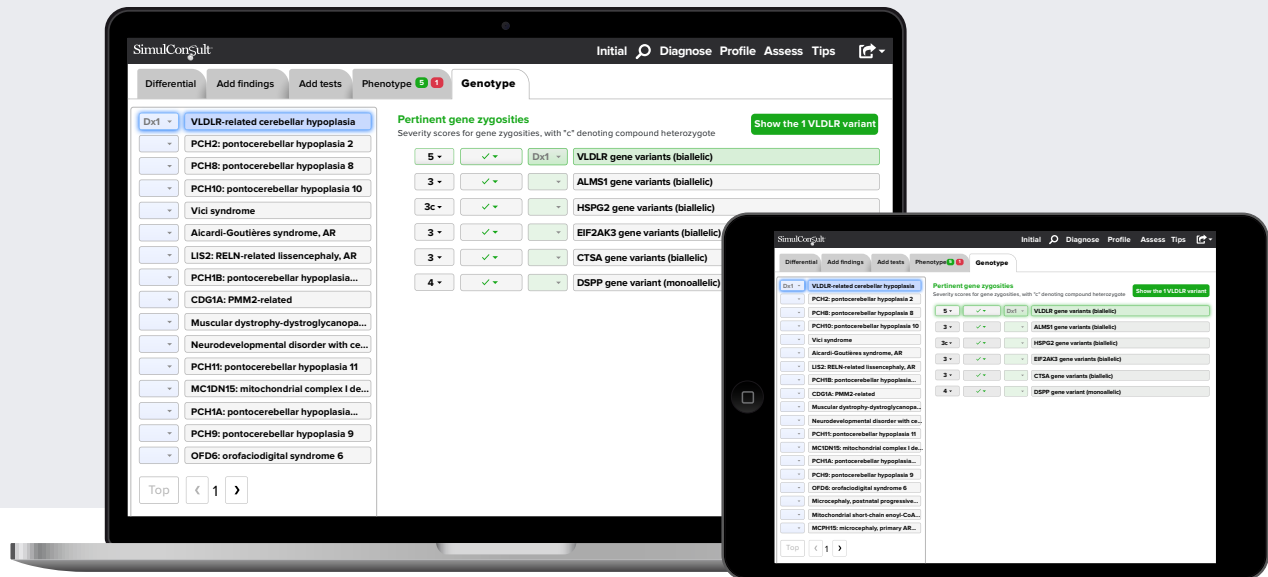


Genome-Phenome Analyzer

Genome Interpretation plus Gene Discovery
with SimulConsult



Empowers you to quickly make diagnoses from genomic results in the clinical context!

Coverage

Covers all chromosomal abnormalities and genes with germline changes convincingly associated with human disease and their clinical and lab findings, as well as non-genetic diseases in their differential diagnosis.

Clear logic

You assess the rationale of the fit between your patient and the disease. It achieves “explainable artificial intelligence” using a human-curated database, it is not a black box.

Platform

Access the software on your computer or tablet.

Focused on your patient

Use your patient's genomic variant table and their clinical information to focus on the pertinent genes. Then get suggestions on useful clinical findings to check and tests to order.

Accurate and cost effective

Top gene in confirmed diagnosis often has >99% pertinence. Can identify multiple genetic diagnoses simultaneously, such as in cases of consanguinity.

Fast

Import variants in seconds and rapidly interpret them in the full clinical context. Quickly prioritize discovery genes, if relevant, and regularly reanalyze undiagnosed and consanguineous patients.

SimulConsult®

To subscribe, visit:
SimulConsult.com

Getting to the diagnosis

Phenome + Genome

DifferentialAdd findingsAdd tests

Phenotype51

PCH2: pontocerebell...

PCH8: pontocerebell...

PCH10: pontocerebell...

Vici syndrome

Aicardi-Goutières sy...

LIS2: RELN-related li...

VLDLR-related cerebellar...

2 year old boy

Pertinent positive findings

≤1m

Nystagmus, non-rotary

@1m

Microcephaly

✓

CT or MRI: brainstem atrophy or hypo...

≤6m

Hyperreflexia

✓

History of a similar disorder in family ...

Annotated Variant Table (Lab-generated)

ALG9	asparagine-linked glycos	chr11:111742146	NM_024740:ex2:c.60+1C>-	NM_024740:rs10708475	het	wt	het	miss
ALMS1	Alstrom syndrome 1	chr2:73799632	NM_015120:ex16:c.C10625G:p.T3542S	rs45501594	het	hom	het	miss
ALMS1	Alstrom syndrome 1	chr2:73613068	NM_015120:ex1:c.72_74del:p.24_25del		hom	het	het	nonfr
CTSA	cathepsin A	chr20:44520261	NM_000308:ex2:c.108_110del:p.36_37del	NM_001127	hom	het	het	nonfr
DSPP	dentin sialophosphoprot	chr4:88537261	NM_014208:ex5:c.A3447T:p.E1149D		het	wt	het	miss
DSPP	dentin sialophosphoprot	chr4:88536321	NM_014208:ex5:c.2507_2509del:p.836_837del		het	wt	wt	nonfr
DSPP	dentin sialophosphoprot	chr4:88537276	NM_014208:ex5:c.3462_3488del:p.1154_1163del		het	wt	wt	nonfr
DSPP	dentin sialophosphoprot	chr4:88536459	NM_014208:ex5:c.2645_2646insTAGTGACAG:p.S882del		het	wt	wt	nonfr
DSPP	dentin sialophosphoprot	chr4:88536868	NM_014208:ex5:c.3054_3155TAGTGACAGCAGCAACAGC		het	wt	wt	nonfr
DSPP	dentin sialophosphoprot	chr4:88537018	NM_014208:ex5:c.T3204C:p.D1068D		het	wt	wt	synom
EIF2AK3	eukaryotic translation in	chr2:88926752	NM_004836:ex1:c.39_41del:p.13_14del		hom	het	het	nonfr
FLG	filaggrin	chr1:152277309	NM_002016:ex3:c.C10053T:p.D3351D		het	wt	wt	synom
FLG	filaggrin	chr1:152283053	NM_002016:ex3:c.C4309T:p.R1437C	rs12750571	het	wt	wt	miss

Specify the pertinent clinical information

Import the annotated variants

DifferentialAdd findingsAdd tests

Phenotype51Genotype

VLDLR-related cerebellar ...

PCH2: pontocerebellar hy...

PCH8: pontocerebellar hy...

PCH10: pontocerebellar h...

Vici syndrome

Aicardi-Goutières syndro...

LIS2: RELN-related lissenc...

PCH1B: pontocerebellar h...

CDG1A: PMM2-related

Muscular dystrophy-dystr...

Pertinent gene zygosity

Severity scores for gene zygosity, with "c" denoting compound heterozygote

5

✓

✓

VLDLR gene variants (biallelic)

3

✓

✓

ALMS1 gene variants (biallelic)

3c

✓

✓

HSPG2 gene variants (biallelic)

3

✓

✓

EIF2AK3 gene variants (biallelic)

3

✓

✓

CTSA gene variants (biallelic)

4

✓

✓

DSPP gene variant (monoallelic)

The clinical correlation of patient findings and genomic results:

- Ranks genes by pertinence to the clinical presentation rather than severity
- Identifies the most pertinent causative genes from among described human disorders (shown in green shading)
- Highlights variants that may be causative in those genes and which variants are implausibly frequent given the known disease incidence
- Identifies further useful clinical or lab findings to make the diagnosis

VLDLR biallelic gene severity score 5

Variant severity score and sequence

chr:pos(HG19)

effect

Zygosity

Peter

Mama

Papa

1000

Local

Report

5

NM_003383.3:c.1249_1255delT...

chr9:2643480

frameshift

100

50

50

Biallelic variant severity score of 5 assigned to variant at chromosomal location chr9:2643480.

5 Base score (biallelic) for frameshift.

Used DM from Pathogenicity field to overrule other values for severity.

Key

Variant could contribute to zygosity for all

Individual is affected

Individual has unknown affected status

Variant frequency seems too high for disease incidence

Dubious zygosity due to poor depth, quality or shares

Hover to see depth, quality and shares

Automated reporting

Phenome + Genome

DifferentialAdd findingsAdd testsPhenotype 1Genotype

Dx1VLDLR-related cerebellar...

PCH2: pontocerebellar...

PCH8: pontocerebellar...

PCH10: pontocerebellar...

Vici syndrome

Alcardi-Goutières syn...

LIS2: RELN-related liss...

PCH1B: pontocerebell...

2 year old boy

Pertinent positive findings

≤1m

@1m

≤6m

✓

✓

Pertinent negative findings

X

Other

Nystagmus, non-rotary

Other

Microcephaly

Other

Hyperreflexia

History of a similar disorder in family or contacts

Reason

CT or MRI: brainstem atrophy or hypoplasia

(none selected)

Reason for testing

Other key finding

DifferentialAdd findingsAdd testsPhenotype 1Genotype

Dx1VLDLR-relate...

(none selected)

Diagnosis 1

Diagnosis 2

Diagnosis 3

Diagnosis 4

Pertinent gene zygosity

Severity scores for gene zygosity, with "c" denoting compound heterozygote

5

3

3c

3

✓

✓

✓

✓

Dx1

VLDLR gene variants (biallelic)

ALMS1 gene variants (biallelic)

HSPG2 gene variants (biallelic)

EIF2AK3 gene variants (biallelic)

Show the 1 VLDLR variant

VLDLR biallelic gene severity score 5

Variant severity score and sequence		chr:pos(HG19)	effect	Zygosity				
				Peter	Mama	Papa	1000	Local
Report	NM_003383.3:c.1249_1255delT...	chr9:2643480	frameshift	100	50	50		

Genome Report Cart: items selected

Reason for testing:
CT or MRI: brainstem atrophy or hypoplasia (onset unknown)

Other findings:
Microcephaly (onset @1 mo)
Nystagmus, non-rotary (onset by 1 mo)
Hyperreflexia (onset by 6 mo)

Diagnosis 1: VLDLR-related cerebellar hypoplasia
VLDLR gene variants (biallelic)
Severity 5 zygosity 100 at chr9:2643480 sequence NM_003383.3:c.1249_1255delTACAAAGT

Show genome report

Automated reporting.

You generate the report after you:

- Select the disease, gene and variant by diagnosis (supports up to 4 diagnoses in a patient)
- Assign findings to be a “reason for testing” or “other key finding”
- Confirm selection in “cart”

Genome report for the 2 year old boy with

Reason for testing:
- CT or MRI: brainstem atrophy or hypoplasia

Other key findings:
- Microcephaly
- Nystagmus, non-rotary
- Hyperreflexia

Consanguinity of parents: 1st cousin
Ethnicity: (unspecified)

Diagnosis # 1

Diagnosis # 1: VLDLR-related cerebellar hypoplasia
Mode of inheritance: Autosomal recessive
Gene symbol (HGNC): VLDLR
Gene name: Very low density lipoprotein receptor
Relevant variant:
Biallelic, shared with both parents: NM_003383.3:c.1249_1255delTACAAAGT
Chromosomal position: chr9:2643480, Effect: frameshift

Pertinent positive findings of the patient for this diagnosis:
- Nystagmus, non-rotary (onset by about 1 month old)
- Hyperreflexia (onset by about 6 months old)
- CT or MRI: brainstem atrophy or hypoplasia (present now)

Pertinent negative findings of the patient for this diagnosis:
- (none entered)

Provider Resources: GeneReviews and OMIM

Prognosis for VLDLR-related cerebellar hypoplasia

At what age do people with this disease have these findings?

Signs and Symptoms	Birth	1 month	3 months	6 months	1 year	3 years	6 years	10 years	15 years	25 years	40 years	60 years	80 years
Ataxia	Few	Few	Some	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most
Intellectual disability	NA	Few	Few	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most
Motor developmental delay	NA	Few	Few	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most
Gait abnormality	NA	NA	NA	NA	Some	Most	Most	Most	Most	Most	Most	Most	Most
Nystagmus, non-rotary	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Eye movement deficit, horizontal	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Hyperreflexia	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Seizures with abnormal movements	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Foot: pes planus	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Cataracts	Few	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some
Dysarthria or abnormal sound character	NA	NA	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some
Stature short	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few

Findings detected by laboratory tests

CT or MRI: pan-cerebellar atrophy or hypoplasia	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
VLDLR gene variants (biallelic)	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
CT or MRI: pontine atrophy or hypoplasia	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
CT or MRI: lissencephaly	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
CT or MRI: brainstem atrophy or hypoplasia	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some

KEY

None or NA	Few is less than or equal to 30%	Some is more than 30%	Most is more than 85%
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PCORI-funded research has shown the report to be well liked by patient families and referring physicians, especially the Prognosis Table, which allows you to quickly answer their question “With this diagnosis, what should I expect?”

Prioritizing discovery genes using clinical context & family history

SimulConsult Initial Diagnose Profile Assess Tips

Discovery genes: unrecognized gene zygosity

Unrecognized ☒ Human phenotypes ☐ Monoallelic phenotypes ☐ Biallelic phenotypes

Sort by ☒ Severity ☐ Alphabetical ☐ Order read

☐ Report 0 PEX11G monoallelic ☒ Report 5 PEX11G biallelic

Select a gene zygosity

Brown genes = ExAC suspicious

Discovery genes
Set variant parameters
Incidental genes
Loss of heterozygosity

PEX11G biallelic gene severity score 5

Variant severity score and sequence	chr:pos(HG19)	effect	Zygosity				
			Peter	Mama	Papa	1000	Local
<input type="checkbox"/> Report 5 NM_080662:ex5:c.C646T:p.L2...	chr19:7542168	missense	100	50	50	0.0351	0.0303

Genome Report Cart: items selected

Reason for testing:
CT or MRI: brainstem atrophy or hypoplasia (onset unknown)

Other findings:
Microcephaly (onset @1 mo)
Nystagmus, non-rotary (onset by 1 mo)
Hyperreflexia (onset by 6 mo)

Diagnosis 1: VLDLR-related cerebellar hypoplasia
VLDLR gene variants (biallelic)
Severity 5 zygosity 100 at chr9:2643480 sequence NM_003383.3:c.1249_1255delTACAAGT

Discovery gene candidate: PEX11G (biallelic)
Severity 5 zygosity 100 at chr19:7542168 sequence NM_080662:ex5:c.C646T:p.L216F

Discovery section of report
Selection of the variant adds discovery section to the “cart” and report

Loss of heterozygosity analysis

SimulConsult Initial Diagnose Profile Assess Tips

Differential Add findings Add tests Phen

Discovery genes
Set variant parameters
Incidental genes
Loss of heterozygosity

Tests by usefulness
Top tests ranked by usefulness account cost and treatability

Loss of heterozygosity analysis

LOC112268459
UVSSA
CRIPAK
NKX1-1
LOC105374348

Load genes

Next: View genes on genotype tab using Diagnose on the top black menu

Use results from a microarray about loss of heterozygosity

- **Select Loss of heterozygosity.** Find “Loss of heterozygosity” under DNA menu
- **Input gene list.** Convert the regions where loss of heterozygosity was found (e.g., chr4 801509 1503857), to a list of genes. Paste in gene list and “Load genes”
- **Review genes.** The green shading will indicate the gene zygositys most pertinent to your patient. Then you can use suggestions of useful clinical or lab findings to distinguish among the diseases in the differential diagnosis