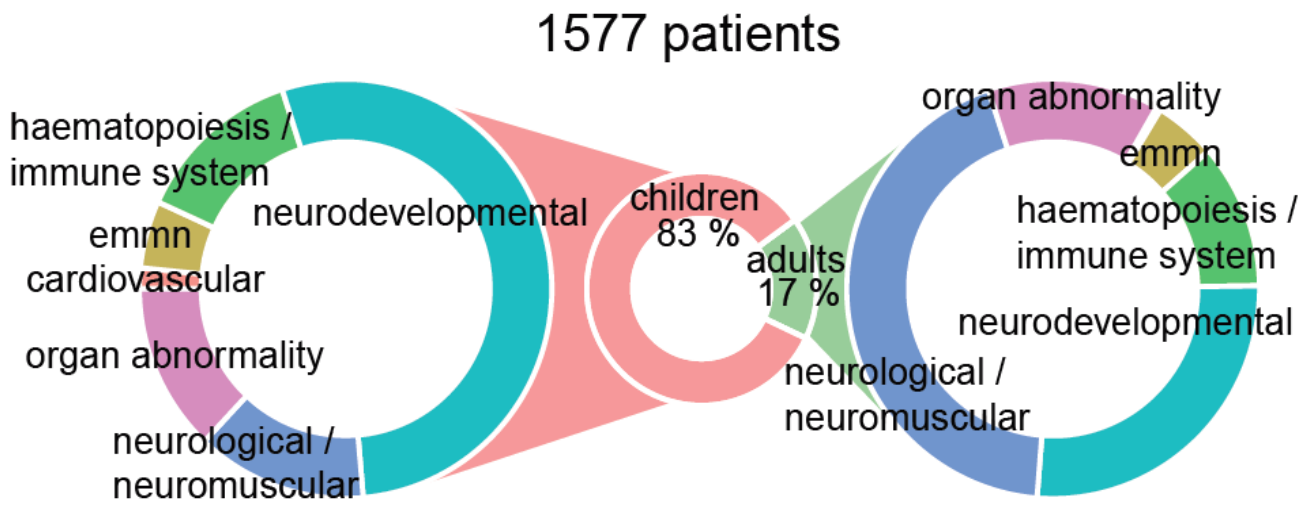
Diagnostic yield: children vs adults





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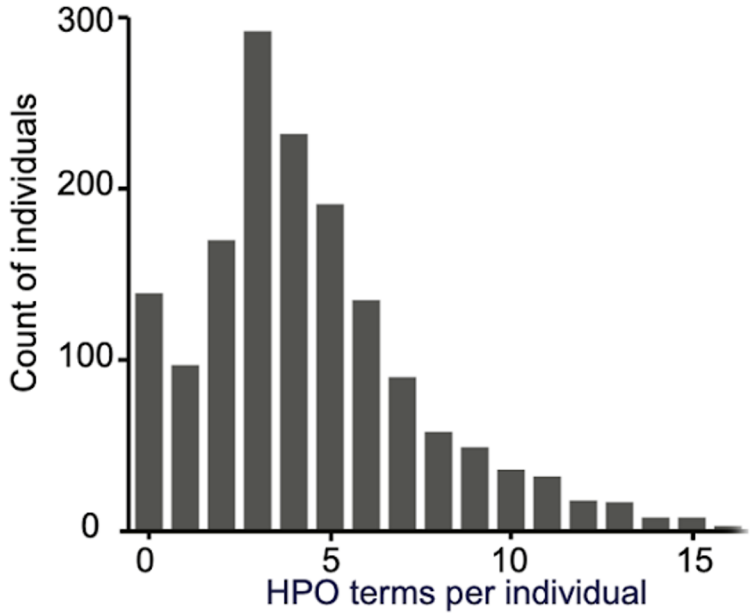
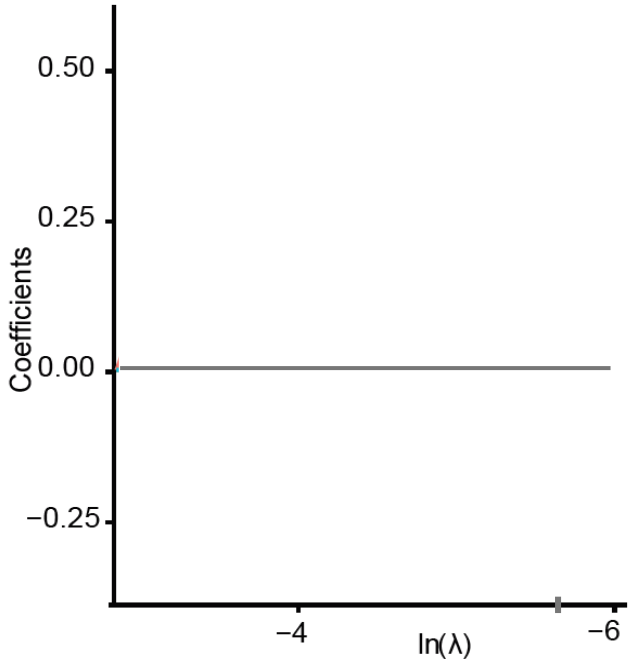
HPO-based prediction of diagnostic yield





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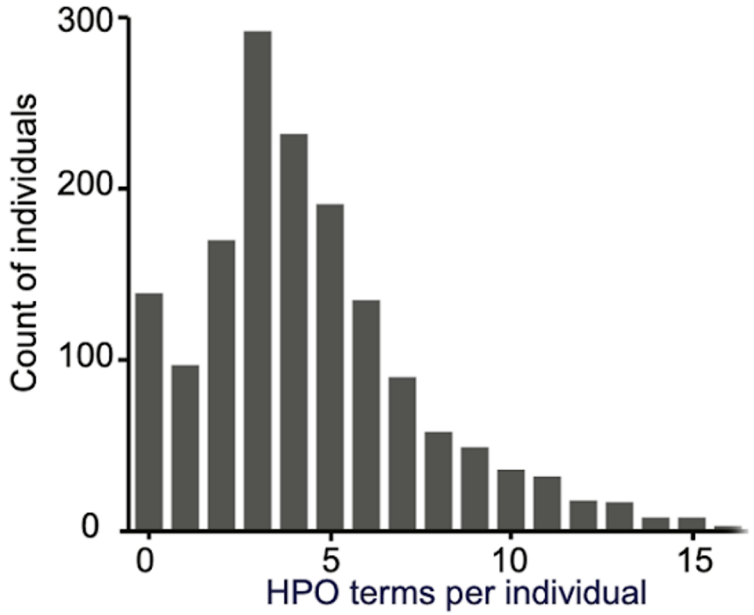

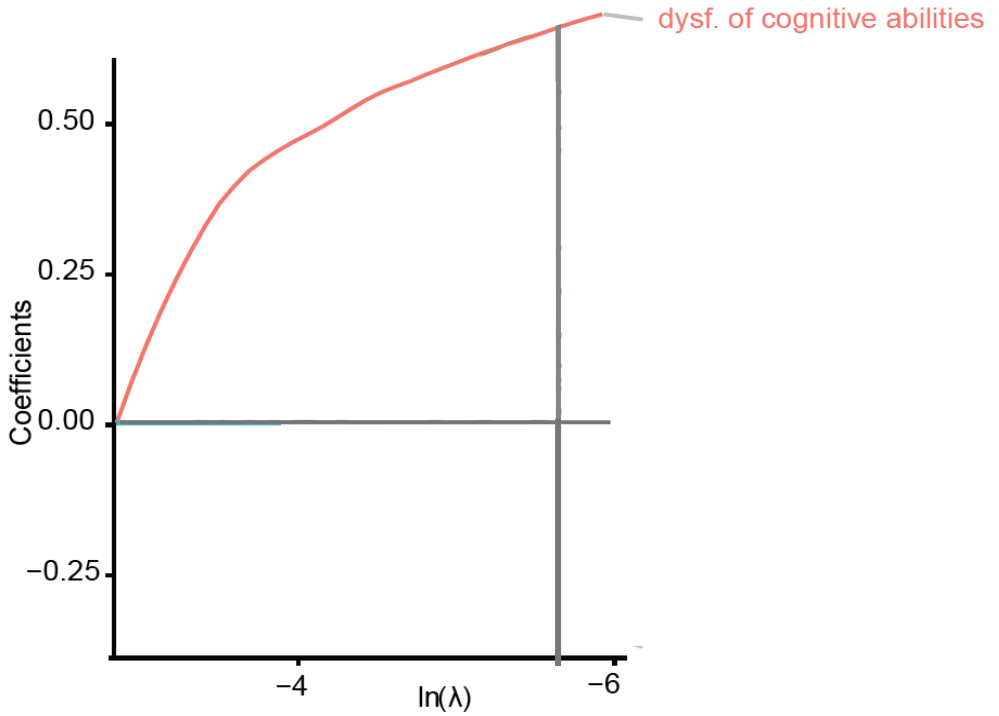

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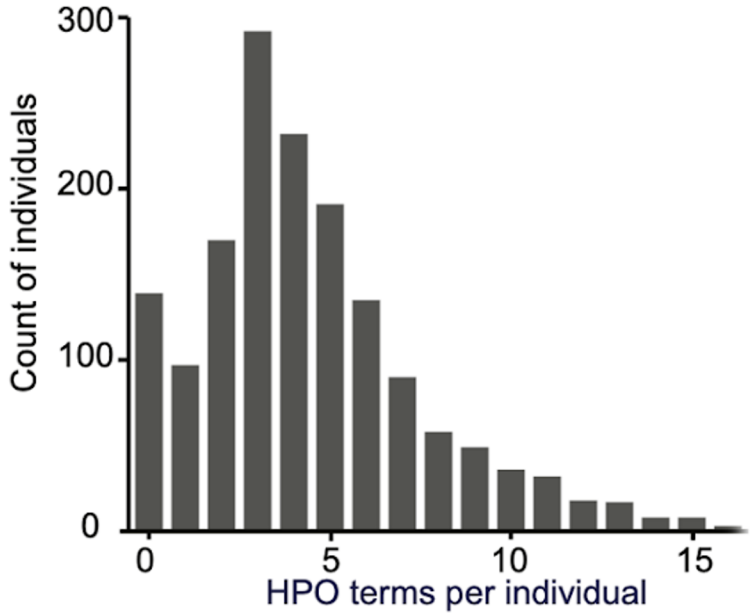

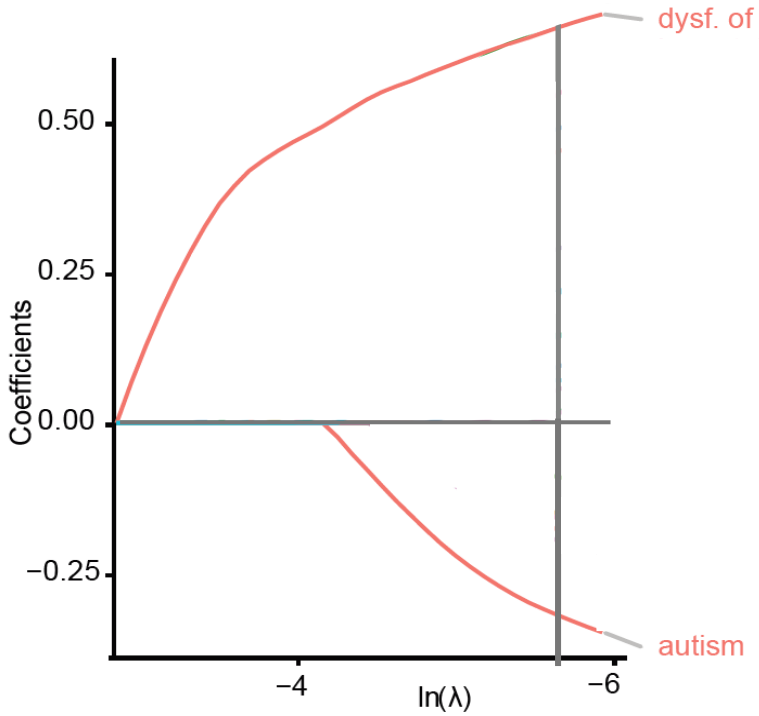

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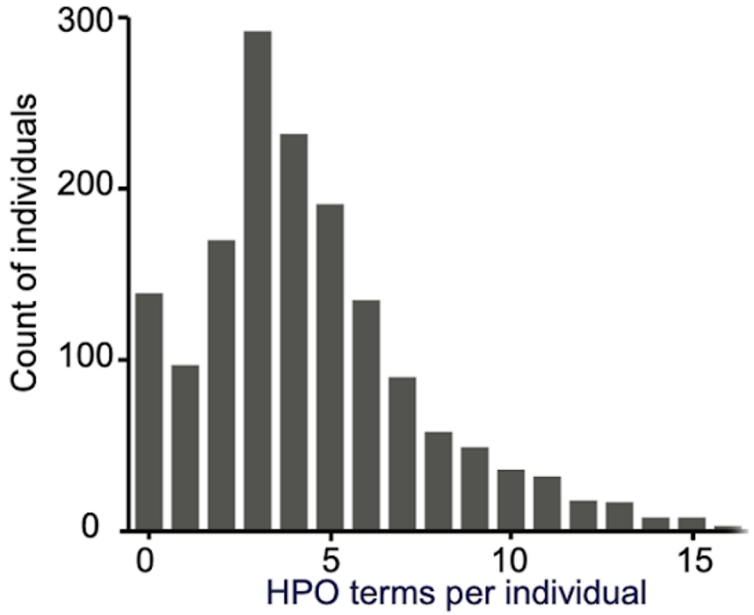

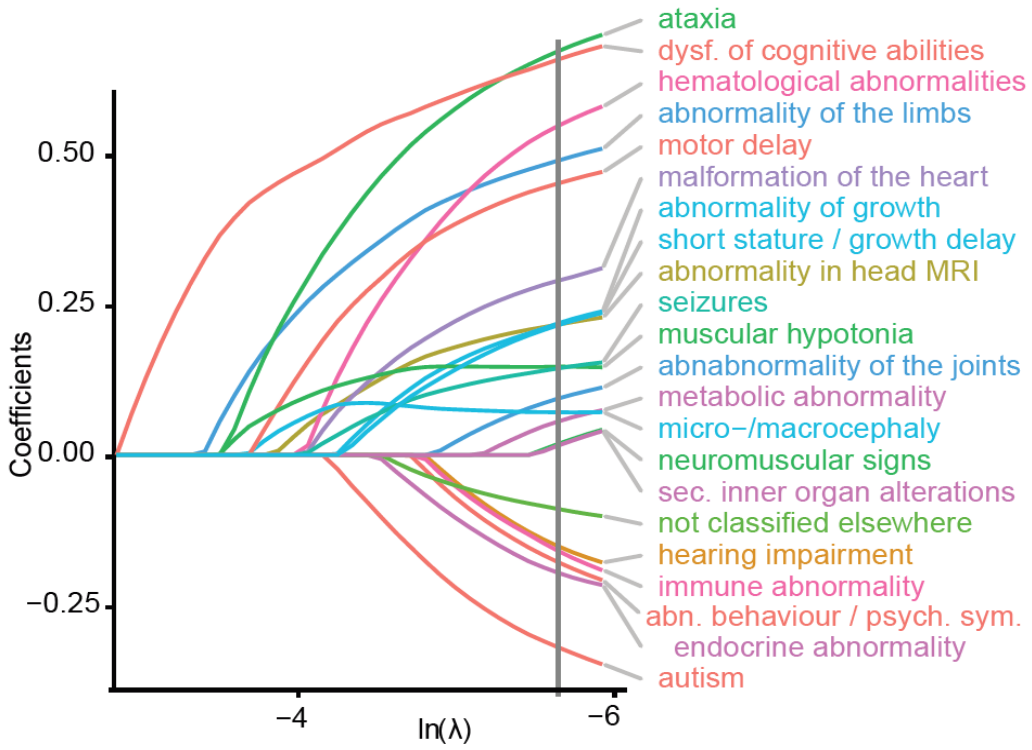

"Dysfunction of higher cognitive abilities", "abnormality of the limbs" and "ataxia" are predictive clinical features of an increased diagnostic yield.

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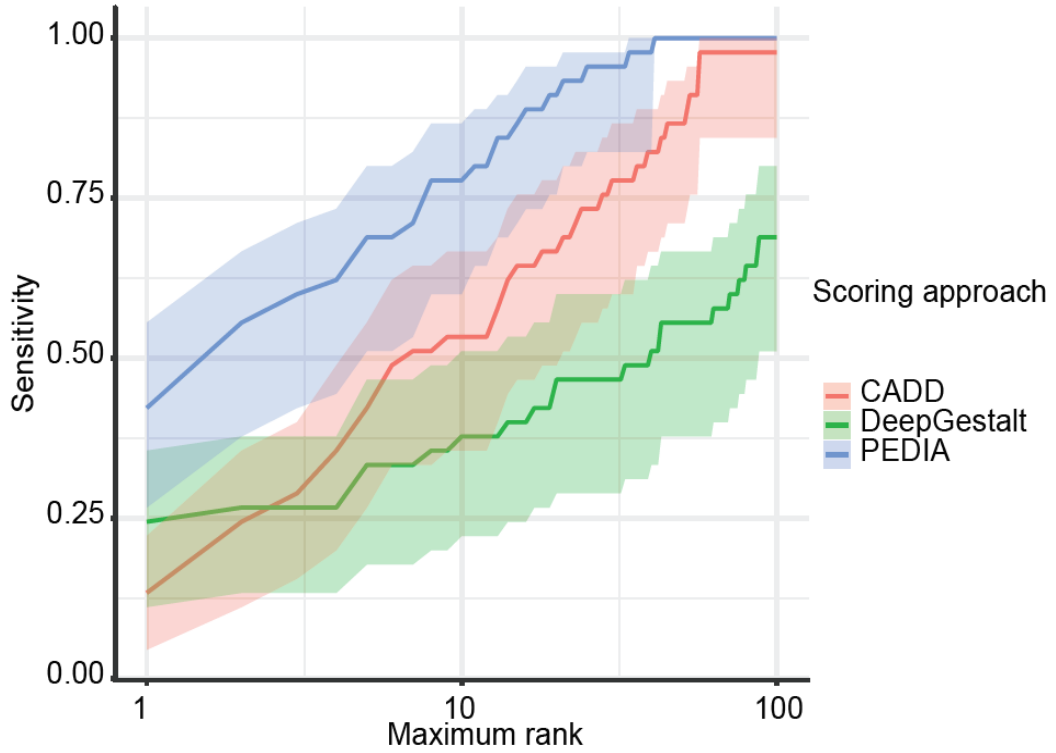
Artificial intelligence-based PEDIA protocol

PEDIA cohort: n=211
88 cases (42%) solved by ES

48/88 supported by AI:

55%



PEDIA: prioritization of exome data by image analysis
Hsieh, Mensah et al., Genet Med. 2019, PMID: 31164752

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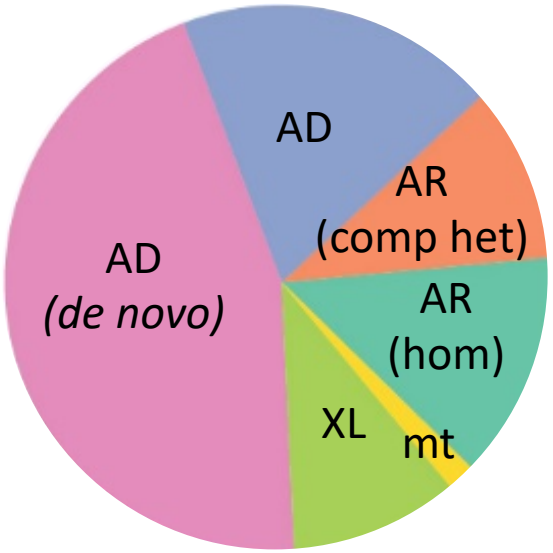
Mode of inheritance (MOI)



Amenable to carrier screening?

73%

The majority of solved cases were due to *de novo* variants

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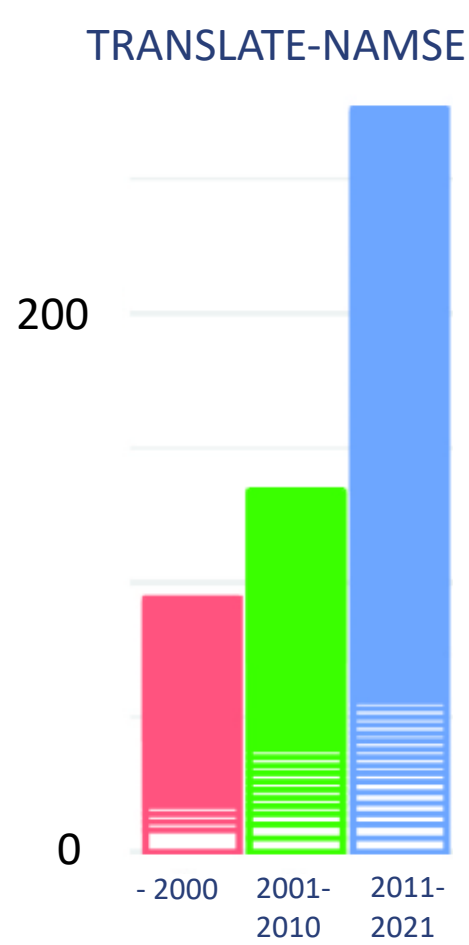
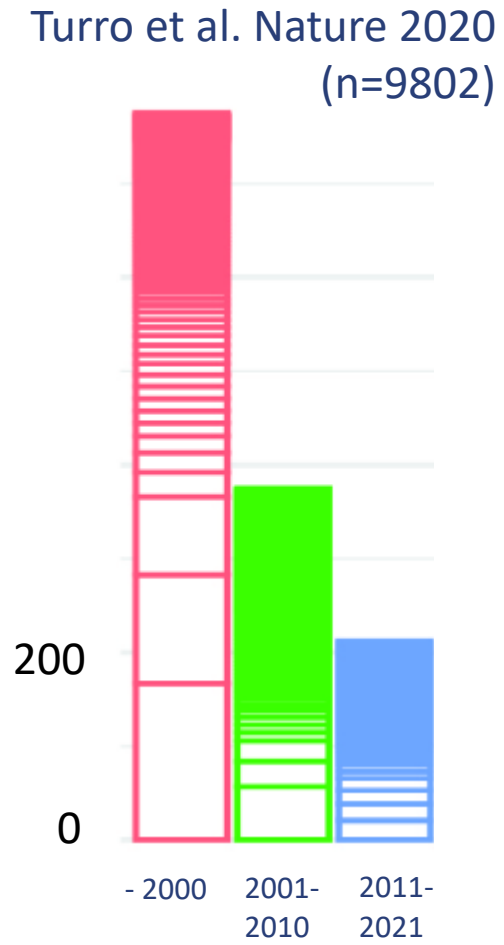
Ultra-rare disorders enriched in the TN cohort





The variants reported in the TN cohort were mostly in recently published genes.

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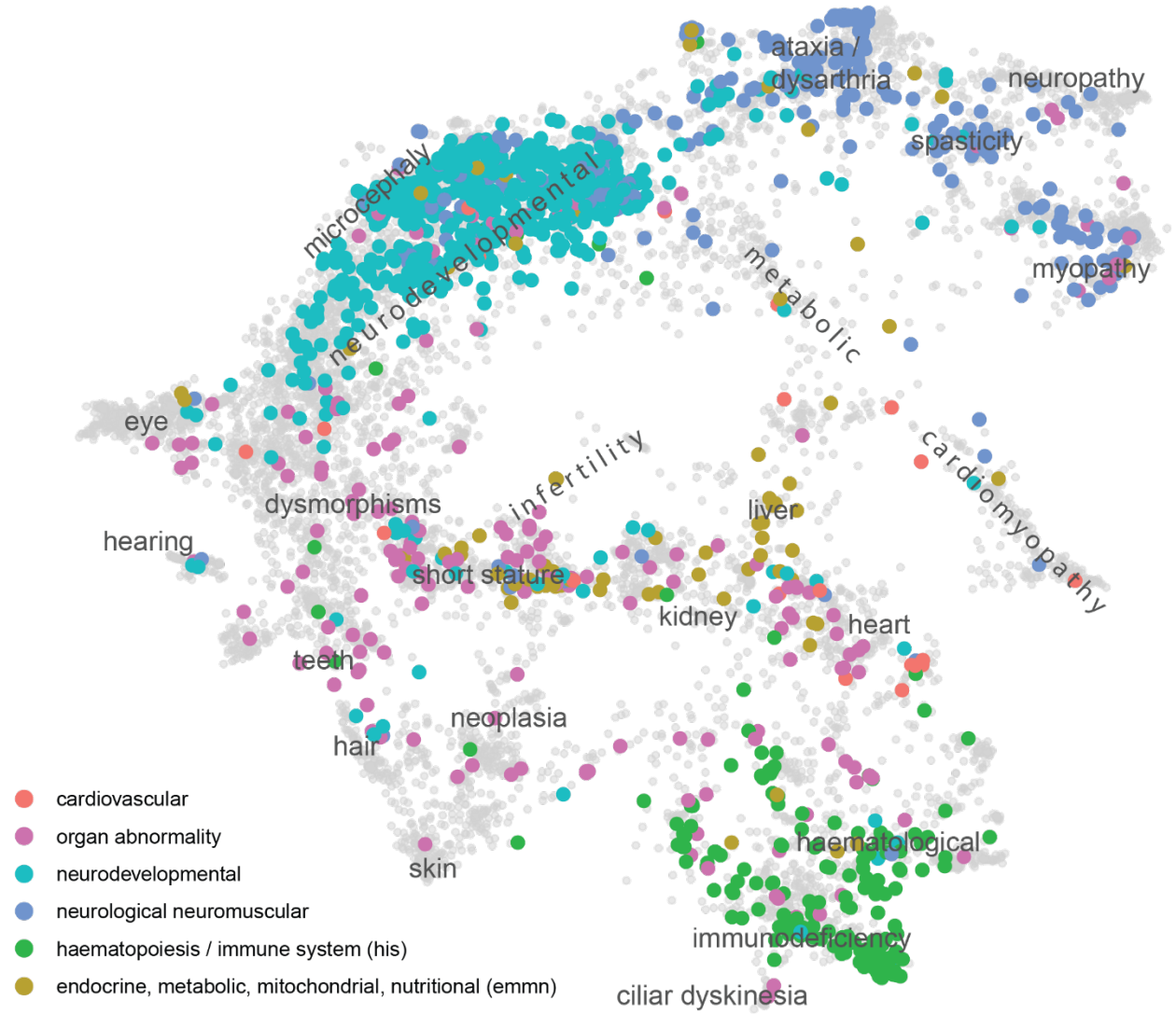
Phenotypes of the TN cohort



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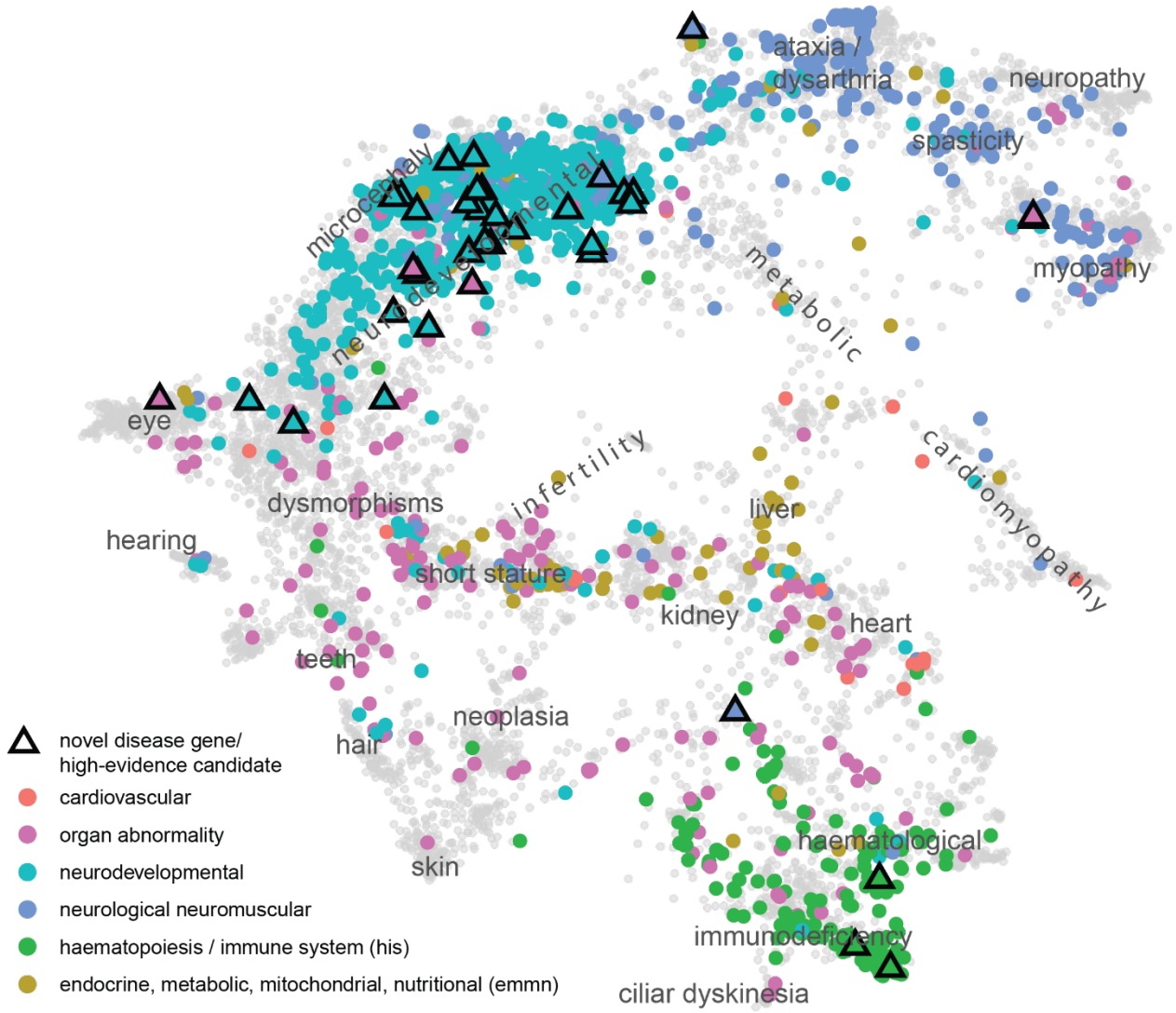
Phenotypes of the TN cohort



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Mandatory criteria for novel disease candidate gene

gene was not previously robustly associated with human phenotype

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Mandatory criteria for novel disease candidate gene

- ✓ gene was not previously robustly associated with human phenotype
- ✓ no other clearly causative disease explanation was found

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Mandatory criteria for novel disease candidate gene

- gene was not previously robustly associated with human phenotype
- no other clearly causative disease explanation was found
- allele frequency of the respective variant was below MAF cutoff/ variant was absent in controls
- inheritance was in accordance with the phenotype in the family/ variant co-segregated with the disease

Evidence score (max. value of 8) was calculated for each gene

Published gene-phenotype associations -> DGG status

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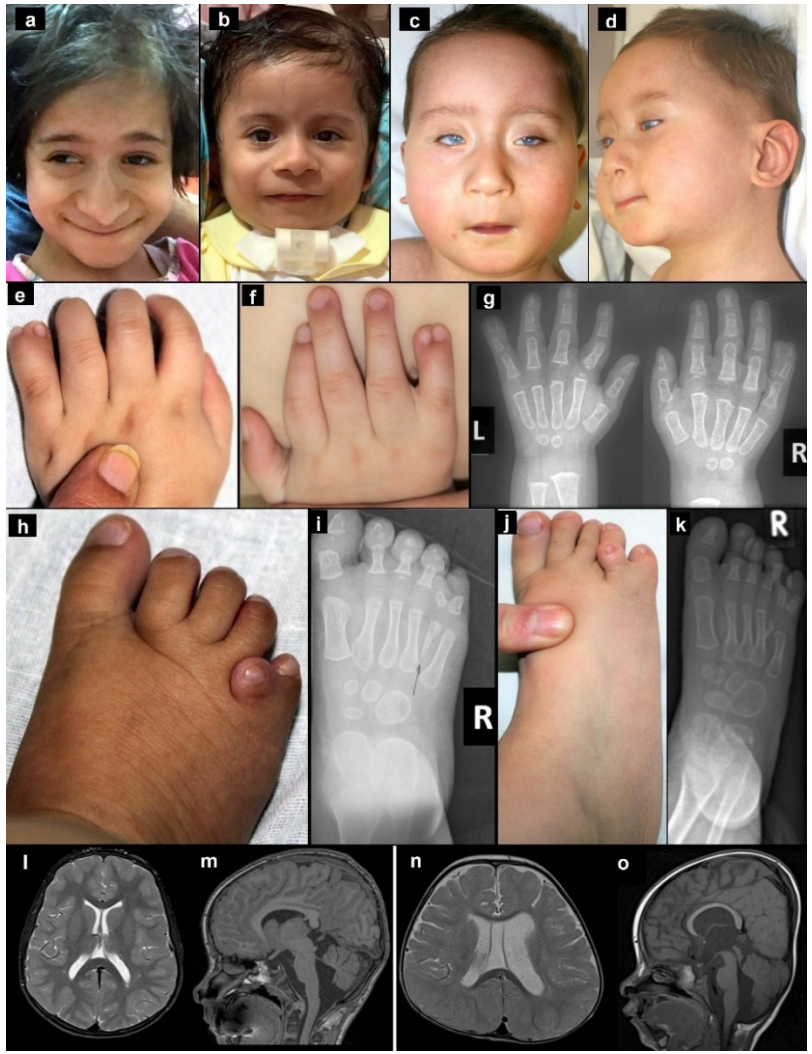
Case reports of particular interest

MAPKAPK5-associated neurodevelopmental disorder



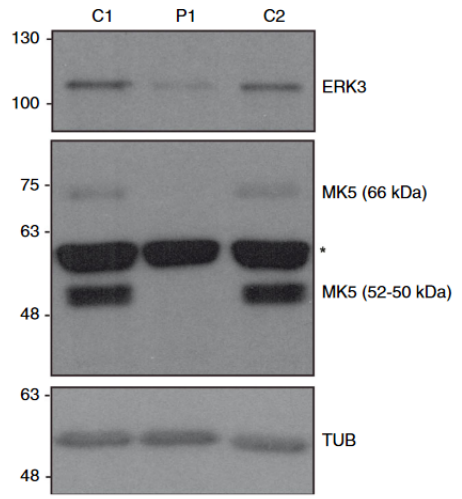
Clinical features:

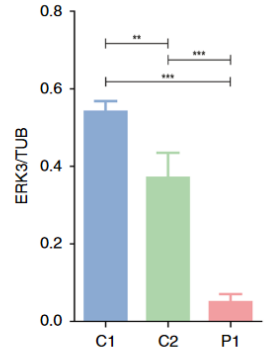
- Severe developmental delay,
- brain anomalies,
- congenital heart defects,
- dysmorphic facial features (narrow palpebral fissures, thin lips, and retromicrognathia)
- distinctive type of synpolydactyly

Exome sequencing revealed biallelic loss-of-function variants in *MAPKAPK5,* encoding the mitogen-activated protein kinase

No expression of MAPKAPK5 protein isoforms and reduced levels of the MAPKAPK5-interacting protein ERK3 were detectable in patient derived cells.

Horn et al., Genet Med. 2021, PMID: 33442026





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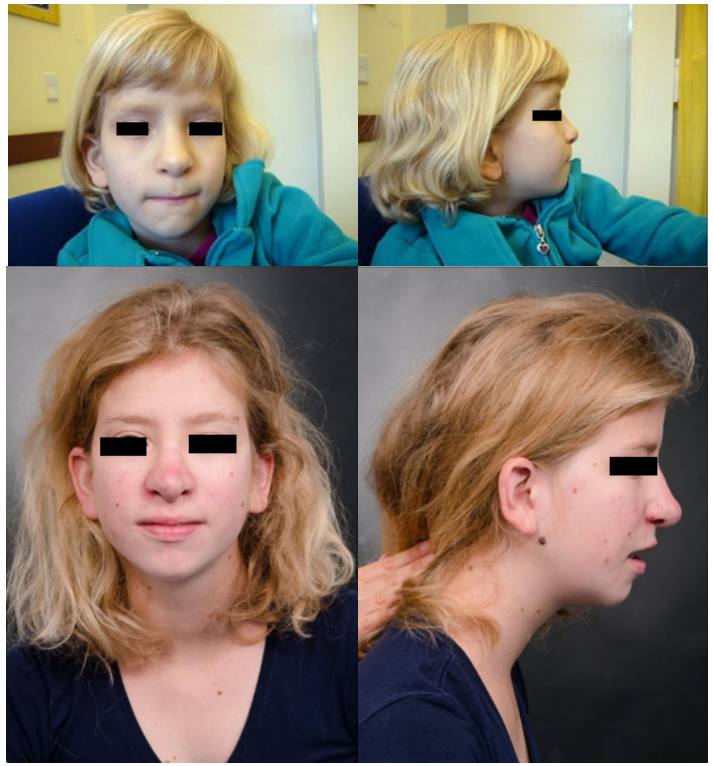
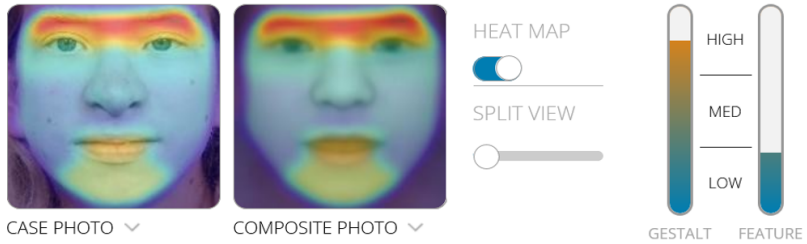
DeepGestalt triggered genome sequencing

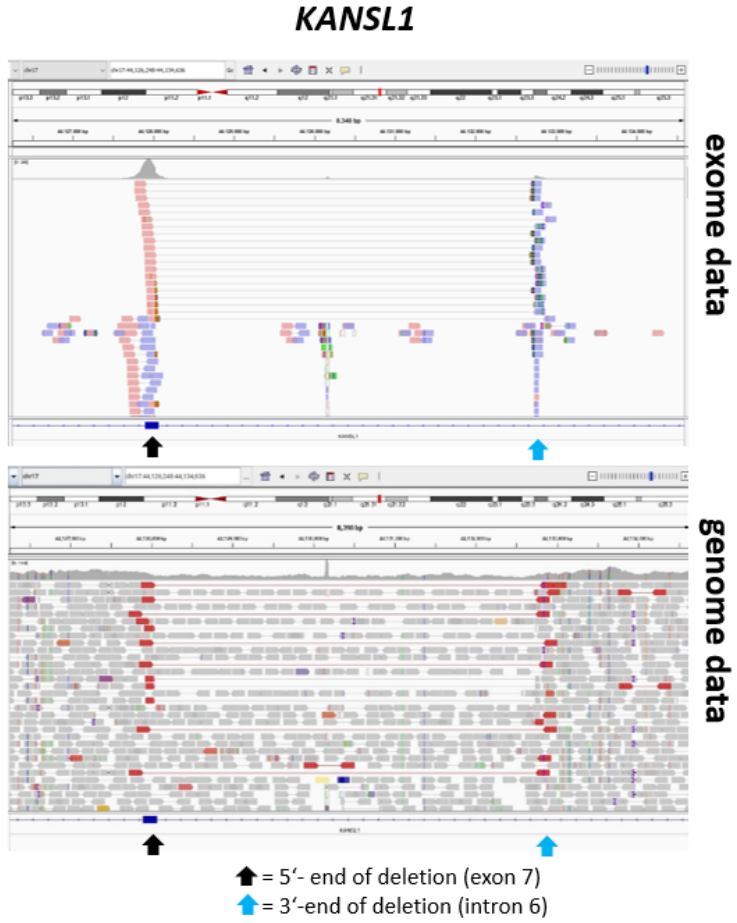


Clinical features:

- Developmental delay / moderate ID (IQ 43)
- Muscular hypotonia
- Dysmorphic facial features (long face, slightly upslanting palpebral fissures, ptosis of the left eye, prominent bulbous nasal tip, low-hanging columella)

Perne et al.
P-ClinG-88





Computer-assisted image analysis led to identification of a intragenic deletion in *KANSL1* (*de novo*, ACMG class V) associated with **Koolen-de Vries syndrome**

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Multi-omics approaches

Fuctional assays for 18 cases classified as uncertain or unsolved

- Analysis of the methylome (n=4)
- Analysis of the transcriptome (n=11)
- Analysis of the proteome (n=3)

Methylation analysis

Epigenetic signatures could clarify the status of *de novo* missense variants as likely to be benign or pathogenic

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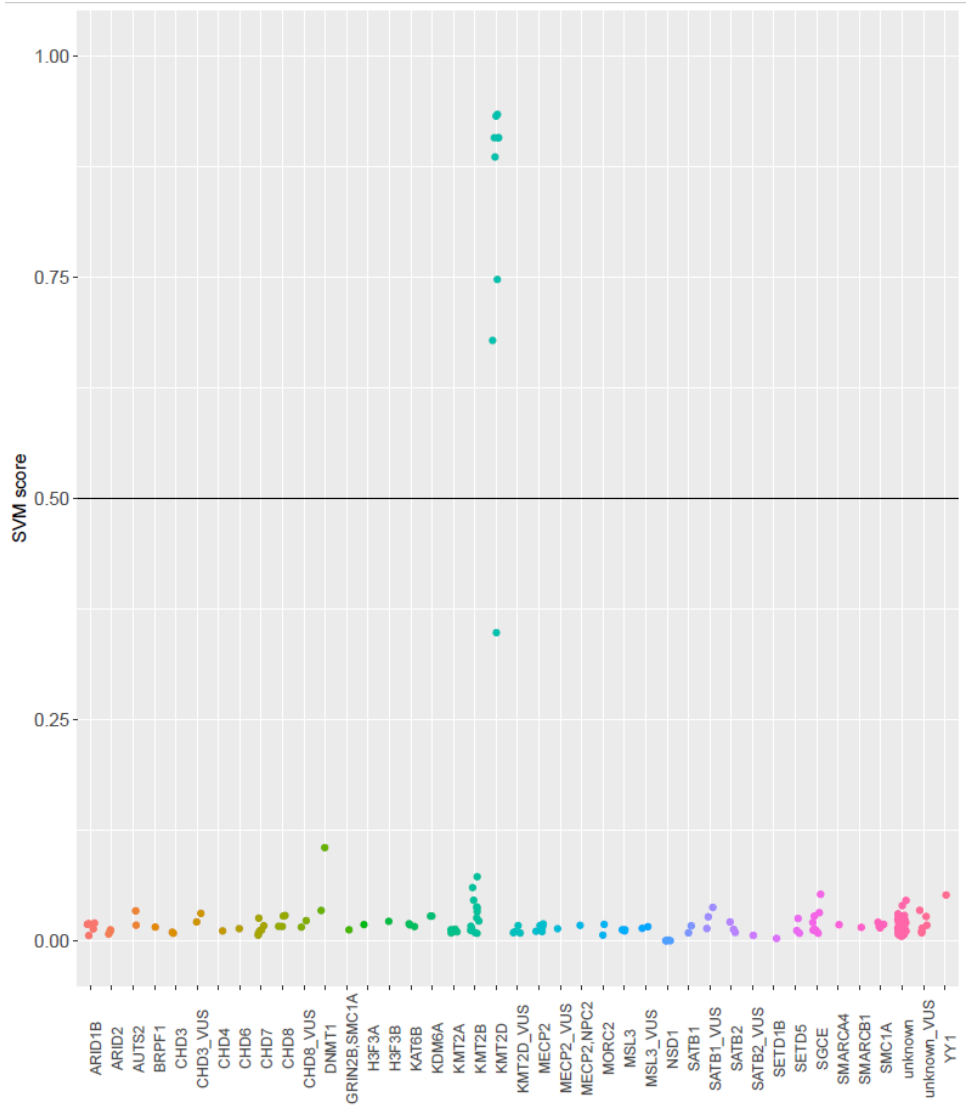
Multi-omics approaches



Methylation analysis

Epigenetic signatures could clarify the status of *de novo* missense variants as likely to be benign or pathogenic

Schreiber et al., Brain. 2021, PMID: 34590685

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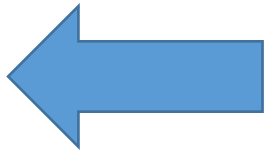
Diagnoses with causal therapeutic implications

- ***ARSA***-associated metachromatic leukodystrophy (MLD)
- ***SLC35C1***-associated congenital disorder of glycosylation (type IIc)
- ***SLC6A8***-associated cerebral creatine deficiency syndrome 1
- ***SLC2A1***-associated GLUT1 deficiency syndrome
- ***PDHA1***-associated pyruvate dehydrogenase E1-alpha deficiency

The gene therapeutic approach with atidarsagene autotemcel has been authorized by EMA in the EU since 17 December 2020.



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SLC6A8-associated creatine deficiency syndrome 1

Clinical features:

- Developmental delay
- Intellectuall disability
- Autism-spectrum disorder
- Muscular hypotonia
- Dysmorphic facial features

(short eye lids, hypertelorism, epicanthus, smooth philtrum)

Brugger M, et al. Gene. 2021.
PMID: 33164824

Brain MRI: delayed meyelination and deficits of white matter

Exome sequencing: heterozygous missense mutation in *SLC6A8*

"During the following 18 months after treatment initiation (at age of nine years) with L-glycine, L-arginine and creatine monohydrate, she showed ***positive effects in her visual-motoric and fine motor function, social behavior*** *(increased self-conciousness, increased attention span),* ***and weight gain*** *(from 4th to the 7th percentile)".*

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Thank you for your attention!

Working group TN Exome analysis

Thank you!

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Averdunk Luisa
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Bender Tim
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Berutti Riccardo
Bettendorf Markus
Betz Regina
Borggräfe Ingo
Bösch Annemarie
Boschann Felix
Brand Fabian
Brugger Melanie
Brunet Theresa
Bufler Philip
Bührer Christoph
Choukair Daniela
Cremer Kirsten
Danyel Magdalena
Demet Önder
Demidov German
Di Donato Nataliya
Ehmke Nadja
Engels Hartmut
Grobe-Einsler Marcus
Graf Elisabeth
Grasemann Corinna
Grigull Lorenz
Groffmann Maximilian
Grundmann Kathrin
Haack Tobias
Hanka Britta
Hanßke Amalia-Mihaela
Hauck Fabian
Heimbach André
Heinen André
Hellenbroich Yorck
Hempel Maja
Herget Theresia
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Kaindl Angela
Kaiser Frank
Kallinich Tillmann
Kaufmann Lilian
Kehrer Martin
Klein Christoph
Klinkhammer Hannah
Klockgether Thomas
Knaus Alexej
Kobeleva Xenia
Körholz Julia
Kotzaeridou Ourania
Krawitz Peter
Kreiss Martina
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Krude Heiko
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Lee-Kirsch Min Ae
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Moosa Shahida
Mücke Martin
Müller-Felber Wolfgang
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Neugebauer Julia
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Okka Kimmich
Okun Pamela M.
Ossowski Stephan
Pantel Jean Tori
Pantelis Karakostas
Pauly Martje
Perne Claudia
Peters Sophia
Reuner Ulrike
Riedhammer Korbinian M.
Riess Olaf
Rillig Franziska
Ripke Annekatrin
Rohlfs Meino
Rudolph Cornelia
Sarah Bernsen
Schaaf Christian P.
Schäfer Valentin
Schlapakow Elena
Schlein Christian
Schmidt Axel
Schramm Christoph
Schröck Evelin
Schröder Sebastian
Schütz Catharina
Schwaibold Eva M. C.
Schwartzmann Sarina
Sczakiel Henrike
Sergio Castro Gomez
Sivalingam Sugirthan
Spielmann Malte
Spier Isabel
Stieber Christiane
Stoltenburg Corinna
Strom Tim
Suter Aude-Annick
Tibelius Alexandra
Ullrich Kurt
Wagner Matias
Weigand Heike
Weiler-Normann Christina
Weinhold Natalie
Weiß Claudia
Westphal Dominik S.
Weydt Patrick
Vill Katharina
Zawada Michal

Patients and their families

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Thank you for your attention!