



GestaltMatcher IN GENOMIC DIAGNOSTICS

NHS Genomic AI Masterclass

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24 June 2025



THIS WORKSHOP



GestaltMatcher

GestaltMatcher
Artificial Intelligence



GestaltMatcher
Database

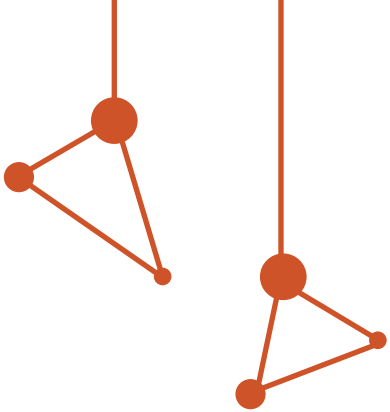


GestaltMatcher
Services

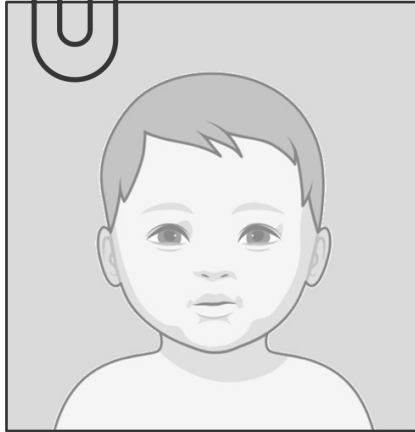


YOUR AI DYSMORPHOLOGIST

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

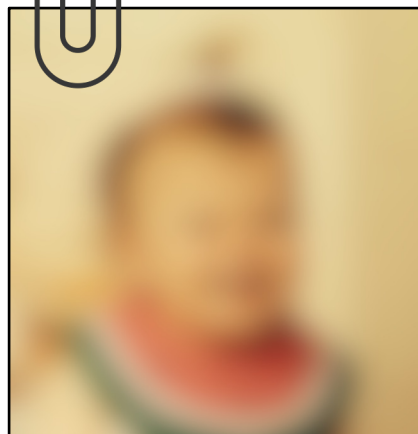
INFECTIONS

- Frequent respiratory infections

GASTROINTESTINAL & ORGANS

- Recurrent diarrhoea
- Hepatosplenomegaly

CASE PRESENTATION



Patient ID 1234567

DoB 01/04/2023

Female

PATIENT RECORD

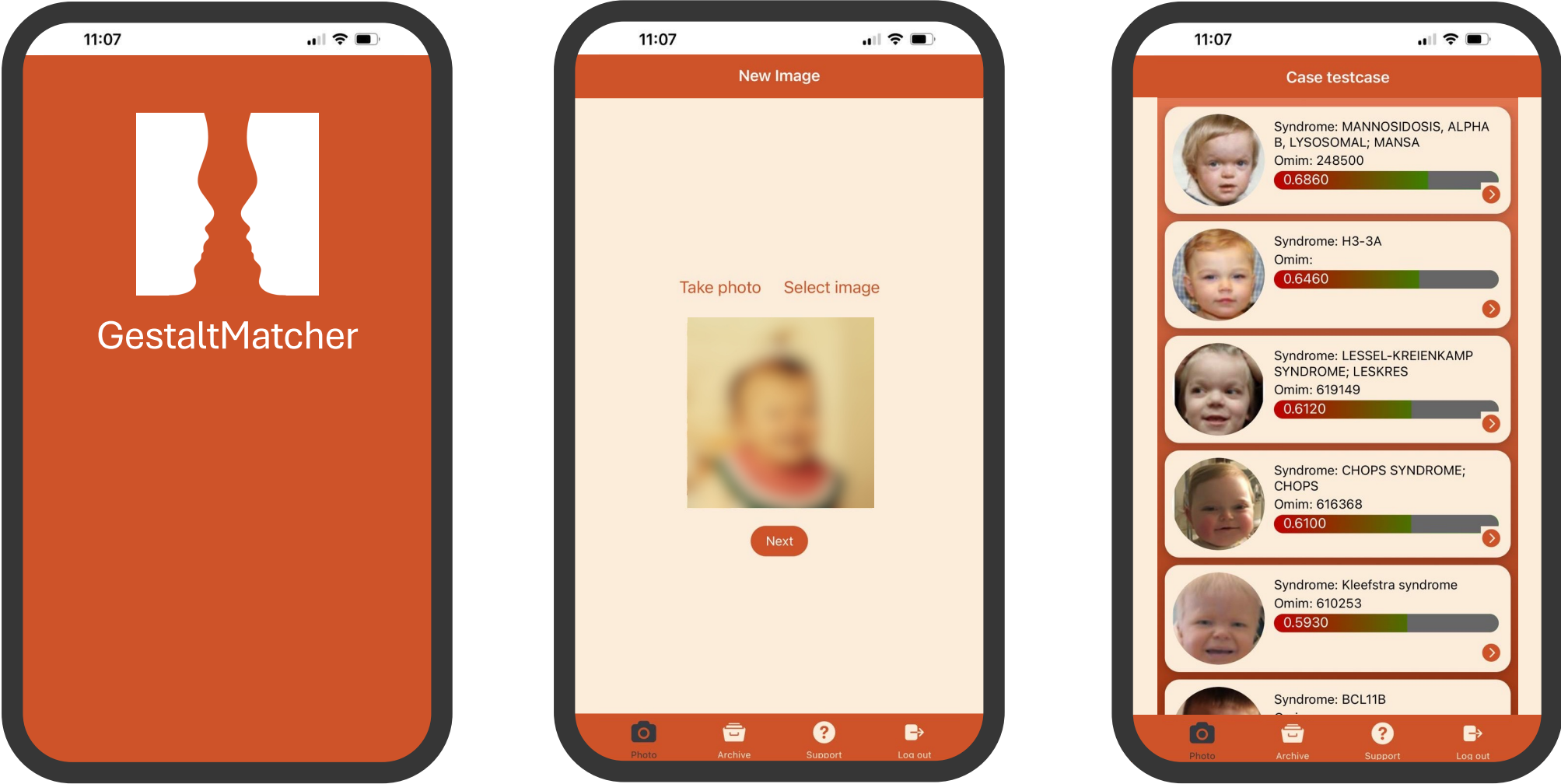
WHAT CONDITION WOULD YOU SUSPECT?

- ? Mucopolysaccharidosis
- ? α -Mannosidosis
- ? Kleeftstra syndrome
- ? Smith-Lemli-Opitz syndrome

WHOM WOULD YOU CONSULT FOR ADVICE?

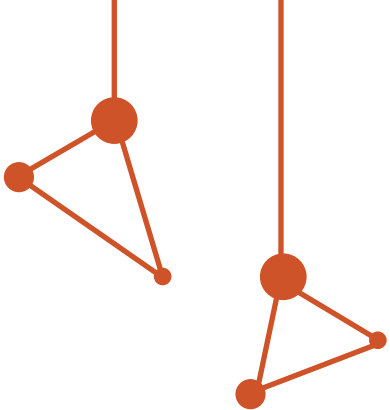
- ? Colleague in your practice / department
- ? Clinical geneticist or dysmorphologist
- ? Syndrome database
- ? Referral to a centre for rare diseases
- ? Dysmorphology atlas
- ? Artificial intelligence

AI TOOL FOR RARE DISEASES

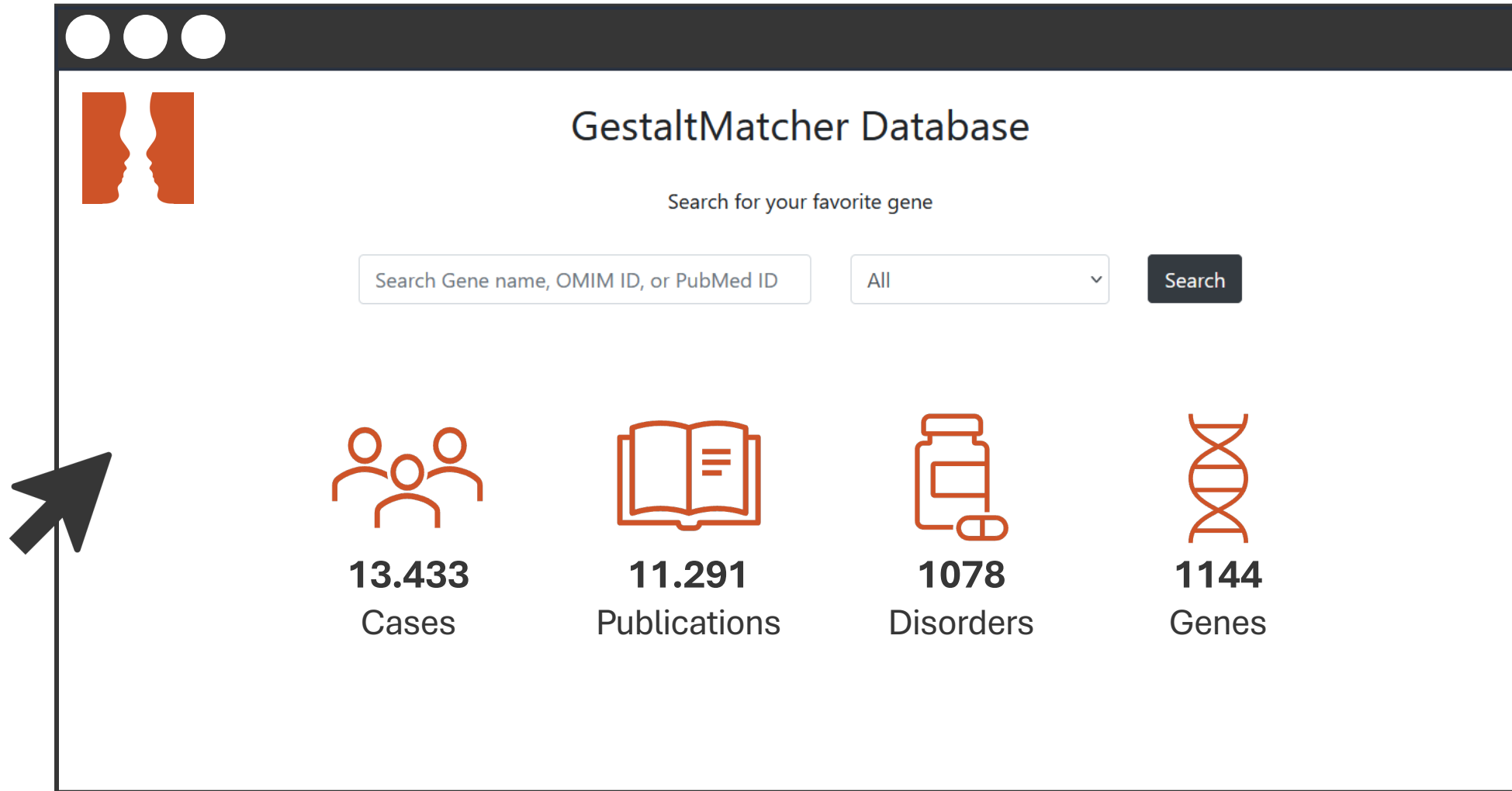


CURATED DATABASE

Data Basis of GestaltMatcher AI



CURATED DATABASE



The screenshot shows the GestaltMatcher Database interface. At the top left is a logo consisting of two orange silhouettes of human heads facing each other. The title 'GestaltMatcher Database' is centered at the top. Below the title is a search bar with the placeholder text 'Search for your favorite gene'. The search bar has a text input field containing 'Search Gene name, OMIM ID, or PubMed ID', a dropdown menu set to 'All', and a 'Search' button. Below the search bar are four categories, each with an icon, a count, and a label: 'Cases' (13.433) with a group of people icon, 'Publications' (11.291) with an open book icon, 'Disorders' (1078) with a pill bottle icon, and 'Genes' (1144) with a DNA double helix icon. A large black mouse cursor arrow points to the left side of the interface.

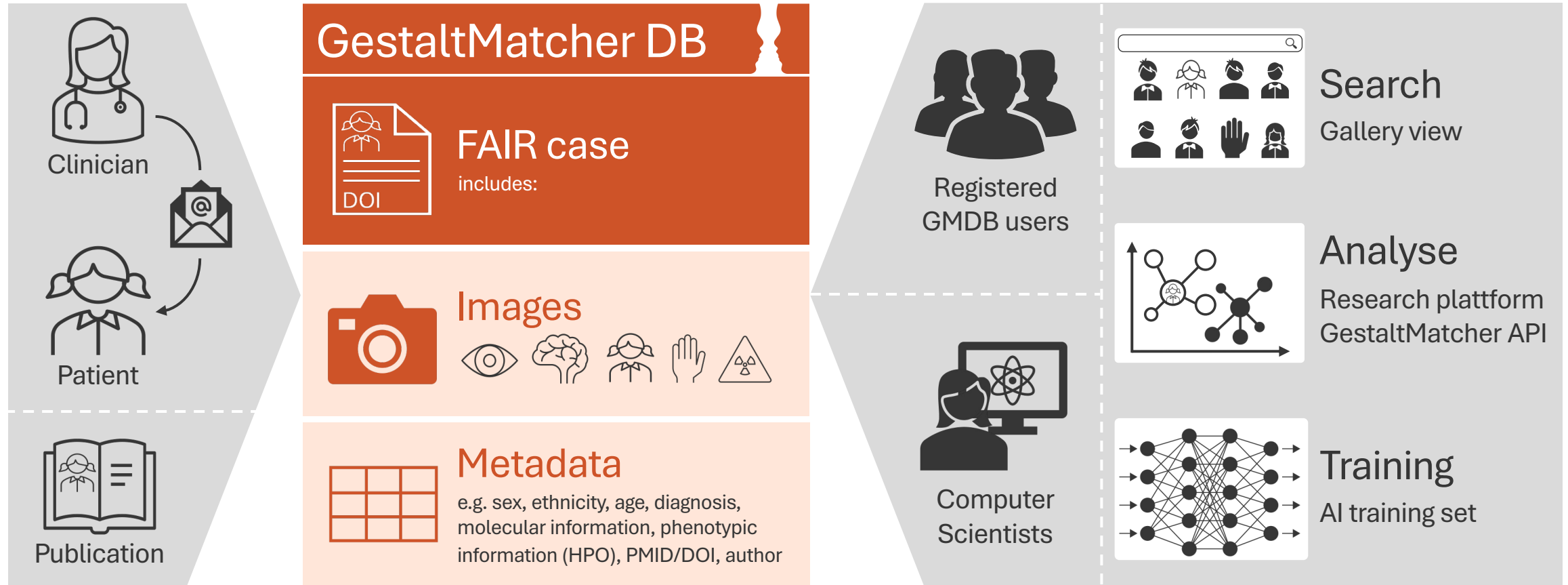
GestaltMatcher Database

Search for your favorite gene

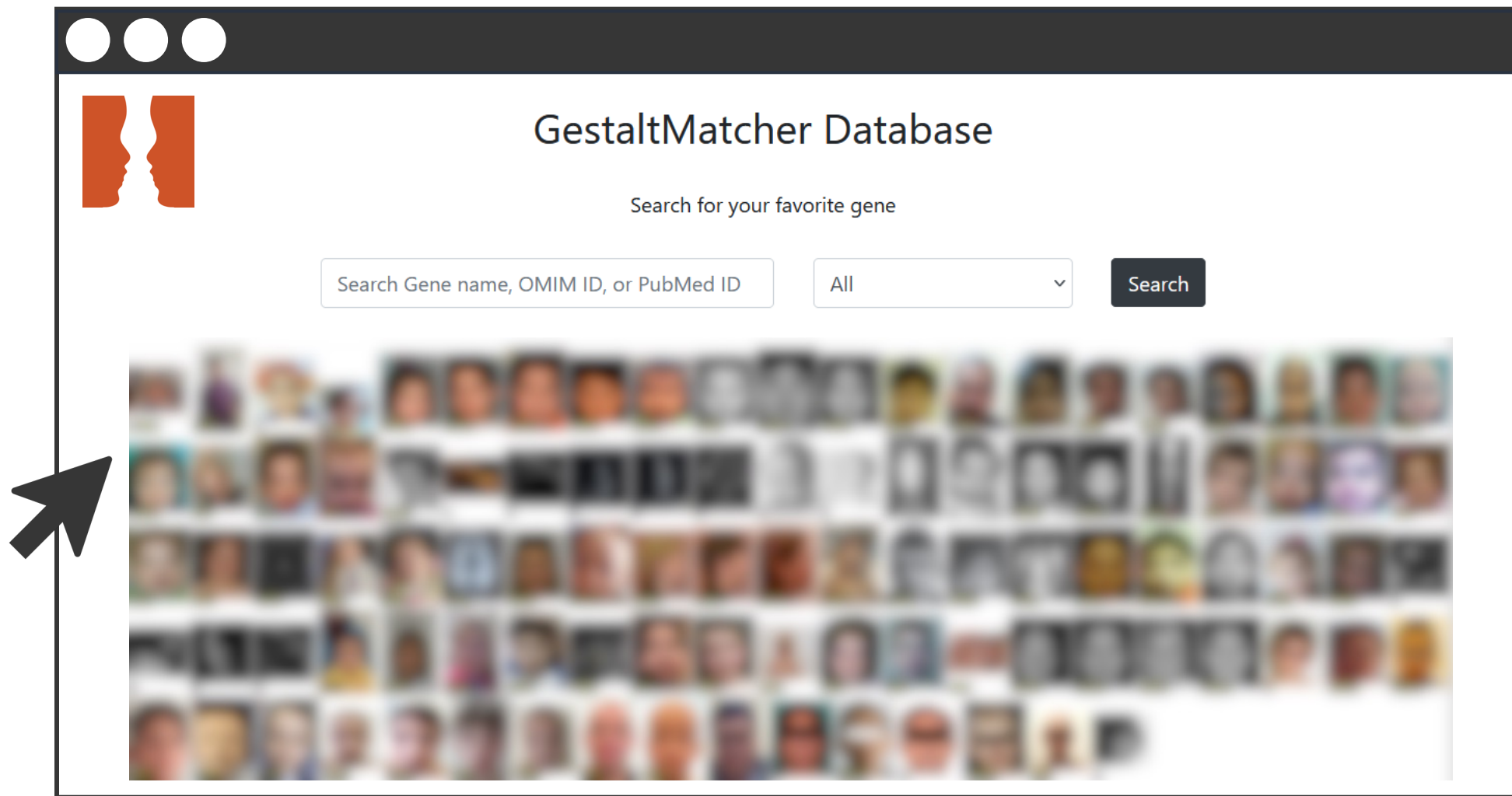
Search Gene name, OMIM ID, or PubMed ID All Search

Category	Count
Cases	13.433
Publications	11.291
Disorders	1078
Genes	1144

CURATED DATABASE

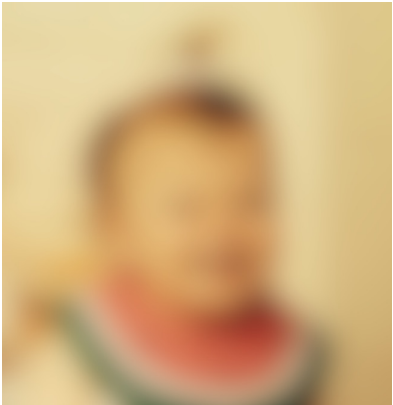


CURATED DATABASE



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; NEPMIA	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](#)

Figure 1

A

Two young children with Alpha-mannosidosis. The child on the left is wearing a yellow and brown patterned sweater, and the child on the right is wearing a blue sweater. They are both looking towards the camera.

B

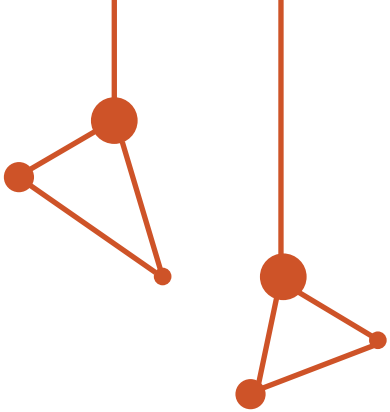
Two young children with Alpha-mannosidosis. The child on the left is wearing a blue sweater and holding a black cat. The child on the right is wearing a white sweater and red pants, holding a red object. They are both looking towards the camera.

 **BMC** Part of Springer Nature

 **Orphanet Journal of Rare Diseases**

TRY IT YOURSELF

Hands-on with GestaltMatcher



GET TO KNOW GMDB



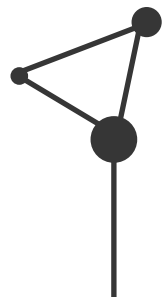
- 1** Go to db.gestaltmatcher.org
- 2** Log in with your credentials
- 3** Explore GMDB (5 min)

SUGGESTIONS

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

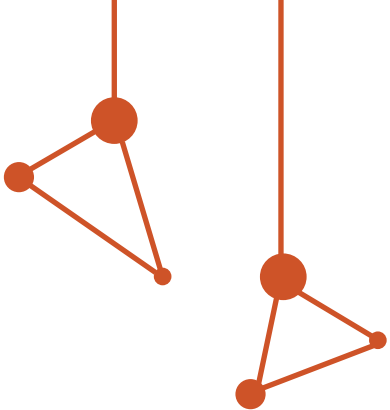
EXPLORE A CASE → Click on an image in the gallery → *View Patient*

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

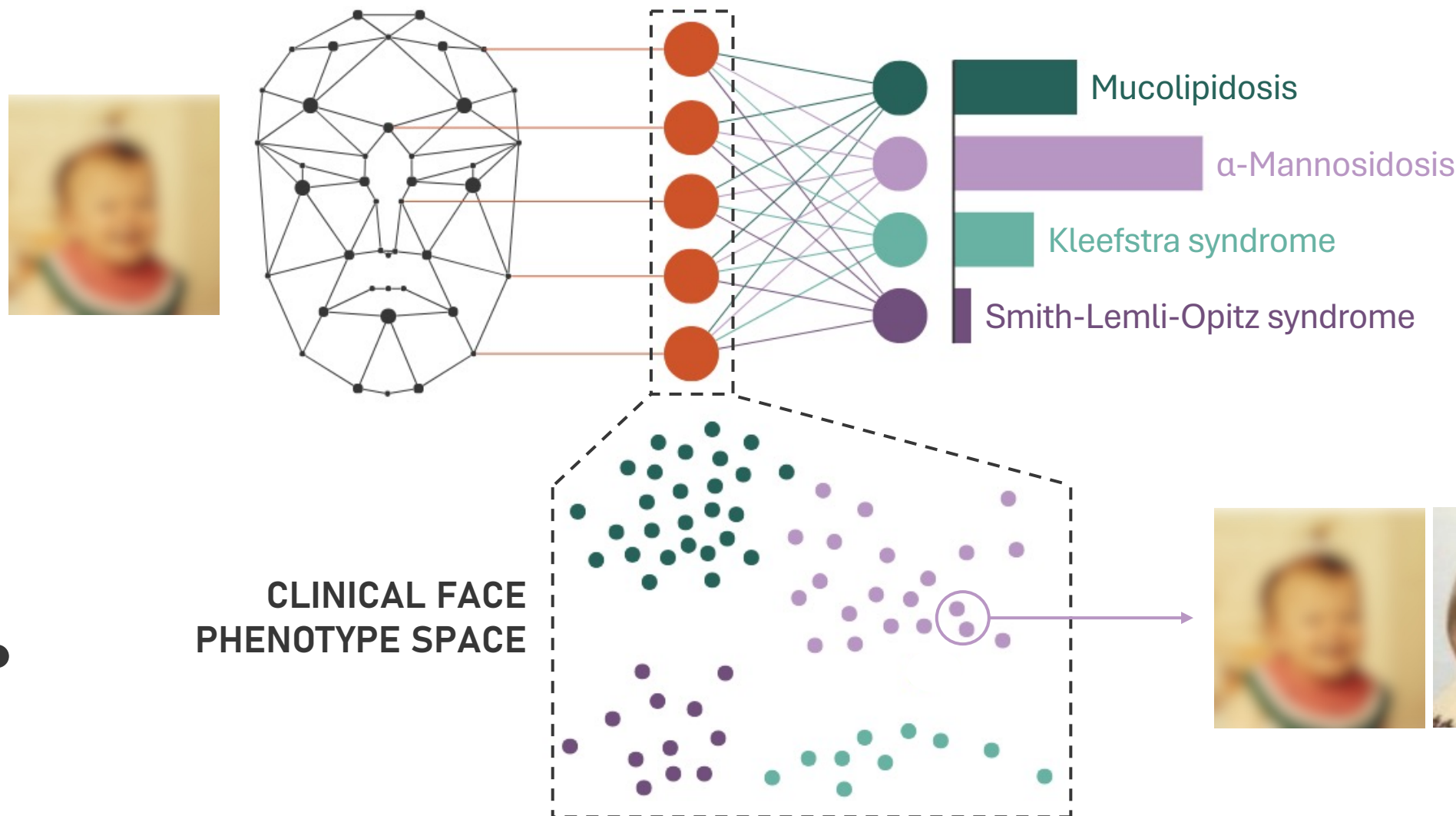


ARTIFICIAL INTELLIGENCE

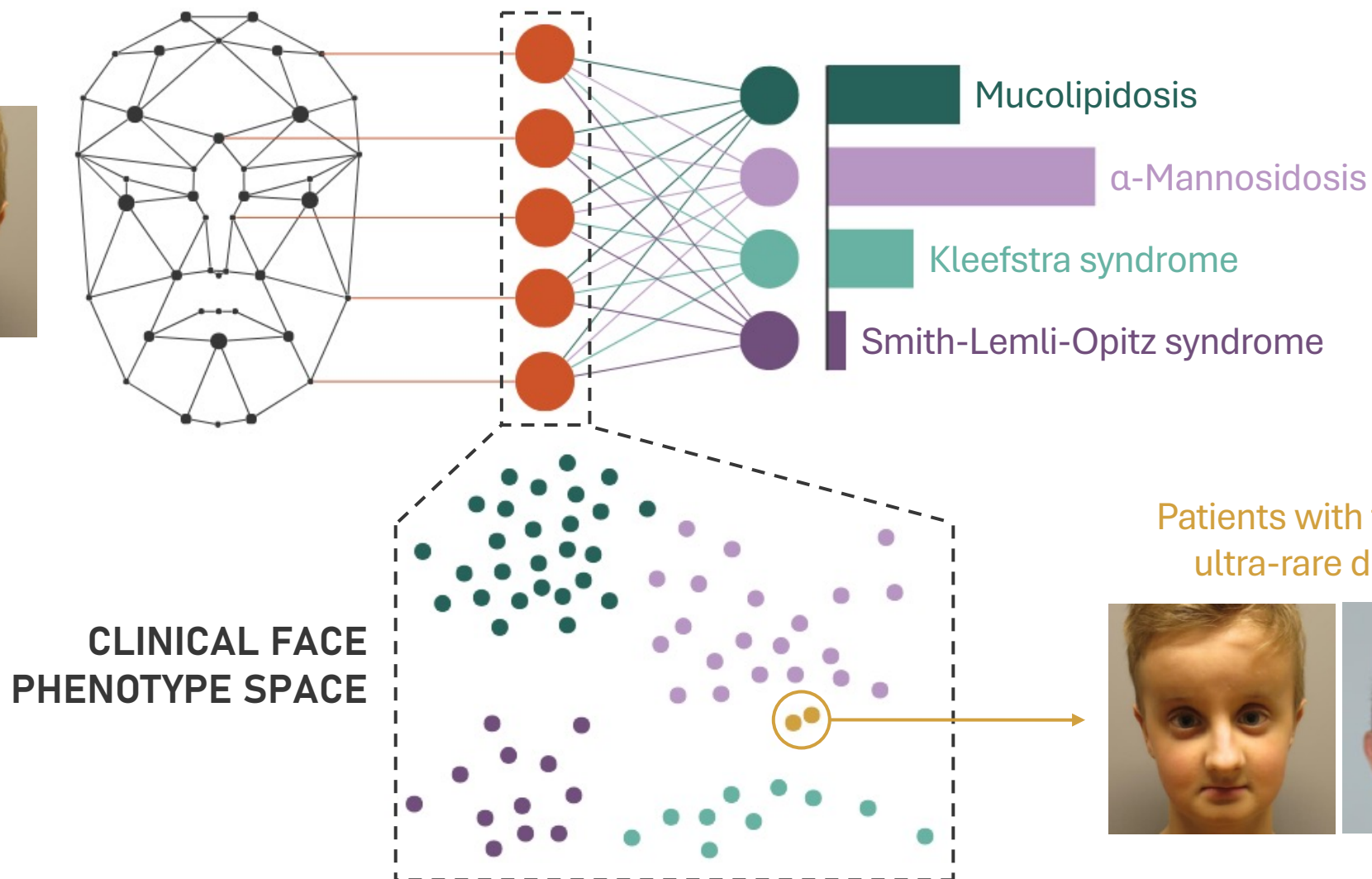
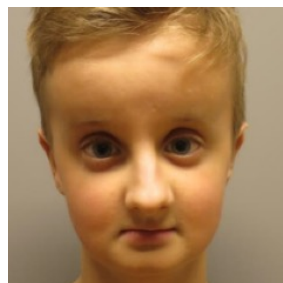
How GestaltMatcher Analyses Facial Features



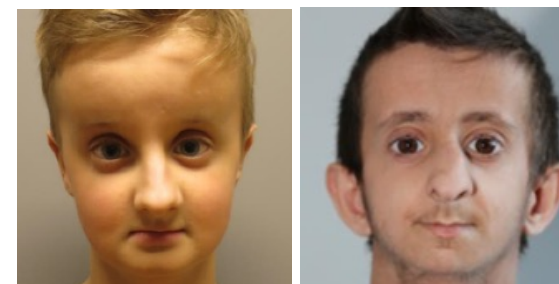
NEXT-GENERATION PHENOTYPING



NEXT-GENERATION PHENOTYPING



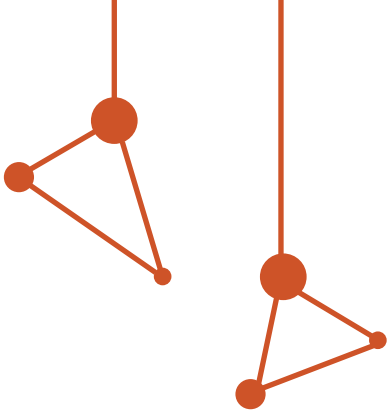
Patients with the same
ultra-rare disorder



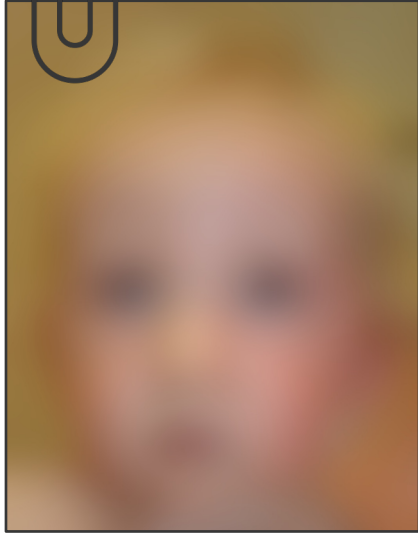
Marbach et al. *Am J Hum Genet* (2019)

TRY IT YOURSELF

Hands-on with GestaltMatcher



CASE EXAMPLE



Patient ID 0000001
DoB 13/08/2024
Male

PATIENT RECORD

CLINICAL NOTES

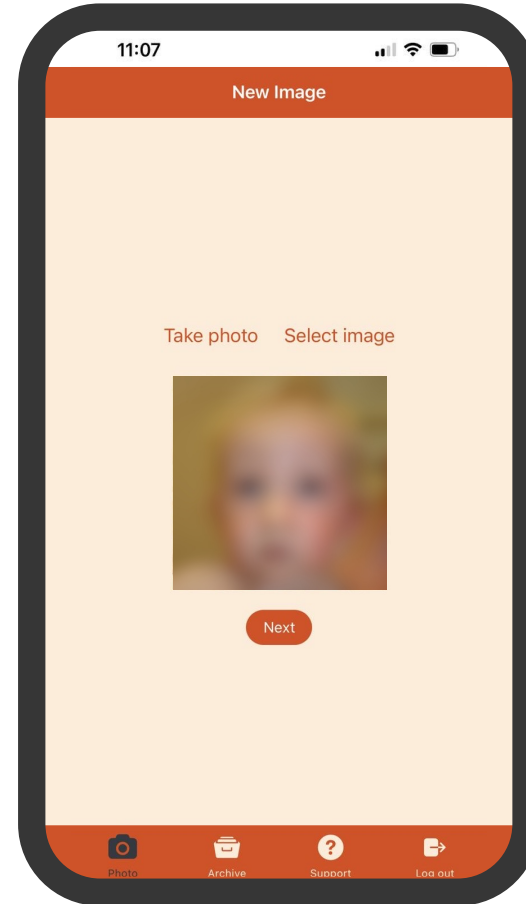
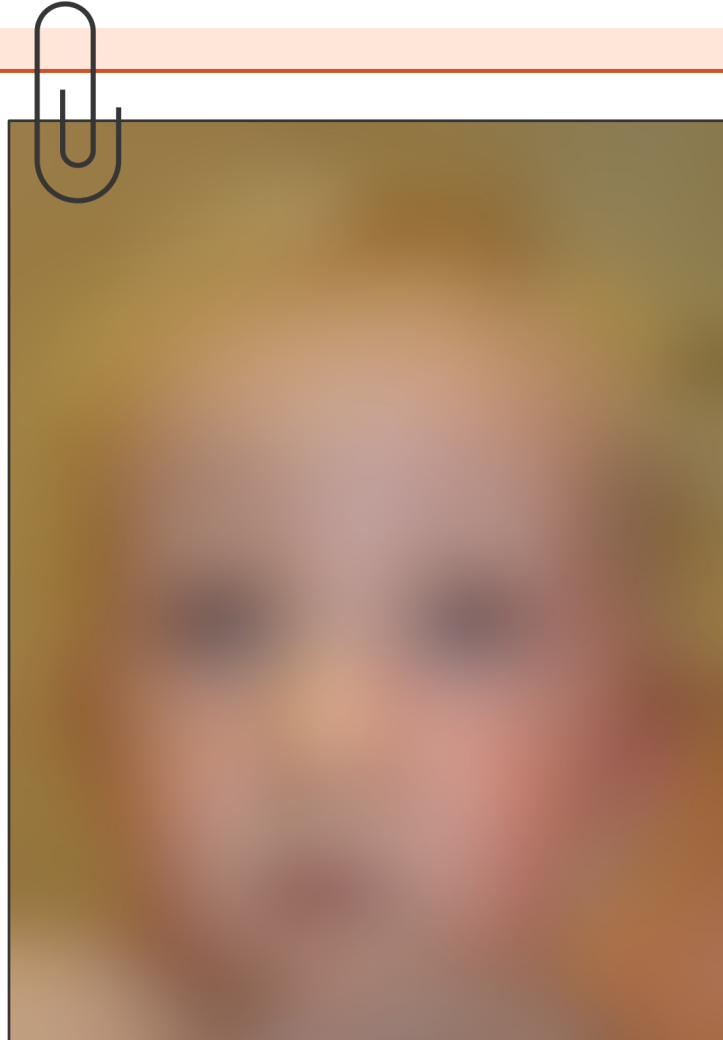
- Muscular hypotonia
- Hypoplastic left heart
- Short stature
- Recurrent otitis media
- Not able to sit without support

FACIAL DYSMORPHISM

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

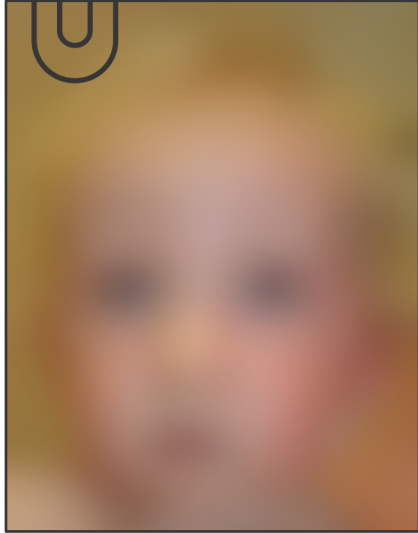
WHAT CONDITION DO YOU SUSPECT?

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



Patient ID 0000001
DoB 13/08/2024
Male

PATIENT RECORD

CLINICAL NOTES

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

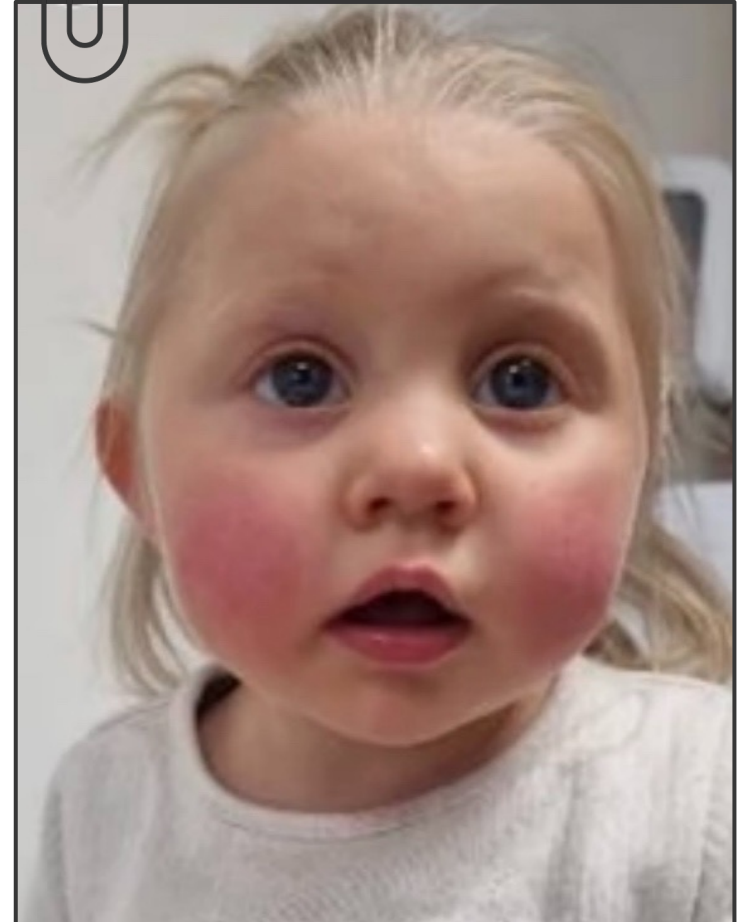
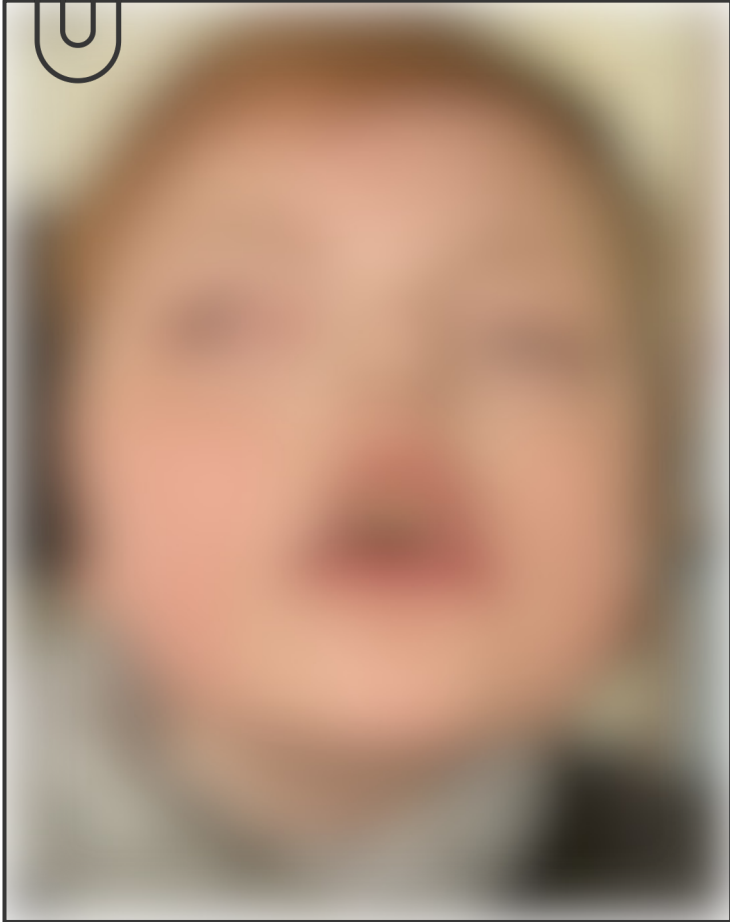
FACIAL DYSMORPHISM

- Long palpebral fissures
- Low-set ears
- Small chin
- Recurrent otitis media

WHAT CONDITION DO YOU SUSPECT?

KABUKI SYNDROME

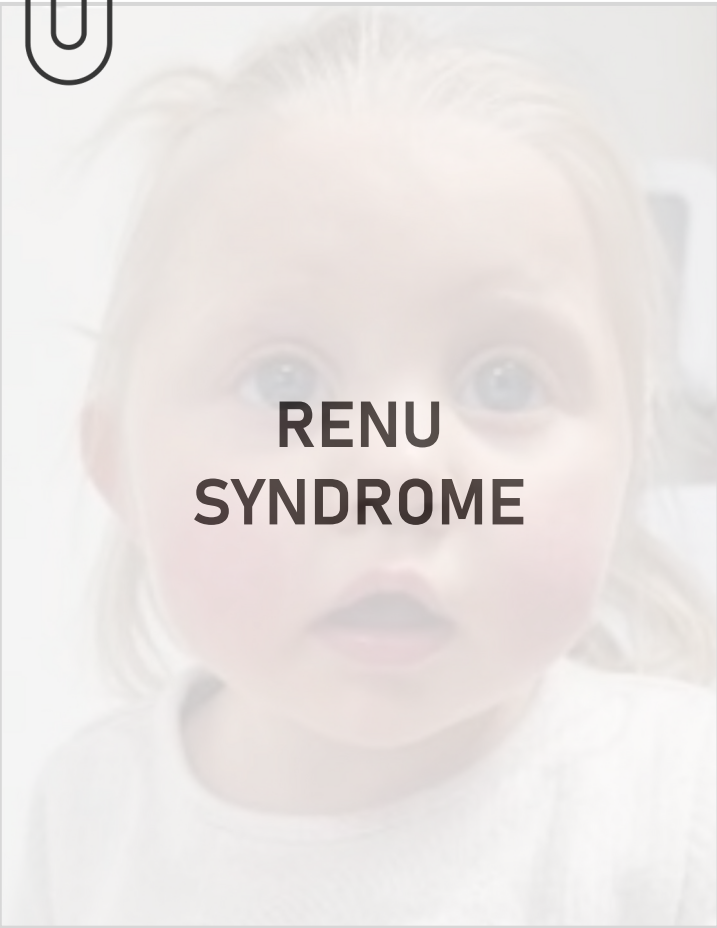
TRY IT YOURSELF



TRY IT YOURSELF



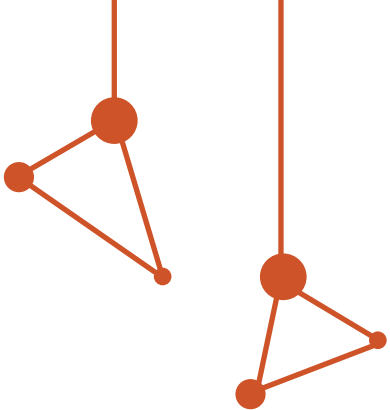
**HYPERPHOSPHATASIA
WITH MENTAL
RETARDATION
SYNDROME**



**RENU
SYNDROME**

VARIANT INTERPRETATION

Support for ACMG PP4 Criterion



A SHIFT IN DIAGNOSTIC REASONING

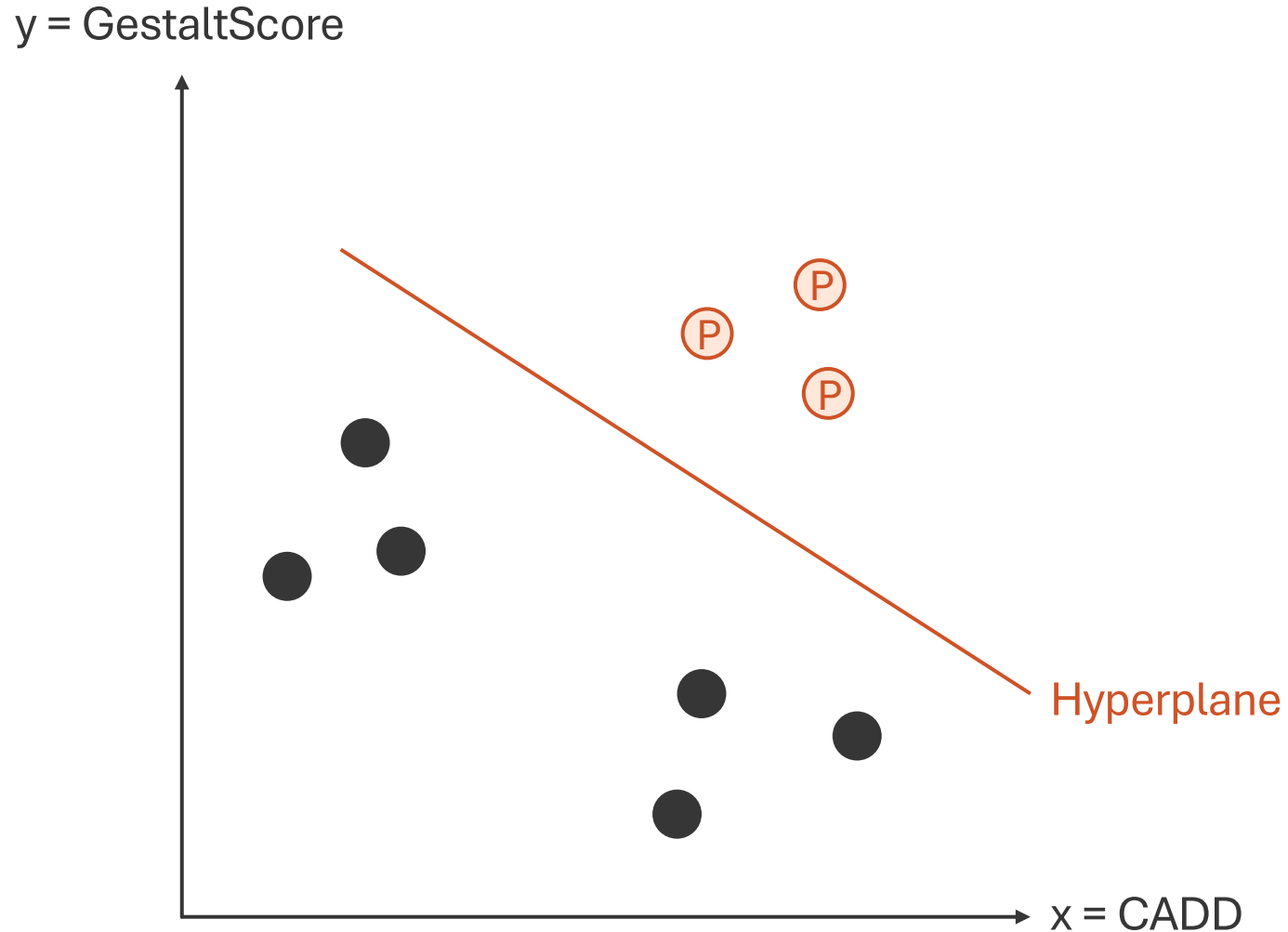
GENOMIC DATA ←———— PHENOTYPE

AMCG PP4

“Patient’s phenotype or family history is **highly specific** for a disease with a single genetic aetiology”



COMBINING SCORES



SUPPORT VECTOR MACHINE

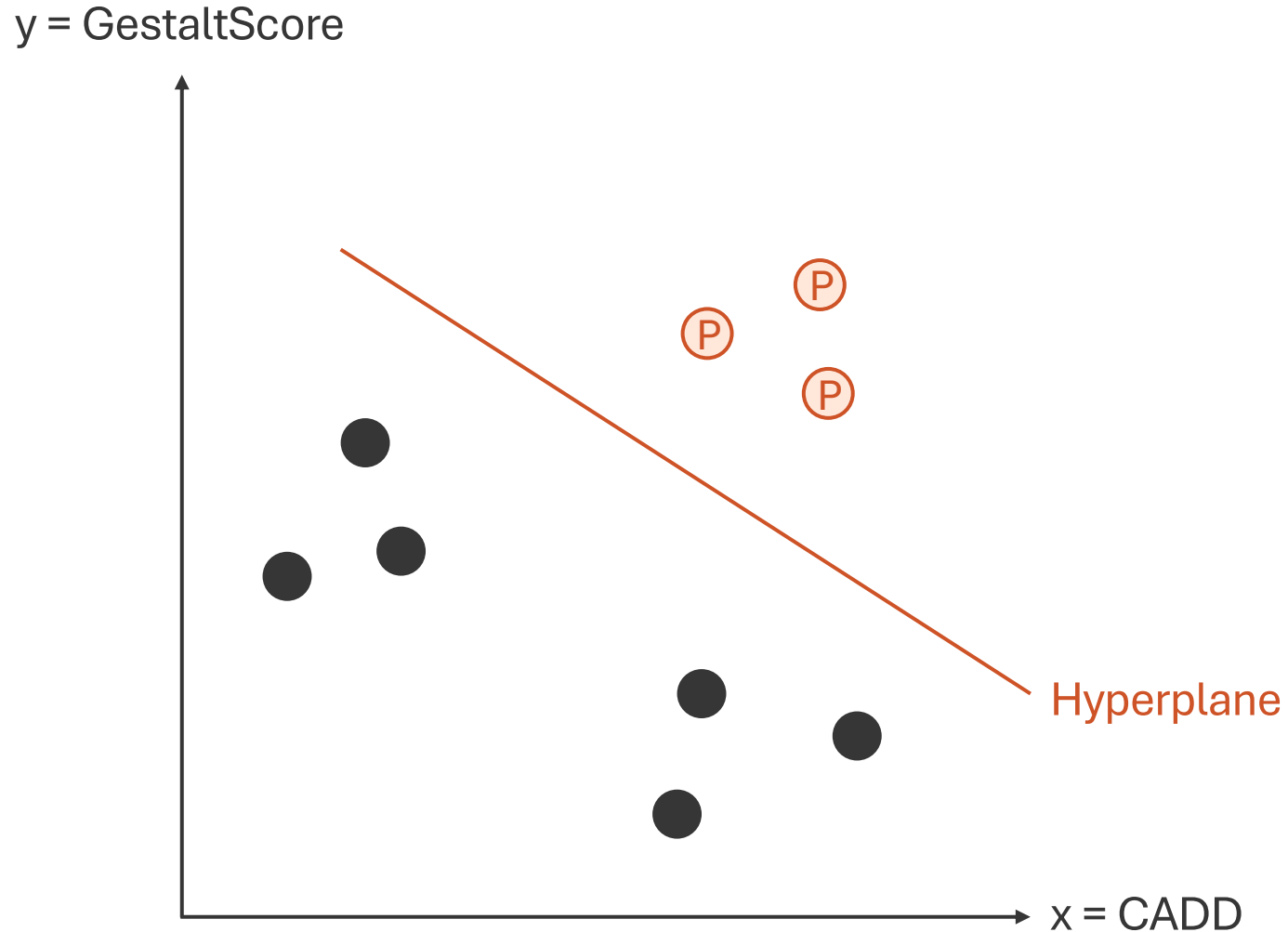
classifies data by finding a
hyperplane
that maximizes distance
between two classes

for example between

Ⓟ pathogenic

● benign

COMBINING SCORES



PEDIA APPROACH

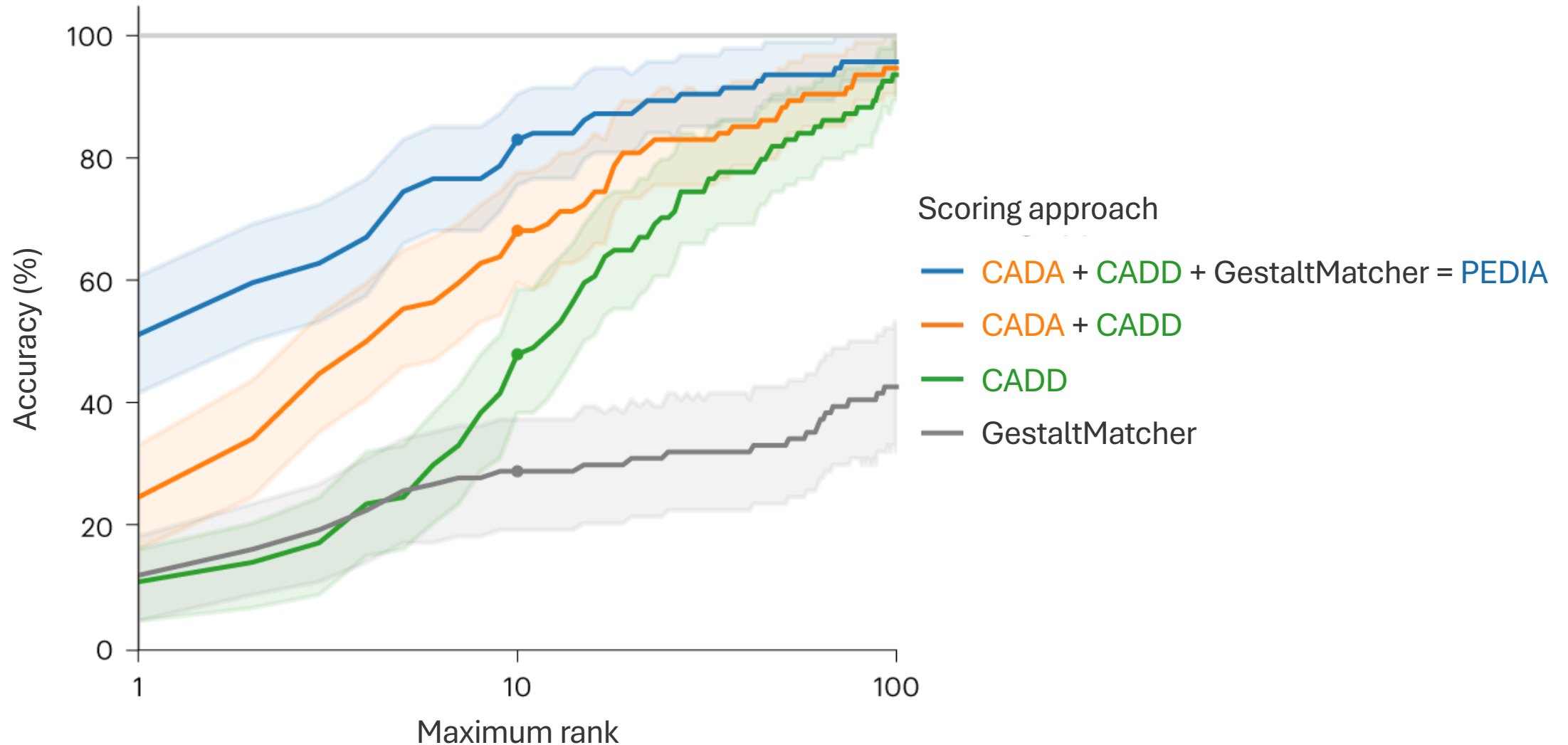
PRIORITIZATION OF EXOME DATA
BY IMAGE ANALYSIS

PEDIA SCORE

$$= \alpha \text{ CADD} + \beta \text{ GestaltScore}$$

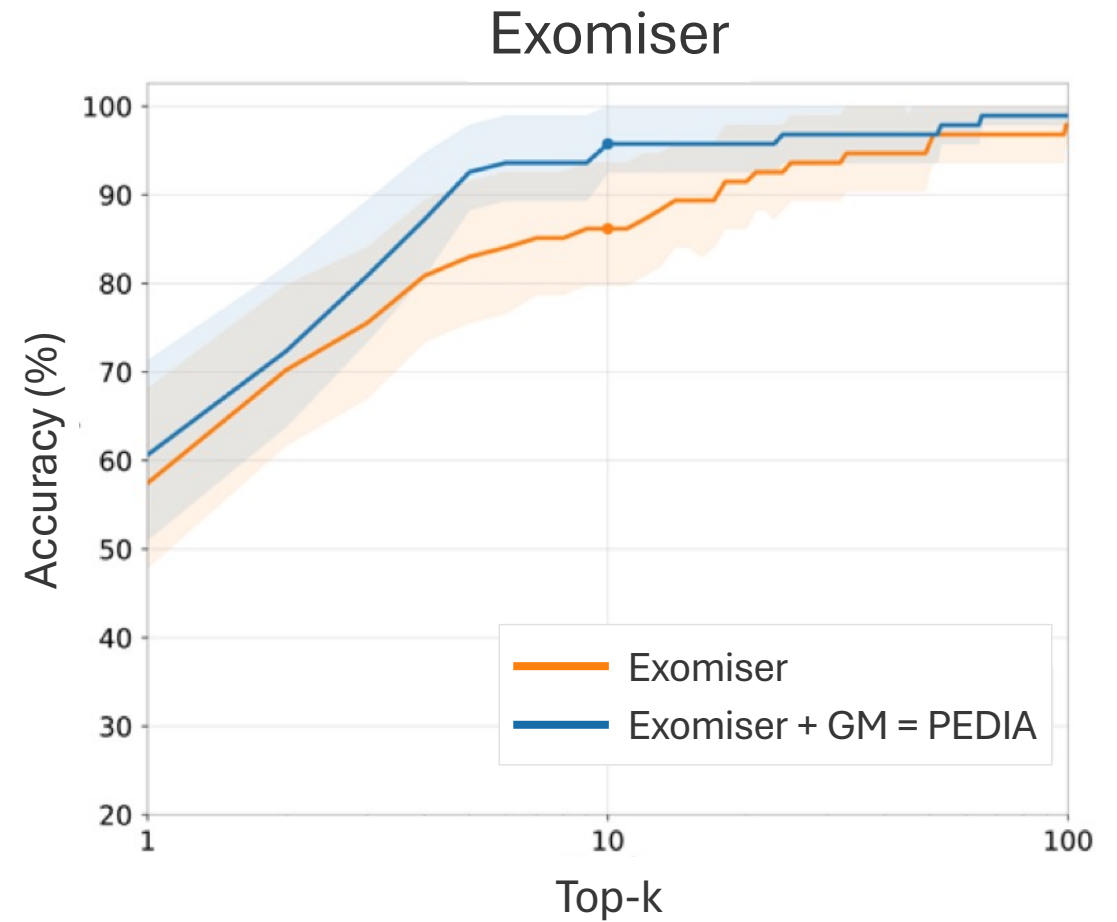
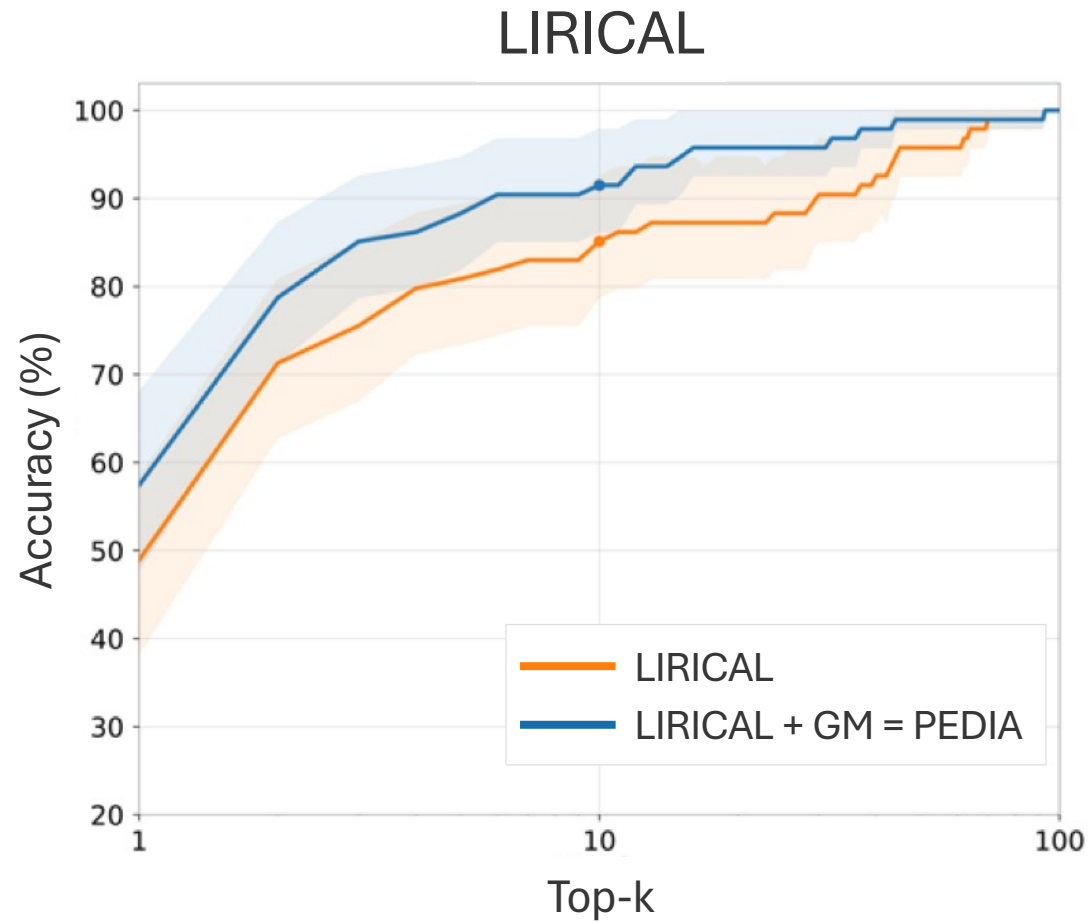
Find ideal combination
of α and β

GESTALT IMPROVES ACCURACY



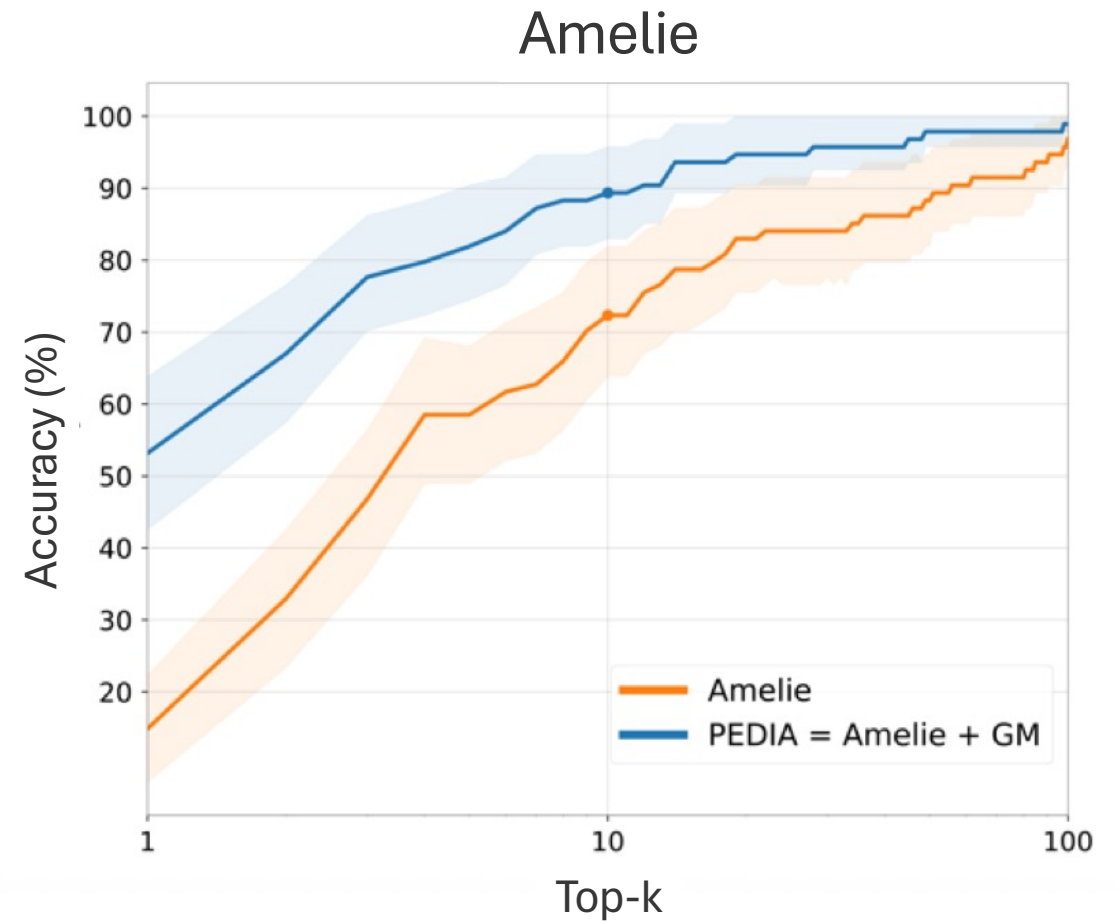
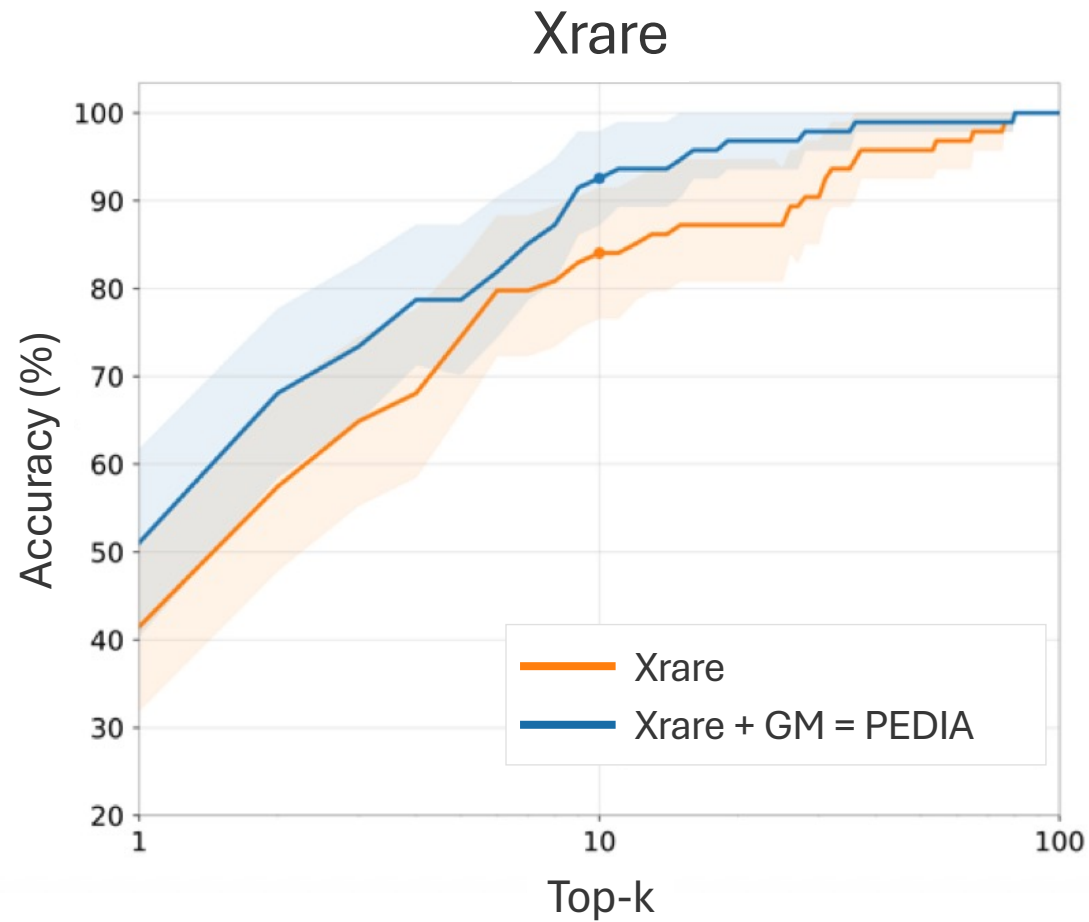
Schmidt et al. *Nat Genet* (2024)

GESTALT IMPROVES ACCURACY



Schmidt et al. *Nat Genet* (2024)

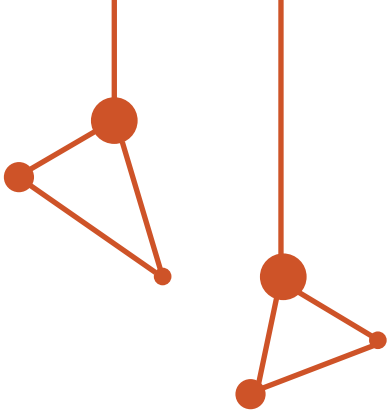
GESTALT IMPROVES ACCURACY



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
<u>Chr9-86585070-A-C</u> [0/1]	<i>HNRPK</i> c.1361+7T>G; p.?	Au-Kline syndrome (AD)	20 / -		2	Likely benign: PM2, BP4 (ClinVar: conflicting)
<u>Chr16-19621652-C-G</u> [0/1]	<i>VPS35L</i> c.938G>C; p.Ser313Ter	Ritscher-Schinzel syndrome (AR)	38 / 1		7	Pathogenic: PVS1, PM2, PP5 (ClinVar: likely pathogenic)
<u>Chr16-19711792-G-C</u> [0/1]	<i>VPS35L</i> c.2886G>C; p.Arg962Ser	Ritscher-Schinzel syndrome (AR)	22.4 / 0.304		7	Likely benign: PM2, BP4, BP1 (ClinVar: VUS)
<u>Chr12-49447863-G-A</u> [0/1]	<i>KMT2D</i> c.571C>T; p.Arg191Trp	Kabuki syndrome (AD)	26.6 / 0.502		25	VUS: PP3, PM2, PP5 (ClinVar: conflicting)



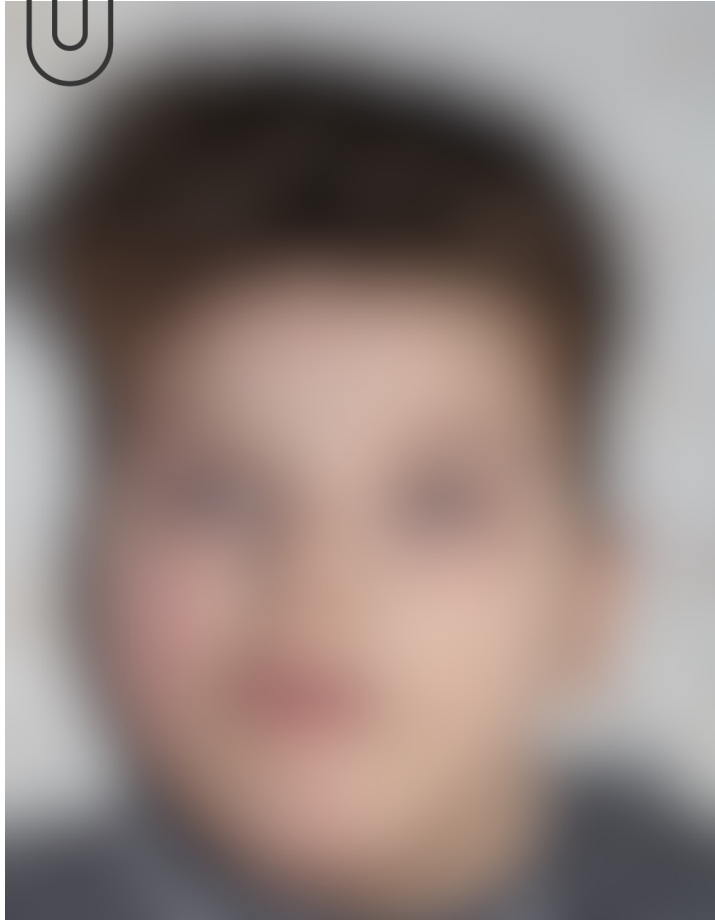
CASE EXAMPLE

Genomic variant	HGVS	Disorder (Mode of Inheritance)	CADD / REVEL	GestaltScore 	Feature Rank (CADA)	ACMG
<u>Chr12-49447863-G-A</u> [0/1]	<i>KMT2D</i> c.571C>T; p.Arg191Trp	Kabuki syndrome (AD)	26.6 / 0.502	0.611 (rank 1)	25	Likely pathogenic: PP4 , PP3, PM2, PP5
<u>Chr9-86585070-A-C</u> [0/1]	<i>HNRPK</i> c.1361+7T>G; p.?	Au-Kline syndrome (AD)	20	0.692 (rank 8)	2	Likely benign: PM2, BP4 (ClinVar: conflicting)
<u>Chr16-19621652-C-G</u> [0/1]	<i>VPS35L</i> c.938G>C; p.Ser313Ter	Ritscher-Schinzel syndrome (AR)	38 / 1	0.794 (rank 71)	7	Pathogenic: PVS1, PM2, PP5 (ClinVar: likely pathogenic)
<u>Chr16-19711792-G-C</u> [0/1]	<i>VPS35L</i> 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
<u>Chr11-71146484-G-T</u> [0/1]	<i>DHCR7</i> c.1365C>A p.Tyr455Ter	Smith-Lemli-Opitz syndrome (AR)	36 / -	0.772 (rank 59)	73	Likely pathogenic: PVS1, PM2, PP5 (ClinVar: pathogenic)
<u>ChrX-132670158-C-</u> [0/1]	<i>GPC3</i> 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]	<i>PIGV, ZDHHC8</i>	?	- / -	0.591 (rank 1)	11	VUS: 1A, 3A, 4L, (5H)
<u>Chr1-27121547-C-A</u> [0/1]	<i>PIGV</i> c.1022C>A; p.Ala341Glu	Mabry syndrome (HPMRS) (AR)	20	0.591 (rank 1)	11	Pathogenic: PM2, PM5, PS3, PP5 (ClinVar: pathogenic)



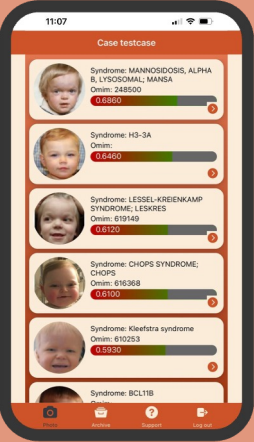
CASE 3

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



SUMMARY

SUGGESTED
GENES / SYNDROMES

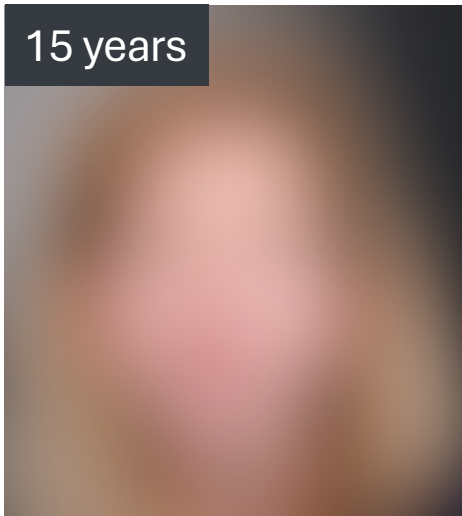
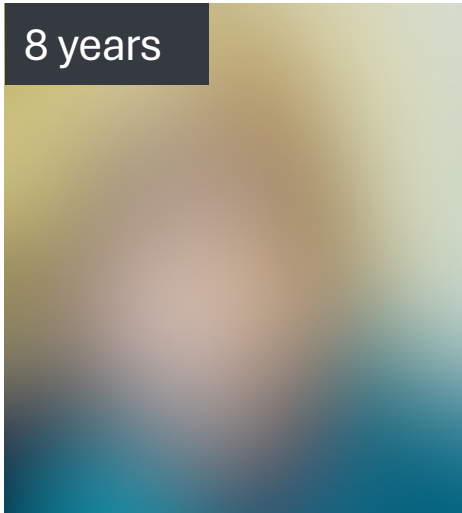


PRIORITIZED
VARIANT
SHORTLIST

GENETIC VARIANTS
(VCF)

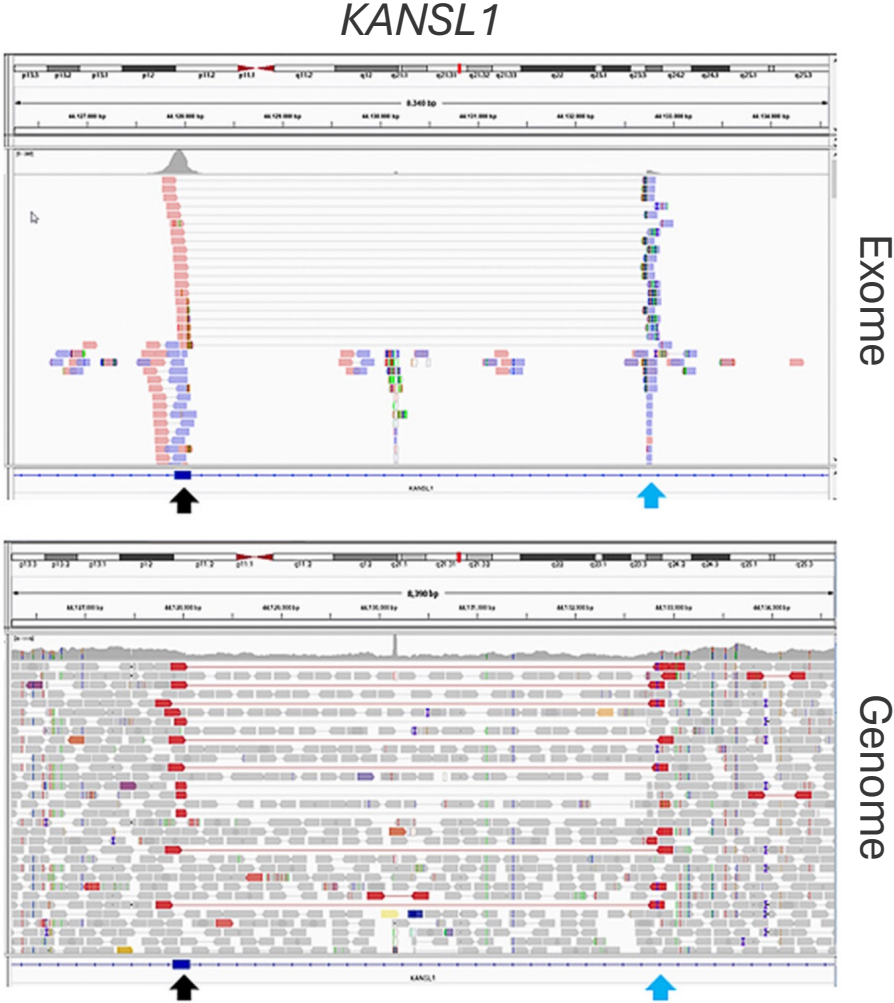
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non_coding_transcript_exon_variant[LOW|50K|6391|transcript[NR  
n.2619C>G|2619/58376|]]|CADD_SNV_OVL_PHRD=1.386|2.576|  
0.614|CADD_SNV_OVL_RawScore=-0.150001|4.00097|  
0.002962|CADD_SNV_PHRD=1.386|CADD_SNV_RawScore=-0.150095|DP=1  
52584|SAS_AFR=0.2196|UK10K_AC=468|UK10K_AFR=0.062|UK10K_AN=7562  
62|UK10K_OVL_AN=7562|VT=SNP GT 110  
1 16151284 rs199848551 G A 100  
AM=|||AC=3|AF=0.000599042|AFR_AF=0|AFR_AF=0|AN=5008|AN=0|SV  
transcript[NM_008569.6|Coding|3/5|c.354C>T|p.(*)38/8278|35  
118/291|]]CADD_SNV_OVL_PHRD=1.15910.002|  
0.002|CADD_SNV_OVL_RawScore=-0.188623|-1.763440|-1.641299|CADD  
=-0.188623|DP=32086|EAS_AFR=0|EUR_AF=0|EXAC_AC_AFR=1|EXAC_AC_AL  
XAC_AC_FIN=0|EXAC_AC_NFE=2|EXAC_AC_OTTH=0|EXAC_AC_SAS=30|EXAC_A  
-04|EXAC_AF_AFR=0.00|EXAC_AF_EAS=4.623e-04|EXAC_AF_FIN=0.00|EX  
00|EXAC_AF_SAS=1.817e-03|EXAC_AN_AFR=10406|EXAC_AN_ALL=121418|1  
EXAC_AN_FIN=6014|EXAC_AN_NFE=60740|EXAC_AN_OTTH=005|EXAC_AN_SAS  
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T_NFE=2|EXAC_HET_OTTH=0|EXAC_HET_SAS=30|EXAC_HOM_AFR=0|EXAC_HOM  
-0|EXAC_HOM_FIN=0|EXAC_HOM_NFE=0|EXAC_HOM_OTTH=0|EXAC_HOM_SAS=0  
=37|EXAC_OVL_AC_AFR=0|EXAC_OVL_AC_EAS=4|EXAC_OVL_AC_FIN=0|EXAC  
AC_OVL_AC_SAS=30|EXAC_OVL_AF_AFR=0.00|EXAC_OVL_AF_EAS=4.623e-04  
VL_AF_EAS=4.623e-04|EXAC_OVL_AF_FIN=0.00|EXAC_OVL_AF_NFE=2.997  
_AF_SAS=1.817e-03|EXAC_OVL_AN_AFR=10406|EXAC_OVL_AN_ALL=121418  
EAS=0052|EXAC_OVL_AN_FIN=6014|EXAC_OVL_AN_NFE=60740|EXAC_OVL  
XAC_OVL_BEST_AC=38|EXAC_OVL_BEST_AFR=1.817e-03|EXAC_OVL_HET_AFR  
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1 161561151 rs74341264 G A 100  
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```

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; BBR SAY

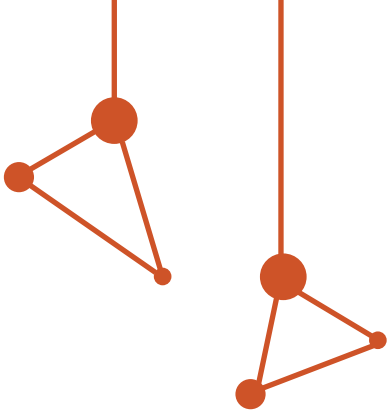
Suggested disorders	
Rank	Disorder
1	KOOLEN-DE VRIES SYNDROME; KDVS
2	OHDO SYNDROME, SBBYS VARIANT; SBBYSS
3	KEIPERT SYNDROME; KPTS
4	Noonan syndrome
5	H4C3



Brand et al. *Hum Mutat* (2022)

OUTLOOK

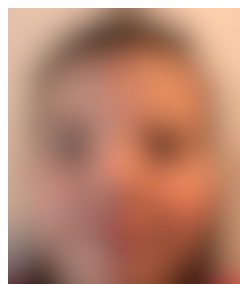
(Your) Future with GestaltMatcher



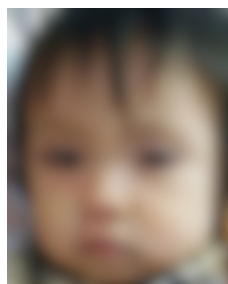
FROM HEAD TO TOE



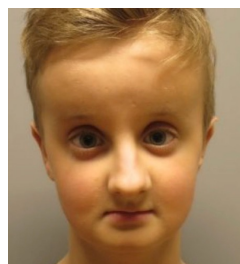
Faces



PIGV



KMT2D



LEMD2



PACS1



Bone2Gene

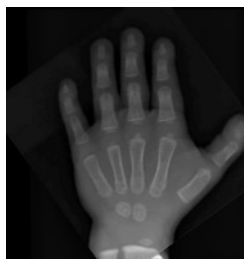
Bones



PRKAR1A



RMRP



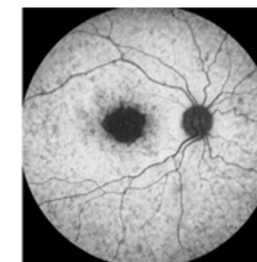
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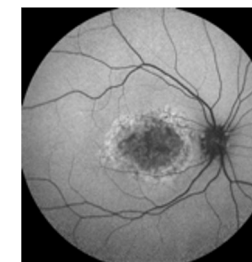
SHOX



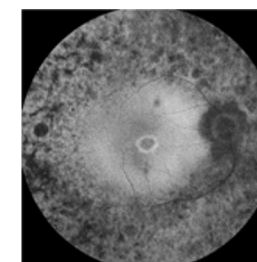
Eyes



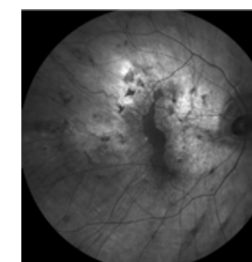
ABCA4



EFEMP1



USH2A



CHM

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

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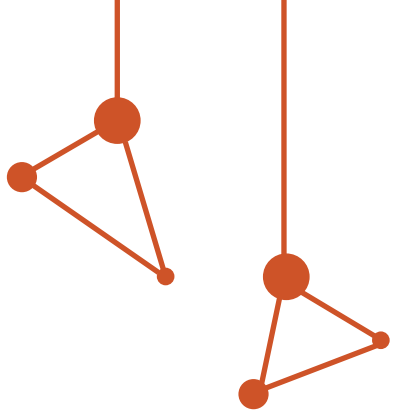
STIFTUNGEN

Wirtgen Invest

GO-Bio
initial | next

THANK YOU!

We hope you enjoyed our session!



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