GestaltMatcher IN GENOMIC DIAGNOSTICS

NHS Genomic AI Masterclass

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THIS WORKSHOP

GestaltMatcher

GestaltMatcher
Artificial Intelligence

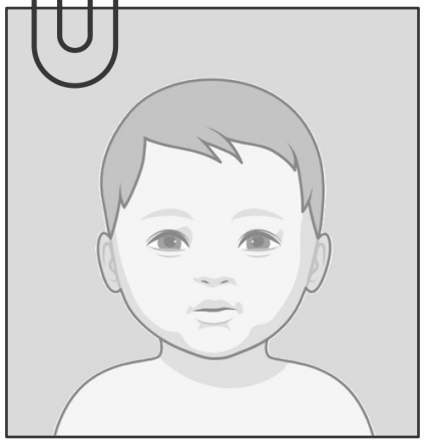
GestaltMatcher
Database

GestaltMatcher
Services

YOUR AI DYSMORPHOLOGIST

Analysing Facial Features with GestaltMatcher AI

CASE PRESENTATION



Patient ID *1234567*

DoB *01/04/2023*

Female

PATIENT RECORD

NEUROLOGICAL

- Gross motor developmental delay
- Intellectual disability
- Ataxia and spastic paraparesis

ENT

- Progressive hearing loss

SKELETON & GROWTH

- Dysostosis (joint contractures, kyphosis, osteopenia)
- Delayed linear growth

INFECTIONS

- Frequent respiratory infections

GASTROINTESTINAL & ORGANS

- Recurrent diarrhoea
- Hepatosplenomegaly

CASE PRESENTATION

Patient ID *1234567*

DoB *01/04/2023*

Female

PATIENT RECORD

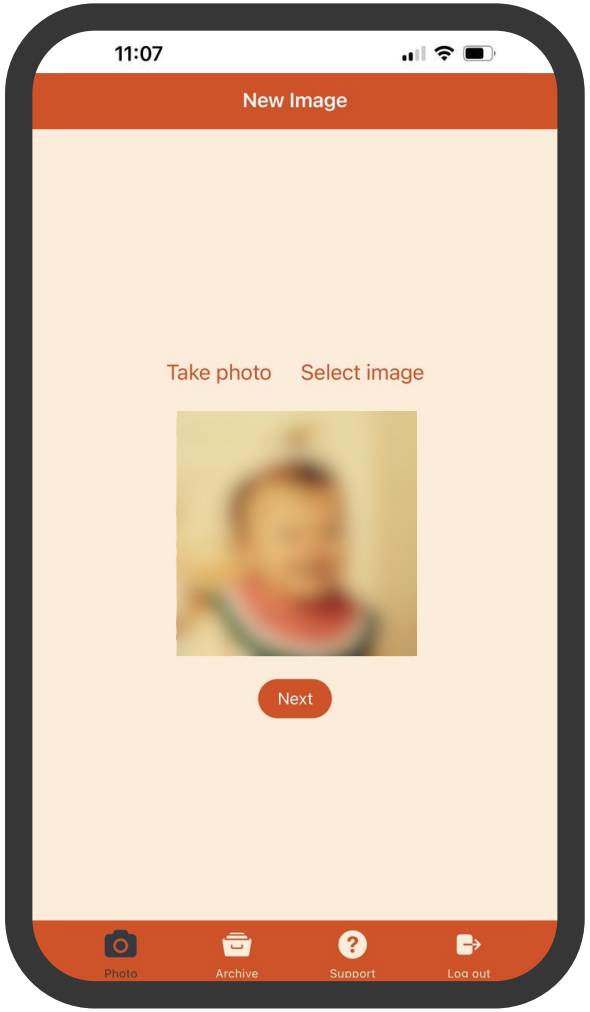
WHAT CONDITION WOULD YOU SUSPECT?

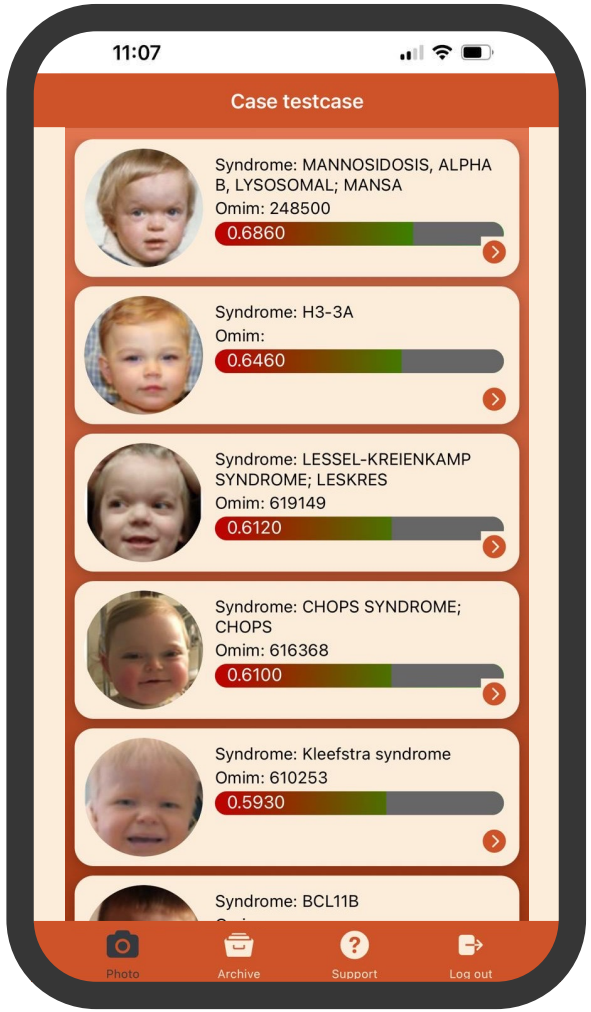
? Mucolipidosis
? α-Mannosidosis
? Kleefstra syndrome
? Smith-Lemli-Opitz syndrome

WHOM WOULD YOU CONSULT FOR ADVICE?

? Colleague in your practice / department
? Clinical geneticist or dysmorphologist
? Syndrome database
? Referral to a centre for rare diseases
? Dysmorphology atlas
? Artificial intelligence

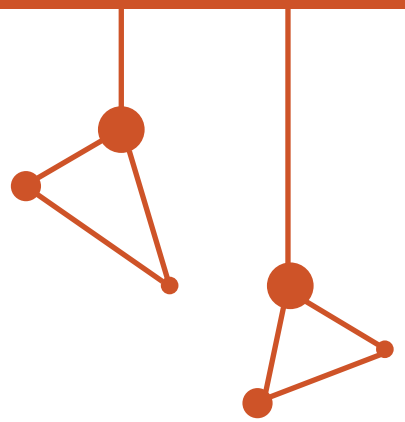
AI TOOL FOR RARE DISEASES



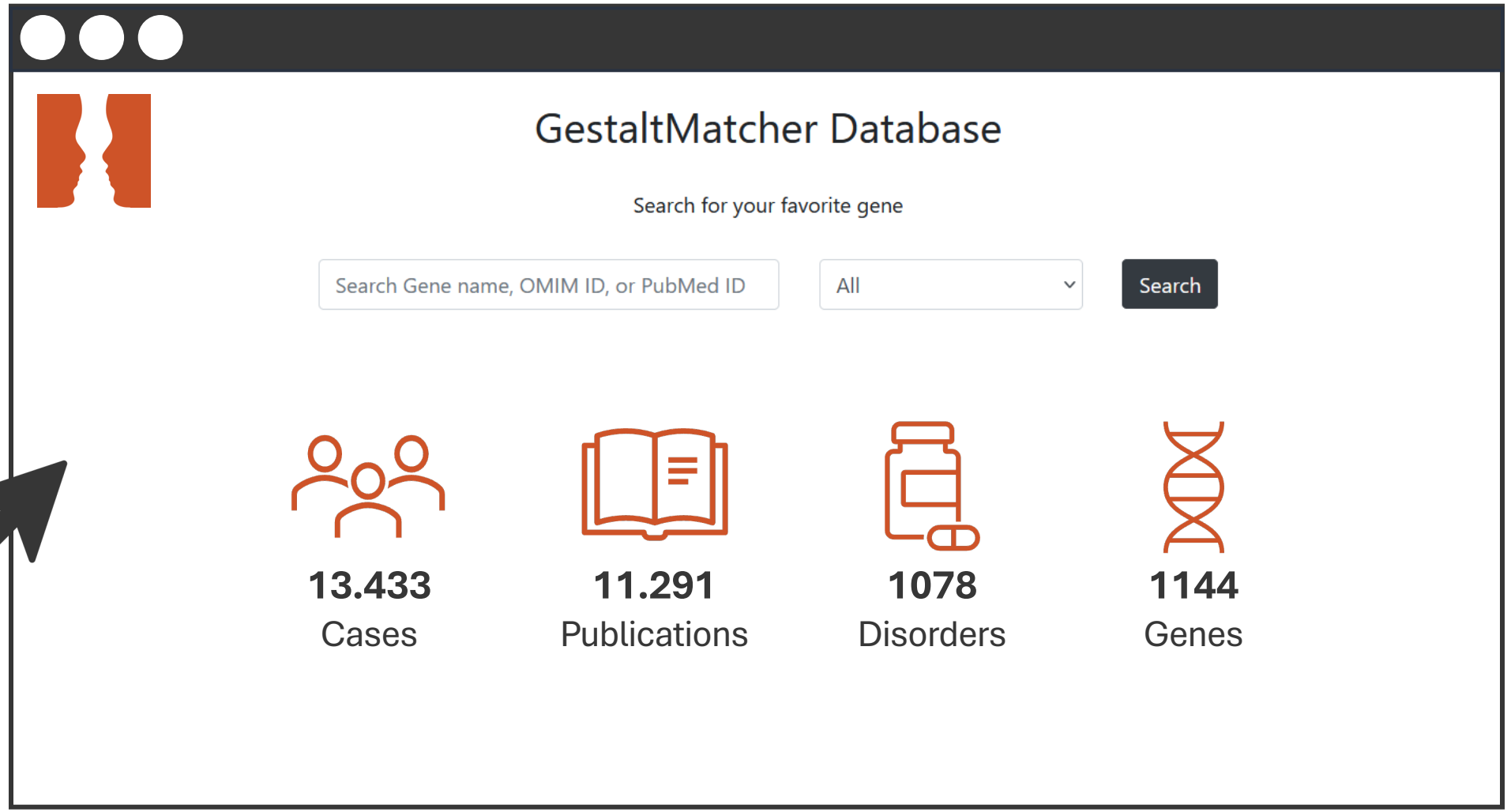


CURATED DATABASE

Data Basis of GestaltMatcher AI



CURATED DATABASE



CURATED DATABASE

Clinician

Patient

Publication

GestaltMatcher DB

DOI

FAIR case

includes:

Images

Metadata

e.g. sex, ethnicity, age, diagnosis, molecular information, phenotypic information (HPO), PMID/DOI, author

Registered GMDB users

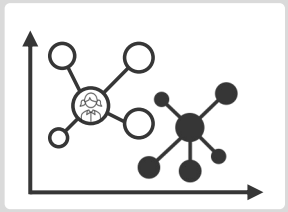
Computer Scientists

Search

Gallery view

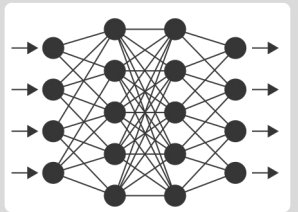
Analyse

Research plattform
GestaltMatcher API

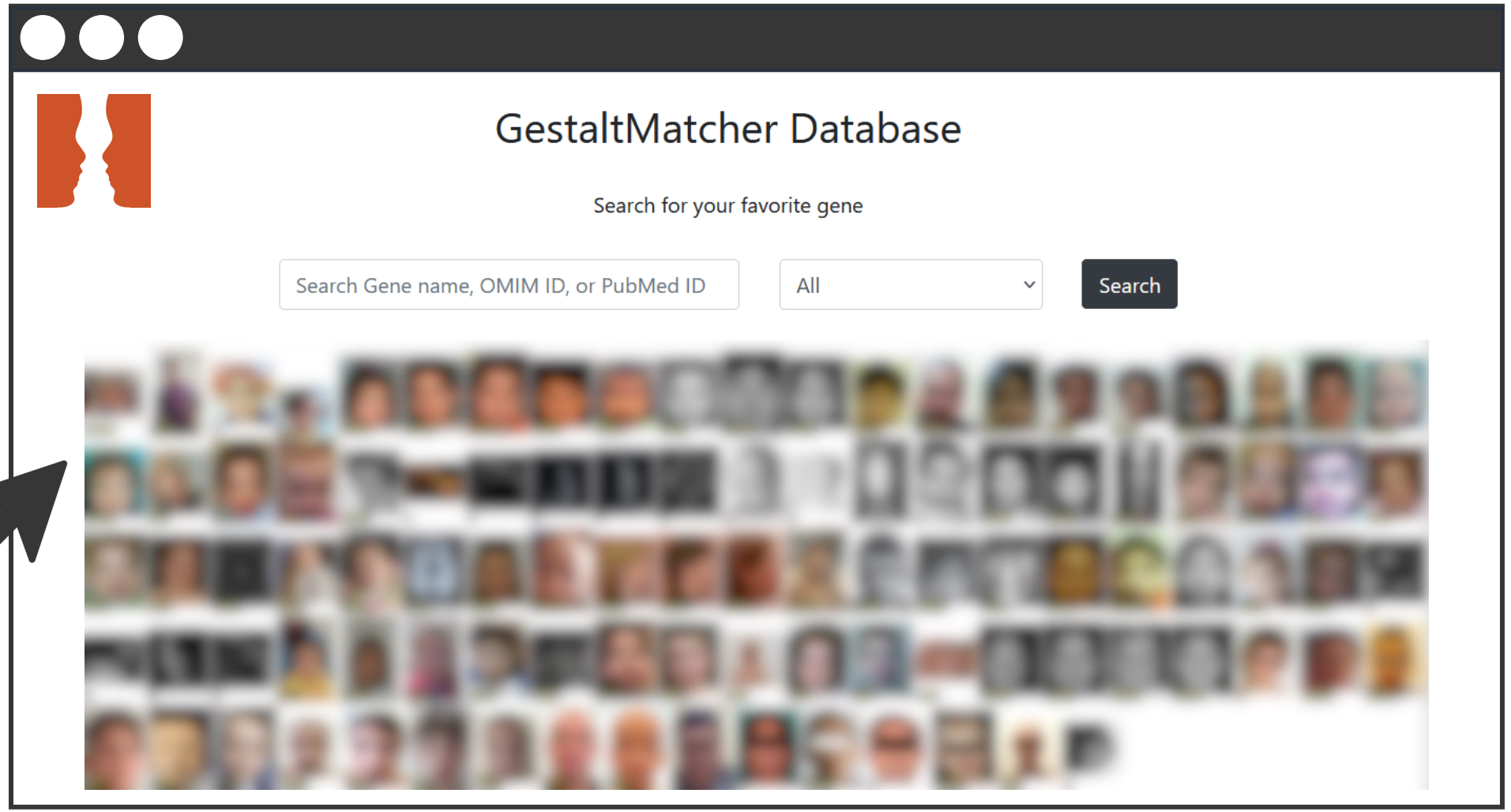


Training

AI training set

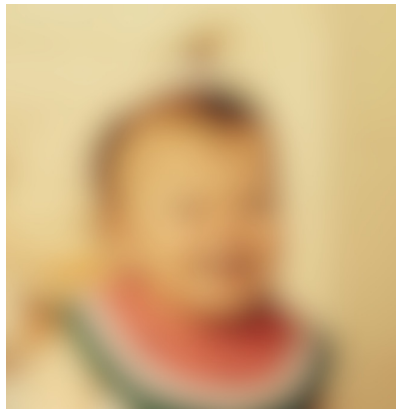


CURATED DATABASE



CURATED DATABASE

Uploaded Image:



Analysis Results:

Model version: v1.1.0

Gallery version: 27.01.2025

Suggested disorders

Rank	Disorder	OMIM	Distance	Most similar patient
1	MANNOSIDOSIS, ALPHA B, LYSOSOMAL; MANSA	248500	0.636	9714
2	NEURODEVELOPMENTAL DISORDER WITH SEVERE MOTOR IMPAIRMENT AND ABSENT LANGUAGE;	617804	0.663	12356

CURATED DATABASE

Patient published in

PubMed: 18651971

Family numbering: -

Corresponding author Dag Malm

DOI: 10.1186/1750-1172-3-21

Diagnosed disorders

OMIM	Disorder	Diagnosed
248500	MANNOSIDOSIS, ALPHA B, LYSOSOMAL	unknown

Molecular Information

Gene	Test	HGVS
MAN2B1 4125	exome sequencing heterozygous	

Phenotypic Information

HPO	Description	Status
HP:0000256	Macrocephaly	Present
HP:0000470	Short neck	Present
HP:0002553	Highly arched eyebrow	Present
HP:0011120	Concave nasal ridge	Present
HP:0011220	Prominent forehead	Present

CURATED DATABASE

Review | Open access | Published: 23 July 2008

Alpha-mannosidosis

Dag Malm & Øivind Nilssen

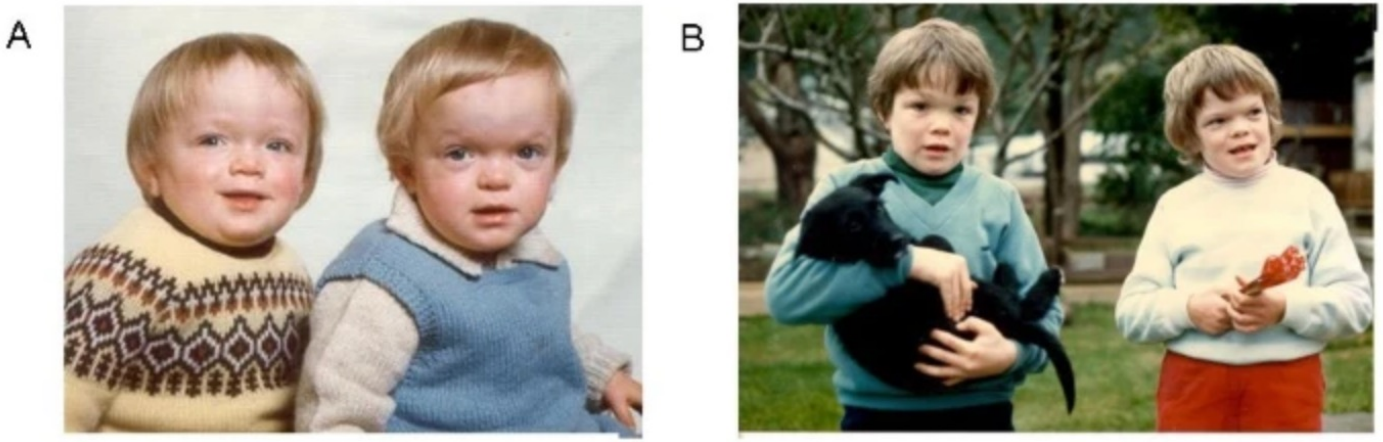
Orphanet Journal of Rare Diseases **3**, Article number: 21 (2008) | Cite this article

35k Accesses | **18** Altmetric | Metrics

BMC Part of Springer Nature

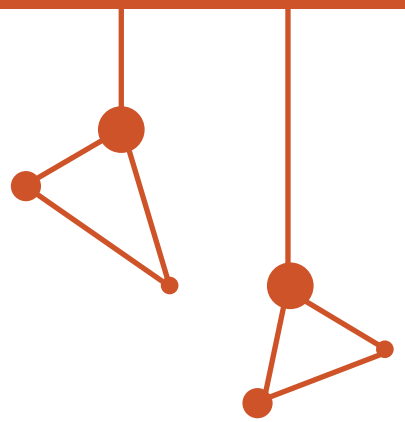
Orphanet Journal of Rare Diseases

Figure 1



TRY IT YOURSELF

Hands-on with GestaltMatcher



GET TO KNOW GMDB

1 Go to *db.gestaltmatcher.org*

2 Log in with your credentials

3 Explore GMDB (5 min)

SUGGESTIONS

SEARCH FOR A GENE OF INTEREST → *Gallery* or *Home* → Type gene/OMIM ID/disorder and *Search*

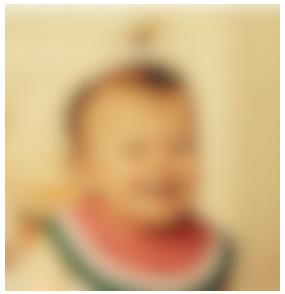
EXPLORE A CASE → Click on an image in the gallery → *View Patient*

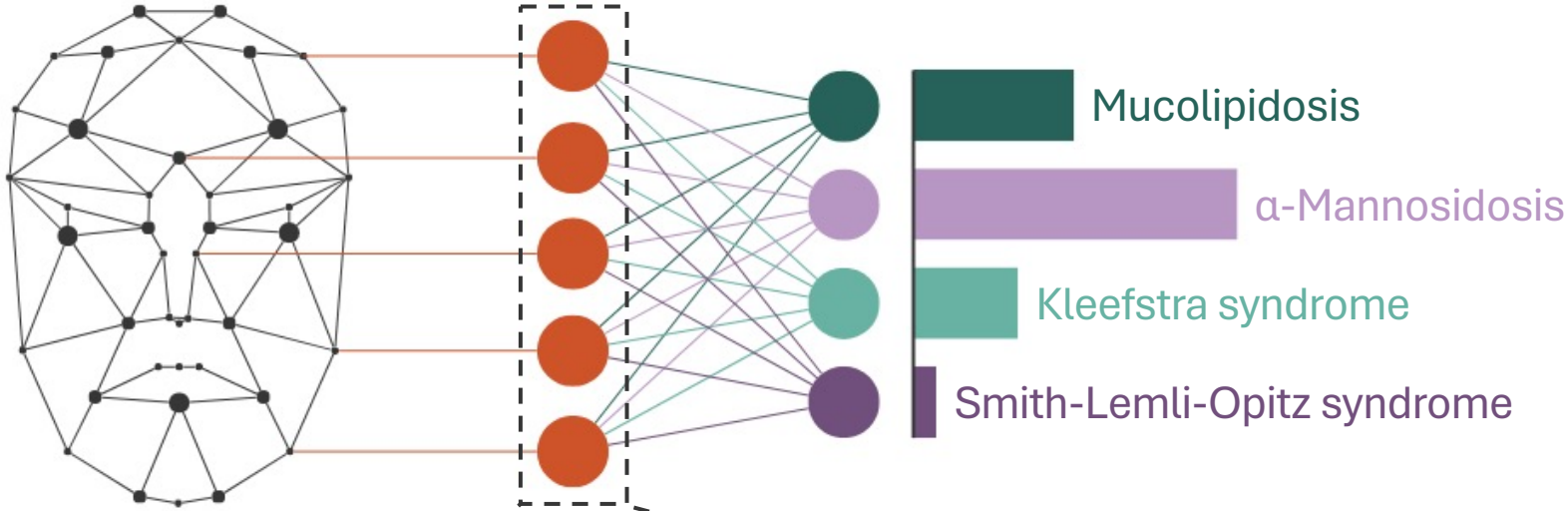
ANALYZE A PHOTO → *My Data* → *Analyze Patient* → Upload a portrait photo → *Send Image*

ARTIFICIAL INTELLIGENCE

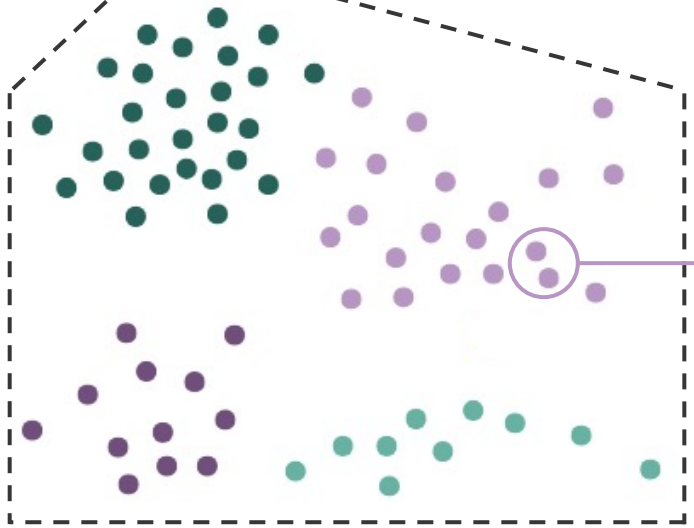
How GestaltMatcher Analyses Facial Features

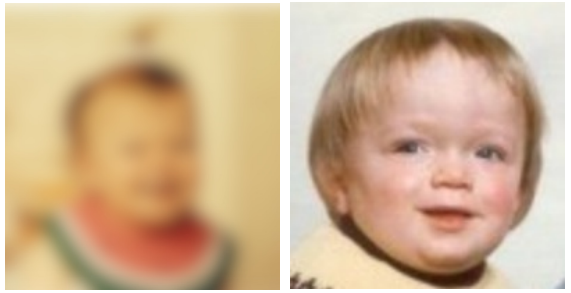
NEXT-GENERATION PHENOTYPING



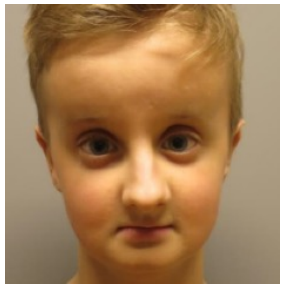


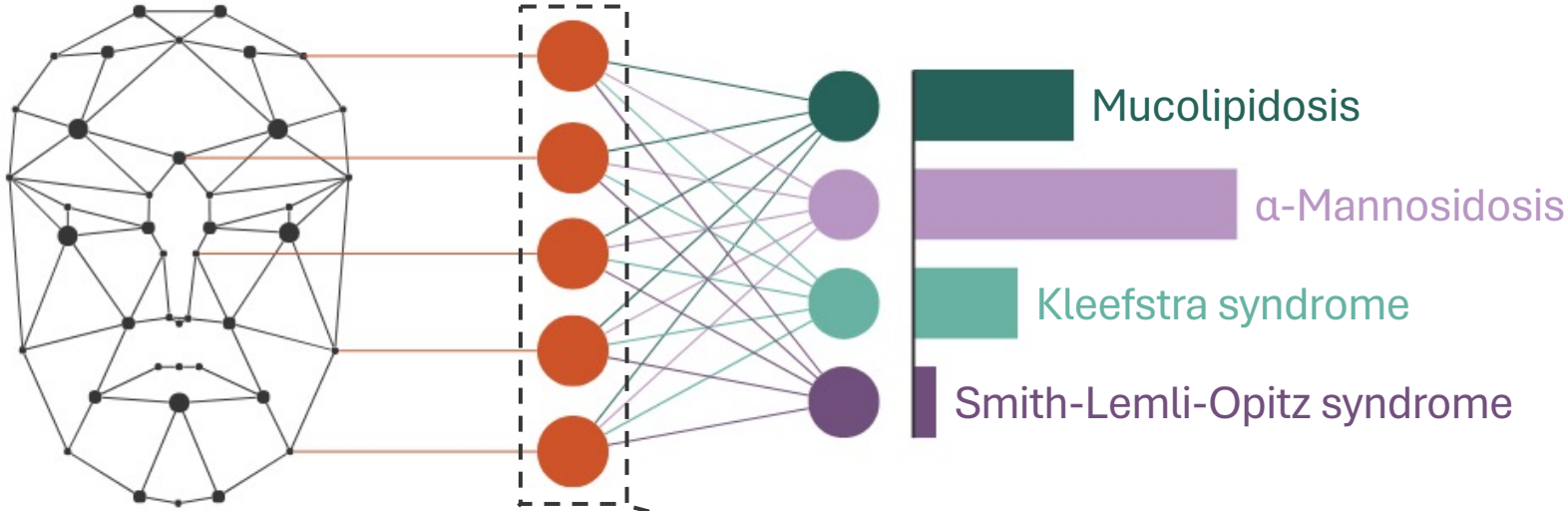
CLINICAL FACE PHENOTYPE SPACE



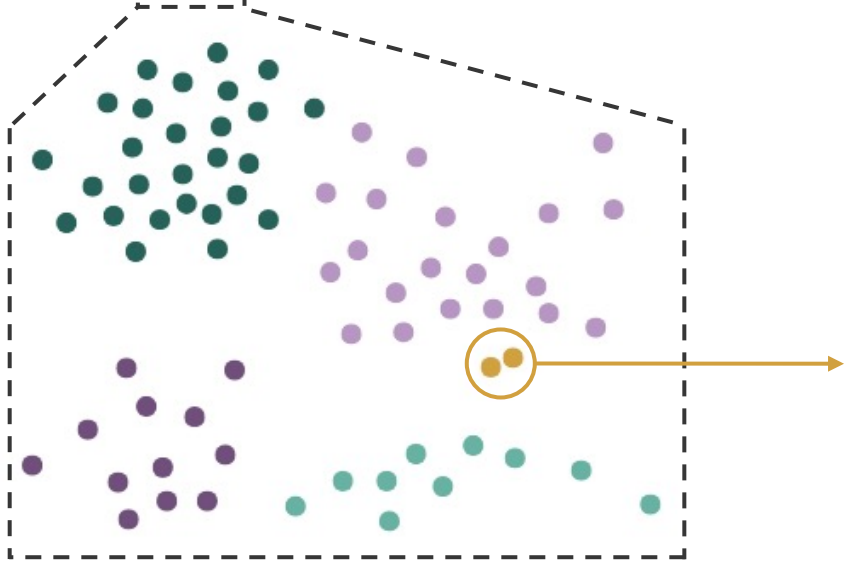


NEXT-GENERATION PHENOTYPING

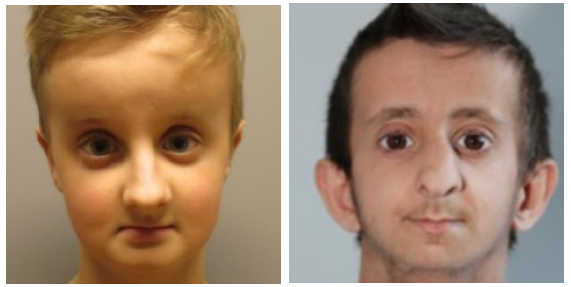




CLINICAL FACE PHENOTYPE SPACE



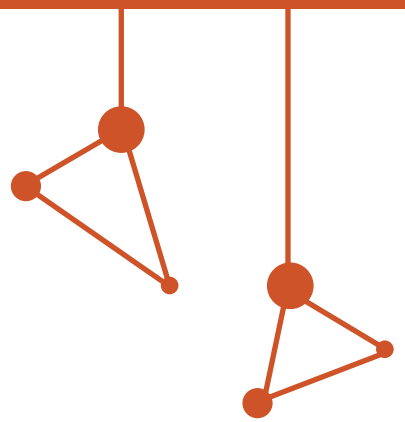
Patients with the same ultra-rare disorder



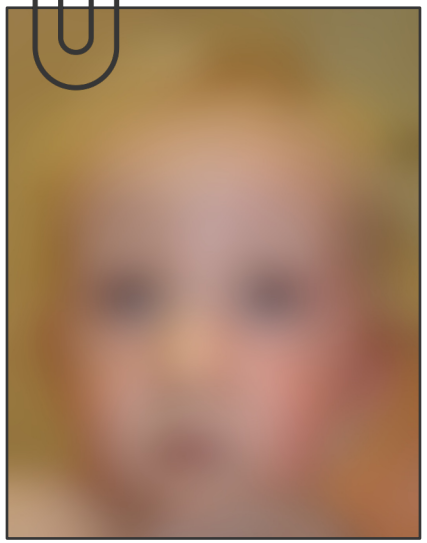
Marbach et al. *Am J Hum Genet* (2019)

TRY IT YOURSELF

Hands-on with GestaltMatcher



CASE EXAMPLE



Patient ID *0000001*

DoB *13/08/2024*

Male

PATIENT RECORD

CLINICAL NOTES

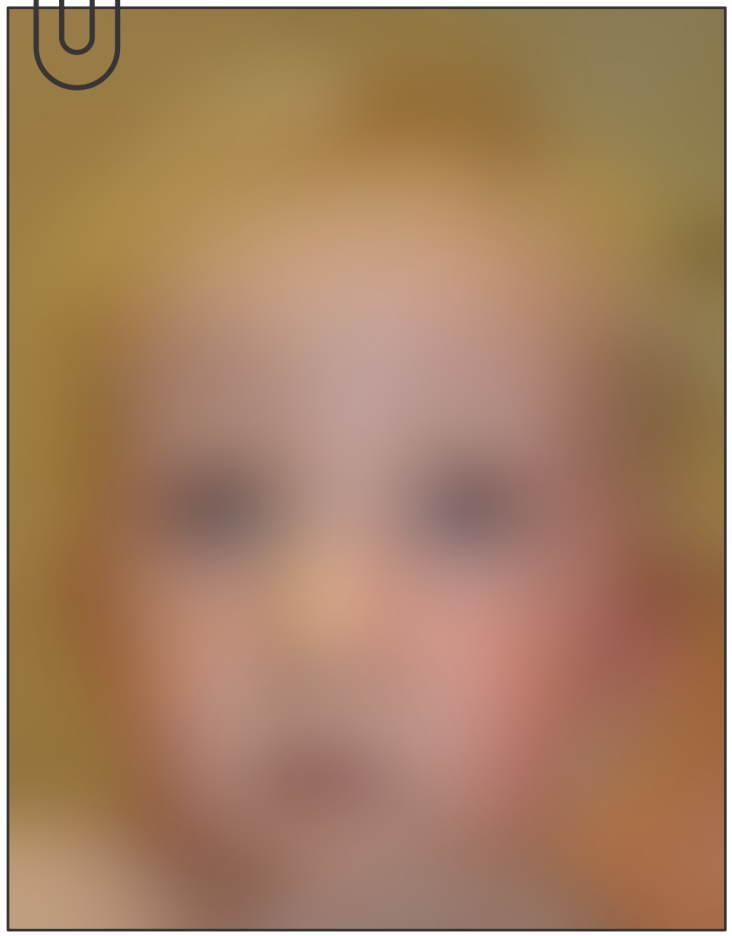
- Muscular hypotonia
- Hypoplastic left heart
- Short stature
- Recurrent otitis media
- Not able to sit without support

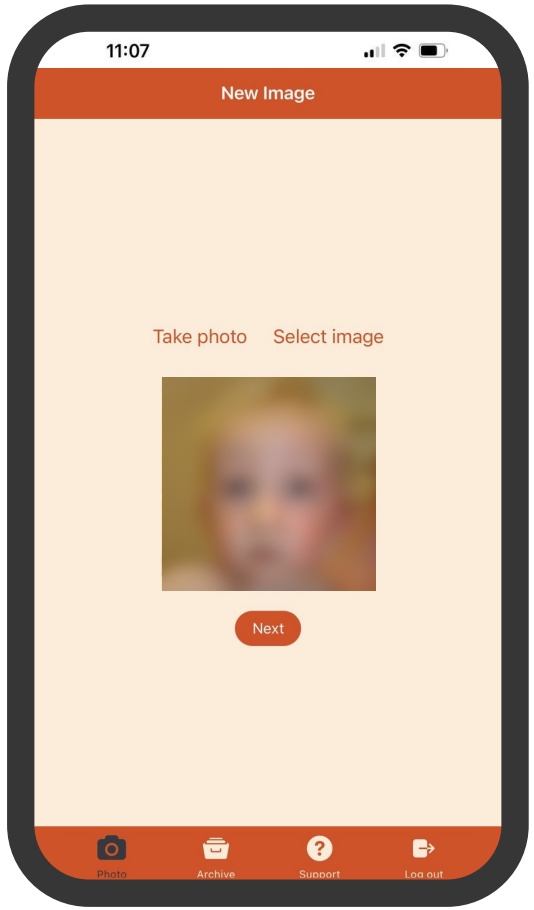
FACIAL DYSMORPHISM

- Long palpebral fissures
- Low-set ears
- Small chin

WHAT CONDITION DO YOU SUSPECT?

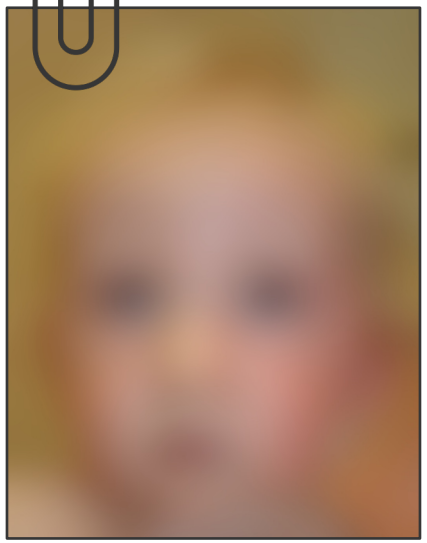
CASE EXAMPLE





1. Open GestaltMatcher app
2. Log in with your credentials
3. Click *Take photo*
4. Take photo and resize
5. Click *Use photo* and *Next*

CASE EXAMPLE



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FACIAL DYSMORPHISM

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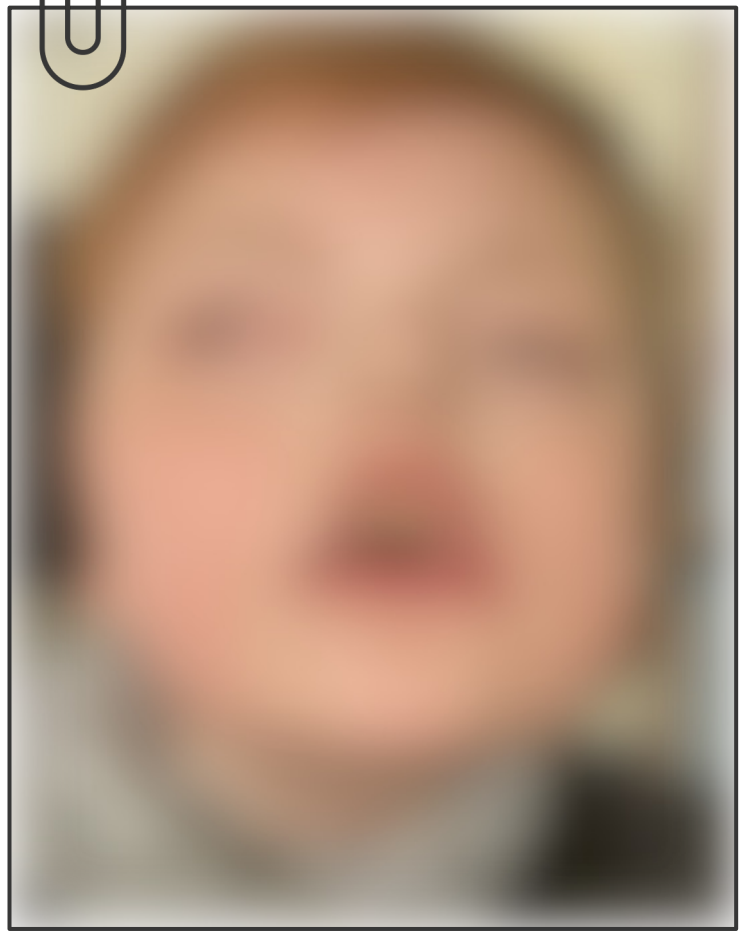
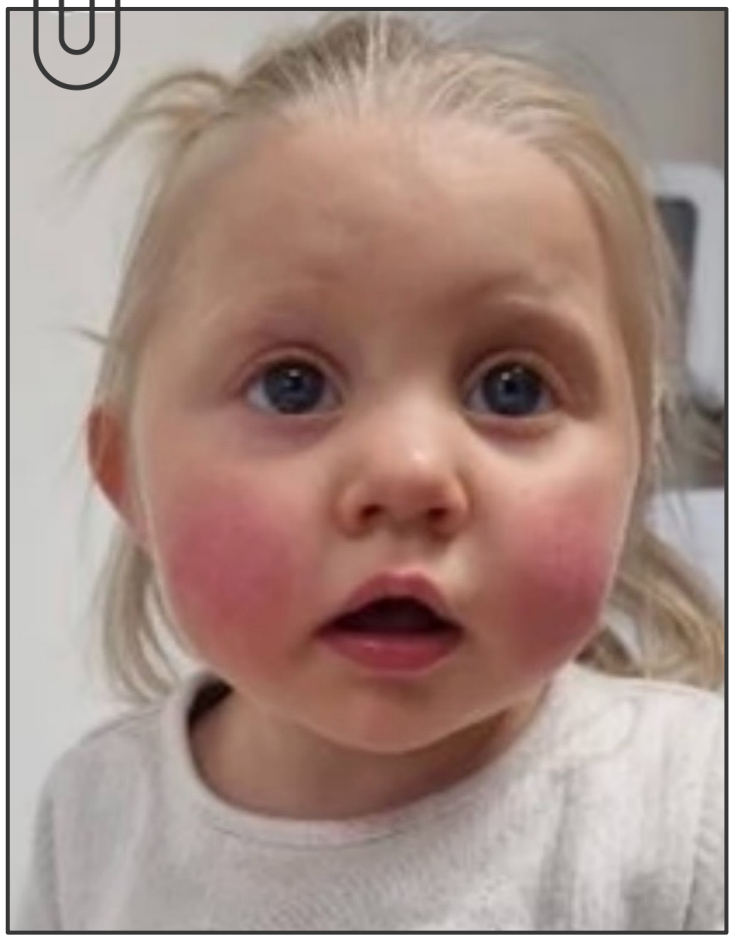
- Recurrent otitis media

WHAT CONDITION DO YOU SUSPECT?

KABUKI SYNDROME

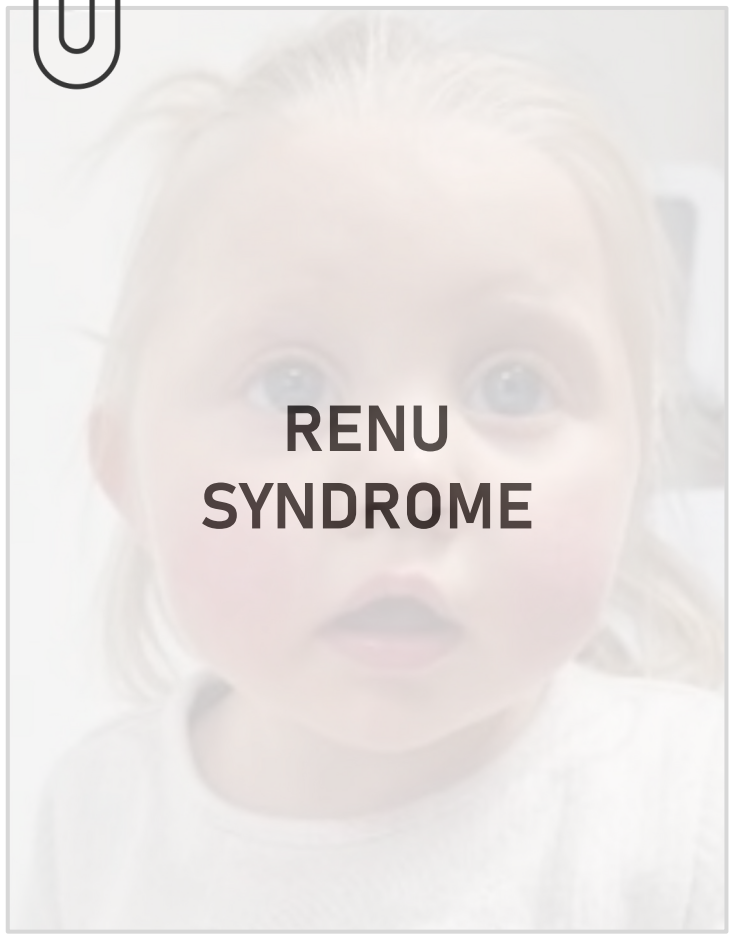
TRY IT YOURSELF





TRY IT YOURSELF

HYPERPHOSPHATASIA WITH MENTAL RETARDATION SYNDROME



RENU SYNDROME

VARIANT INTERPRETATION

Support for ACMG PP4 Criterion

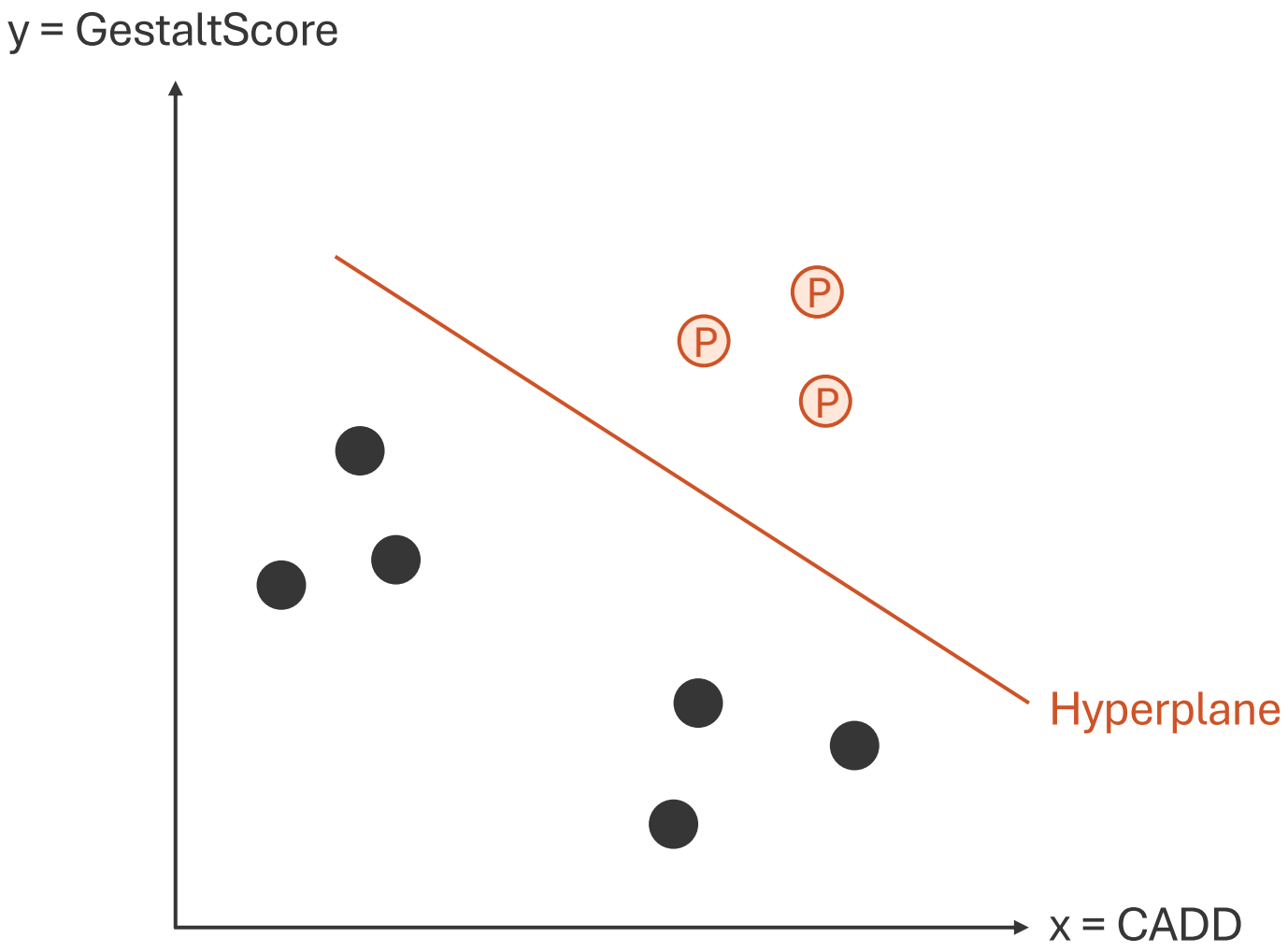
A SHIFT IN DIAGNOSTIC REASONING

GENOMIC DATA ⟵ **PHENOTYPE**

AMCG PP4

"Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology"

COMBINING SCORES



SUPPORT VECTOR MACHINE

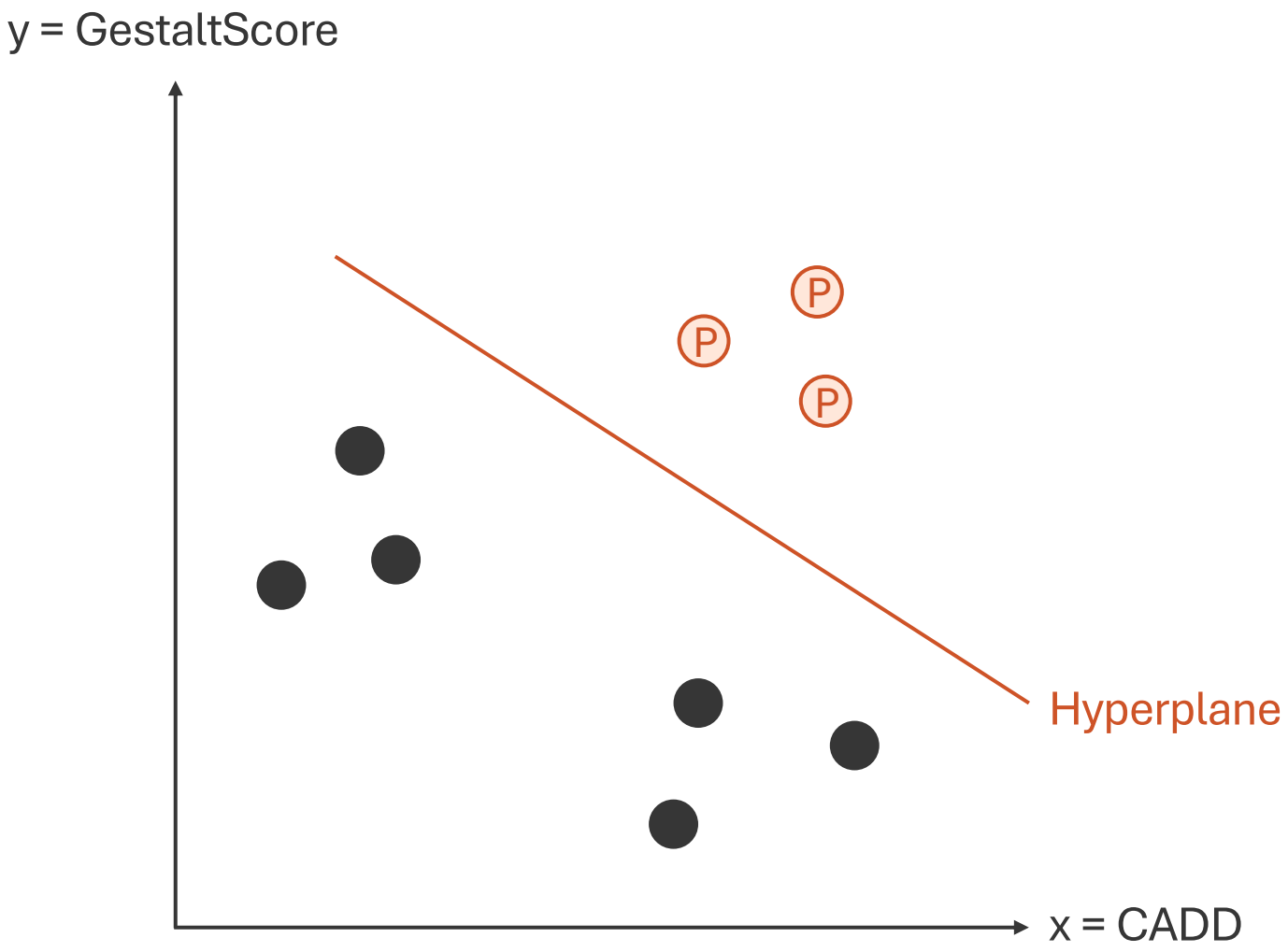
classifies data by finding a hyperplane that maximizes distance between two classes

for example between

P pathogenic

benign

COMBINING SCORES



PEDIA APPROACH

PRIORITIZATION OF EXOME DATA
BY IMAGE ANALYSIS

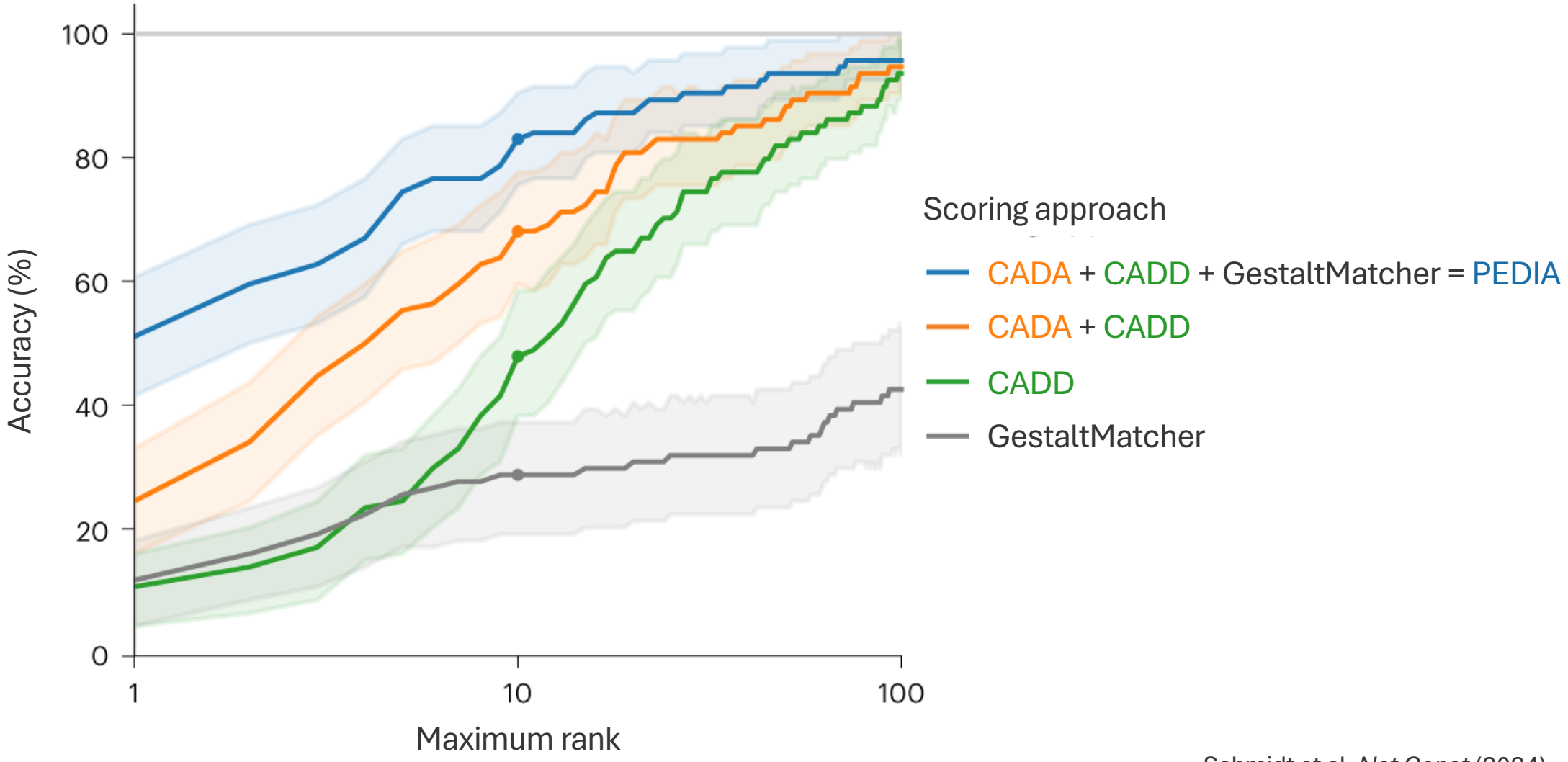
PEDIA SCORE

= α CADD + β GestaltScore

↓

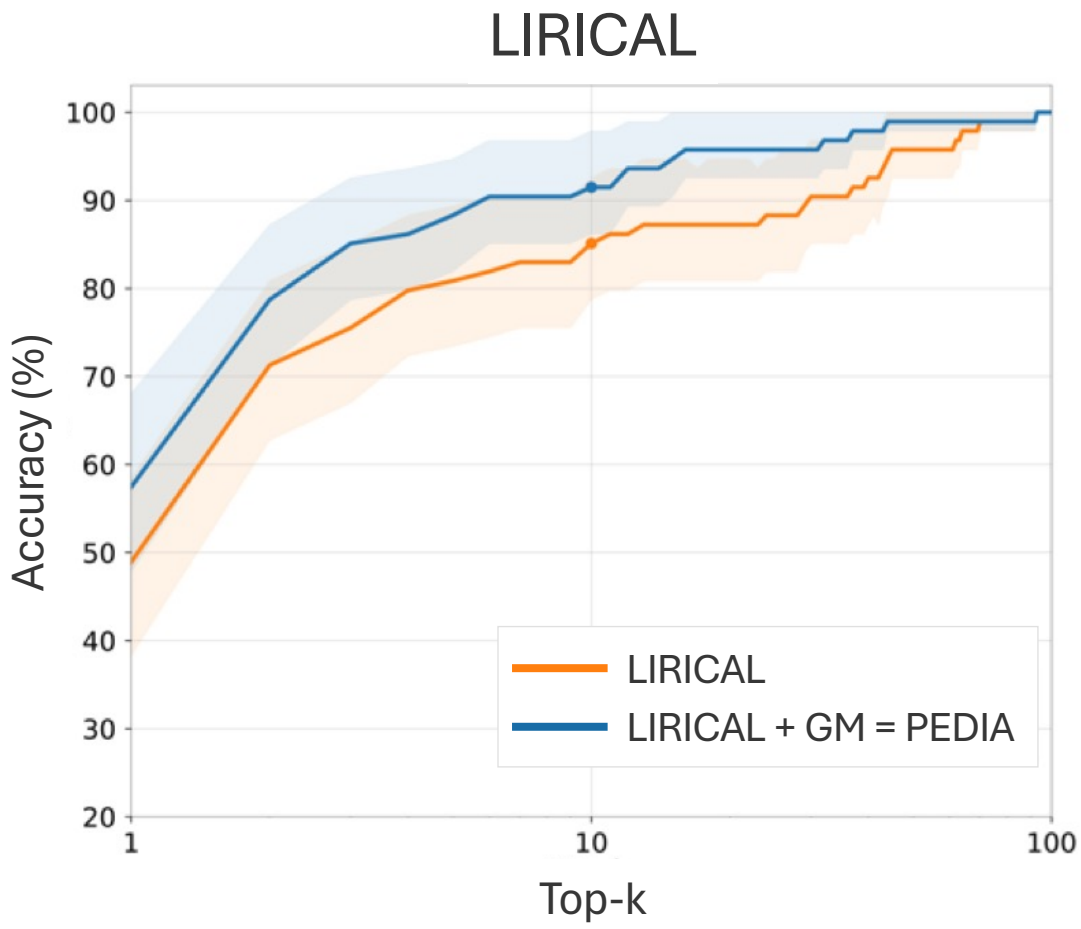
Find ideal combination
of α and β

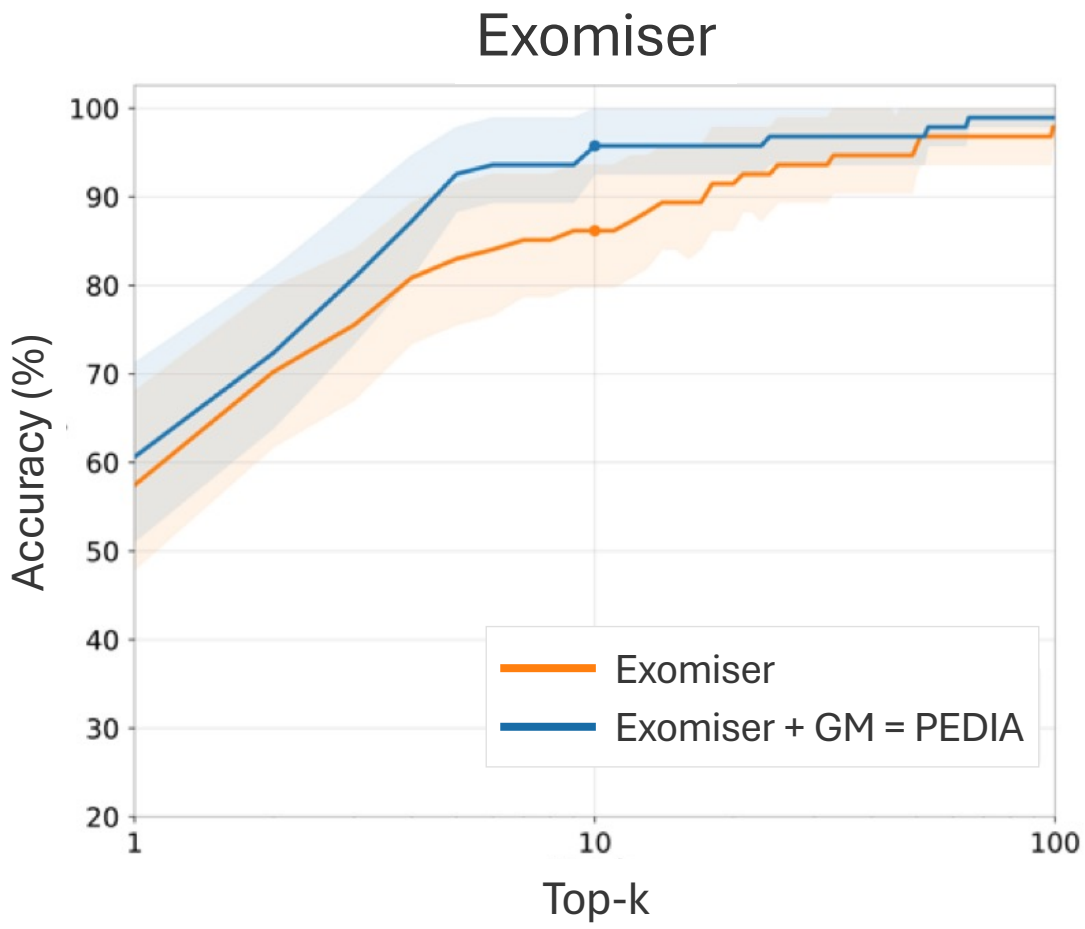
GESTALT IMPROVES ACCURACY



Schmidt et al. *Nat Genet* (2024)

GESTALT IMPROVES ACCURACY





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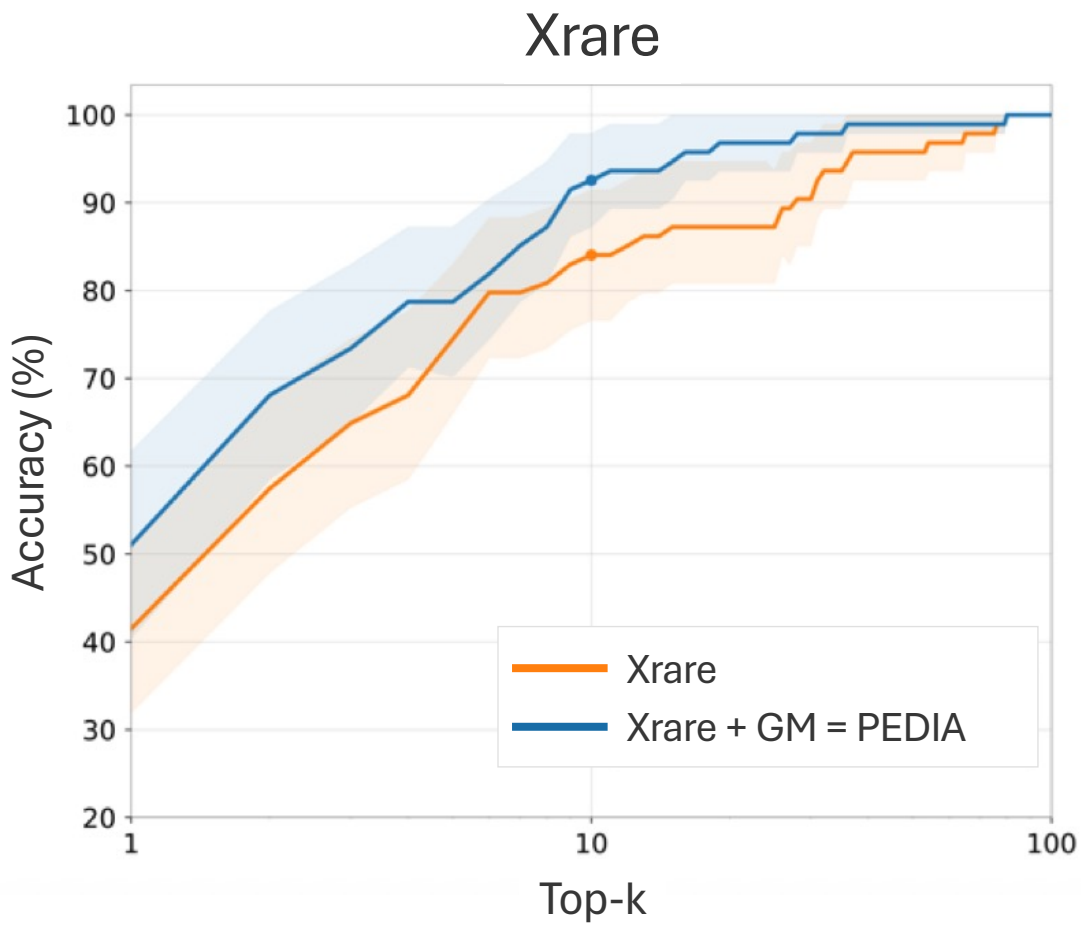
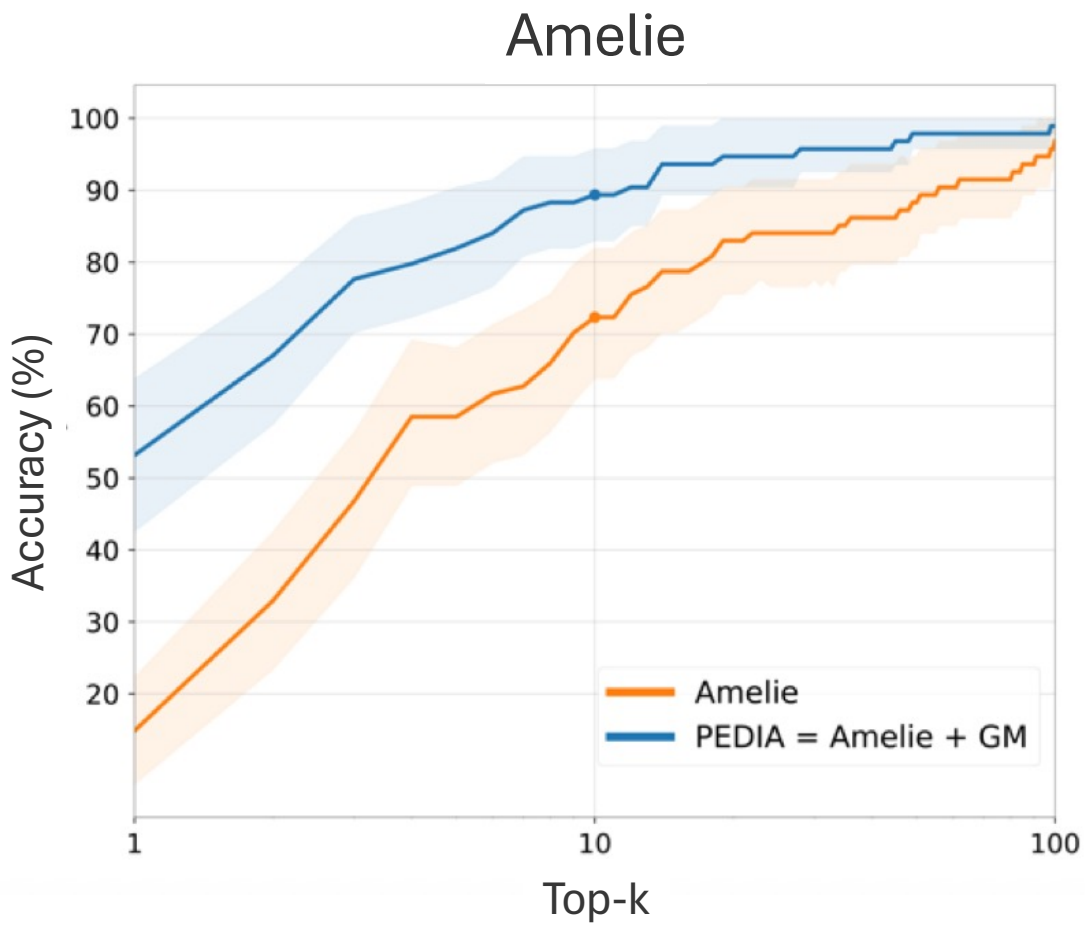
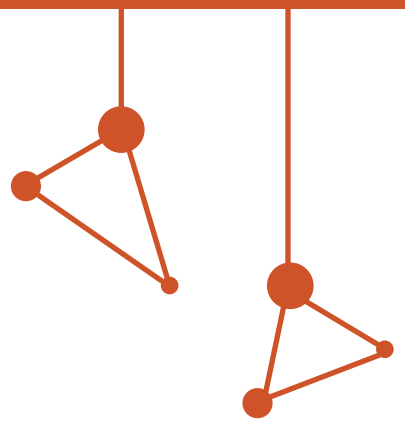




Schmidt et al. *Nat Genet* (2024)

TRY IT YOURSELF

Variant Analysis with GestaltMatcher



CASE EXAMPLE

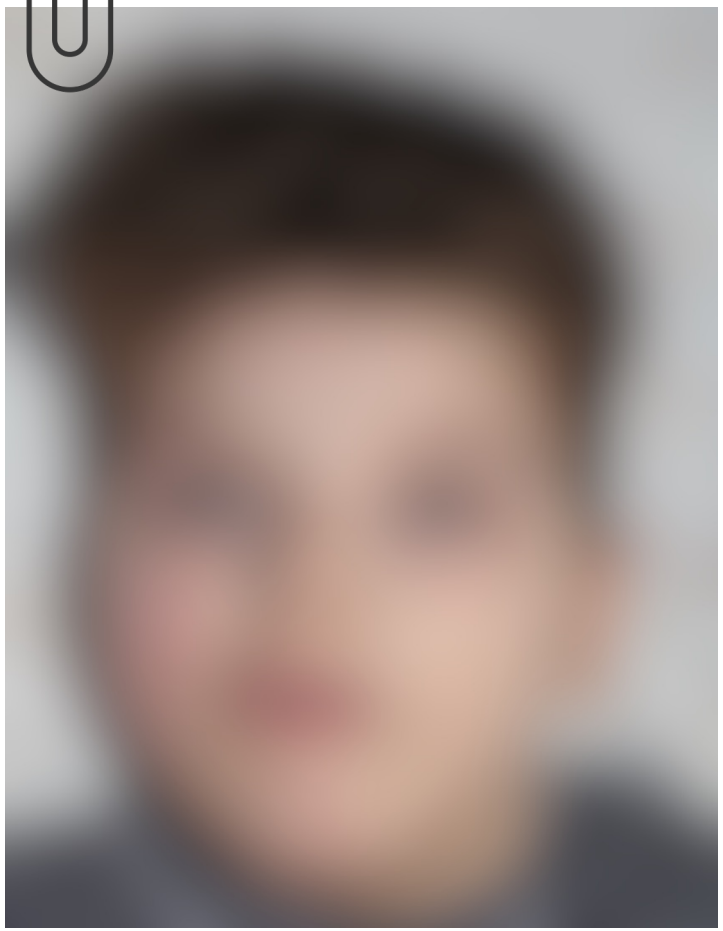
Genomic variant	HGVS	Disorder (Mode of Inheritance)	CADD / REVEL	GestaltScore	Feature Rank (CADA)	ACMG
Chr9-86585070-A-C [0/1]	*HNRPK* c.1361+7T>G; p.?	Au-Kline syndrome (AD)	20 / -		**2**	Likely benign: PM2, BP4 (ClinVar: conflicting)
Chr16-19621652-C-G [0/1]	*VPS35L* c.938G>C; p.Ser313Ter	Ritscher-Schinzel syndrome (AR)	38 / 1		**7**	Pathogenic: PVS1, PM2, PP5 (ClinVar: likely pathogenic)
Chr16-19711792-G-C [0/1]	*VPS35L* c.2886G>C; p.Arg962Ser	Ritscher-Schinzel syndrome (AR)	22.4 / 0.304		**7**	Likely benign: PM2, BP4, BP1 (ClinVar: VUS)
Chr12-49447863-G-A [0/1]	*KMT2D* c.571C>T; p.Arg191Trp	Kabuki syndrome (AD)	26.6 / 0.502		**25**	VUS: PP3, PM2, PP5 (ClinVar: conflicting)

CASE EXAMPLE

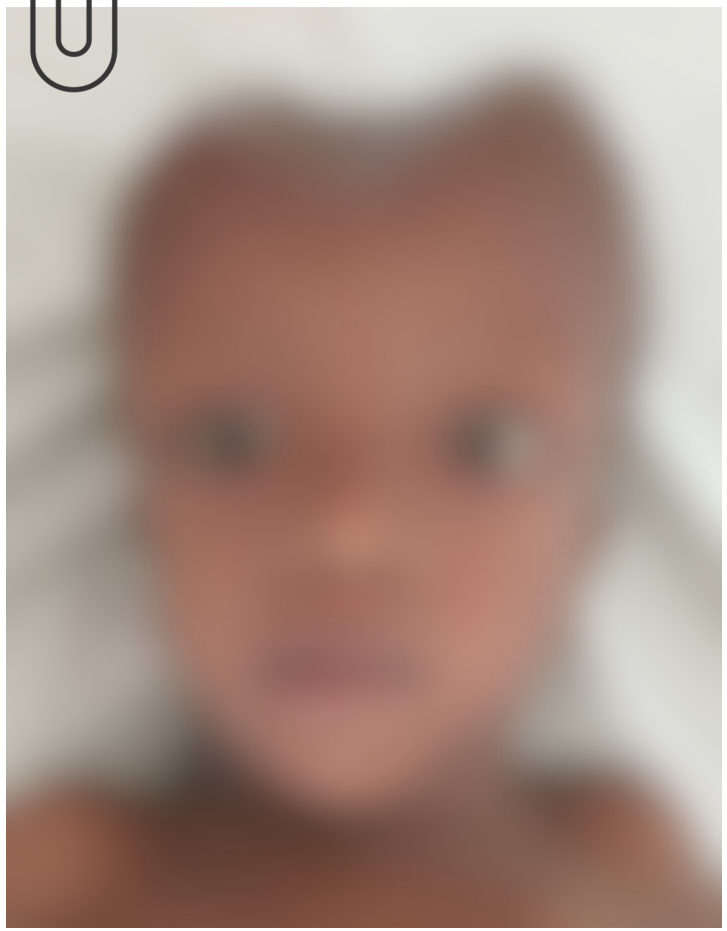
Genomic variant	HGVS	Disorder (Mode of Inheritance)	CADD / REVEL	GestaltScore ↑	Feature Rank (CADA)	ACMG
Chr12-49447863-G-A [0/1]	*KMT2D* c.571C>T; p.Arg191Trp	Kabuki syndrome (AD)	26.6 / 0.502	**0.611 (rank 1)**	25	**Likely pathogenic: PP4**, PP3, PM2, PP5
Chr9-86585070-A-C [0/1]	*HNRPK* c.1361+7T>G; p.?	Au-Kline syndrome (AD)	20	**0.692 (rank 8)**	2	Likely benign: PM2, BP4 (ClinVar: conflicting)
Chr16-19621652-C-G [0/1]	*VPS35L* c.938G>C; p.Ser313Ter	Ritscher-Schinzel syndrome (AR)	38 / 1	**0.794 (rank 71)**	7	Pathogenic: PVS1, PM2, PP5 (ClinVar: likely pathogenic)
Chr16-19711792-G-C [0/1]	*VPS35L* c.2886G>C; p.Arg962Ser	Ritscher-Schinzel syndrome (AR)	22.4 / 0.304	**0.794 (rank 71)**	7	Likely benign: PM2, BP4, BP1 (ClinVar: VUS)

TRY IT YOURSELF

CASE 2



CASE 3



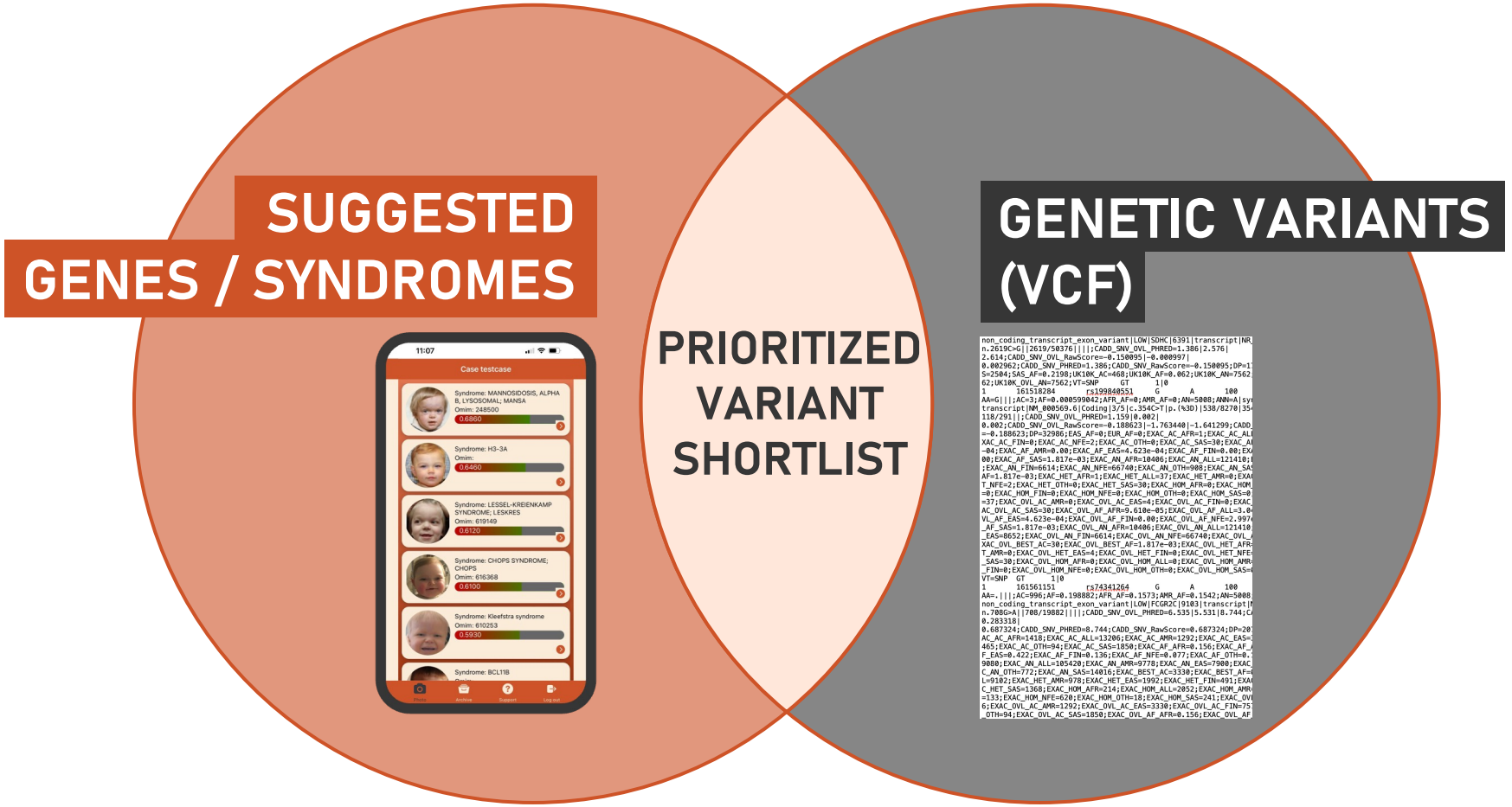
CASE 2

Genomic variant	HGVS	Disorder (Mode of Inheritance)	CADD / REVEL	GestaltScore	Feature Rank (CADA)	ACMG
Chr11-71146484-G-T [0/1]	*DHCR7* c.1365C>A p.Tyr455Ter	Smith-Lemli-Opitz syndrome (AR)	36 / -	**0.772 (rank 59)**	73	Likely pathogenic: PVS1, PM2, PP5 (ClinVar: pathogenic)
ChrX-132670158-C- [0/1]	*GPC3* c.1737del; p.His580ThrfsTer48	Simpson-Golabi-Behmel syndrome (XLR)	34 / -	**0.663 (rank 7)**	1772	VUS: PVS1, PM2
Chr1:27123380-27223003_del 99 kB deletion [0/1]	*PIGV, ZDHHC8*	?	- / -	**0.591 (rank 1)**	11	VUS: 1A, 3A, 4L, (5H)
Chr1-27121547-C-A [0/1]	*PIGV* c.1022C>A; p.Ala341Glu	Mabry syndrome (HPMRS) (AR)	20	**0.591 (rank 1)**	11	Pathogenic: PM2, PM5, PS3, PP5 (ClinVar: pathogenic)

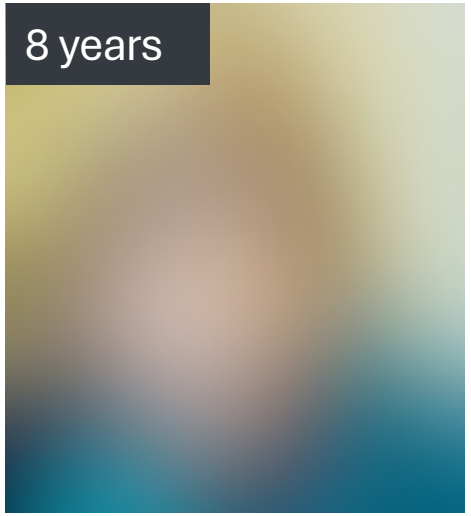
CASE 3

Genomic variant	HGVS	Disorder (Mode of Inheritance)	CADD / REVEL	GestaltScore	Feature Rank (CADA)	ACMG
Chr12-124233333-G-C [0/1]	*ATP6V0A2* c.1935+1G>C; p.?	Cutis Laxa syndrome (AR)	33 / -	**0.632 (rank 2)**	73	Likely pathogenic: PVS1, PM2
Chr12-124218508-C-CT [0/1]	*ATP6V0A2* c.688dup; p.Trp230Lysfs*10	Cutis Laxa syndrome (AR)	- / -	**0.632 (rank 2)**	73	Likely pathogenic: PVS1, PM2
Chr12-112888129-G-A [0/1]	*PTPN11* c.145G>A; p.Gly49Arg	Noonan syndrome (AD)	27 / 0.304	**0.814 (rank 1)**	658	Likely pathogenic: PP3, PM1, PM2 (ClinVar: VUS)
Chr16-3832738-T-C [0/1]	*CREBB* c.1406A>G; p.Gln469Arg	Menke-Hennekam syndrome (AD)	20	**0.566 (rank 12)**	3	VUS (ClinVar: conflicting)

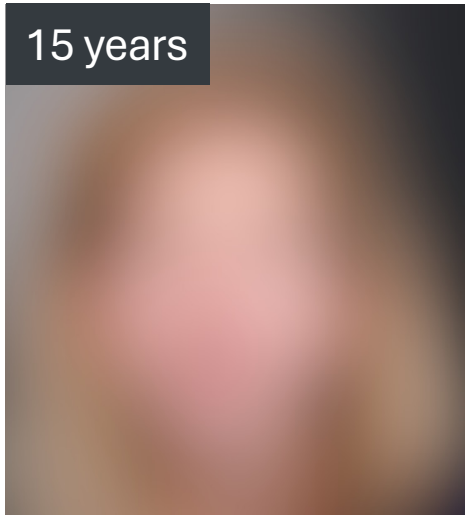
SUMMARY


SUGGESTED GENES / SYNDROMES
11:07
Case testcase
Syndrome: MANNOSIDOSIS, ALPHA B, LYSOSOMAL; MANSA
Omim: 248500
0.6860
Syndrome: H3-3A
Omim:
0.6460
Syndrome: LESSEL-KREIENKAMP SYNDROME; LESKRES
Omim: 619149
0.6120
Syndrome: CHOPS SYNDROME; CHOPS
Omim: 616368
0.6100
Syndrome: Kleefstra syndrome
Omim: 610253
0.5930
Syndrome: BCL11B
PRIORITIZED VARIANT SHORTLIST
GENETIC VARIANTS (VCF)

USE CASE IN VARIANT ANALYSIS

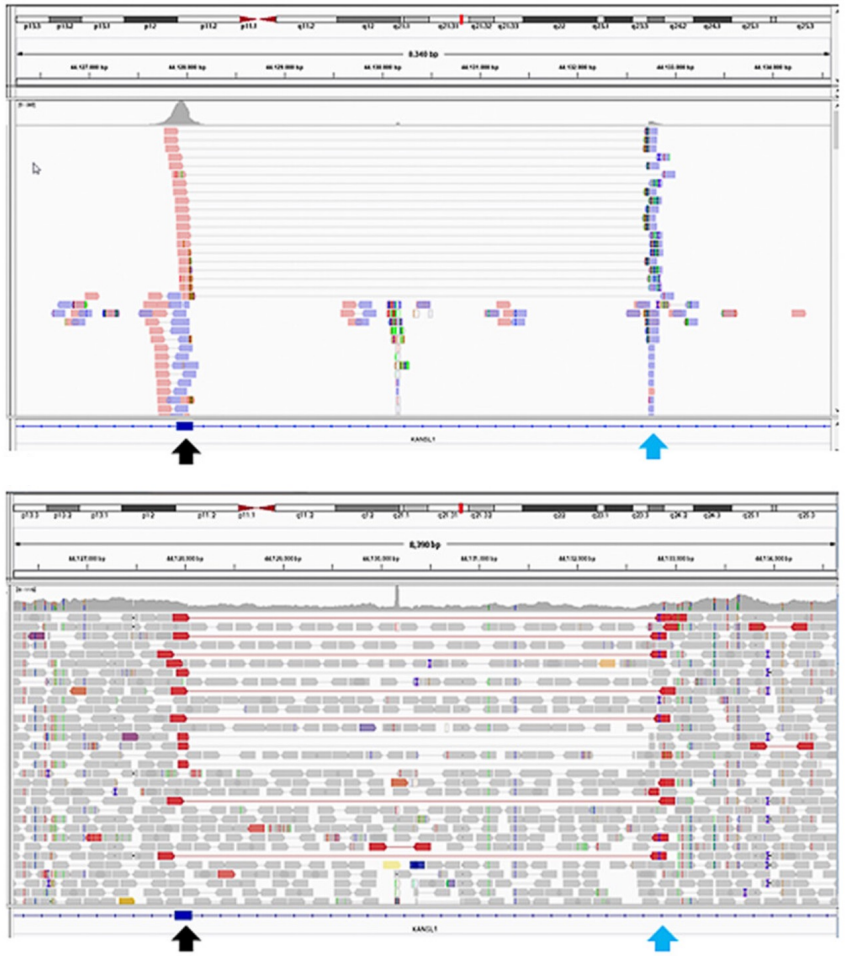


Suggested disorders	
Rank	**Disorder**
1	KOOLEN-DE VRIES SYNDROME; KDVS
2	Cardiofaciocutaneous syndrome
3	FOCAL DERMAL HYPOPLASIA; FDH
4	OHDO SYNDROME, SBBYS VARIANT; SBBYSS
5	BARBER-SAY SYNDROME; BBRSAY



Suggested disorders	
Rank	**Disorder**
1	KOOLEN-DE VRIES SYNDROME; KDVS
2	OHDO SYNDROME, SBBYS VARIANT; SBBYSS
3	KEIPERT SYNDROME; KPTS
4	Noonan syndrome
5	H4C3

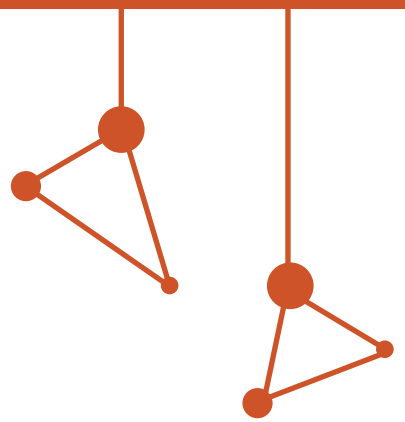
KANSL1



Brand et al. *Hum Mutat* (2022)

OUTLOOK

(Your) Future with GestaltMatcher



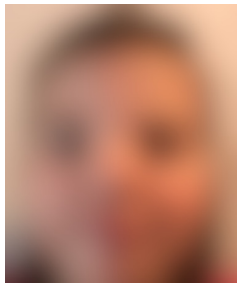
FROM HEAD TO TOE

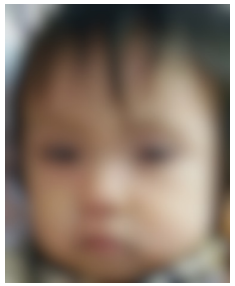
GestaltMatcher

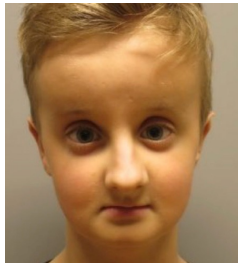
Bone2Gene

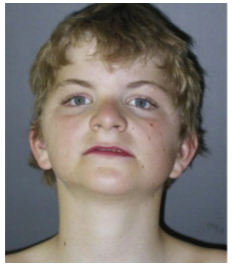
Eye2Gene

Faces

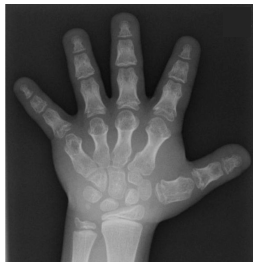

PIGV

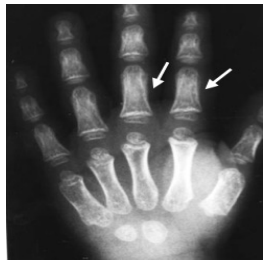

KMT2D

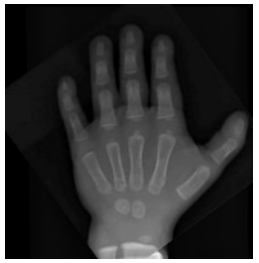

LEMD2

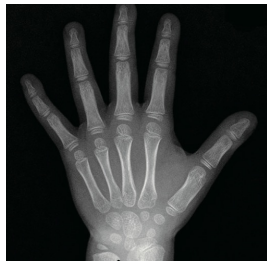

PACS1

Bones

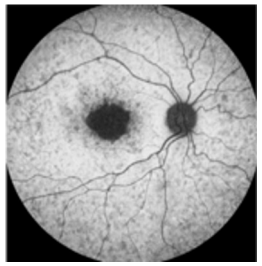

PRKAR1A


RMRP


PIGV


SHOX

Eyes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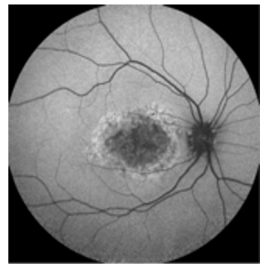
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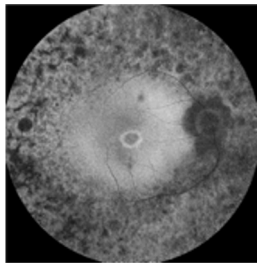
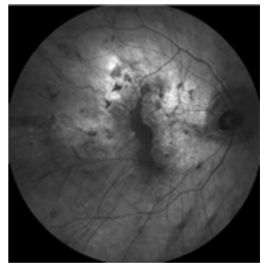

USH2A


CHM

Pontikos, Woof, et al. (2025) *Nat Mach Intel*

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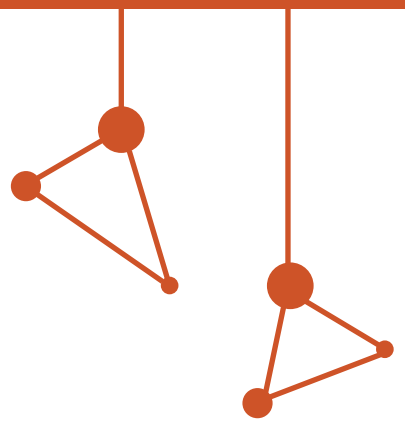
STIFTUNGEN Wirtgen Invest

GO-Bio initial | next

THANK YOU!



We hope you enjoyed our session!

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