
The Human Phenotype Ontology (HPO)

Andreas Laner	(MGZ München; laner@mgz-muenchen.de)
Sebastian Köhler	(Charité – Universitätsmedizin Berlin; drseb.github.io .)
Peter Robinson	(Jackson Lab; peter.robinson@jax.org)

- History of HPO
- Current status
- Applications
- Workshop/ Demonstration



Why phenotypes matter ?

- Phenotypic abnormality = clinical feature
- Constellation / Pattern of phenotypes / clinical features defines a disease:

... is a rare developmental disorder defined by the combination of **aplasia cutis congenita of the scalp vertex** and **terminal transverse limb defects**. In addition, **vascular anomalies** such as **cutis marmorata telangiectatica** ... are recurrently seen.

OMIM

WILLIAMS-BEUREN SYNDROME; WBS

Alternative titles; symbols

CHROMOSOME 7q11.23 DELETION SYNDROME, 1.5- TO 1.8-MB
WILLIAMS SYNDROME; WMS; WS

Cytogenetic location: [7q11.23](#) *Genomic coordinates (GRCh38):* [7:72,700,000-77,900,000](#)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
7q11.23	Williams-Beuren syndrome	194050	AD	#

Clinical Synopsis

▼ TEXT

A number sign (#) is used with this entry because Williams-Beuren syndrome (WBS) is a contiguous gene deletion syndrome resulting from the hemizygous deletion of 1.5 to 1.8 Mb on chromosome 7q11.23.

For a discussion of the genes deleted in this syndrome and possible genotype/phenotype correlations, see below.

▼ Description

Williams-Beuren syndrome is a multisystem disorder caused by hemizygous deletion of 1.5 to 1.8 Mb on chromosome 7q11.23, which contains approximately 28 genes. [Pober \(2010\)](#) reviewed the clinical features of Williams-Beuren syndrome as well as the genomic and genetic basis and clinical management. [🔗](#)

See also the distal chromosome 7q11.23 deletion syndrome ([613729](#)), which occurs between the WBS region and the MAGI2 gene ([606382](#)).

▼ Clinical Features

[Williams et al. \(1961\)](#) described a syndrome characterized by supravalvular aortic stenosis (SVAS), mental retardation, and distinctive facial features. [Beuren et al. \(1962\)](#) described a similar syndrome with the additional features of dental anomalies and peripheral pulmonary artery stenosis. Two features of the syndrome had been described as distinct entities: supravalvular aortic stenosis

- Free text phenotypic description
- Very expressive

OMIM

Clinical Synopsis (CS) section

WILLIAMS-BEUREN SYNDROME; WBS

Alternative titles; symbols

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- Free text phenotypic description
- Very expressive

INHERITANCE

- Autosomal dominant

GROWTH

Height

- Short stature

Weight

- Abnormal weight gain

Other

- Intrauterine growth retardation (IUGR)

HEAD & NECK

Face

- Medial eyebrow flare

- Flat midface

- Periorbital fullness (puffy eyes)

- Epicanthal folds

- Long philtrum [P](#)

Ears

- Sensorineural hearing loss, mild to moderate

- Hyperacusis

- Phonophobia

- Abnormal brain auditory evoked responses (BAER)

- Decreased or absent ipsilateral acoustic reflex response to maximum stimulation

Eyes

- Stellate pattern of iris

- Strabismus

- Altered visual acuity

Nose

- Depressed nasal bridge [P](#)

- Anteverted nares [P](#)

Mouth

- Thick lips

Teeth

- Hypodontia

- Microdontia [P](#)

CARDIOVASCULAR

Heart

- Supravalvular aortic stenosis

(Un)Controlled Vocabularies

- Non-standardized method for describing phenotypes
- Not designed to be machine interpretable
- Spelling problems

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Incomplete:

Fulltext contains
phenotype information;
absent in **CS**

Inconsistent:

No handling of synonyms

`'Height: short stature'`

`'Reduced adult height'`

`'Final adult height, 84-128cm'`

(Un)Controlled Vocabularies

- Non-standardized method for describing phenotypes
- Not designed to be machine interpretable
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CS contains symptoms such as:

`'Heart: Prolonged QTc interval'`
or
`'T-wave abnormalities'`

Imagine query for

`'ECG Abnormalities'` , how to ensure the examples above are found?

(Un)Controlled Vocabularies

- Non-standardized method for describing phenotypes
- Not designed to be machine interpretable
- Spelling problems

E.g.:

hypereflexia	-	hyperreflexia
congential	-	congenital
defecency	-	deficiency



Homonyms

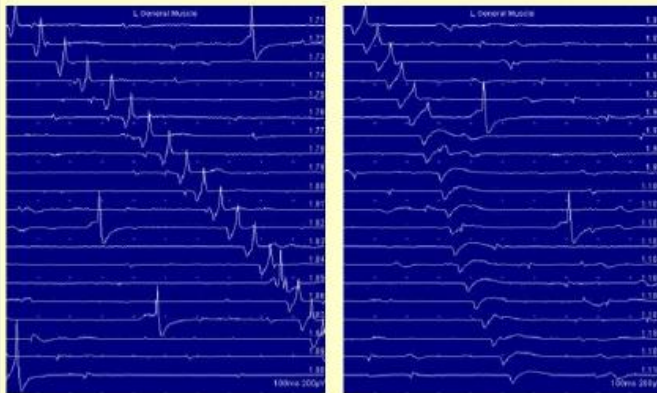
... fibrillation ...

fibrillation \neq fibrillation

= muscle fibrillation

= ventricular fibrillation

Fibrillation to PSW



Fib and intermediate shapes

Transformation is complete



Motivation for HPO Development

OMIM Query	Number of Results
large bones	264
large bone	785
enlarged bones	87
enlarged bone	156
big bones	16
huge bones	4
massive bones	28
hyperplastic bones	12
hyperplastic bone	40
bone hyperplasia	134
increased bone growth	612

Washington et al. *PLoS Biology* (2009)

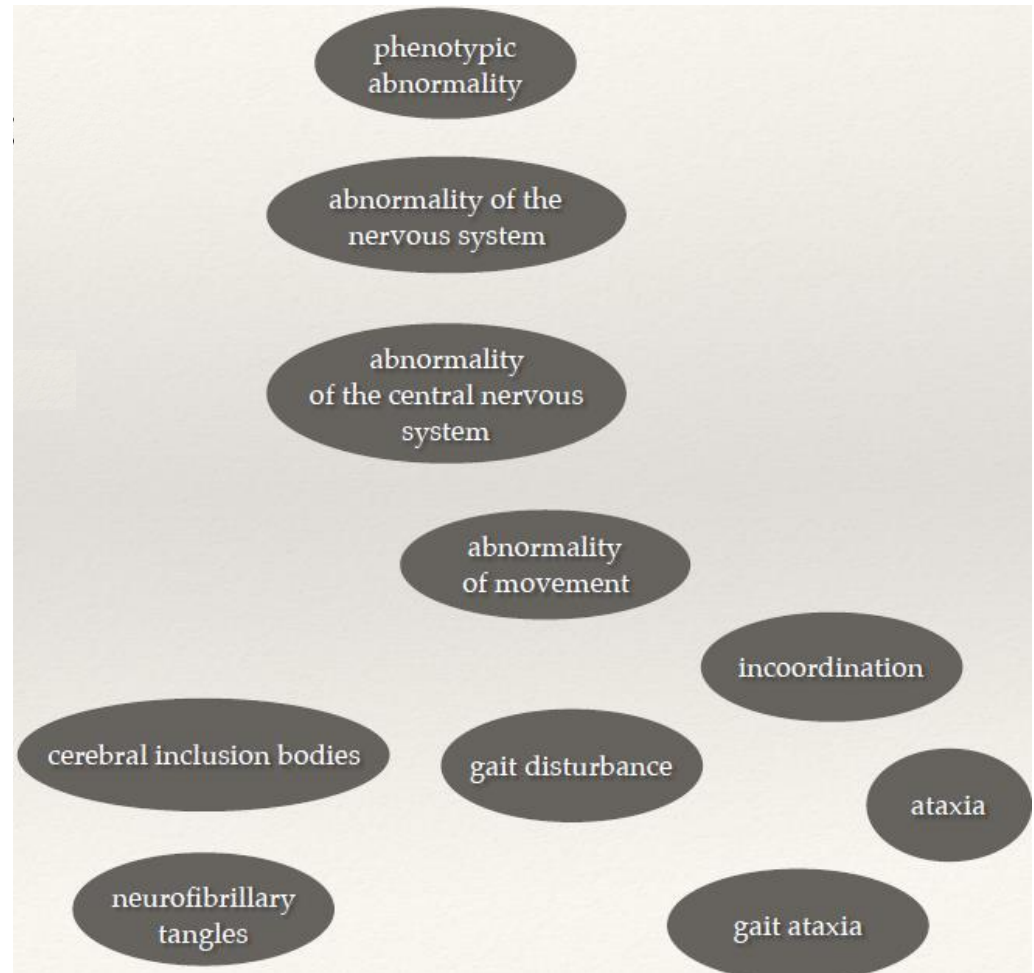
Linking human diseases to animal models using ontology-based phenotype annotation

Goal of HPO

- Computer-interpretable clinical features
 - Compare diseases based on clinical features
 - Compare patients based on clinical features
 - Compare patients with diseases based on clinical features
 -
 - Prioritization of variants in high throughput sequencing assays
- Easy to use and freely available

The Human Phenotype Ontology (HPO)

- Description of **phenotypic abnormalities** (=clinical features) in humans
- Synonyms merged into one term
- Creation of textual and logical definitions for each term



The Human Phenotype Ontology (HPO)

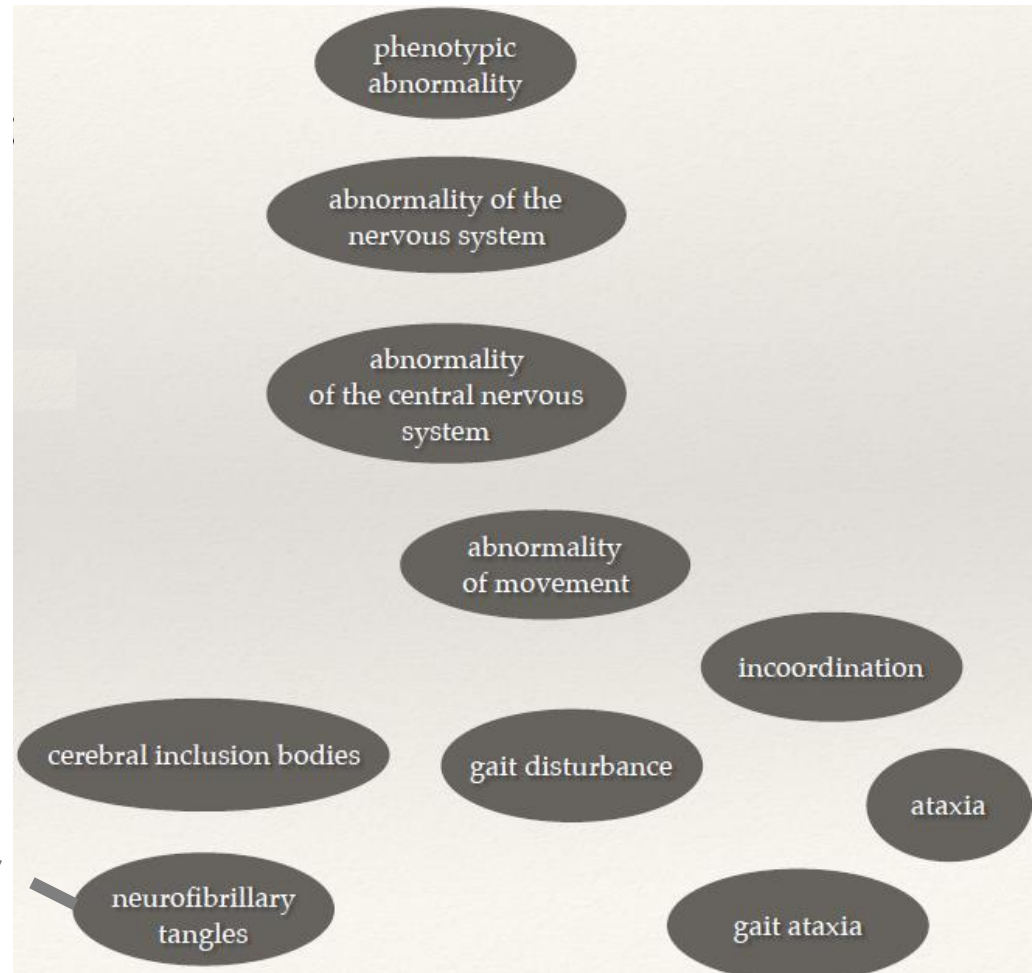
id: HP:0002185

name: Neurofibrillary tangles

def: Pathological protein aggregates formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate in an insoluble form. [HPO:sdoelken]

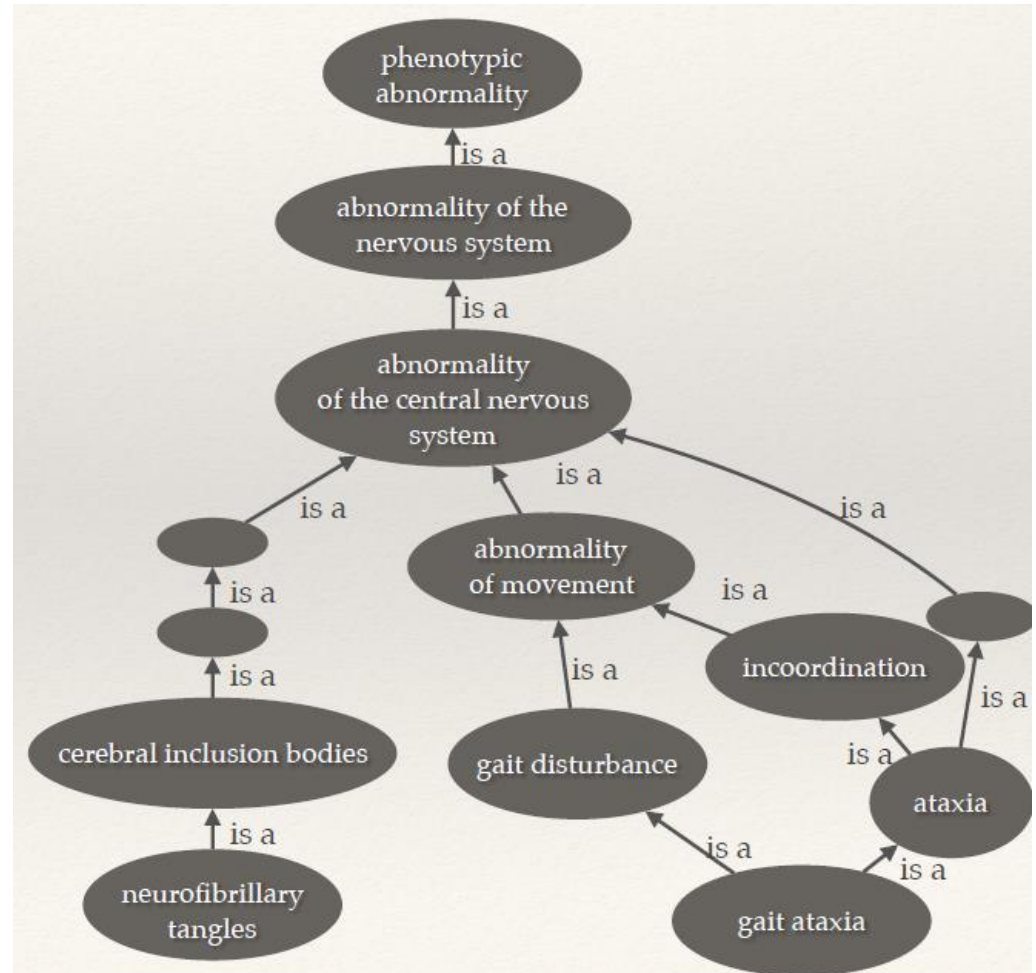
synonym: Neurofibrillary tangles may be present EXACT []

synonym: Paired helical filaments EXACT []



The Human Phenotype Ontology (HPO)

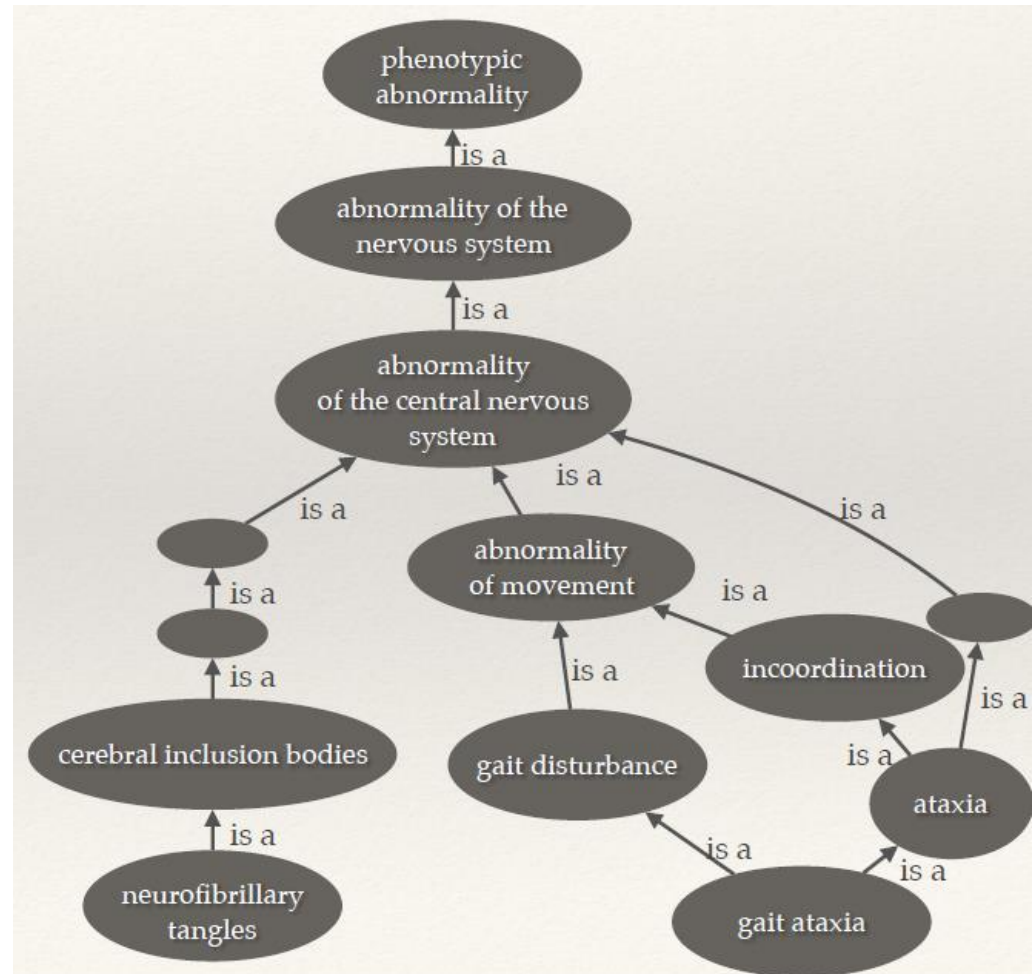
- ➡ Semantic relations
(is a subclass of)
- ➡ From top to bottom terms get more specific



Annotation of diseases

- ➡ HPO terms are used to **annotate** (describe) diseases
 - E.g. *neurofibrillary tangles* is used to annotate Alzheimer Disease
- ➡ Note: Annotation with *neurofibrillary tangles* induces annotation to all ancestor terms

Köhler et al.
The Human Phenotype Ontology project: linking molecular biology and disease through phenotype data; NAR (2014)



Current Status

➡ 4 root classes

- **Phenotypic abnormality**
- Mode of Inheritance
- Clinical modifier
- Mortality/ Aging





➡ Over 13.000 terms in HPO

➡ Over 156.000 annotations of > 7.700 rare diseases
(OMIM, Orphanet, DECIPHER)

➡ Over 133.000 annotations of > 3.100 common diseases

Recent projects

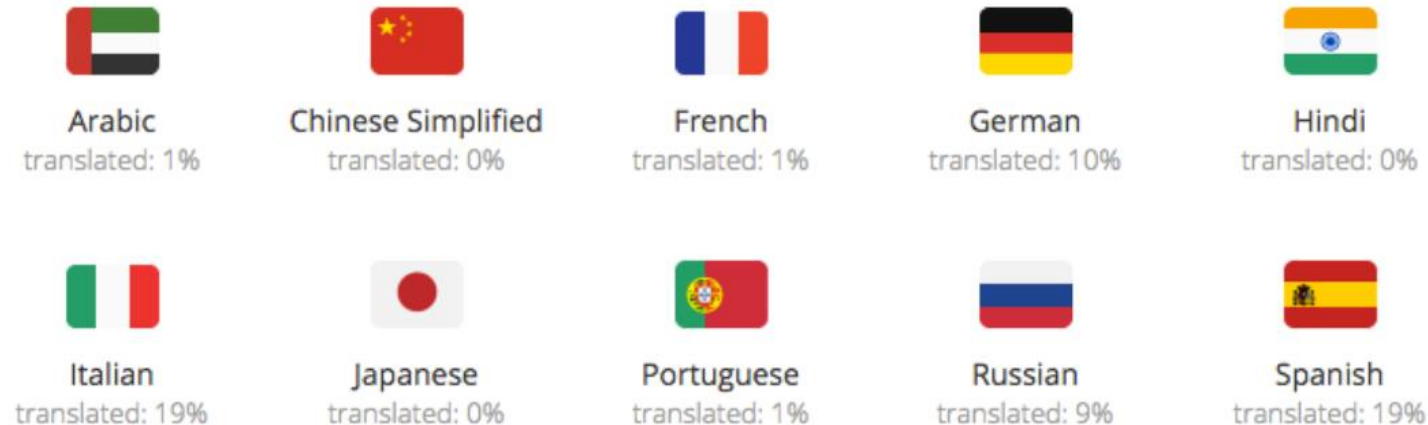
► Translations of labels, synonyms and textual definitions (crowdsourcing)

Plain language for describing human diseases		
We have developed the Human Phenotype Ontology (HPO) , a vocabulary to describe human disease features (phenotypes). The HPO now includes synonyms that patients, doctors, and machines can all understand.		
		
Apert's syndrome		
	Plain language	Medical term
	Webbed toes	Syndactyly
	Deformity due to premature fusing of skull bones	Cranio-synostosis
	Wide-set eyes	Ocular hypertelorism

Recent projects

- ➡ Translations of labels, synonyms and textual definitions (crowdsourcing)

Needs Translation:



- ➡ Numbers from 2017
- ➡ The HPO team needs help to get HPO available in our language as well

Sebastian Köhler (Charité – Universitätsmedizin Berlin; [drseb.github.io](https://github.com/drseb))

Sources of HPO Terms


The screenshot shows the Human Phenotype Ontology (HPO) website. The browser address bar highlights the URL <https://hpo.jax.org/app/>. The website header includes the HPO logo and navigation links: Tools, Downloads, and Help. The main content area features a search bar with the term "seizure" entered. Below the search bar, a dropdown menu displays "Terms (49)" and "Diseases (58)".

The Human Phenotype Ontology

The Human Phenotype Ontology (HPO) provides a standard term in the HPO describes a phenotypic abnormality, such as **Atrial septal defect**. The HPO project and others have developed software for research. The HPO is a flagship product of the **Monarch Initiative**, an NIH-supported initiative, a central component of one of the **13 driver projects** in the **Global Alliance for Genomics and Health**.

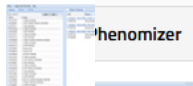
[Learn More About HPO](#)

Monarch Initiative

 Cross-species genomic and phenotypic analysis

[Explore Monarch!](#)

Phenomizer

 Rank disease differential diagnosis by clinical features

[Learn How!](#)

Seizure Search Results

Terms (49)

- HP:0001250 **Seizures**
- HP:0007359 **Focal seizures**
- HP:0002197 **Generalized seizures**
- HP:0011153 **Focal motor seizures**
- HP:0011146 **Dialectic seizures**
- HP:0002121 **Absence seizures**
- HP:0002069 **Generalized tonic-clonic seizures**
- HP:0002373 **Febrile seizures**
- HP:0011145 **Symptomatic seizures**
- HP:0011148 **Absence seizures with special features**

Diseases (58)

- ORPHA **Aldosterone-producing Adenoma With Seizures And Neurological Abnormalities**
- OMIM **Arthrogryposis, Mental Retardation, And Seizures**
- OMIM **Deafness, Onychodystrophy, Osteodystrophy, Mental Retardation, And Seizures...**
- OMIM **Dentatorubral-pallidoluysian Atrophy Naito-oyanagi Disease Haw River Syndro...**
- OMIM **Developmental Delay And Seizures With Or Without Movement Abnormalities**
- OMIM **Dyskinesia, Seizures, And Intellectual Developmental Disorder**
- OMIM **Epilepsy With Grand Mal Seizures On Awakening**
- OMIM **Epilepsy, Idiopathic Generalized, Susceptibility To, 10**
- ORPHA **Facial Asymmetry-temporal Seizures Syndrome**
- OMIM **Febrile Seizures, Familial, 11**

Evaluate variants based on the predicted pathogenicity

[View tool!](#)

Create structured patient phenotype profiles

[Check it out!](#)

Sources of HPO Terms

compbio.charite.de/hpover/showterm?id=HP:0000118#id=HP:0001250

hpo charite

VAMP UCSC Genome Browse... MGZ NGL Resources & Tools - C... Breast Cancer Informa... BIOBASE product logi... View all genes - Intern... View user account #00... Google kalender BRCA Exchange

Enter search terms ...

Infopage for HPO class

Seizures

<p>Primary ID</p> <p>HP:0001250</p> <p>Alternative IDs</p> <p>HP:0002306, HP:0002182, HP:0002348, HP:0001275, HP:0002466, HP:0002125, HP:0002417, HP:0010520, HP:0006997, HP:0002391, HP:0002437, HP:0002434, HP:0001303, HP:0002479, HP:0002432, HP:0002279, HP:0002430, HP:0002431, HP:0002794</p> <p>PURL</p> <p>http://purl.obolibrary.org/obo/HP_0001250</p>	<p>Synonyms</p> <p>Epilepsy</p> <p>Seizure</p> <p>Seizures</p>	<p>Textual definition</p> <p>Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.</p> <p>Logical definition</p> <p>Currently we do not have logical definition for this class. Feel free to suggest a logical definition at our github tracker.</p>
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<p>Superclasses</p> <p>Abnormality of nervous system physiology</p>	<p>Subclasses</p> <p>Multifocal seizures</p> <p>Focal seizures</p> <p>Epileptic spasms</p> <p>Dialeptic seizures</p> <p>Symptomatic seizures</p> <p>Status epilepticus</p> <p>Generalized seizures</p> <p>Febrile seizures</p>
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Sources of HPO Terms

1715 associated diseases

Disease id	Disease name
ORPHA:2930	Cronkhite-Canada syndrome
ORPHA:127	Borjeson-Forssman-Lehmann syndrome
ORPHA:1951	Epilepsy-telangiectasia syndrome
OMIM:612582	CHROMOSOME 6PTER-P24 DELETION SYNDROME
ORPHA:5	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
OMIM:311400	PAINE SYNDROME

Export to Excel  Export to CSV 

1174 associated genes

Gene	Associated diseases
CLPP (8192)	PERRAULT SYNDROME 3 (OMIM:614129)
NHLRC1 (378884)	MYOCLONIC EPILEPSY OF LAFORA (OMIM:254780)
GPHN (10243)	Hereditary hyperekplexia (ORPHA:3197), HYPEREKPLEXIA, HEREDITARY (OMIM:149400), MOLYBDENUM COFACTOR DEFICIENCY, COMPLEME... (OMIM:615501)
TACO1 (51204)	MITOCHONDRIAL COMPLEX IV DEFICIENCY (OMIM:220110)
UBA5 (79876)	SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESS... (OMIM:617133), EPILEPTIC ENCEPHALOPATHY, EARLY INFANTIL... (OMIM:617132)
CLN8 (2055)	CEROID LIPOFUSCINOSIS, NEURONAL, 8, NORT... (OMIM:610003), CEROID LIPOFUSCINOSIS, NEURONAL, 8 (OMIM:600143), Progressive epilepsy-intellectual disabi... (ORPHA:1947)
NAT10	

Export to Excel  Export to CSV 

Sources of HPO Terms

https://mseqdr.org/search_phenotype.php

ontobee

VAMP UCSC Genome Browser MSeqDR L-SDB Resources & Tools - C... Breast Cancer Informa... BIOBASE product logi... View all genes - Intern... View user account #00... Google Kalender BRCA Exchange Orphanet

About GBrowse MSeqDR-L-SDB Tools Phenome Collaboration Submission MSeqDR PhenoTips Hello! Guest! Please [Login](#) or [Register](#)! [Clinician Mode](#)

MSeqDR

Genomic Search Enter search term here. Mouse-over for examples.

Human Disease and Phenotype Search

Search term, single or multiple lines...

Batch Search:

1	SEIZURES	Term ID	HPO Disorder	Detail	Matched Field	Top Match
1:1	SEIZURES	HP:0001250	Seizures	Term:HP:0001250 Seizures Synonym: Epilepsy Definition: Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures. Tree level: 5	Name or Synonym	2
1:2	SEIZURES	HP:0001327	Photomyoclonic seizures	Term:HP:0001327 Photomyoclonic seizures Synonym: Definition: Tree level: 8	Name or Synonym	1
1:3	SEIZURES	HP:0002069	Generalized tonic-clonic seizures	Term:HP:0002069 Generalized tonic-clonic seizures Synonym: Generalised tonic-clonic seizures Definition: Generalized tonic-clonic seizures are generalized seizures with bilateral symmetrical tonic contraction then bilateral clonic contractions of somatic muscles usually associated with autonomic phenomena. Tree level: 7	Name or Synonym	1
1:4	SEIZURES	HP:0002121	Absence seizures	Term:HP:0002121 Absence seizures Synonym: Definition: Recurrent absence seizures are generalized seizures and are characterized by a loss of consciousness, thus, are a form of dialeptic seizures. Tree level: 7	Name or Synonym	1
1:5	SEIZURES	HP:0002123	Generalized myoclonic seizures	Term:HP:0002123 Generalized myoclonic seizures Synonym: Myoclonic epilepsy, progressive Definition: Seizures with sudden, brief (< 100 msec) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal). Tree level: 7	Name or Synonym	1
1:6	SEIZURES	HP:0002173	Hypoglycemic seizures	Term:HP:0002173 Hypoglycemic seizures Synonym: Definition: Tree level: 7	Name or Synonym	1
				Term:HP:0002197 Generalized seizures		

Adoption of HPO

Table 1. A selection of public-facing clinical databases using HPO to annotate patient data for disease-gene discovery projects

Name	URL
PhenomeCentral	phenomecentral.org
DDD (Deciphering Developmental Disorders)	www.ddduk.org
DECIPHER (Database of genomic variation and Phenotype in Humans using Ensembl Resources)	decipher.sanger.ac.uk
ECARUCA (European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations)	http://umcecaruca01.extern.umcn.nl:8080/ecaruca/ecaruca.jsp
The 100 000 Genomes Project	https://www.genomicsengland.co.uk/
Geno2MP (Exome sequencing data linked to phenotypic information from a wide variety of Mendelian gene discovery projects)	http://geno2mp.gs.washington.edu
NIH UDP (Undiagnosed Diseases Program)	available via phenomecentral.org
NIH UDN (Undiagnosed Diseases Network)	available via phenomecentral.org
HDG (Human Disease Gene Website series)	www.humandiseasegenes.com
Phenopolis(an open platform for harmonization and analysis of sequencing and phenotype data)	https://phenopolis.github.io
GenomeConnect (Patient portal developed by ClinGen (67))	www.genomeconnect.org
FORGE Canada & Care4Rare Consortium	available via phenomecentral.org
RD-Connect	platform.rd-connect.eu
Genesis	thegenesisprojectfoundation.org

Adoption of HPO

Table 2. Tools and applications using HPO

Tool	
<i>Phenotype-driven differential diagnosis</i>	<i>Cross-species phenotype analysis</i>
Phenomizer	PhenoDigm
BOQA	MouseFinder
FACE2GENE	Monarch
Phenolyzer	PhenomeNet
<i>Phenotype-driven exome/genome analysis</i>	UberPheno
Exomiser	MORPHIN
PhenIX	PhenogramViz
Phevor	<i>Phenotype knowledge resources and databases</i>
PhenoVar	Orphanet
eXtasy	MalaCards
OMIMExplorer	NIH genetic testing registry
Phen-Gen	OMIM
Geno2MP	dcGO
Genomiser	ClinVar
SimReg	GeneSetDB
ontologySimilarity	MSeqDR
<i>Functional and network analysis</i>	DIDA (digenic diseases database)
TopGene/ToppFunn	Genetic and Rare Diseases (GARD) Information Center
WebGestalt	<i>Visualization</i>
SUPERFAMILY	PhenoStacks
GREAT	PhenoBlocks
Random walk on heterogeneous network	DECIPHER (phenogram)
PANDA	phenogrid
PREDICT	ontologyPlot
<i>Clinical data management and analysis</i>	
Phenotips	
Patient Archive	
GENESIS (GEM.app)	

Adoption of HPO

Table 2. Tools and applications using HPO

Tool

Phenotype-driven differential diagnosis

→ Phenomizer
BOQA
FACE2GENE
Phenolyzer

Phenotype-driven exome/genome analysis

→ Exomiser
→ PhenIX
Phevor
PhenoVar
eXtasy
OMIMExplorer
Phen-Gen
Geno2MP
Genomiser
SimReg
ontologySimilarity

Functional and network analysis

TopGene/ToppFunn
WebGestalt
SUPERFAMILY
GREAT
Random walk on heterogeneous network
PANDA
PREDICT

Clinical data management and analysis

→ Phenotips
Patient Archive
GENESIS (GEM.app)

Cross-species phenotype analysis

PhenoDigm
MouseFinder
Monarch
PhenomeNet
UberPheno
MORPHIN
PhenogramViz

Phenotype knowledge resources and databases

Orphanet
MalaCards
NIH genetic testing registry
OMIM
dcGO
ClinVar
GeneSetDB
MSeqDR
DIDA (digenic diseases database)
Genetic and Rare Diseases (GARD) Information Center
Visualization
PhenoStacks
PhenoBlocks
DECIPHER (phenogram)
phenogrid
ontologyPlot

Phenotyp-driven Differential Diagnosis

Phenomizer: Search for diseases or differential diagnosis with HPO terms

compbio.charite.de/phenomizer/

UCSC Genome Browse... Befundverwaltung Praena Arztbriefe MGZ Intranet gnomAD browser VAMP HGMD start page European Journal of H... http://compbio.charit... ClinVar

Menu. Support the Phenomizer. Help. The Phenomizer

Features. Diseases. Ontology.

Enter feature... search. reset.

HPO id.	Feature.
HP:0010704	1-2 finger syndactyly
HP:0005767	1-2 toe complete cutaneous syndactyly
HP:0010711	1-2 toe syndactyly
HP:0010706	1-3 finger syndactyly
HP:0001459	1-3 toe syndactyly
HP:0010707	1-4 finger syndactyly
HP:0010712	1-4 toe syndactyly
HP:0006088	1-5 finger complete cutaneous syndactyly
HP:0010708	1-5 finger syndactyly
HP:0010713	1-5 toe syndactyly
HP:0030300	10 pairs of ribs
HP:0000878	11 pairs of ribs
HP:0030306	11 thoracic vertebrae
HP:0001233	2-3 finger syndactyly
HP:0005709	2-3 toe cutaneous syndactyly
HP:0004691	2-3 toe syndactyly
HP:0010709	2-4 finger syndactyly
HP:0005768	2-4 toe cutaneous syndactyly
HP:0010714	2-4 toe syndactyly
HP:0010692	2-5 finger syndactyly
HP:0010715	2-5 toe syndactyly
HP:0008083	2nd-5th toe middle phalangeal hypoplasia
HP:0011939	3-4 finger cutaneous syndactyly
HP:0006097	3-4 finger syndactyly
HP:0009779	3-4 toe syndactyly
HP:0010710	3-5 finger syndactyly
HP:0010716	3-5 toe syndactyly

Page 1 of 424 Features 1 - 27 of 11442

Patient's Features.

HPO.	Feature. ▲	Modifier.	Num diseases.
------	------------	-----------	---------------

News

Info

- The Phenomizer is developed and maintained by [Sebastian Köhler](#) (see [group website](#) for more info).
- The Phenomizer [Orphanet](#) uses the latest Orphanet date and a different algorithm for ranking the differential diagnoses.

Please cite the following papers when you use this tool/HPO in your publications.

[Köhler et al., Clinical diagnostics in human genetics with semantic similarity searches in ontologies.](#)
Am J Hum Genet (2009) vol. 85 (4) pp. 457-64

[Köhler et al., The Human Phenotype Ontology in 2017.](#)
Nucleic Acids Research (2017) doi: <https://doi.org/10.1093/nar/gkw1039>

Clear. Mode of inheritance. Get diagnosis.

Phenotyp-driven Differential Diagnosis

Phenomizer: Search for diseases or differential diagnosis with HPO terms

Menu. ▾ Support the Phenomizer. Help.

The Phenomizer

Features. Diseases. Ontology.

Foot deformity search. reset.

HPO id.	Feature.
HP:0001760	Abnormality of the foot
HP:0001776	Bilateral talipes equinovarus
HP:0005656	Positional foot deformity
HP:0001839	Split foot
HP:0010219	Structural foot deformity
HP:0001884	Talipes calcaneovalgus
HP:0008081	Valgus foot deformity

Page 1 of 1

Features 1 - 7 of 7

Patient's Features. Diagnosis. ✕

HPO.	Feature. ▲	Modifier.	Num diseases.
category.: Abnormality of limbs (1 Item)			
HP:0001760	Abnormality of the foot	observed.	1200 of 7994
category.: Abnormality of the eye (1 Item)			
HP:0000648	Optic atrophy	observed.	358 of 7994
category.: Abnormality of the integument (1 Item)			
HP:0001000	Abnormality of skin pigmentation	observed.	463 of 7994
category.: Abnormality of the nervous system (3 Items)			
HP:0001251	Ataxia	observed.	467 of 7994
HP:0001249	Intellectual disability	observed.	1242 of 7994
HP:0012675	Iron accumulation in brain	observed.	0 of 7994

Clear.

Mode of inheritance.

Get diagnosis.

Phenotyp-driven Differential Diagnosis

Phenomizer: Search for diseases or differential diagnosis with HPO terms

Menu ▾ Support the Phenomizer. Help.

Features. Diseases. Ontology.

Enter feature...
HPO id. Feature.
HP:0010704 1-2 finger syndactyly
HP:0005767 1-2 toe complete cutaneous syndactyly
HP:0010711 1-2 toe syndactyly
HP:0010706 1-3 finger syndactyly
HP:0001459 1-3 toe syndactyly
HP:0010707 1-4 finger syndactyly
HP:0010712 1-4 toe syndactyly
HP:0006088 1-5 finger complete cutaneous syndactyly
HP:0010708 1-5 finger syndactyly
HP:0010713 1-5 toe syndactyly
HP:0030300 10 pairs of ribs
HP:0000878 11 pairs of ribs
HP:0030306 11 thoracic vertebrae
HP:0001233 2-3 finger syndactyly
HP:0005709 2-3 toe cutaneous syndactyly
HP:0004691 2-3 toe syndactyly
HP:0010709 2-4 finger syndactyly
HP:0005768 2-4 toe cutaneous syndactyly
HP:0010714 2-4 toe syndactyly
HP:0010692 2-5 finger syndactyly
HP:0010715 2-5 toe syndactyly
HP:0008083 2nd-5th toe middle phalangeal hypoplasia
HP:0011939 3-4 finger cutaneous syndactyly
HP:0006097 3-4 finger syndactyly
HP:0009779 3-4 toe syndactyly
HP:0010710 3-5 finger syndactyly
HP:0010716 3-5 toe syndactyly

search. reset.

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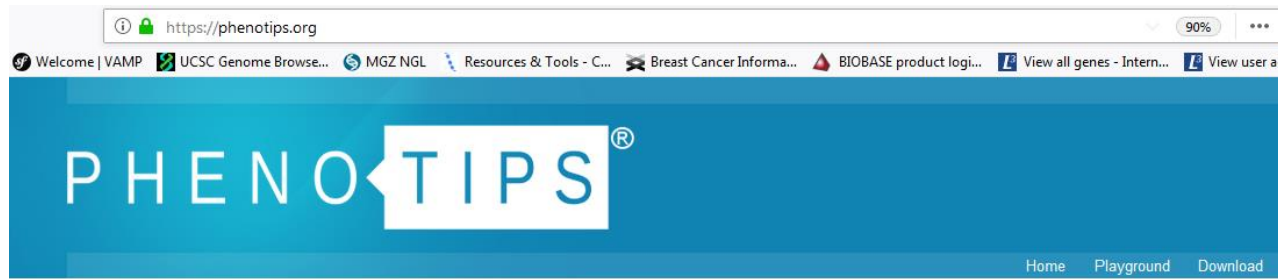
Patient's Features. Diagnosis. Diagnosis.

Algorithm: resnik (Unsymmetric). 6 Features.

<input type="checkbox"/>	p-value. ▲	Disease Id.	Disease name.	Genes.
<input checked="" type="checkbox"/>	0.2535	OMIM:136600	FRIEDREICH ATAXIA, SO-CALLED, WITH OPTIC ATROPHY AND SENSORINEURALDEAFNESS	
<input checked="" type="checkbox"/>	0.2535	OMIM:614499	#614499 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 34; MRT34	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2535	OMIM:614329	%614329 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 31; MRT31	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2535	OMIM:614254	#614254 MENTAL RETARDATION, AUTOSOMAL DOMINANT 8; MRD8	MBD5 (55777), CA
<input checked="" type="checkbox"/>	0.2535	OMIM:300387	#300387 MENTAL RETARDATION, X-LINKED 63; MRX63; MENTAL RETARDATION, X-LINKED 68; MRX68	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:136610	#136610 FRAGILE SITE 2Q11	
<input checked="" type="checkbox"/>	0.2535	OMIM:614256	#614256 MENTAL RETARDATION, AUTOSOMAL DOMINANT 10; MRD10	CACNG2 (10369),
<input checked="" type="checkbox"/>	0.2535	OMIM:300849	#300849 MENTAL RETARDATION, X-LINKED 41; MRX41; MENTAL RETARDATION, X-LINKED 48; MRX48	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:611090	#611090 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 12; MRT12	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2535	OMIM:300046	MENTAL RETARDATION, X-LINKED 23	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:611095	MENTAL RETARDATION, AUTOSOMAL RECESSIVE 9; MRT9	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2535	OMIM:612581	#612581 MENTAL RETARDATION, AUTOSOMAL DOMINANT 4; MRD4	MBD5 (55777), CA
<input checked="" type="checkbox"/>	0.2535	OMIM:300419	#300419 MENTAL RETARDATION, X-LINKED, WITH OR WITHOUT SEIZURES, ARX-RELATED; MRXARX; ME...	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:612580	#612580 MENTAL RETARDATION, AUTOSOMAL DOMINANT 3; MRD3	MBD5 (55777), CA
<input checked="" type="checkbox"/>	0.2535	OMIM:300803	#300803 MENTAL RETARDATION, X-LINKED 97; MRX97; MRXZ	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:309530	MENTAL RETARDATION, X-LINKED 1	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:614257	#614257 MENTAL RETARDATION, AUTOSOMAL DOMINANT 11; MRD11	MBD5 (55777), CA
<input checked="" type="checkbox"/>	0.2535	OMIM:300047	MENTAL RETARDATION, X-LINKED 20	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.2535	OMIM:136630	MENTAL RETARDATION, FRA12A TYPE	DIP2B (57609)
<input checked="" type="checkbox"/>	0.2535	OMIM:614249	#614249 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 18; MRT18	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2535	OMIM:611093	#611093 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 7; MRT7; MENTAL RETARDATION, AUTOSOM...	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2535	OMIM:614020	#614020 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 14; MRT14	METTL23 (124512)
<input checked="" type="checkbox"/>	0.2766	OMIM:311050	OPTIC ATROPHY 2	
<input checked="" type="checkbox"/>	0.3300	OMIM:300210	#300210 MENTAL RETARDATION, X-LINKED 58; MRX58	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.3300	OMIM:300355	%300355 MENTAL RETARDATION, X-LINKED 73; MRX73	ZNF711 (7552), IL1
<input checked="" type="checkbox"/>	0.3300	OMIM:300115	%300115 MENTAL RETARDATION, X-LINKED 50; MRX50	ZNF711 (7552), IL1

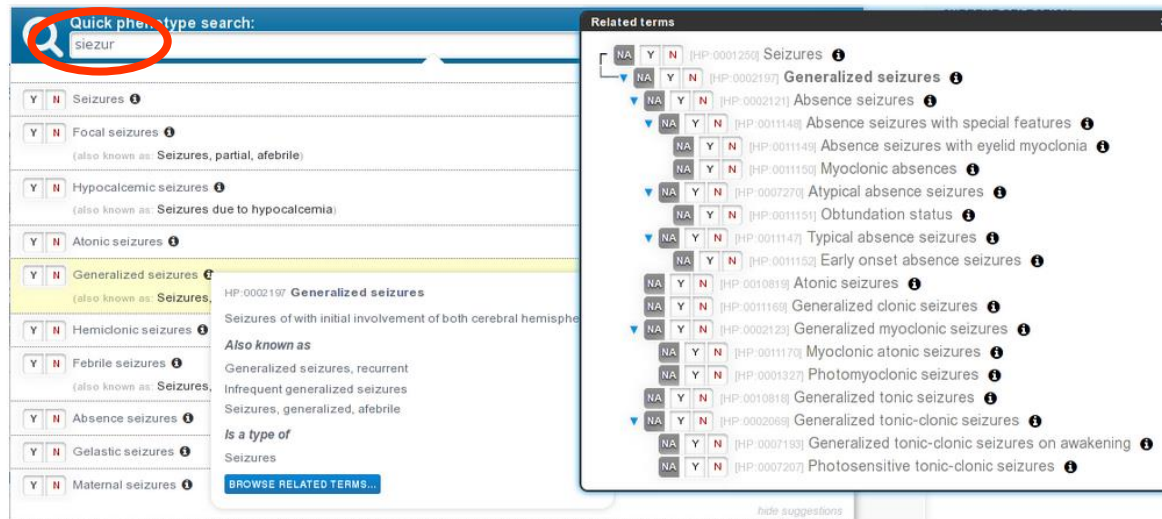
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Improve Differential Diagnosis. Download Results.

Clinical Data Management and Analysis

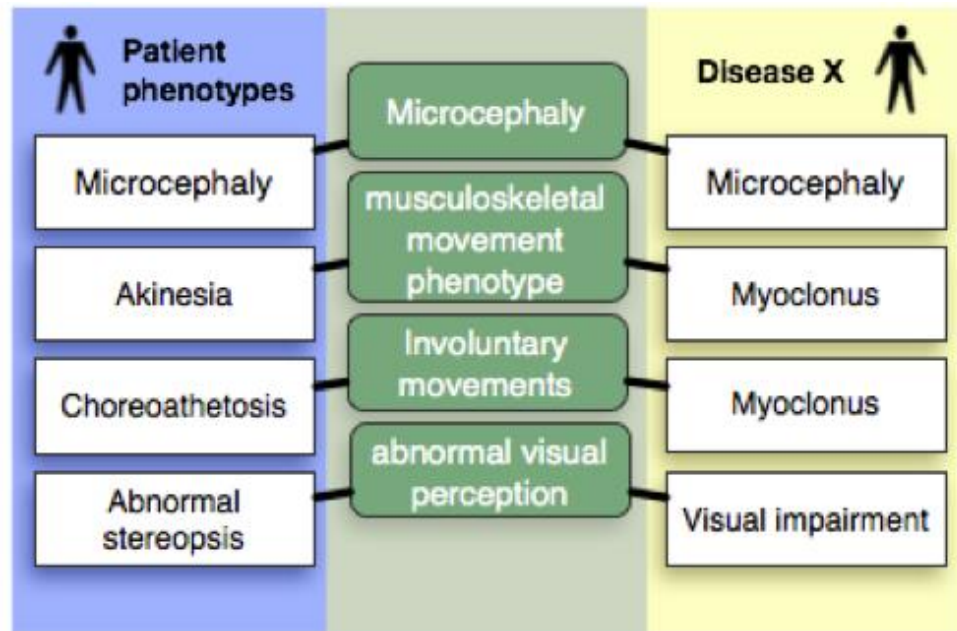


PhenoTips® is a software tool for collecting and analyzing phenotypic information of patients with genetic disorders.

- Free and open source
- Web-based application
- Easy to customize
- Standardized phenotyping using the Human Phenotype Ontology (HPO)
- Error-tolerant, predictive search of the ontology
- Real-time evaluation of the informational value of the phenotypic description via the Monarch Phenotype Profile Analysis
- Powerful built-in pedigree editor
- Measurements and growth curves
- Diagnosis assistance based on the entered data



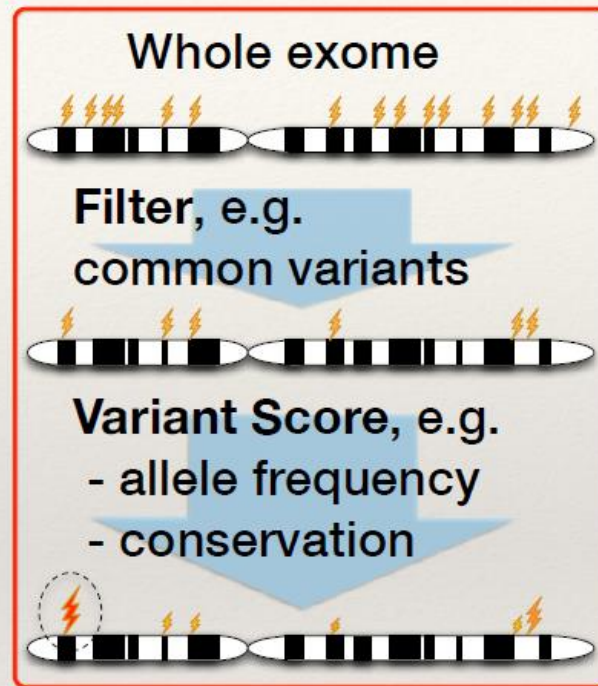
Adoption of HPO



- ❖ Basic idea of ontological search: Do not need exact match! But semantically similar diseases score well.
- ❖ Image a BLAST-search for sets of clinical features. (Phenomizer)

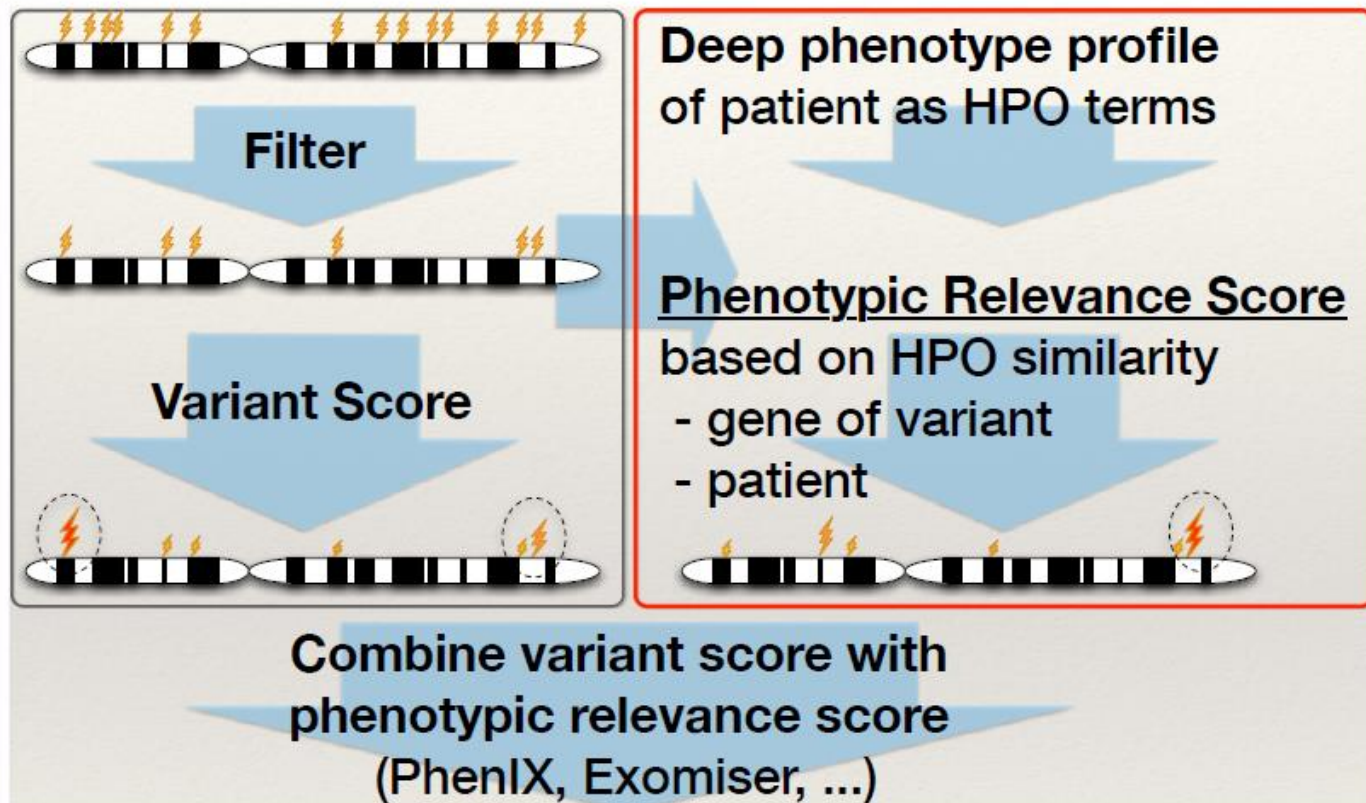
Clinical Genomics

- ❖ “Standard” clinical exome pipeline



- ❖ Predicts causative variant based on information in genome of patient and background genomic data
- ❖ Each human genome harbors about 100 genuine loss-of-function SNVs with ~20 genes completely inactivated (3) and around 50-100 CNVs. (DG MacArthur et al., *Science* 2012)

Clinical Genomics

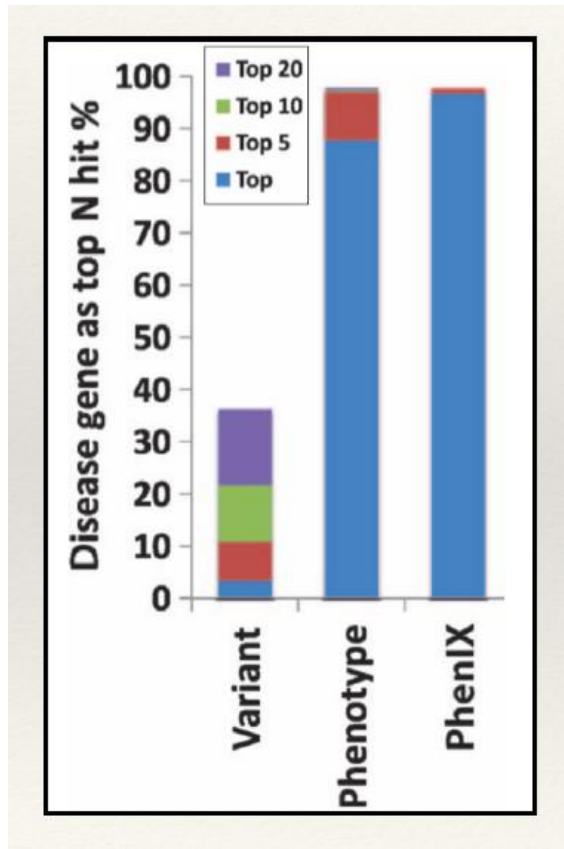


Robinson, Köhler, et al.
Improved exome prioritization of disease genes through cross-species phenotype comparison
Genome Research (2013)

Zemojtel, Köhler et al.
Effective diagnosis of genetic disease by computational phenotype analysis of the disease-associated genome
Science Translational Medicine (2014)

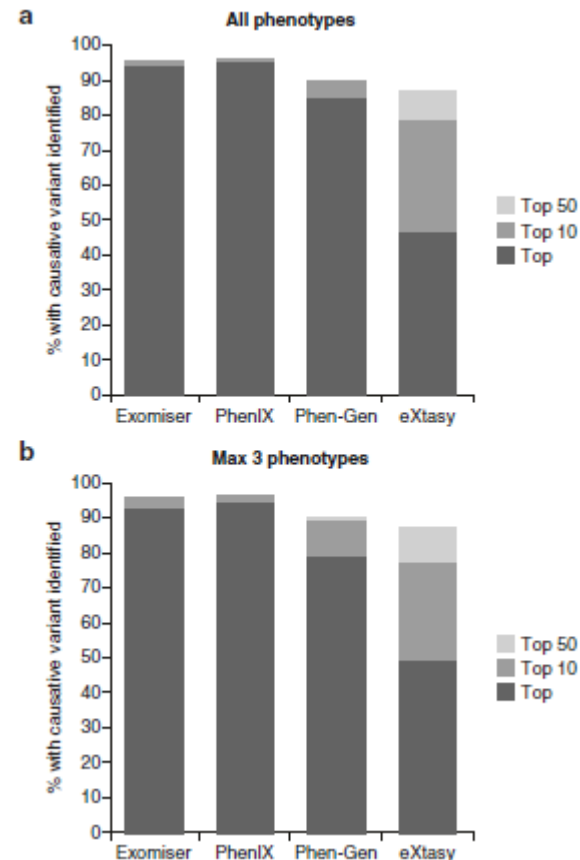
Clinical Genomics

Performance

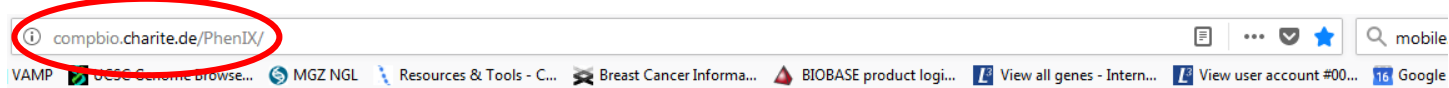


Combination of variant score and phenotype score is key

Other tools



Phenotyp-driven Exome/Genome Analysis



How does PhenIX work?

PhenIX, **Phenotypic Interpretation of eXomes**, is a pipeline for ranking (prioritizing) candidate genes in exomes or VCF panels with comprehensive coverage of human Mendelian disease genes. It ranks genes based on predicted variant pathogenicity as well as phenotypic similarity of diseases associated with the genes harboring these variants to the phenotypic profile of the individual being investigated, based on analysis powered by the [Human Phenotype Ontology \(HPO\)](#).

What input does PhenIX require?

PhenIX requires a VCF file mapped to hg19/Gchr37, as well as a list of HPO terms representing the phenotype observed in the patient. The PhenIX server is designed to work with single sample VCF files, but locally installable versions are available on a collaborative basis that offer additional functionality for pedigree filtering and prioritization based on other data sources.

Run PhenIX online:

HPO term (s):

VCF file: Keine Datei ausgewählt.

Mode of inheritance:

Frequency cutoff:

Number of candidates to show:

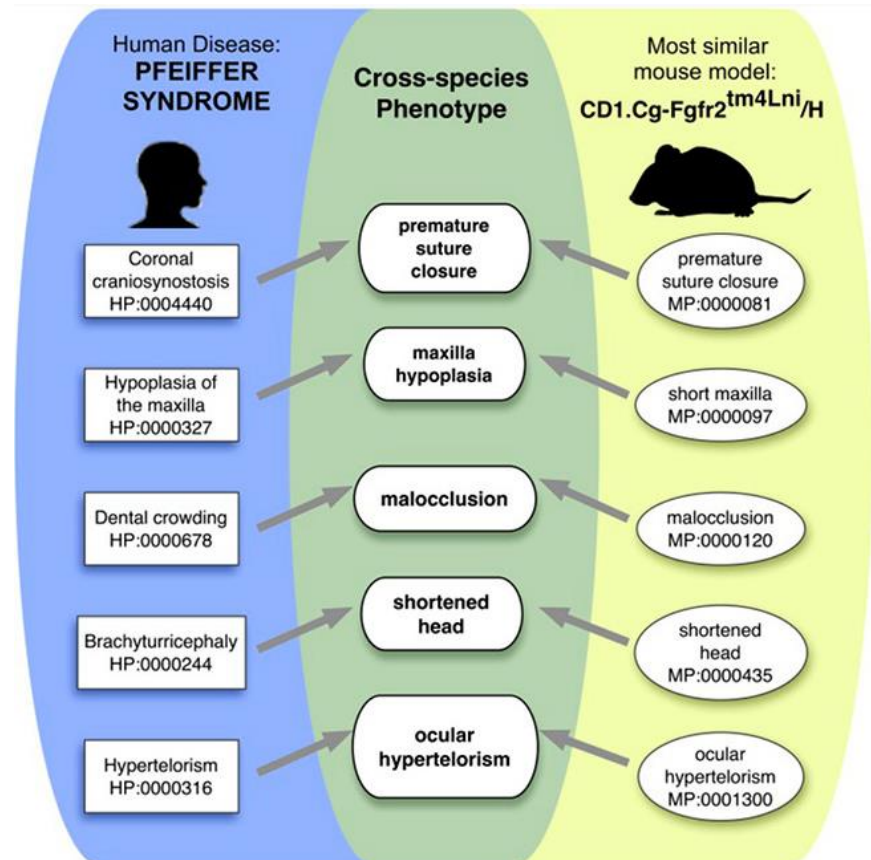
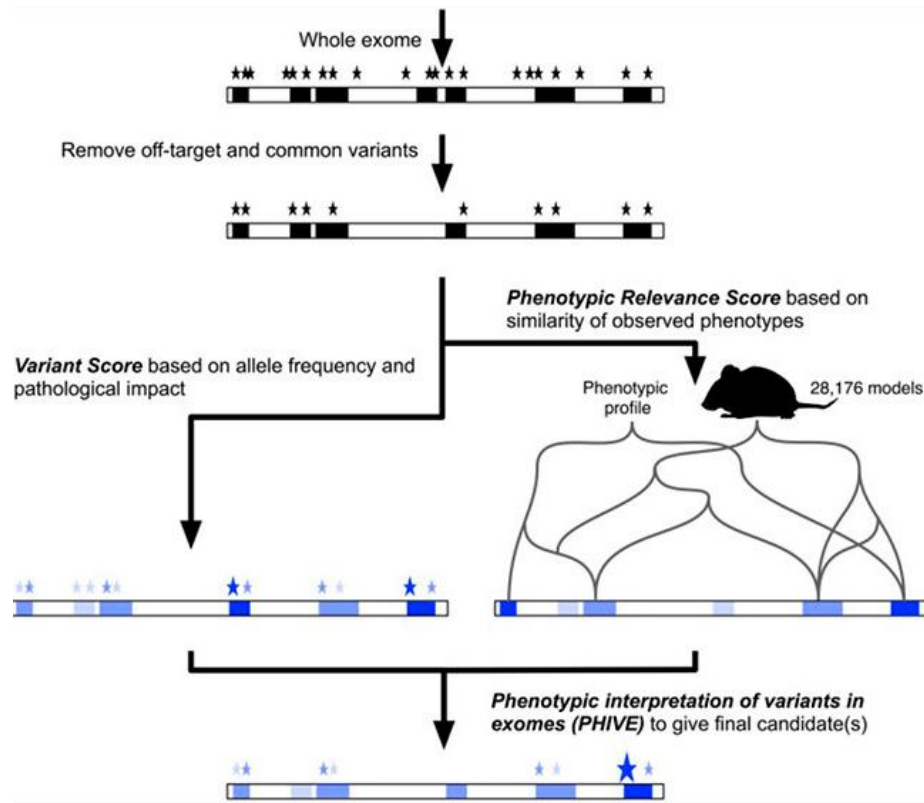
After you submit your data, the VCF file, the HPO terms, and the other parameters will be uploaded to our server. Do not hit the refresh or back button during this time.

[Human Phenotype Ontology \(HPO\)](#) terms are autocompleted (e.g. typing 'polyd' will autocomplete to 'polydactyly'). Users can enter the term name (e.g., "Dry skin") or a synonym (e.g., "Xerosis"). In the case of problems in trying to find the correct HPO term, we recommend using the [PhenExplorer](#) tool. HPO IDs from PhenExplorer can directly serve as inputs to PhenIX.

The input VCF file is stored with memory and not written to a hard disk. Neither the sequence data nor the phenotype data is stored for longer than the HTTP session. PhenIX is freely available for academic users or for private use. Other users are requested to contact us to obtain a license.

Phenotyp-driven Exome/Genome Analysis

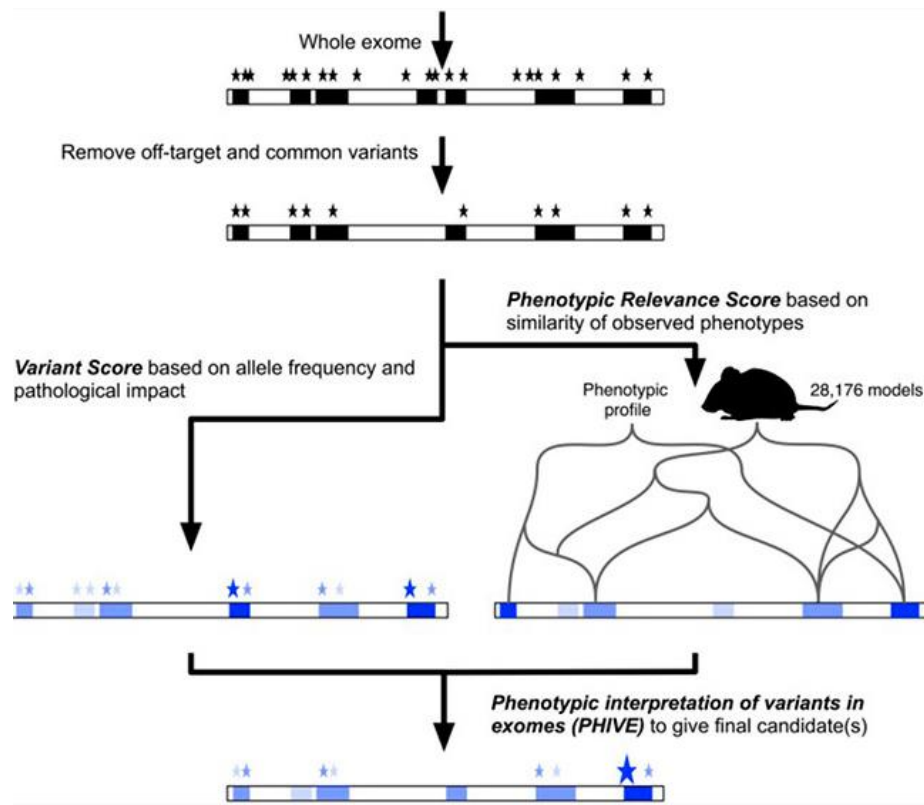
Exomiser – filtered genes assigned a phenotypic relevance score based on comparison with mouse and zebrafish models with mutations in orthologous genes



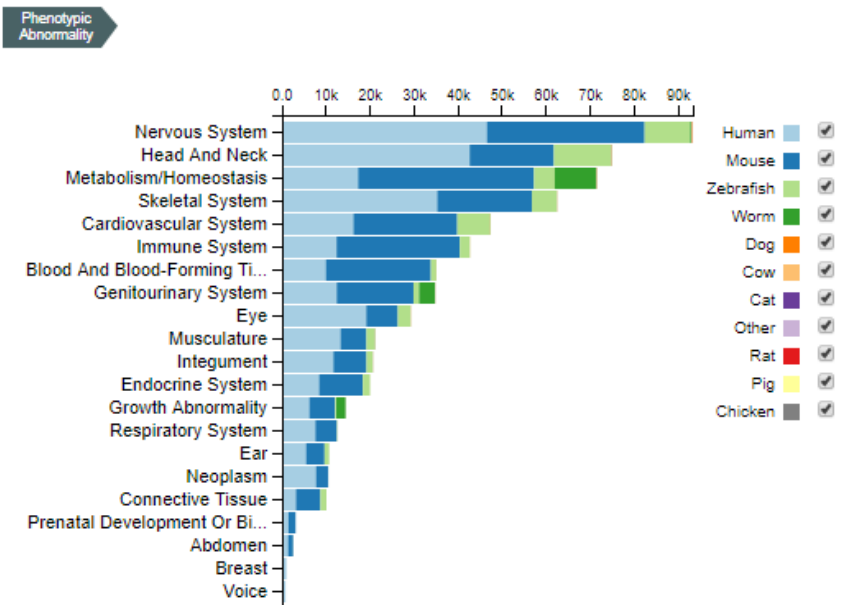
Genes with variants that survive the initial filtering steps are screened for mouse models with phenotypic to the human disease

Phenotyp-driven Exome/Genome Analysis

Exomiser – filtered genes assigned a phenotypic relevance score based on comparison with mouse and zebrafish models with mutations in orthologous genes



Number of Phenotype Gene Associations Per Species



genes with variants that survive the initial filtering steps are then screened for mouse models with phenotypic to the human disease

Summary

HPO – a controlled vocabulary of phenotypic abnormalities for human genetics

- Freely available
- Open source

Novel approaches towards:

- Differential diagnosis tools (e.g. Phenomizer)
- Variant prioritization tools (e.g. Exomiser)
- Standard patient description in projects world-wide

Caveat: Phenotyp-driven variant prioritization

- Phenotypes in your patient (may) change over time
- Phenotypes are not always expressed / observed or described properly (two diseases)
- Phenotypes are not determined for (very) rare diseases (OMIM updates)
- Phenotypes are not very selective for e.g. mental retardation (Phenomizer; e.g. „intellectual disability“ + „seizures“ + „developmental delay“)

... Challenges to (H)WPO



The famous Bavarian “Wolpertinger”