Variant Effect Prediction Training Course

Johor (Malaysia), August 27-30, 2018

Human Phenotype Ontology (HPO)

There are several standards to describe, and store in databases, phenotypic characteristics of an individual (patient). The Human Phenotype Ontology (HPO) is a standard which recently gained a lot of traction and it is used by many databases.

The aim of this task is gaining experience in using the Human Phenotype Ontology (HPO) to describe phenotypes using tools/resources available on the internet. Experience will be gained by visiting a few sites and performing some simple tasks/queries. Note there are many more sites where similar information/tools can be found. Feel free to try others as well. Ultimately, use the one you like best, i.e. easiest to work with to get the results you need!

Our advise is to try;

- Ontobee HPO browser (http://www.ontobee.org/ontology/HP)
  Ontobee includes some other standards as well
- HPO website (http://human-phenotype-ontology.github.io/),
- Phenotips (http://phenotips.org/)

When you are new to HPO it might be good to first get a feeling about HPO and its structure. Using the resources mentioned, try to find the HPO description and code of some standard phenotypic characteristics. While working, note the tree-based structure of HPO with less detail above and more detail below.

When you have some experience, or want a more demanding task, please ask for a manuscript containing detailed phenotype descriptions, find the respective HPO codes and mail the result to the LOVD-team (LOVD@JohanDenDunnen.nl, lsdbs@lovd.nl). Your work will then be used to update the respective database records in the "Global Variome shared LOVD" (http://databases.lovd.nl/shared) with the detailed descriptions you generated.

For all **ToTry's** note that you can query the resource for anything you are interested in. The examples we give is just for those that lacking inspiration. We encourage participants to bring their own cases, get to HPO-based phenotype descriptions and submit them to e.g. the "Global Variome shared LOVD".

Beginners

ToTry: just take some phenotype descriptions you know/work with and see how specific they are or check how many descriptions are linked to term.

Browsing phenotype characteristics

1) go to Ontobee and using the "Keywords" query box try: big head

- what is the associated HPO term,? Macrocephaly at birth
- what the HPO code? HP_0004488
- check the class hierarchy, are there sub-classes? No, only superclass

Class: Macrocephaly at birth

Term IRI: http://purl.obolibrary.org/obo/HP_0004488

Definition: The presence of an abnormally large skull with onset at birth. [database_cross_reference: HPO:probinson][database_cross_reference: HPO:probinson]

Annotations

- **database_cross_reference:**UMLS:C1836599
- **has_broad_synonym:**Congenital large head; Big head present since birth; Big head present at birth; Large head present at birth; Large head present since birth
- **has_exact_synonym:**Congenital macrocephaly; Large cranium present at birth; Congenital large cranium; Big skull present at birth; Big skull present since birth; Congenital large skull; Large skull present since birth; Big cranium present at birth; Large cranium present since birth; Big cranium present since birth; Large skull present at birth; Head circumference large for gestational age
- **has_obo_namespace:**human_phenotype
- **http://www.geneontology.org/formats/oboInOwl#id:**HP:0004488
- **in_subset:**http://purl.obolibrary.org/obo/hp#hposlim_core

Class Hierarchy

Thing
+ Phenotype
+ abnormal phenotype
+ Phenotypic abnormality
+ Abnormality of the skeletal system
+ Abnormality of skeletal morphology
+ Abnormal axial skeleton morphology
+ Abnormality of the skull
+ Abnormality of skull size
+ Increased head circumference
+ Macrocephaly
- Progressive macrocephaly
- Relative macrocephaly
- Postnatal macrocephaly
- Macrocephaly at birth

2) now try: macrocephaly

- note you now immediately get the more detailed subclasses, how many?

Class Hierarchy

Thing
+ Phenotype
+ abnormal phenotype
+ Phenotypic abnormality
+ Abnormality of the skeletal system
+ Abnormality of skeletal morphology
+ Abnormal axial skeleton morphology
+ Abnormality of the skull
+ Abnormality of skull size
+ Increased head circumference
- Macrocephaly
- Progressive macrocephaly
- Relative macrocephaly
- Macrocephaly at birth
- Postnatal macrocephaly

3) try some other terms like “scoliosis”, “intellectual disability”

Class: Scoliosis

Term IRI: http://purl.obolibrary.org/obo/HP_0002650

Definition: The presence of an abnormal lateral curvature of the spine. [database_cross_reference: HPO:probinson][database_cross_reference: HPO:probinson]

Annotations

- **database_cross_reference:**UMLS:C0037932; Fyler:4160; UMLS:C0700208; SNOMEDCT_US:64217002; SNOMEDCT_US:111266001; MSH:D013121
- **has_alternative_id:**HP:0002770; HP:0003415; HP:0003303; HP:0003317
- **has_broad_synonym:**Curvature of spine; Curved spine
- **has_exact_synonym:**Abnormal curving of the spine
- **has_obo_namespace:**human_phenotype
- **http://www.geneontology.org/formats/oboInOwl#id:**HP:0002650
- **in_subset:**http://purl.obolibrary.org/obo/hp#hposlim_core

Equivalents

- has part some (lateral and rotional curvature and (inheres in some vertebral column) and (has modifier some abnormal) and (has modifier some pathological))

Class Hierarchy

Thing
+ Phenotype
+ abnormal phenotype
+ Phenotypic abnormality
+ Abnormality of the skeletal system
+ Abnormality of skeletal morphology
+ Abnormal axial skeleton morphology
+ Abnormality of the vertebral column
+ Abnormality of the curvature of the vertebral column
+ Kyphosis
+ Hyperlordosis
+ Abnormal cervical curvature
- Camptocormia
- Abnormally straight spine
- Scoliosis
+ Kyphoscoliosis
+ Thoracic scoliosis
+ Thoracolumbar scoliosis
- Progressive congenital scoliosis
- Compensatory scoliosis

Term IRI: http://purl.obolibrary.org/obo/HP_0001249

Definition: Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70. [database_cross_reference: HPO:probinson][database_cross_reference: HPO:probinson]

Annotations

- **database_cross_reference:**SNOMEDCT_US:91138005; MSH:D008607; SNOMEDCT_US:228156007; UMLS:C4020876; UMLS:C0917816; UMLS:C0423903; UMLS:C0025362; UMLS:C3714756; UMLS:C1843367; SNOMEDCT_US:247578003
- **has_alternative_id:**HP:0002382; HP:0000730; HP:0002402; HP:0001267; HP:0007154; HP:0002316; HP:0002499; HP:0007176; HP:0002543; HP:0002458; HP:0002482; HP:0002192; HP:0002386; HP:0002122; HP:0006833; HP:0001286; HP:0003767; HP:0007180
- **has_exact_synonym:**Mental retardation, nonspecific; Mental deficiency; Mental-retardation; Mental retardation; Nonprogressive intellectual disability; Intellectua disability; Nonprogressive mental retardation
- **has_obo_namespace:**human_phenotype
- **has_related_synonym:**Poor school performance; Low intelligence; Dull intelligence
- **http://www.geneontology.org/formats/oboInOwl#id:**HP:0001249
- **http://www.w3.org/2000/01/rdf-schema#comment:**This term should be used for children at least five years old. For younger children, consider the term Global developmental delay (HP:0001263).

Equivalents

- has part some (disrupted and (inheres in some cognition) and (has modifier some abnormal))

Class Hierarchy

Thing
+ Phenotype
+ abnormal phenotype
+ Phenotypic abnormality
+ Abnormality of the nervous system
+ Abnormality of nervous system physiology
+ Neurodevelopmental abnormality
+ Specific learning disability
- Developmental regression
+ Developmental stagnation
+ Neurodevelopmental delay
- Intellectual disability
- Intellectual disability, mild
- Intellectual disability, profound
- Intellectual disability, moderate
- Intellectual disability, progressive
- Intellectual disability, borderline
- Intellectual disability, severe

4) try “abnormal nose” and “nose” and compare the results

abnormal nose has synonyms

- how many hits do you get with the query “nose”? >100

Class: Abnormal nasal morphology

Term IRI: http://purl.obolibrary.org/obo/HP_0005105

Annotations

- **database_cross_reference:**Fyler:4870; UMLS:C4025252
- **has_exact_synonym:**Abnormal of nasal shape; Abnormal nose morphology; Abnormal of shape of nose; Abnormal of morphology of nose
- **has_obo_namespace:**human_phenotype
- **http://www.geneontology.org/formats/oboInOwl#created_by:**peter
- **http://www.geneontology.org/formats/oboInOwl#creation_date:**2008-03-25T05:21:00Z
- **http://www.geneontology.org/formats/oboInOwl#id:**HP:0005105
- **http://www.w3.org/2000/01/rdf-schema#comment:**This is a category for overall abnormal morphology that may be replaced later with more exact descriptions.

Equivalents

- has part some (morphology and (inheres in some nasal bone) and (has modifier some abnormal))

Class Hierarchy

Thing
+ Phenotype
+ abnormal phenotype
+ Phenotypic abnormality
+ Abnormality of head or neck
+ Abnormality of the head
+ Abnormality of the face
+ Abnormality of the nose
+ Abnormality of the choanae
+ Abnormality of the nasal septum
+ Epistaxis
+ Abnormality of the nasal bridge
+ Abnormality of the nasal mucosa
+ Abnormality of the nasopharynx
- Nasal obstruction
+ Abnormality of the sense of smell
+ Abnormality of the nares
+ Abnormality of the nasolabial region
+ Abnormality of the nasal cavity
+ Abnormality of the nasal skeleton
- Abnormality of nasal hair
- Abnormality of nasalis muscle
- Abnormality of procerus muscle
more...
- Abnormal nasal morphology
- Bulbous nose
- Slender nose
- Wide nose
- Pear-shaped nose
- Prominent nose
- Narrow nose
+ Anteverted nares
- Long nose
- Short nose
+ Midline defect of the nose
+ Aplasia/Hypoplasia involving the nose
- Proboscis
+ Fullness of paranasal tissue
- Pyriform aperture stenosis

Keywords: nose Search terms

Terms with 'nose' included in their label:

1. http://purl.obolibrary.org/obo/UBERON_0000004 **(UBERON)**:
   - **nose** *in Ontobee*: HP
2. http://purl.obolibrary.org/obo/UBERON_0012128 **(UBERON)**:
   - **nose** tip *in Ontobee*: HP
3. http://purl.obolibrary.org/obo/UBERON_0015476 **(UBERON)**:
   - **nose** skin *in Ontobee*: HP
4. http://purl.obolibrary.org/obo/UBERON_0019306 **(UBERON)**:
   - **nose** epithelium *in Ontobee*: HP
5. http://purl.obolibrary.org/obo/GO_0043584 **(GO)**:
   - **nose** development *in Ontobee*: HP
6. http://purl.obolibrary.org/obo/HP_0000421 **(HP)**:
   - **Nose**bleed *in Ontobee*: HP
   - **Nose** bleeding *in Ontobee*: HP
   - Bloody **nose** *in Ontobee*: HP
   - Frequent **nose**bleeds *in Ontobee*: HP
7. http://purl.obolibrary.org/obo/HP_0012720 **(HP)**:
   - **Nose** cancer *in Ontobee*: HP
   - Neoplasm of the **nose** *in Ontobee*: HP
   - Neoplasia of the **nose** *in Ontobee*: HP
   - Tumor of the **nose** *in Ontobee*: HP
8. http://purl.obolibrary.org/obo/CHEBI_2181 **(CHEBI)**:
   - L-fucopyra**nose** *in Ontobee*: HP
9. http://purl.obolibrary.org/obo/CHEBI_48206 **(CHEBI)**:
   - fucopyra**nose** *in Ontobee*: HP
10. http://purl.obolibrary.org/obo/HP_0000366 **(HP)**:
    - Abnormality of the **nose** *in Ontobee*: HP
    - Anomaly of the **nose** *in Ontobee*: HP
    - Deformity of the **nose** *in Ontobee*: HP
    - Malformation of the **nose** *in Ontobee*: HP
11. http://purl.obolibrary.org/obo/HP_0000414 **(HP)**:
    - Bulbous **nose** *in Ontobee*: HP
    - Potato **nose** *in Ontobee*: HP
12. http://purl.obolibrary.org/obo/HP_0000417 **(HP)**:
    - Slender **nose** *in Ontobee*: HP
13. http://purl.obolibrary.org/obo/HP_0000445 **(HP)**:
    - Wide **nose** *in Ontobee*: HP
    - Broad **nose** *in Ontobee*: HP
    - Increased breadth of **nose** *in Ontobee*: HP
    - Increased width of **nose** *in Ontobee*: HP
14. http://purl.obolibrary.org/obo/HP_0000447 **(HP)**:
    - Pear-shaped **nose** *in Ontobee*: HP
15. http://purl.obolibrary.org/obo/HP_0000448 **(HP)**:
    - Prominent **nose** *in Ontobee*: HP
    - Big **nose** *in Ontobee*: HP
    - Disproportionately large **nose** *in Ontobee*: HP
    - Increased size of **nose** *in Ontobee*: HP
    - Large **nose** *in Ontobee*: HP
    - Pronounced **nose** *in Ontobee*: HP
    - Hyperplasia of **nose** *in Ontobee*: HP
    - Hypertrophy of **nose** *in Ontobee*: HP

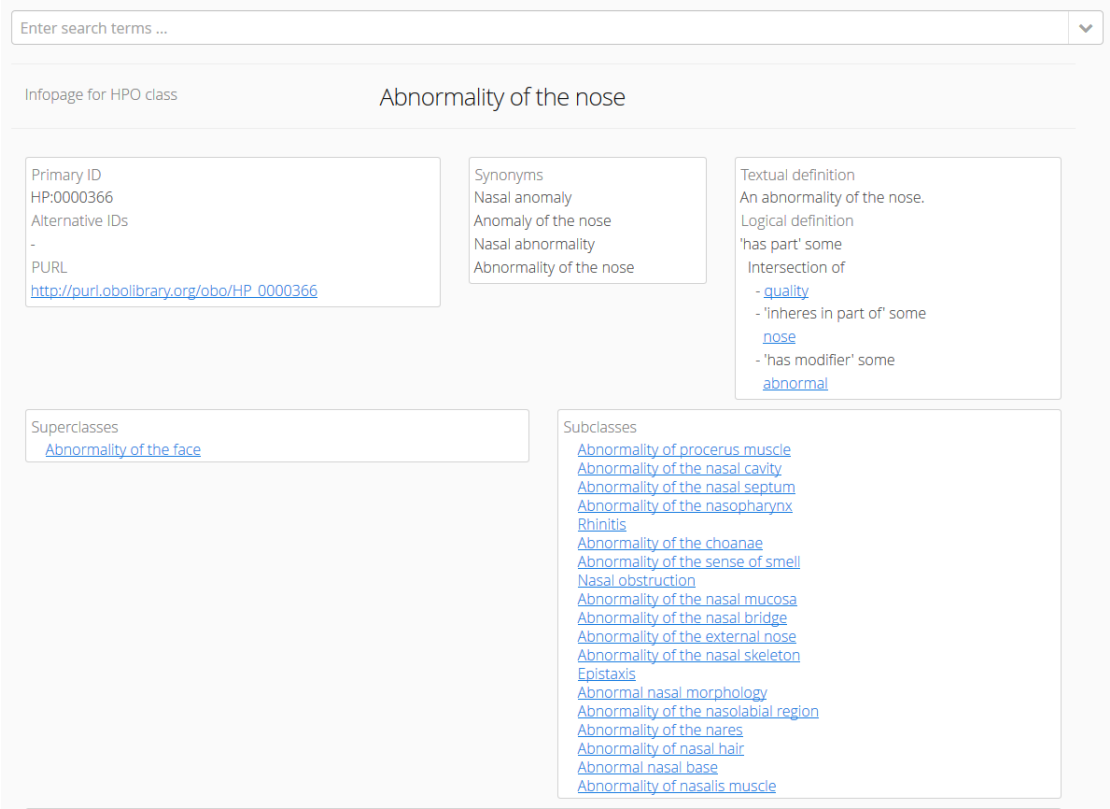
"Nose"

5) try some other general terms like "mouth" and "lip"/"lips"

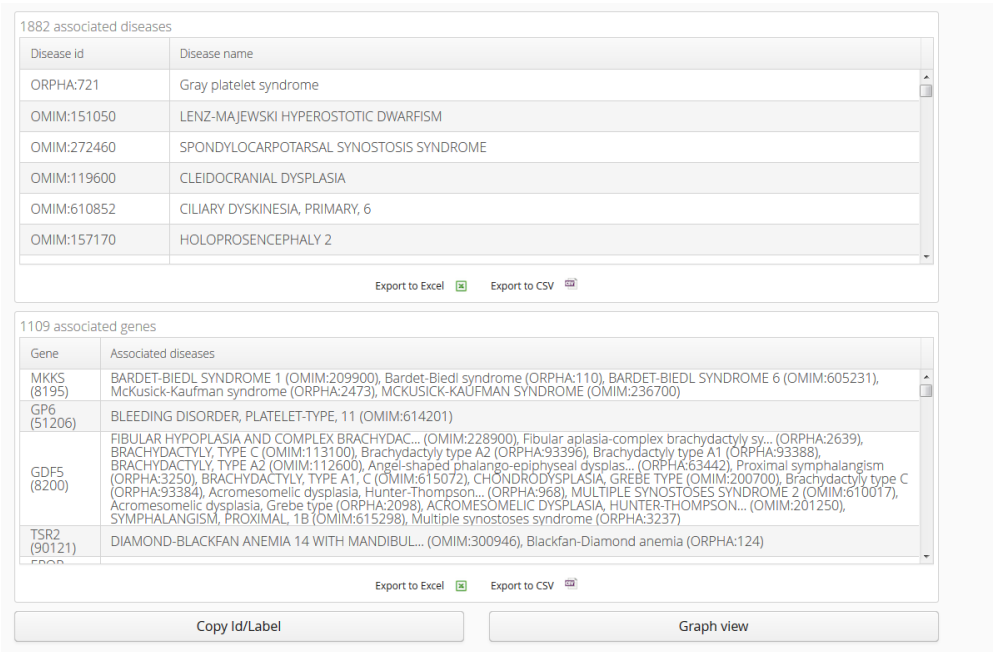
Lips < Lip > Mouth

6) go to the HPO website (http://compbio.charite.de/hpoweb/showterm?id=HP:0000118#id=HP_0000118), try the same queries and compare the results
- what do you notice?

Other structure, only HP terms of course. Subclass and superclass displayed, Synonyms, ID and textual description all are the same.



BUT: in addition, associated genes and diseases are listed!



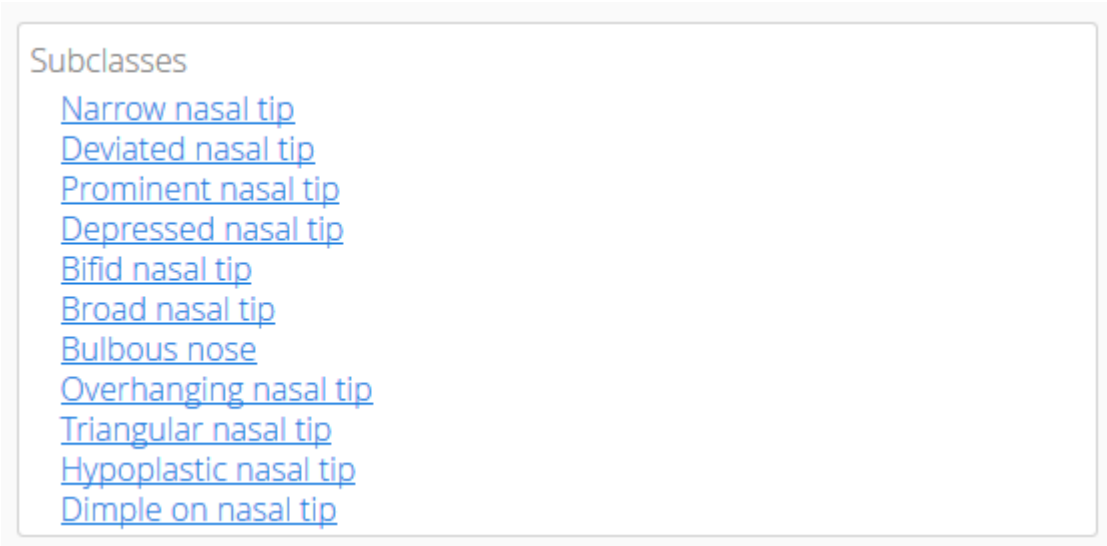
Generating a HPO-based phenotype description

Alternative for 7) and 8)
ask for a manuscript containing phenotype descriptions. For features checked but not present use "no scoliosis (-HP:0002650)", for features which are not known use "loss ability to walk not known (?HP:0006957)" The disadvantage of this task is we cannot quickly give the "correct" answer, the advantage is you help us to improve the phenotype descriptions in the GV shared database.

7) an individual has coronal craniosynostosis (left and right), hypertelorism, a grooved nasal tip, down slanting palpebral fissures, a high arched palate, agenesis of the corpus callosum, a mild learning disability, Sprengel deformity, grooved nails, brachydactyly, syndactyly of the 2nd and 3rd left toes, low set ears, wiry hair, ptosis (left eye only), undescended testes (left and right), mild pectus excavatum, duplication of the distal phalanx of the right thumb, postaxial polydactyly and an inguinal hernia.

- what are the HPO codes for these features?

coronal craniosynostosis (left and right): Bicoronal synostosis HP:0011318
hypertelorism: hypertelorism HP:0000316
grooved nasal tip: No HPO term, use superclass like Abnormality of the nasal tip HP:0000436 OR try to specify:



down slanting palpebral fissures: down slanting palpebral fissures HP:0000494
high arched palate: high palate HP:0000218
agenesis of the corpus callosum: agenesis of corpus callosum HP:0001274
Sprengel deformity: Sprengel anomaly HP:0000912
grooved nails: Ridged nail HP:0001807
brachydactyly: brachydactyly HP:0001156
syndactyly of the 2nd and 3rd left toes: 2-3 toe syndactyly HP:0004691 (note: "left" is not available
low set ears: Low-set ears HP:0000369
wiry hair: NOT AVAILABLE: superclass would be Abnormality of hair texture; semantic similar term would be Coarse hair HP:0002208
ptosis (left eye only): Unilateral ptosis HP:0007687

undescended testes (left and right): Bilateral cryptorchidism HP:0008689
mild pectus excavatum: Pectus excavatum (Mild is missing) HP:0000767
duplication of the distal phalanx of the right thumb: (Right is missing) Duplication of the distal phalanx of the thumb HP:0009612
postaxial polydactyly: Postaxial polydactyly HP:0100259
inguinal hernia: inguinal hernia HP:0000023

- can all features be described using HPO? NO, example grooved nasal tip

- can all features be described down to the detail you have? No, example 2-3 toe syndactyly HP:0004691 LEFT

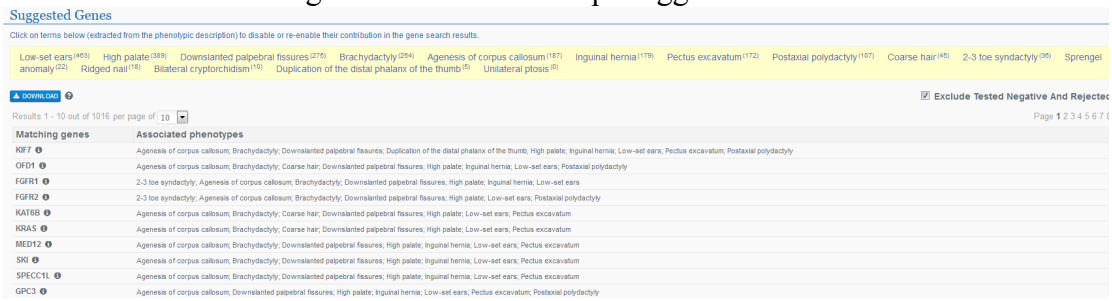
8) go to the PhenoTips website, select the "Playground", the "Create new patient", select "None" for "Please select one of the available studies" and click "Select". Enter the features described for the individual under 7). Save your result.

- which matching disorders (OMIM) does PhenoTips suggest?

%227330 FACIODIGITOGENITAL SYNDROME, AUTOSOMAL RECESSIVE
#311200 OROFACIODIGITAL SYNDROME I
101805 ACROFACIAL DYSOSTOSIS, CATANIA TYPE
#300472 CORPUS CALLOSUM, AGENESIS OF, WITH MENTAL RETARDATION, OCULAR COLOBOMA, AND MICROGNATHIA
#614437 CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IB
#213980 CRANIOFACIAL DYSMORPHISM, SKELETAL ANOMALIES, AND MENTAL RETARDATION SYNDROME
#219200 CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IIA
#609640 FRIAS SYNDROME
#163950 NOONAN SYNDROME 1
249630 MENTAL RETARDATION, BUENOS AIRES TYPE
104350 AMASTIA, BILATERAL, WITH URETERAL TRIPLICATION AND DYSMORPHISM
263540 POLYDACTYLY, POSTAXIAL, WITH DENTAL AND VERTEBRAL ANOMALIES
#130720 LATERAL MENINGOCELE SYNDROME
301950 BRANCHIAL ARCH SYNDROME, X-LINKED
#166250 OSTEOGLOPHONIC DYSPLASIA
#258860 OROFACIODIGITAL SYNDROME IV
%235255 MULLERIAN DERIVATIVES, PERSISTENCE OF, WITH LYMPHANGIECTASIA AND POSTAXIAL POLYDACTYLY
#303600 COFFIN-LOWRY SYNDROME
#180700 ROBINOW SYNDROME, AUTOSOMAL DOMINANT 1
601976 OTOFACIOOSSEOUS-GONADAL SYNDROME

- remove or add a few phenotypic features. Look at the list of matching disorders. More phenotypes do not necessarily narrow the possible diseases/genes. Playing around with the order of the HPO terms shows which terms are in favor for or against a specific disease. **NOTE:** the algorithm does not "exclude" a disease completely if one or more terms do not fit, it allows for some "false" HPOterms (the individual could also have two diseases).

- which matching Genes does PhenoTips suggest



- save the result, open the file (unfortunately the HPO codes are not given).

You can use the result to submit your data to a gene variant databases or to include in a manuscript.

9) go to the Phenomizer website (compbio.charite.de/phenomizer/) and try the same exercise.

The results are similar but different. There is no "gold standard" for prioritizing diseases/genes with HPO.

Andreas Laner & Johan den Dunnen, August 2018