

# The SysNDD Documentation

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## Preface

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This documentation is intended to describe the SysNDD<sup>1</sup> project and provide instructions for regular user show to use the tool and for curator status users how to perform reviews and how to enter data.

### History of SysID and SysNDD

SysNDD is based on its predecessor SysID<sup>2</sup>, conceived by Annette Schenck and Christiane Zweier in 2009 and published in 2016 [Kochinke et al., 2016]. Christiane Zweier has been involved in establishing and updating SysID from its start. She has since performed and coordinated curation and regular updates.

The PHP based SysID web tool (Yii 2 framework) was however not further developed and maintained besides necessary bugfixes. After the maintenance agreement for the original server at the CMBI at Radboud University in Nijmegen ran out, the installation was moved to a virtual server at the Department for BioMedical Research (DBMR) at the University Bern. The former link from the initial publication is re-directed so it still works. The legacy code base was updated to allow installation and security fixes and to be uploaded to a GitHub repository (SysID)<sup>3</sup>. After the first SysNDD native updates to the curated entities, we display a warning popup on the SysID page to show that the content is not curated any more.

In 2019 the chance arose to integrate the SysID curation effort with the Orphanet resource, supported by ERN ITHACA. In the process of aligning the curation and naming conventions for genes, diseases and phenotypes we decided to redesign the database and web tool.

### The SysNDD concept

SysNDD contains our latest update of the manually curated catalogue of published gene-disease-associations implicated in neurodevelopmental disorders (NDD).

To allow interoperability and mapping between gene-, phenotype- or disease-oriented databases, we center our approach around curated gene-inheritance-disease units, so called entities. These entities are classified into different confidence status (categories: “Definitive”, “Moderate”, “Limited”, “Refuted”) according to the degree of underlying scientific evidence. Furthermore, manually curated information on associated phenotypes is provided.

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<sup>1</sup><https://sysnnd.dbmr.unibe.ch/>

<sup>2</sup><https://www.sysid.dbmr.unibe.ch/>

<sup>3</sup><https://github.com/berntpopp/SysID>

The entries in SysNDD are currently updated every 3-4 months and can be utilized for a broad spectrum of tasks from both research and diagnostics.

One of our goals is to incorporate the SysID/ SysNDD data<sup>4</sup> into other gene/ disease-relationship databases like the Orphanet ontology (first results: id-genes.orphanet.app<sup>5</sup>).

Bernt Popp (scientist at the Institute of Human Genetics at the University Hospital Leipzig, Germany) developed and programmed the SysNDD tool and will be integrating further functionality including variants associated with entities in future updates.

## Support and Funding

The current SysNDD database development is supported by:

- DFG (Deutsche Forschungsgemeinschaft) grant PO2366/2-1 to Bernt Popp<sup>6</sup>.
- DFG (Deutsche Forschungsgemeinschaft) grant ZW184/6-1 to Christiane Zweier<sup>7</sup>.
- ERN ITHACA<sup>8</sup> through Alain Verloes<sup>9</sup>.

The previous SysID database and data curation was supported by:

- The European Union's FP7 large scale integrated network GenCoDys (HEALTH-241995) to Martijn A Huynen<sup>10</sup> and Annette Schenck<sup>11</sup>.
- VIDI and TOP grants (917-96-346, 912-12-109) from The Netherlands Organisation for Scientific Research (NWO) to Annette Schenck<sup>12</sup>.
- DFG (Deutsche Forschungsgemeinschaft) grants ZW184/1-1 and -2 to Christiane Zweier<sup>13</sup>.
- the IZKF (Interdisziplinäres Zentrum für Klinische Forschung) Erlangen to Christiane Zweier<sup>14</sup>.
- ZonMw grant (NWO, 907-00-365) to Tjitske Kleefstra.

## 1 Curating gene-disease relationships

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As the name implies a rare disease affects only very few individuals. However, there are many unique causes of rare diseases, thus many individuals are affected by such a disease. Due to the rarity of each single entity, effective management, surveillance and treatment is challenging. So is finding the correct diagnosis, which is often described as the “diagnostic odyssey”.

Rare diseases often have a genetic cause, making high-throughput sequencing (next-generation sequencing; NGS) a central part of finding the molecular diagnosis.

<sup>4</sup><https://sysndd.dbmr.unibe.ch/>

<sup>5</sup><https://id-genes.orphanet.app/ithaca/>

<sup>6</sup><https://orcid.org/0000-0002-3679-1081>

<sup>7</sup><https://orcid.org/0000-0001-8002-2020>

<sup>8</sup><https://ern-ithaca.eu/>

<sup>9</sup><https://orcid.org/0000-0003-4819-0264>

<sup>10</sup><https://orcid.org/0000-0001-6189-5491>

<sup>11</sup><https://orcid.org/0000-0002-6918-3314>

<sup>12</sup><https://orcid.org/0000-0002-6918-3314>

<sup>13</sup><https://orcid.org/0000-0001-8002-2020>

<sup>14</sup><https://orcid.org/0000-0001-8002-2020>

## 1.1 Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) affect about 2% of children. They represent a clinically and genetically extremely heterogeneous disease group comprising amongst other developmental delay (DD), intellectual disability (ID) and autism spectrum disorder (ASD) and developmental and epileptic encephalopathies (DEE).

## 1.2 Genetic heterogeneity

The huge genetic heterogeneity is evident when looking at the published gene-disease associations over time. Thus the question arises:

How can we keep track of this fast development and have the information at hand when we need it in the clinic or when analysing sequencing data?

While the answer to this question is easy:

We need curated databases to catalogue and summarise the wealth of published information.

The task at hand is not only laborious but also requires expertise and consistence.

## 1.3 Expert curation

In our opinion, the curation of gene-disease relationships in rare disease such as NDDs requires clinical and scientific proficiency in the respective field. This implies that clinician scientists involved in counseling, diagnostics and research of NDDs are predestined for this task.

To reduce workload and dependence on single experts, a distributed effort in larger consortia and collaboration between different work groups is needed.

In the course of updating SysID we had the great chance to contribute our data to Orphanet to create a European ID/NDD specific reference list. With support from the „ITHACA Workgroup: intellectual disability“ ([id-genes.orphanet.app](https://id-genes.orphanet.app)<sup>15</sup>) in 2019 we started working with the Orphanet team which is part of the Gene Curation Coalition (GenCC).

Additionally, we are able to recruit expert curators from ERN ITHACA<sup>16</sup> to contribute to re-curation of old data and updating new data in SysNDD.

## 1.4 Technical concepts

In addition to a pool of experts, the right tools are needed.

We defined “gene-inheritance-disease” units as “entities” which represent the central curation effort. The components of these entities are normalized using widely used and standardized ontology terms (e.g. HGNC identifier for genes, OMIM or MONDO for disease and inheritance from HPO). This allows inter-operability and linking to other data sources.

Based on this concept we developed a new database scheme, which allows entities to be systematically and reproducibly cataloged. The database is abstracted into a JSON API, which allows structured programmatic access to the underlying data.

Finally, the API feeds the web tool which can be used to easily search, filter, download and visualize the database contents in modern web browsers.

<sup>15</sup><https://id-genes.orphanet.app/ithaca%5D>

<sup>16</sup><https://ern-ithaca.eu/>

## 1.5 Outlook

- The SysNDD database will improve the understanding and curation of rare NDD entities.
- SysNDD will enable systems biology and network analyses.
- Our long-term goal is incorporation of the high-quality, manually curated SysNDD data into European and international gene disease relationship databases,
- thus, improving diagnostics and care for individuals with rare NDDs.

## 2 Web tool

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The SysNDD web tool is available from <https://sysnnd.dbmr.unibe.ch/> on a server hosted at the Department for BioMedical Research (DBMR<sup>17</sup>) (University of Bern) and the web address <https://sysnnd.org/> redirects to this server.

The web tool uses the Vue.js<sup>18</sup> (v2.6) JavaScript framework with BootstrapVue to generate a Bootstrap v4 website frontend.

### 2.1 Landing page

The landing page is designed as simple Bootstrap v4 website with:

- 1) a navigation menu at the top,
- 2) the main site content, which changes with navigation to other routes, and
- 3) a footer navigation bar at the bottom

Screenshot of the landing page with elements marked:

The landing page content displays different elements to give a quick overview and allow fast navigation:

- a centered search input at the top,
- a box (left side top) with current gene statistics divided by association category and inheritance patterns (*Details*),
- a box (left side bottom) showing a table of the five last entities entered into the database,
- an explanatory text on the right.

### 2.2 Main navigation menu

The main navigation allows quick access to all sub-pages.

The *Tables* button triggers a dropdown menu with links to:

- *Entities* table view
- *Genes* table view
- *Phenotypes* table view
- *Panels* table view

1) top menu →

2) content

3) footer →

Welcome to SysNDD,  
the expert curated database of gene disease relationships in **neurodevelopmental disorders** (NDD).

Search by genes, entities and diseases using names or identifiers

**Current database statistics (last update: 11/14/2022)**

Category	Count	Details
Definitive	1719	[show]
Moderate	91	[show]
Limited	1427	[show]
not applicable	1	[show]

Category	Count	Details
Definitive	1566	[show]
Moderate	57	[show]
Limited	1256	[show]

New entities					
Entity	Symbol	Disease	Inh.	Category	NDD
symbol:3028	CACSEB	Menke-Hennekam syndrome	○	●	●
symbol:3027	HOMER2	Intellectual disability	○	●	●
symbol:3026	GNAD3	Neurodevelopmental disorder with insensitivity to Gαq/13 protein	○	●	●
symbol:3025	HNA2D	Intellectual developmental disorder with language delay	○	●	●
symbol:3024	DOCK8	Neurodevelopmental disorder with immune deficiency	○	●	●

NDD comprise **developmental delay** (DD), **intellectual disability** (ID) and **autism spectrum disorder** (ASD).  
This clinically and genetically extremely **heterogeneous** disease group affects **about 2% of newborns**.  
SysNDD aims to empower clinical diagnostics, counseling and research for NDDs through **expert curation**.  
We define "gene-inheritance-disease" units as "**entities**", which are color coded throughout the website: **Entity** | **Gene** | **Inheritance** | **Disease**.  
The clinical entities are divided into different "**Categories**", based on the strength of their association with NDD phenotypes. They are represented using these differently colored stoplight symbols:  
Definitive: ●, Moderate: ○, Limited: □, Refuted: ■.  
The classification criteria used for the categories are detailed in our Documentation on GitHub.  
In the **Panel** views, which are aggregated by gene, we assign the highest category of associated entities to the gene.  
The SysNDD tool allows browsing and download of tabular views for curated NDD entity components in the **Tables** section. It offers multiple **Analyses** sections for genes, phenotypes and comparisons with other curation efforts.

Figure 1: Landing page

SysNDD

Tables

Analyses

About

Login

Entities

Genes

Phenotypes

Panels

Welcome to SysNDD,  
the expert curated database of gene disease relationships in **neurodevelopmental disorders** (NDD).

Figure 2: Navigation menu: Tables

The *Analyses* button triggers a dropdown menu with links to:

- *Compare curations* view
- *Correlate phenotypes* view
- *Entries over time* view
- *NDD Publications* view
- *Functional clusters* view

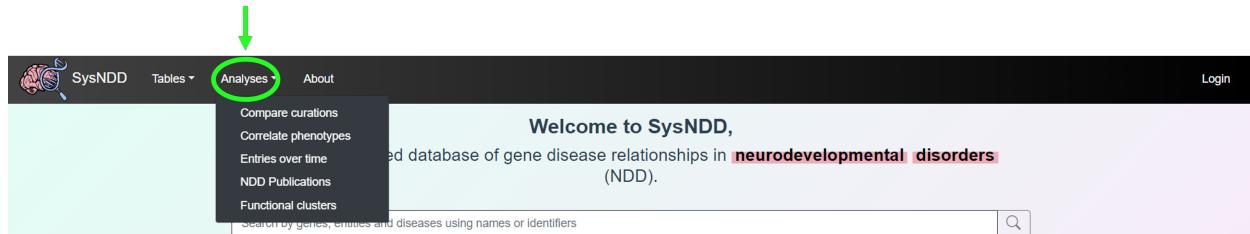


Figure 3: Navigation menu: Analyses

The *About* button directs you to further information on:

- SysNDD and its creators
- Citation Policy
- Support and Funding
- News and Updates
- Credits and acknowledgement
- Help and FAQ
- Disclaimer
- Contact



Figure 4: Navigation menu: About

If not on the landing page, a search bar also appears on the navigation menu.

If not logged in, the right side of the menu shows a button which directs you to the *Login* page. When logged in as a registered user the menu shows your username and additional links to page views depending on your user rights:

<sup>17</sup><https://www.dbmr.unibe.ch/>

<sup>18</sup><https://vuejs.org/>

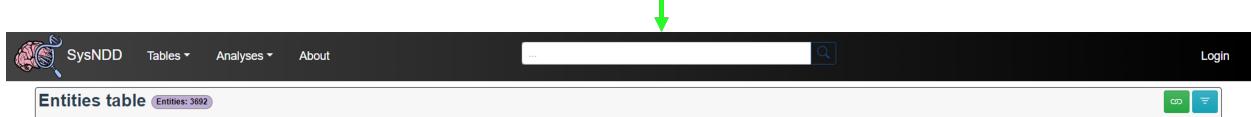


Figure 5: Navigation menu: search bar

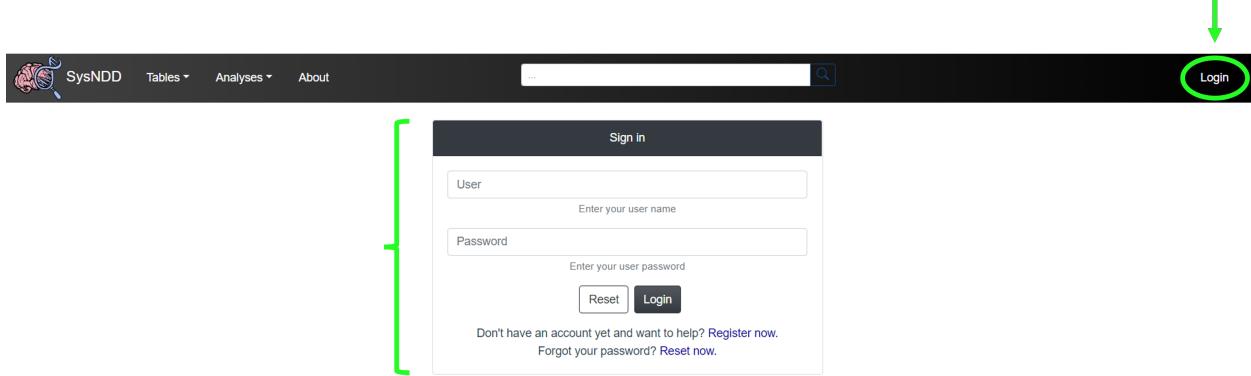


Figure 6: Navigation menu: Login

## 2.3 Footer navigation menu

The footer navigation shows logos with links to:

- 1) the license applied to SysNDD
- 2) our GitHub repository
- 3) the SysNDD API view
- 4) the DFG funder website
- 5) the website of the University of Bern hosting our server
- 6) the ERN-ITHACA website



Figure 7: Footer navigation

## 2.4 Table views

We provide tabular representations with search, filtering, sorting and pagination functionality for different aspects of the entity concept.

### 2.4.1 Entities table

The *Entities* table is intended to provide an overview centered on the entity concept.

Entity id	Symbol	Disease ontology	Hpo mode of inherit...	Category	Ndd phenotype	Details
sysndd:1	ABCC9	Hypertrichotic osteochondrodysplasia (C)	AD	B	✓	Show
sysndd:2	ABCC9	Cardiomyopathy, dilated, 10	AD	B	✗	Show
sysndd:3	ABCC9	✓Atrial fibrillation, familial, 12	AD	B	✗	Show
sysndd:4	ABCD1	Adrenoleukodystrophy	XR	B	✓	Show
sysndd:5	ABCD4	Methylmalonic aciduria and homocystine	AR	B	✓	Show
sysndd:6	ABHD5	Chanarin-Dorfman syndrome	AR	B	✓	Show
sysndd:7	ACAD9	Mitochondrial complex I deficiency, muscle	AR	B	✓	Show
sysndd:8	ACO2	Infantile cerebellar-retinal degeneration	AR	B	✓	Show
sysndd:9	ACOX1	Peroxisomal acyl-CoA oxidase deficiency	AR	B	✓	Show
sysndd:10	ACSF3	Combined malonic and methylmalonic ac...	AR	B	✓	Show

Figure 8: Entities view

#### 2.4.2 Genes table

The *Genes* table is intended to provide a gene-centered overview.

Symbol	Category	Hpo mode of inherit...	Ndd phenotype	Entities count	Details
AZML1	B	AD	✓	1	Show
AAAS	B	AR	✓	1	Show
AACS	B	AR	✓	1	Show
AARS1	B, B	AR, AD	✓, ✗	2	Show
AARS2	B, B	AR, AR	✓, ✓	2	Show
AASS	B	AR	✓	1	Show
ABAT	B	AR	✓	1	Show
ABC13	B	AD	✓	1	Show
ABC2	B	AR	✓	1	Show
ABC5	B	AR	✓	1	Show

Figure 9: Genes view

#### 2.4.3 Phenotypes table

The *Phenotypes* table provides the possibility to filter for phenotype combinations annotated to the entities. The ‘AND/ OR’ switch allows the user to change the logic how phenotype combinations are requested:

- AND: only entities having all selected phenotypes annotated are shown
- OR: all entities having any of the selected phenotypes annotated are shown

The *Entities*, *Genes* and *Phenotypes* tables all have the additional two features (top right corner):

- 1) Green icon that allows the user to copy the link to the page

Phenotype search (Associated entities: 3233)						
Intellectual disability				AND	xlsx	Per page: 10
Entity id	Symbol	Disease ontology	Hpo mode of inherit...	Category	Ndd phenotype	Details
sysndd:1	ABCC9	Hypertrichotic osteochondrodysplasia [C]	AD	●	✓	Show
sysndd:4	ABCD1	Adrenoleukodystrophy	XR	●	✓	Show
sysndd:5	ABCD4	Methylmalonic aciduria and homocysteine	AR	●	✓	Show
sysndd:6	ABHD5	Chanarin-Dorfman syndrome	AR	●	✓	Show
sysndd:7	ACAD9	Mitochondrial complex I deficiency, non-...	AR	●	✓	Show
sysndd:8	ACO2	Infantile cerebellar-retinal degeneratio...	AR	●	✓	Show
sysndd:9	ACOX1	Proxosomal acyl-CoA oxidase deficiency	AR	●	✓	Show
sysndd:10	ACSF3	Combined malonic and methylmalonic ac...	AR	●	✓	Show
sysndd:11	ACSL4	Intellectual developmental disorder, X...	XR	●	✓	Show
sysndd:12	ACTB	Berauts-Winter syndrome 1	AD	●	✓	Show

Figure 10: Phenotypes view

- 2) Yellow icon that allows the use to remove all filters on the table (icon turns blue when all filters are off)

Entities table (Entities: 3238)						
Search any field by typing here						Logout
Entity id	Symbol	Disease ontology	Hpo mode of inherit...	Category	Ndd phenotype	Details
sysndd:810	RBM28	?Alopecia, neurologic defects, and endocr...	AR	●	✓	Show
sysndd:2057	TRIM36	?Anencephaly 1	AR	●	✓	Show
sysndd:3570	ERGIC1	?Arthrogryposis multiplex congenita 2, m...	AR	●	✓	Show
sysndd:3870	CDH2	?Attention deficit/hyperactivity disorder 2	AR	●	✓	Show
sysndd:752	TRIM32	?Bardet-Biedl syndrome 11	AR	●	✓	Show
sysndd:137	CEP290	?Bardet-Biedl syndrome 14	AR	●	✓	Show
sysndd:1658	WDPBP1	?Bardet-Biedl syndrome 15	AR	●	✓	Show
sysndd:1101	BBIP1	?Bardet-Biedl syndrome 18	AR	●	✓	Show
sysndd:125	CCDC78	?Centronuclear myopathy 4	AD	●	✓	Show
sysndd:1916	ATP8A2	?Cerebellar ataxia, mental retardation, and...	AR	●	✓	Show

Figure 11: Entities, Genes and Phenotypes tables - additional features

#### 2.4.4 Panels table

The *Panels* table is intended for users to be able to create lists of NDD-associated genes. Additionally, the columns in the lists can be configured. Finally, the configuration can be downloaded as an Excel file with information on the exact query in the meta sheet and the requested information in the data sheet. These files can then be used as ‘virtual panels’ to filter genetic variants derived from high-throughput sequencing in external analysis tools.

Panel compilation and download		Genes: 2842						
Category	All	Columns	category inheritance symbol					
Inheritance	All	Per page	10					
Sort	symbol	« < > »	1 2					
Category	Inheritance	Symbol	Hgnc id	Entrez id	Ensembl gene id	Ucsc id	Bed hg19	Bed hg38
Limited	Autosomal domi...	A2ML1	HGNC:23336	144568	ENSG00000166...	uc001quz.6	chr12:8975068...	chr12:8822621...
Limited	Autosomal recess...	AAAS	HGNC:13666	8086	ENSG00000094...	uc001scr.5	chr12:53701240...	chr12:53307456...
Limited	Autosomal recess...	AACS	HGNC:21298	65985	ENSG00000081...	uc001uhc.4	chr12:12554992...	chr12:12506543...
Definitive	Autosomal recess...	AARS1	HGNC:20	16	ENSG00000090...	uc002eeyn.2	chr16:70286198...	chr16:70251983...
Limited	Autosomal recess...	AARS2	HGNC:21022	57505	ENSG00000124...	uc010jza.2	chr6:44267391...	chr6:44298731...
Limited	Autosomal recess...	AASS	HGNC:17366	10157	ENSG00000008...	uc003vkb.4	chr7:121715701...	chr7:122064583...
Limited	Autosomal recess...	ABAT	HGNC:23	18	ENSG00000183...	uc002czc.5	chr16:8768422...	chr16:8674596...
Limited	Autosomal domi...	ABCA13	HGNC:14638	154664	ENSG00000179...	uc003toq.2	chr7:48211055...	chr7:48171458...
Definitive	Autosomal recess...	ABCA2	HGNC:32	20	ENSG00000107...	uc064xhf.1	chr9:139901686...	chr9:137007234...
Limited	Autosomal recess...	ABCA5	HGNC:35	23461	ENSG00000154...	uc002jig.3	chr17:67240452...	chr17:69244311...



Figure 12: Panels view

## 2.5 Single entry pages

Single entry pages refer to the directed pages associated with each entity, gene or disease ontology. These are accessed clicking on the entity (purple), gene (orange) or disease (green) buttons associated with each entry.

Entity id	Symbol	Disease ontology	Hpo mode of inherit...	Category	Ndd phenotype	Details
syands:3874	DOCK3	Neurodevelopmental disorder with impaired	AR	B	✓	Show

Figure 13: Single entry pages

### 2.5.1 Entity

The *Entity* page aims to provide information on the gene, disease (with the OMIM link), inheritance pattern and NDD status associated with a particular entity. The synopsis and phenotypes of the disease as well as the relevant links to publications (including GeneReviews if available) are also provided.

### 2.5.2 Gene

The *Gene* page aims to provide further information on 1) the gene of interest with links to other platforms such as Entrez, Ensembl, UCSC, CCDS, UniProt, OMIM gene, MGI, RGD and STRING, and 2) the entities associated with the gene in a table format.

**Entity:** sysndd:1

**Gene Symbol:** ABCC9

**Disease:** Hypertrichotic osteochondrodysplasia (Cantu syndrome) [OMIM:239850]

**Inheritance:** AD

**NDD:** Yes

**Association Category:** 1

**Clinical Synopsis:** activating, gain-of-function mutations: congenital hypertrichosis, neonatal macrosomia, distinct osteochondrodysplasia, cardiomegaly; activating mutations; mild speech delay in most, learning difficulties or ID in a small percentage

**Publications:** PMID:21376300, PMID:22608503, PMID:22610116

**Genereviews:** PMID:25275207

**Phenotypes:**

- Macrocephaly
- Abnormality of the skeletal system
- Intellectual disability
- Intellectual disability, mild
- Abnormal heart morphology
- Intellectual disability, moderate
- Abnormality of the integument

Figure 14: Entity page

**Gene:** HGNC:69

**HGNC Symbol:** ABCC9

**Gene Name:** ATP binding cassette subfamily C member 9

**Entrez:** 10060

**Ensembl:** ENSG00000069431

**UCSC:** uc001mr.2

**CCDS:** CCDS86693, CCDS8694

**UniProt:** O65076

**OMIM gene:** 601439

**MGI:** MGI:1352630

**RGD:** RGD:3787

**STRING:** 9606.ENSP0000261200

**Associated (Entities: 4)**

Entity id	Symbol	Disease ontology	Hpo mode of inherit...	Category	Ndd phenotype	Details
sysndd:1	ABCC9	Hypertrichotic osteochondrodysplasia (Cantu syndrome)	AD	1	Yes	Show
sysndd:2	ABCC9	Cardiomyopathy, dilated, TO	AD	2	No	Show
sysndd:3	ABCC9	Atrial fibrillation, familial, 12	AD	3	No	Show
sysndd:376	ABCC9	Intellectual disability and myopathy syndrome	AR	4	Yes	Show

Figure 15: Gene page

### 2.5.3 Disease ontology

The *Ontology* page aims to provide further information on 1) the inheritance pattern of a disease as well as links to other platforms such as OMIM, DOID, MONDO and Orphanet, and 2) the entities associated with it in a table format.

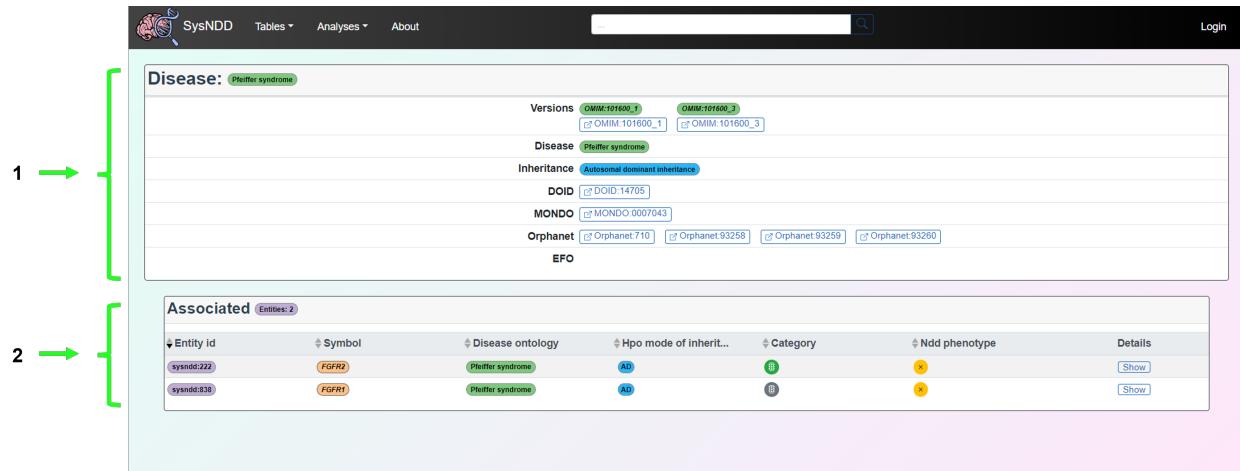


Figure 16: Ontology page

## 2.6 Analyses views

The *Analysis* views are intended to provide the user with a more comprehensive picture of SysNDD comparisons with other curations, phenotype correlations, SysNDD entries over time, NDD publications, and functional gene clusters.

### 2.6.1 Compare curations

The *Compare curations* view is composed of three tabs:

- 1) *Overlap*
- 2) *Similarity*
- 3) *Table*

The *Overlap* tab includes an upset plot (alternative for venn diagrams, please compare: [upset.app](https://upset.app)<sup>19</sup>) to show the overlap between SysNDD and other selected NDD curation efforts.

The *Similarity* tab includes a matrix plot of the cosine similarity between different curation efforts for neurodevelopmental disorders.

The *Table* tab displays a table format for comparing the presence of a gene in different neurodevelopmental disorder curation efforts. This tab also includes the option to download the comparison table as an Excel file. The filter removal button is in the upper right corner.

<sup>19</sup><https://upset.app>



Figure 17: Compare curations view: *Overlap* tab

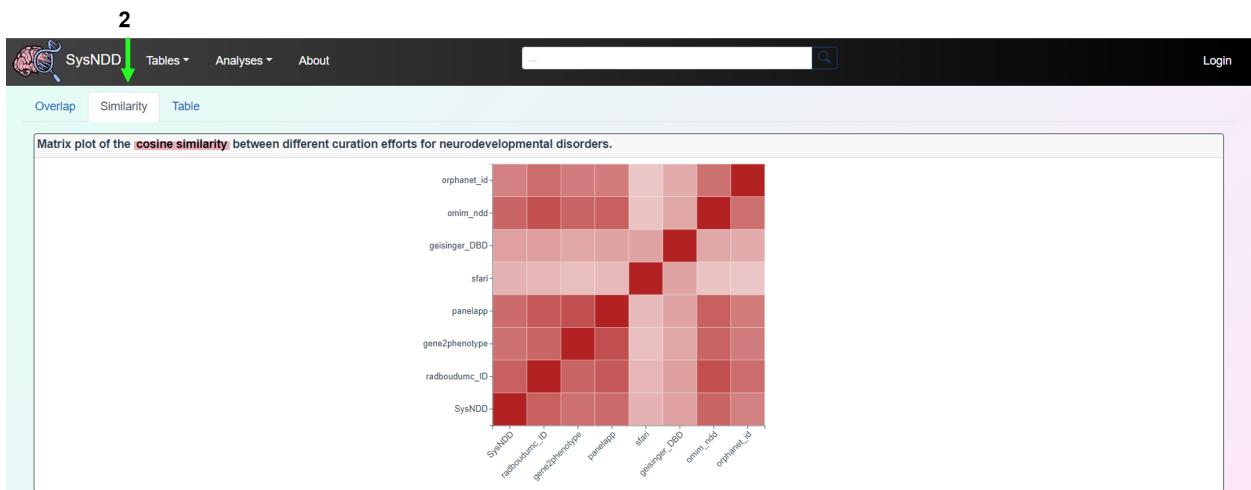


Figure 18: Compare curations view: *Similarity* tab

3

Comparing the presence of a gene in different **curation efforts** for neurodevelopmental disorders. (Genes: 4600)

Search any field by typing here

Per page: 10 | 1 | 2 | > | >>

Symbol	Sysndd	Radboudumc id	Gene2phenotype	Panelapp	Sfari	Geisinger dbd	Omim ndd	Orphanet Id
AZML1	✓	✗	✗	✓	✗	✗	✗	✓
AAAS	✓	✓	✓	✓	✗	✓	✓	✓
AACS	✓	✗	✗	✗	✗	✗	✗	✗
AARS1	✓	✓	✓	✓	✓	✓	✓	✓
AARS2	✓	✗	✗	✗	✗	✗	✗	✗
AASS	✓	✓	✓	✓	✗	✗	✓	✗
ABAT	✓	✓	✓	✓	✓	✗	✓	✗
ABCA10	✗	✗	✗	✗	✓	✗	✗	✗
ABCA13	✓	✗	✗	✗	✓	✗	✗	✗
ABCA2	✓	✓	✗	✓	✗	✗	✓	✗

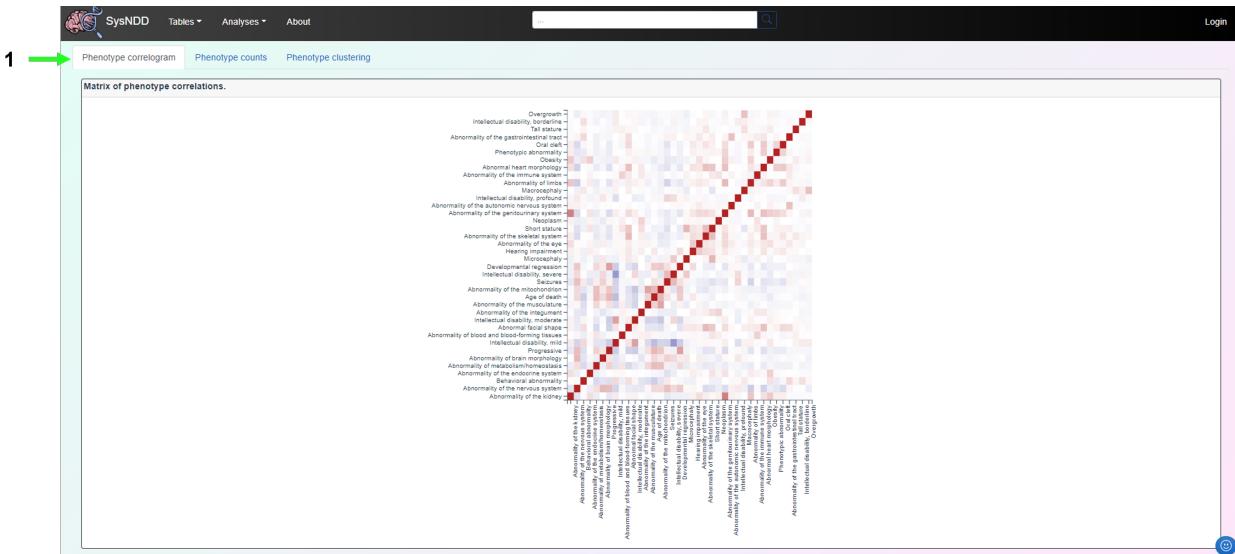
Figure 19: Compare curations view: *Table* tab

## 2.6.2 Correlate phenotypes

*Correlate phenotypes* view is composed of three tabs:

- 1) *Phenotype correlogram*
- 2) *Phenotype counts*
- 3) *Phenotype clustering*

The *Phenotype correlogram* tab displays a matrix of correlations of different phenotypes.

Figure 20: Correlate phenotypes view: *Phenotype correlogram* tab

The *Phenotype counts* tab shows a bar plot of phenotype counts.

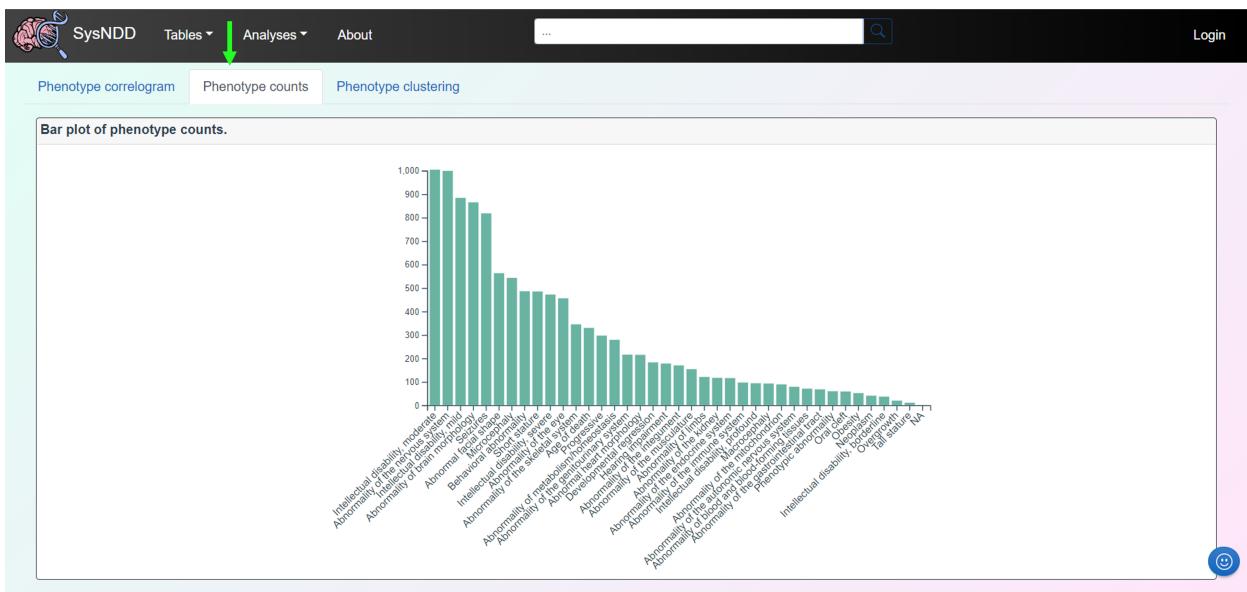


Figure 21: Correlate phenotypes view: *Phenotype counts* tab

The *Phenotype clustering* tab shows clusters of entities based on the manually curated phenotype annotations from SysNDD. Multiple correspondence analysis (MCA) is performed utilizing the “MCA” function from the FactoMineR<sup>20</sup> R package, with the number of dimensions retained set to 15, the qualitative supplementary variables set to inheritance terms, and the quantitative supplementary variables set to phenotype counts divided into ID-related and non-ID-related phenotypes (indicator of “syndromicity”). Then, hierarchical clustering is performed using the “HCPC” function from the FactoMineR package. By clicking on the different colored bubbles on the panel to the left, the user can select the respective clusters. When clicking a cluster the entity count is displayed in the upper part along the cluster name. The link in this panel’s lower section leads to a view of the Entity table that is restricted to the entities in the selected cluster. The right-hand panel displays a table containing either (1) the *Qualitative input variables* representing the phenotypes, (2) the *Qualitative supplementary variables* (independent) representing inheritance patterns, or (3) the *Quantitative supplementary variables* (independent) representing the count of phenotypes, all with variable name, p-values, and v-test values.

### 2.6.3 Entries over time

The *Entries over time* view displays the changes in NDD entity numbers since curation began. The plot can be aggregated by either genes or entities and categorized according to inheritance or category.

### 2.6.4 NDD Publications

*-content coming soon-*

### 2.6.5 Functional clusters

The *Functional clusters* view displays gene clusters of functionally enriched interacting proteins, along with their corresponding ontology annotations. Using the “get\_clusters” function from the STRINGdb<sup>21</sup> R

<sup>20</sup><http://factominer.free.fr/>

<sup>21</sup><https://rdrr.io/bioc/STRINGdb>

3

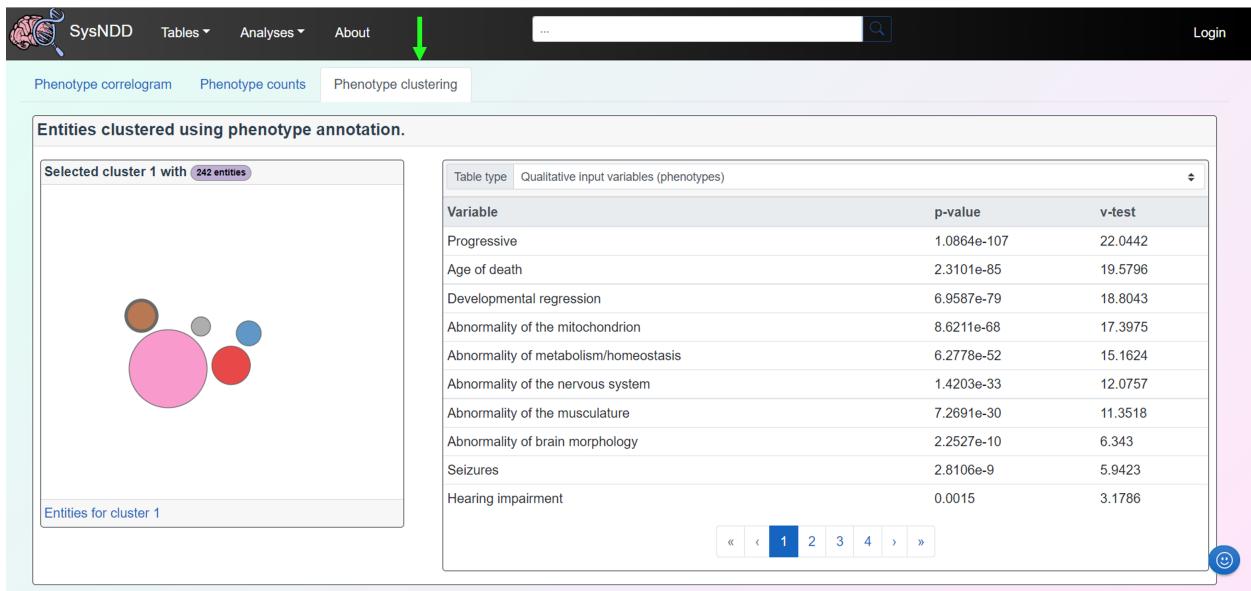


Figure 22: Correlate phenotypes view: *Phenotype clustering* tab

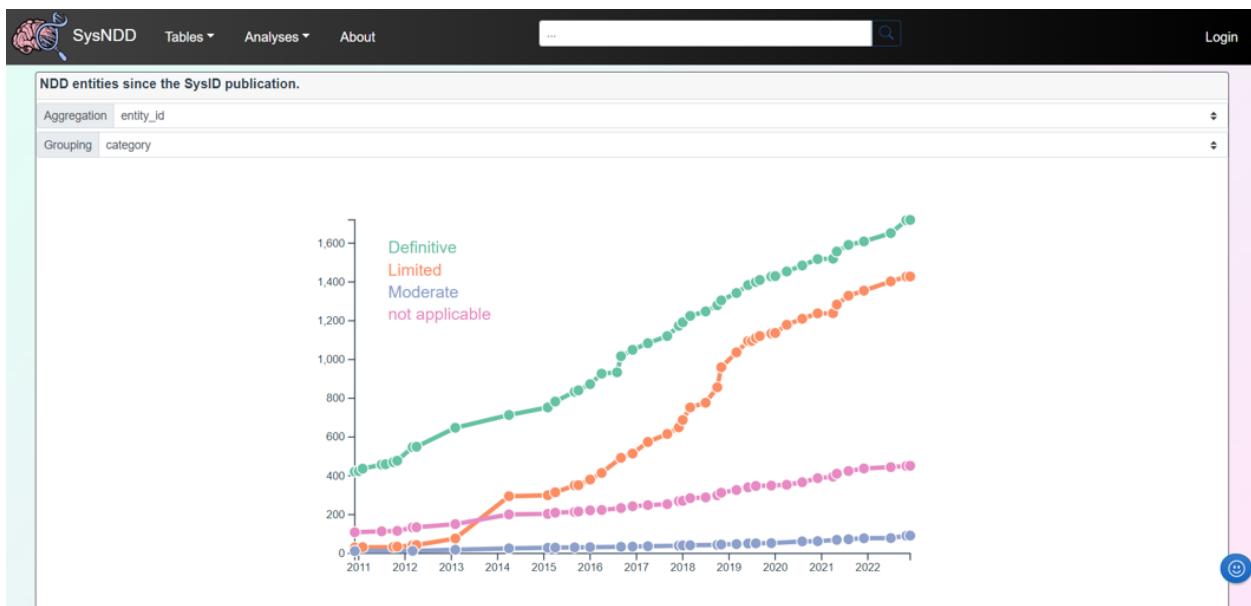


Figure 23: Entries over time view

package and the “walktrap” clustering algorithm from the igraph<sup>22</sup> R package, we perform clustering. By clicking on the different colored bubbles on the panel to the left, the user can select the respective main- or sub-clusters. When clicking a cluster the gene count is displayed in the upper part along the cluster name. The link in this panel’s lower section leads to a view of the Gene table that is restricted to the genes in the selected cluster. The right-hand panel displays a table with either (1) the *Term enrichment* including the ontology annotations, the number of enriched genes, the FDR-corrected p-value, and a link to the corresponding ontology term or (2) the gene *Identifiers* with links to the respective single entry page and to the STRING<sup>23</sup> website of the protein.

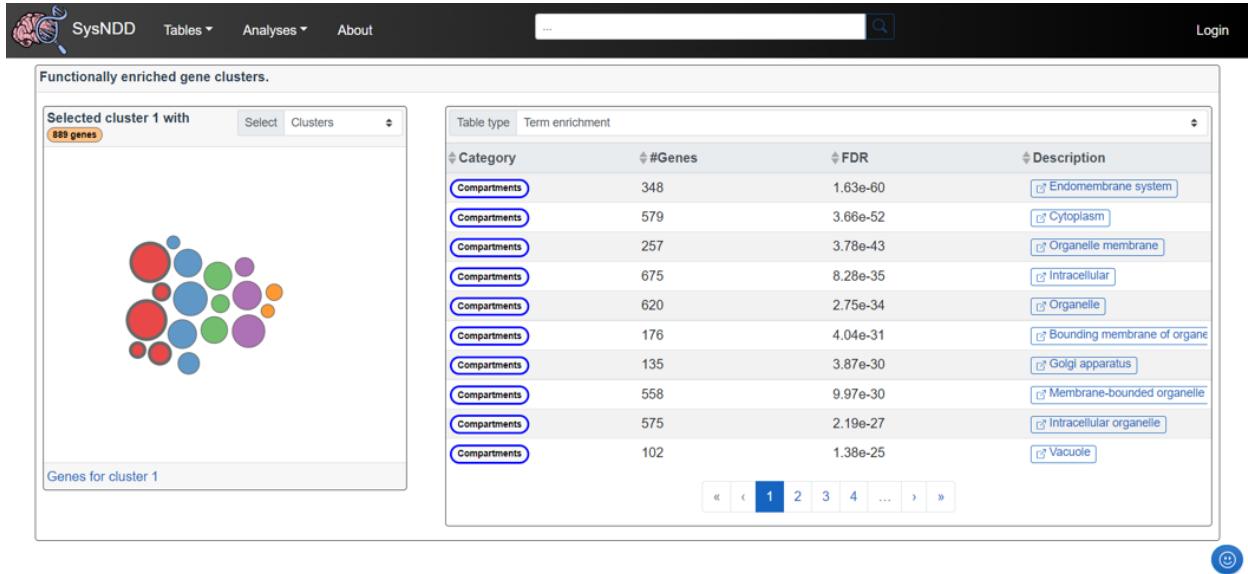


Figure 24: Functional clusters view

## 2.7 About page

The website’s About page provides general information about the project, such as its creators, funding sources, the status of updates, and how to get help.

## 2.8 Help & Feedback

A smiley face button (in blue, bottom right) is present on every page of SysNDD and directs users to the following assistance and feedback functions:

- Button **1** allows the user to cite the page (quotation mark icon), copies the recommended citation text to the clipboard and automatically creates a snapshot of the website in the internet archive for reproducibility (Wayback Machine - Internet Archive<sup>24</sup>)
- Button **2** directs the user to a form for positive feedback (thumbs up icon)
- Button **3** directs the user to a form for improvement suggestions (thumbs down icon)
- Button **4** directs the user to the SysNDD documentation (book icon)
- Button **5** directs the user to the SysNDD GitHub discussions page for questions and help (question mark icon)

<sup>22</sup><https://igraph.org/>

<sup>23</sup><https://string-db.org/>

<sup>24</sup><https://archive.org/web/>

Welcome to SysNDD,  
the expert curated database of gene disease relationships in **neurodevelopmental disorders** (NDD).

Search by genes, entities and diseases using names or identifiers

**Current database statistics (last update: 11/14/2022)**

Entities		
Category	Count	Details
Definitive	1719	<a href="#">show</a>
Moderate	91	<a href="#">show</a>
Limited	1427	<a href="#">show</a>
not applicable	1	<a href="#">show</a>

Genes (links to Panels)		
Category	Count	Details
Definitive	1566	<a href="#">show</a>
Moderate	57	<a href="#">show</a>
Limited	1256	<a href="#">show</a>

New entities					
Entity	Symbol	Disease	Inh.	Category	NDD
Syndd:3878	CREBBP	Menke-Hennekam syndrome 1	AD	<span style="color: green;">●</span>	<span style="color: green;">✓</span>

NDD comprise **developmental delay** (DD), **intellectual disability** (ID) and **autism spectrum disorder** (ASD).

This clinically and genetically extremely **heterogeneous** disease group affects **about 2% of newborns**.

SysNDD aims to empower clinical diagnostics, counseling and research for NDDs through **expert curation**.

We define "gene-inheritance-disease" units as "**entities**", which are color coded throughout the website:

Entity:	Gene	Inheritance	Disease
---------	------	-------------	---------

The clinical entities are divided into different "**Categories**", based on the strength of their association with NDD phenotypes. They are represented using these differently colored stoplight symbols:

- Definitive: ●
- Moderate: ●
- Limited: ●
- Refuted: ●

The classification criteria used for the categories are detailed in our [Documentation](#) on GitHub.

In the **Panel** views, which are aggregated by gene, we assign the highest category of

Figure 25: Help & Feedback

## 2.9 Login page

The Login page shows a simple form with inputs for the (1) user name and their (2) password, (3) buttons to reset the form and (4) links to registration and password reset.

### 2.9.1 Register user page

This page can be used to apply for a SysNDD account by entering the following information:

- 1) desired username
- 2) institutional e-mail
- 3) ORCID identifier
- 4) first name
- 5) family name
- 6) description of your interest in SysNDD and why you want to participate in the curation effort

and (7) accepting the terms of use.

The (8) buttons allow resetting or submitting the form.

After submitting your application, the curators will receive an email to review it. You will receive an e-mail with your login information and instructions after your application has been confirmed.

### 2.9.2 Reset password page

Users who have forgotten their password can reset it by entering the e-mail address they registered with on this page.

Upon submission the e-mail account will receive a message with a one-time link allowing the user to enter a new password.

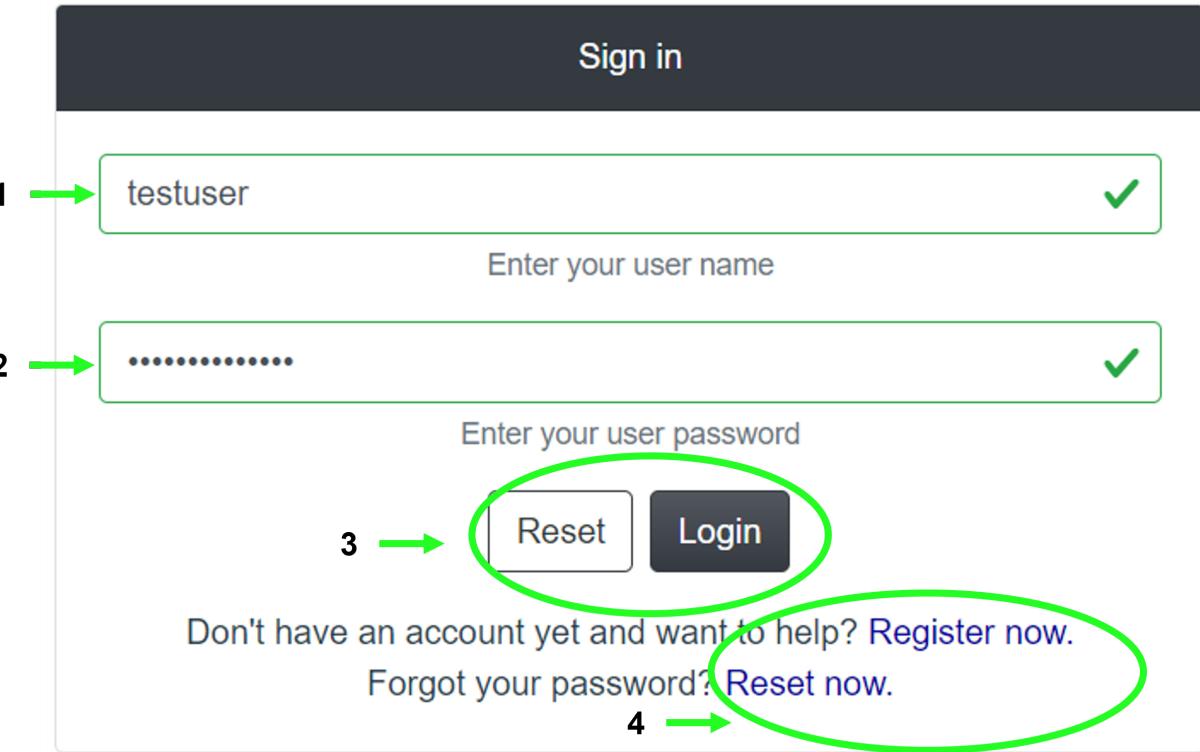


Figure 26: Login modal

## 2.10 Mobile website

The Vue.js framework enables native cross platform development. Together with the Bootstrap CSS library, this enables the SysNDD web app to integrate seamlessly on smaller mobile screens.

The layout breaks to mobile view at 768 pixels width and minimises the navigation and footer menus:

All tables in mobile views break to a stacked view (column names become the first column in a cell and values the second column) to best use display space:

The table controls and search inputs are further displayed at the top in this view.

The *Analyses* pages on mobile are best viewed in landscape mode:

## 2.11 Progressive Web App (PWA)

The SysNDD web app can also be installed on mobile devices using the Progressive Web App (PWA<sup>25</sup>) technology. This is supported in all Chromium-based modern browsers (Chrome, Edge, Opera, etc.) on all common operating systems (Windows, Linux, macOS and Android). Additionally new Safari versions on iOS show some support for PWA.

PWAs are faster because they cache files. They offer more screen space for the app. Future integrations of this feature in SysNDD will enable offline use.

To install the PWA on Android devices follow these steps:

- 1) Visit the SysNDD website at <https://sysndd.dbmr.unibe.ch/>. You will see a message offering to add the PWA to your home screen:

<sup>25</sup>[https://en.wikipedia.org/wiki/Progressive\\_web\\_application](https://en.wikipedia.org/wiki/Progressive_web_application)

Register new SysNDD account

1 →   
Enter your preferred user name (min 5 chars)

2 →   
Enter your institutional mail account

3 →   
Enter your ORCID

4 →   
Enter your first name

5 →   
Enter your family name

6 →   
Please describe why you want to help with SysNDD

7 →  I accept the terms and use

← 8

Figure 27: Register modal

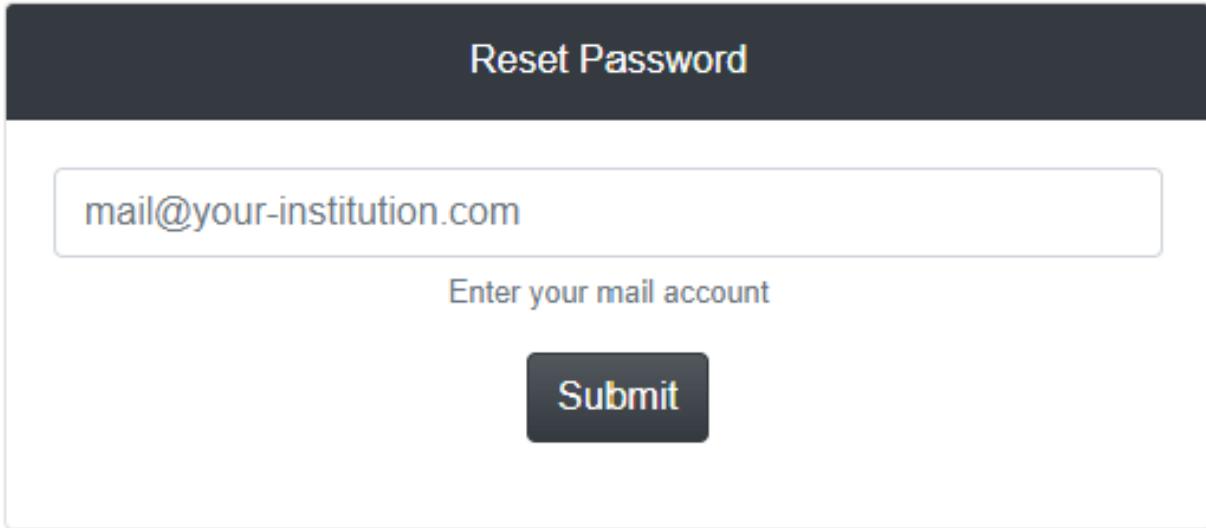


Figure 28: Reset modal

- 2) After clicking the previous message, confirm the installation by clicking “Install” in the following prompt:
- 3) A message will confirm the installation:
- 4) Following app symbol will be available on one of your screens:
- 5) Clicking this will open SysNDD in PWA mode (no browser address bar, instead custom coloured top bar):

## 2.12 Performance

Modern Javascript frameworks like Vue.js, which we use for the SysNDD website, offer rich user experience. The generated single-page applications can be slower than server side rendered pages.

With SysNDD we are engaged to provide a fast user experience by reducing component and request sizes and applying techniques like lazy loading and code splitting in the frontend with parallelisation in the api.

A quick overview on the current website performance can be obtained on PageSpeed Insights (or “Lighthouse” in the chrome development console):

<https://pagespeed.web.dev/report?url=https%3A%2F%2Fsysndd.dbmr.unibe.ch%2F><sup>26</sup>

## 2.13 Security

SysNDD is engaged to offer highest security standards for all web tools. We use HTTPS with Transport Layer Security (TLS) and follow the Mozilla recommendations for web server settings.

A quick overview for our security settings for the SysNDD website can be obtained on Mozilla Observatory:

<https://observatory.mozilla.org/analyze/sysndd.dbmr.unibe.ch>

<sup>26</sup>[https://pagespeed.web.dev/report?url=https%3A%2F%2Fsysndd.dbmr.unibe.ch%2F&form\\_factor=desktop](https://pagespeed.web.dev/report?url=https%3A%2F%2Fsysndd.dbmr.unibe.ch%2F&form_factor=desktop)



SysNDD



Welcome to SysNDD,  
the expert curated database  
of gene disease relationships  
in **neurodevelopmental  
disorders** (NDD).

Search the SysNDD-db by genes,



### Current gene statistics (last update: 5.6.2022)

Category Definitive

Count [1567](#)

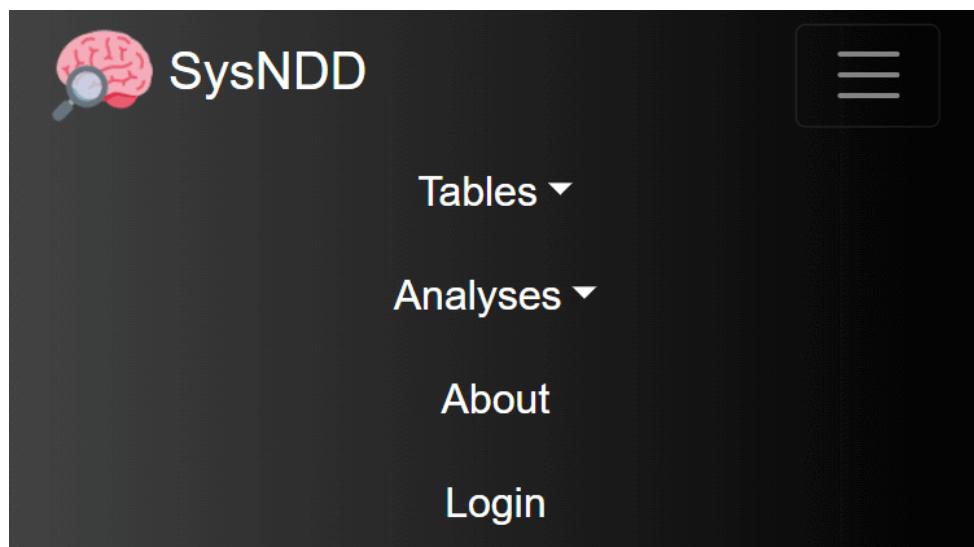
Details [show](#)

Category Limited

Count [1275](#)

Details [show](#)

### New entities



**Welcome to SysNDD,**  
the expert curated database  
of gene disease relationships  
in **neurodevelopmental**  
**disorders** (NDD).

Search the SysNDD-db by genes,



**Current gene statistics (last update: 5.6.2022)**

**Category** Definitive

**Count** 1567

**Details** [show](#)

Figure 30: Mobile navbar  
24

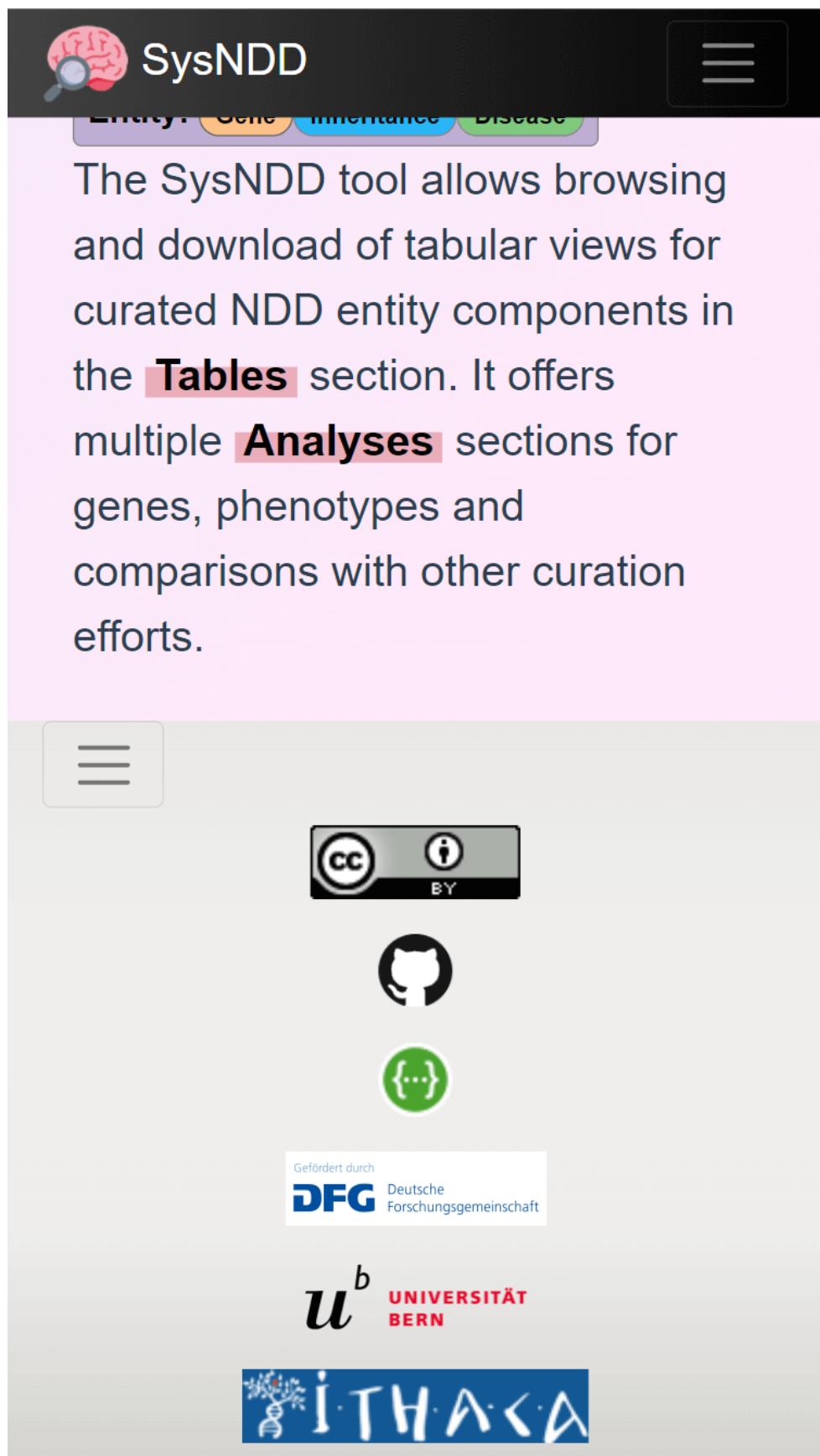


Figure 31: Mobile footer  
25



# SysNDD

**Entities table** Entities: 3629

Search any field by typing here

Per page 10 ▾

« < 1 2 > »

.. Entity id ..

.. Symbol ..

.. Disease ontology na... ..

.. Hpo mode of inherit... .. ▾

.. Category .. ▾

.. Ndd phenotype word .. ▾

**Entity id** sysnidd:1

**Symbol** ABCC9

**Disease ontology name** Hypertrichotic osteochondro-

<b>Entity id</b>	sysnidd:1
<b>Symbol</b>	ABCC9
<b>Disease ontology name</b>	Hypertrichotic osteochondro-

Figure 32: Stacked table  
26

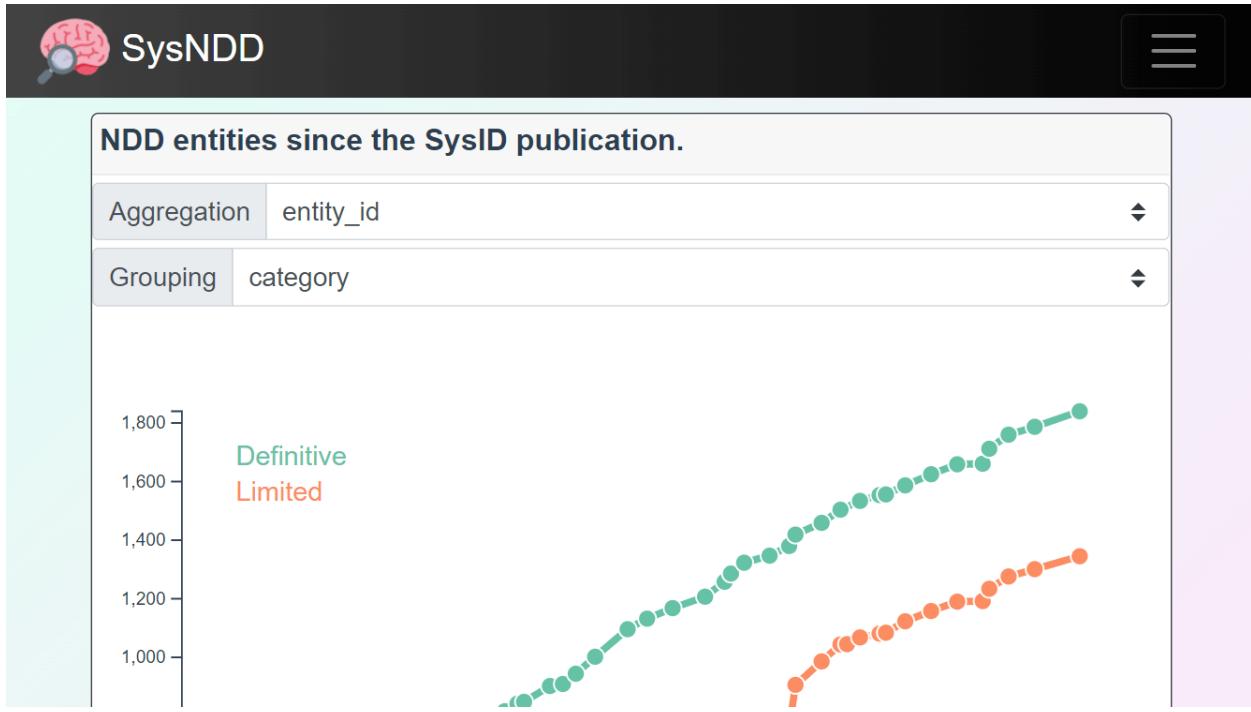


Figure 33: Landscape mode

### 3 API

---

The SysNDD api (application programming interface) is available from <https://sysnnd.dbmr.unibe.ch/API>.

The api is written in R using the plumber package<sup>27</sup>.

We intend to follow the Swagger/ OpenAPI<sup>28</sup> and JSON:API<sup>29</sup> specifications.

The api scripts run in a Docker container using the official “rocker/tidyverse” image (version 4.2.0).

As R is single threaded, we deploy multiple instances of the api container. These are bundled together using HAProxy<sup>30</sup> load balancer.

The api is rate limited through our NGINX<sup>31</sup> web server configuration with a rate limit of 10 requests per second (10r/s; equals 1 request every 100 milliseconds) per requesting ip. The configuration allows bursts of up to 30r/s but introduces a delay after 10 requests to enforce the rate limit.

#### 3.0.1 Endpoints

The SysNDD api currently contains all endpoints for external and internal usage in one api script. This may change with future releases.

The api is structured into different components based on the SysND concept:

<sup>27</sup><https://www.rplumber.io/>

<sup>28</sup><https://swagger.io/specification/>

<sup>29</sup><https://jsonapi.org/>

<sup>30</sup><http://www.haproxy.org/>

<sup>31</sup><https://www.nginx.com/>

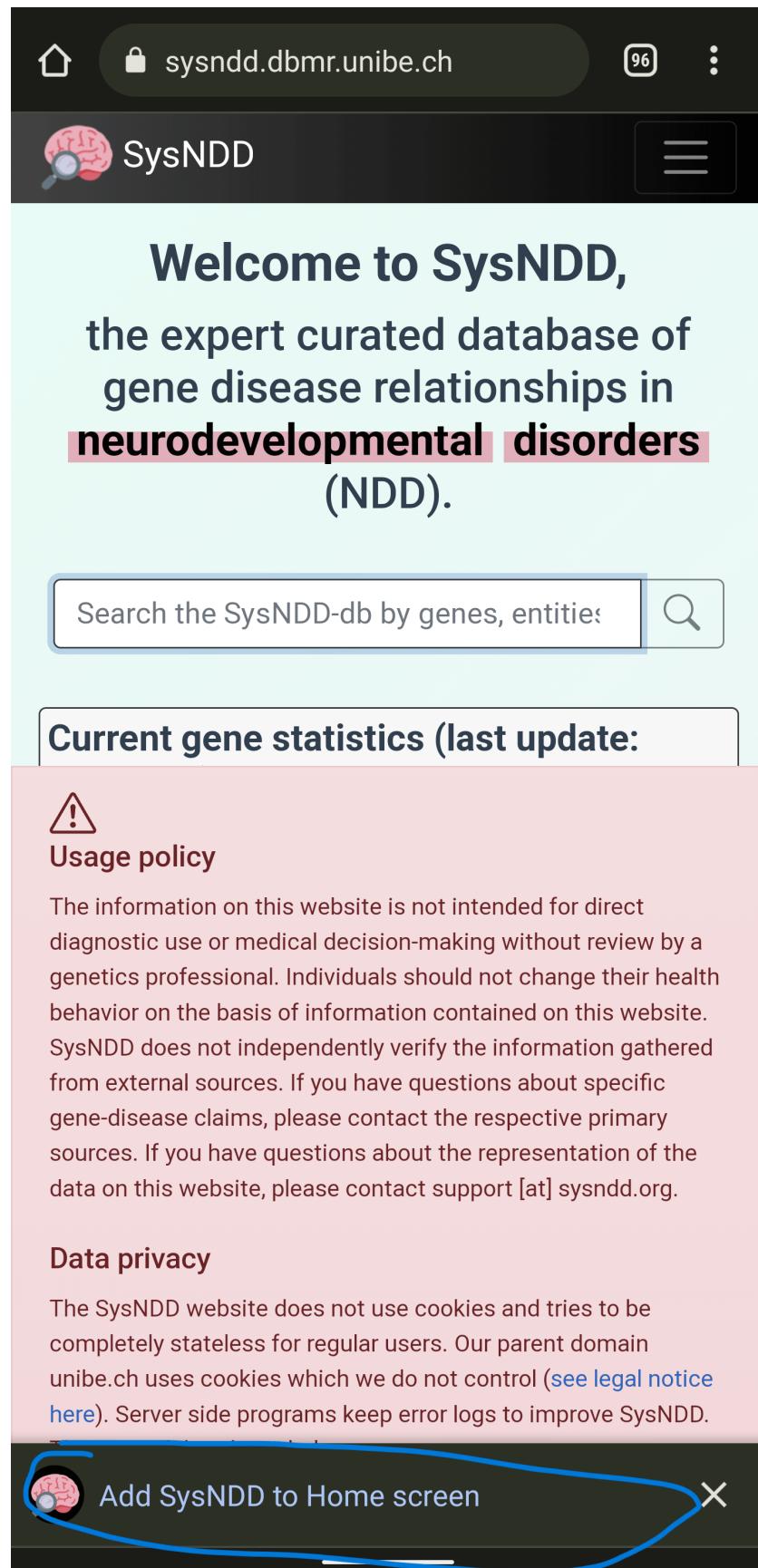


Figure 34: PWA add  
28

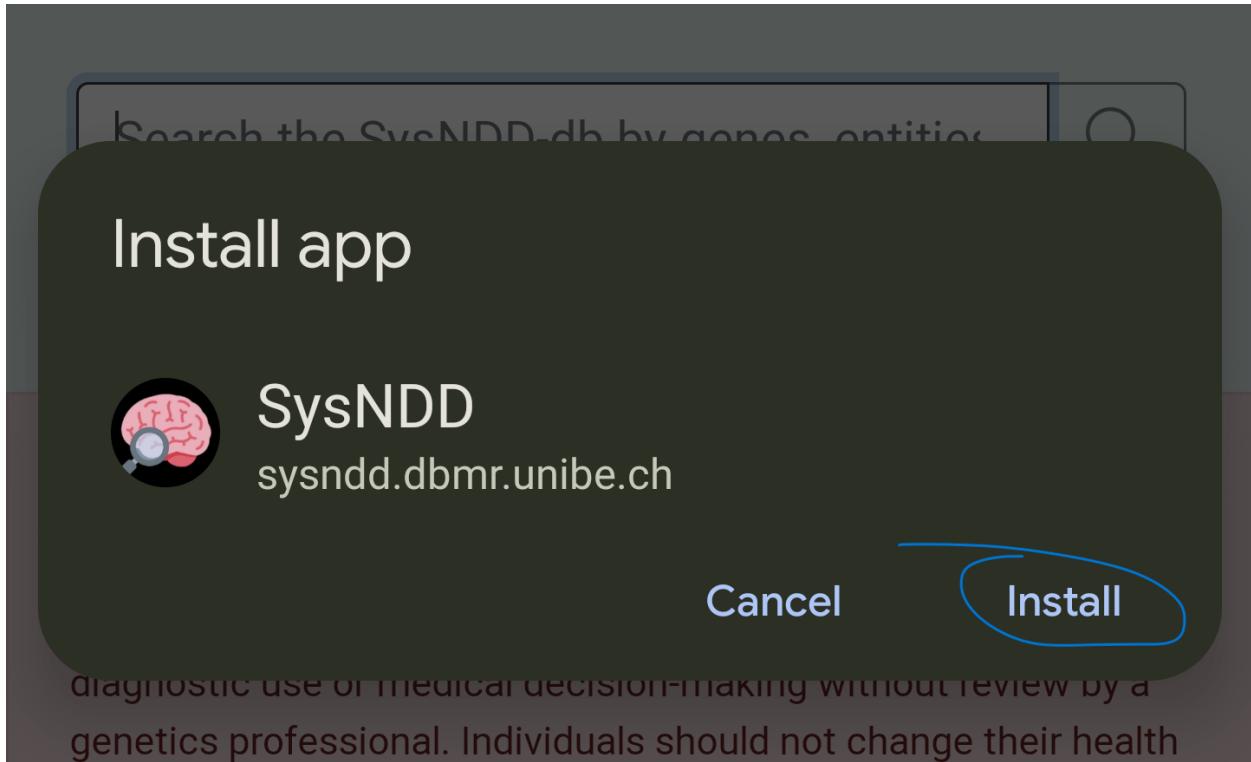


Figure 35: PWA install

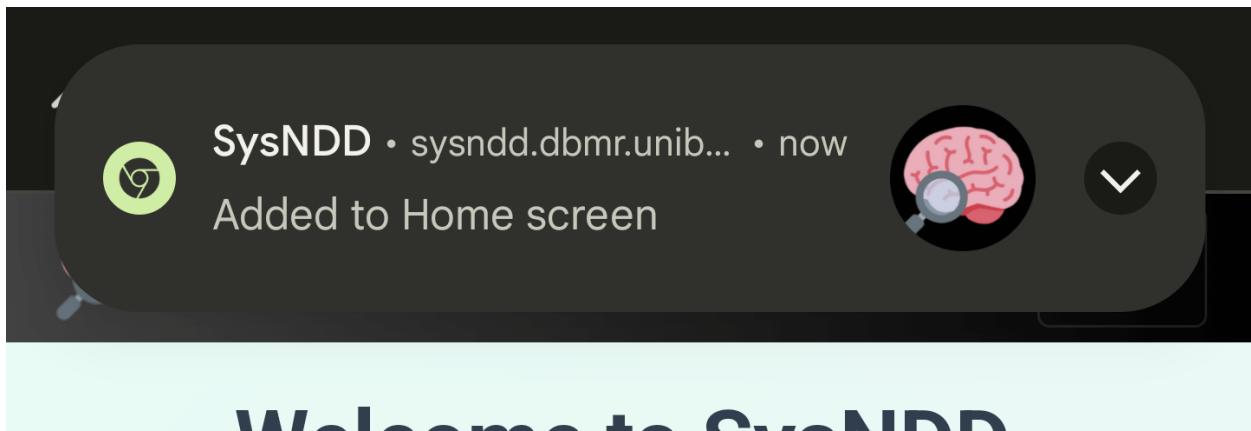


Figure 36: PWA added



Figure 37: App symbol

- entity: Entity related endpoints
- review: Reviews related endpoints
- status: Status related endpoints
- re\_review: Re-review related endpoints
- publication: Publication related endpoints
- gene: Gene related endpoints
- ontology: Ontology related endpoints
- inheritance: Inheritance related endpoints
- phenotype: Phenoptype related endpoints
- panels: Gene panel related endpoints
- comparisons: NDD gene list comparisons related endpoints
- search: Database search related endpoints
- list: Database list related endpoints
- statistics: Database statistics
- user: User account related endpoints
- authentication: Authentication related endpoints

The endpoints are documented and can be tested using the Swagger/ OpenAPI user interface at <https://sysndd.dbmr.unibe.ch/API>. Here one can generate cURL requests to use in external software.

### 3.0.2 Usage policy

The SysNDD api powers the web tool for everyday users. We also provide the SysNDD api free to allow users to use the SysNDD data and build on it by creating software or services that connect to our platform.

Usage requirements:

- optimize your requests to stay in the above described limits
- be sensible about re-using data (e.g., store your requests until data is updated on our server)
- use pagination where possible instead of requesting large data chunks (e.g., restrict usage of “all” option in large, potentially blocking list endpoints like “entity” and “gene”)
- if you require more api ressources please get in contact

Updates and disclaimer:

The screenshot shows the SysNDD mobile application interface. At the top, there is a header bar with the time (11:31), signal strength, battery level (91%), and the SysNDD logo. To the right of the logo is a menu icon. The main content area features a welcome message: "Welcome to SysNDD, the expert curated database of gene disease relationships in neurodevelopmental disorders (NDD)." Below this is a search bar with the placeholder "Search the SysNDD-db by genes, entities" and a magnifying glass icon. A large box titled "Current gene statistics (last update: 6/5/2022)" displays two categories: "Definitive" (1567 entries) and "Limited" (1275 entries), each with a "Details" button. Another box titled "New entities" shows a single entry: Entity sysnnd:3755, Symbol ABCC9, Disease Intellectual disability and myopathy sy., Inh. AR, and Category Definitive.

11:31 4G+ 91%

SysNDD

Welcome to SysNDD,  
the expert curated database of  
gene disease relationships in  
neurodevelopmental disorders  
(NDD).

Search the SysNDD-db by genes, entities

Current gene statistics (last update:  
6/5/2022)

Category Definitive  
Count 1567  
Details [show](#)

Category Limited  
Count 1275  
Details [show](#)

New entities

Entity sysnnd:3755  
Symbol ABCC9  
Disease Intellectual disability and myopathy sy.  
Inh. AR  
Category

Figure 38: PWA screenshot  
31

- We provide the SysNDD api as is.
- Due to the current development status (version 0.X.Y) we may update or modify the api any time. These changes may affect your use of the api or the way your integration interacts with the api.

### 3.0.3 Authentication and authorization

The SysNDD api uses JSON Web Tokens (JWT<sup>32</sup>) to implement stateless authentication and authorization.

The api user can manually (test purposes) request a token by entering their login credentials in the input form provided at the “api/auth/authenticate” endpoint:

Figure 39 shows the Swagger UI interface for the 'GET /api/auth/authenticate' endpoint. The 'user\_name' field is highlighted with a green circle and labeled '1'. The 'password' field is highlighted with a green circle and labeled '2'. The 'Execute' button at the bottom is highlighted with a green circle and labeled '3'.

Figure 39: Authenticate endpoint

This endpoint will generate and respond with and JWT token:

```
[{"token": "eyJhbGciOiJIUzI1NiJ9.eyJleHAiOjE2NTQ2NzcxMDgsImhdCI6MTY1NDY3MzUwOCwidXNlc19pZCI6NCwidXNlc19uYW1lIjo1VGVzdHvzZXI1LCJlbWFpbCI6ImJ1cm50LnBvcHAubWRAZ21haWwuY29tIiwidXNlc19yb2xIiyoUmV2aW3ZXiiLCJ1c2VyX2NyZWFOZWNQoiIyMDiyLTA1LTmxIiwiYWJicmV2aWFoaw9uIijo1VFUiLCJvcnNpZCI6bnVsblH0.fETYpoSfIC2QTg8A2tkCLeuV2mJi2F1zmyQRp1_DiqE"}]
```

Figure 40 shows the response body of the JWT token, which contains a single JSON object with a 'token' key. The token value is a long string of characters. There are 'Copy' and 'Download' buttons next to the response body.

Figure 40: JWT token

This Bearer token can then be copied and entered in the OpenAPI/ Swagger authorize modal, which opens after clicking the “Authorize” modal button at the upper right corner:

After entering the token in the respective field (1) and clicking the “Authorize” submission button the modal will change and show the login status. This field can be closed now:

The user is now fully authenticated and can access the endpoints requiring user rights:

The token is valid for 60 minutes. It can be refreshed using the endpoint “api/auth/refresh”.

## 4 Database structure

<sup>32</sup><https://jwt.io/>

# SysNDD API 0.1.0 OAS3

<https://sysndd.dbmr.unibe.ch/alb/openapi.json>

This is the API powering the SysNDD website and allowing programmatic access to the database contents.

[Terms of service](#)

[API Support - Website](#)

[Send email to API Support](#)

[CC BY 4.0](#)



Figure 41: Authorize button

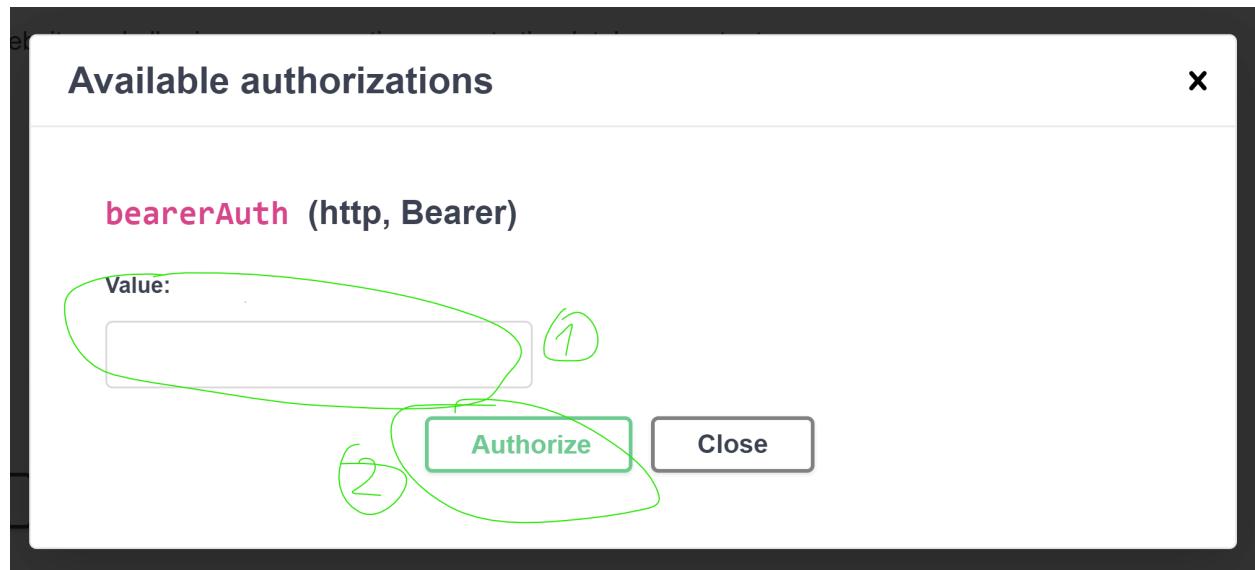


Figure 42: Authorize modal prompt

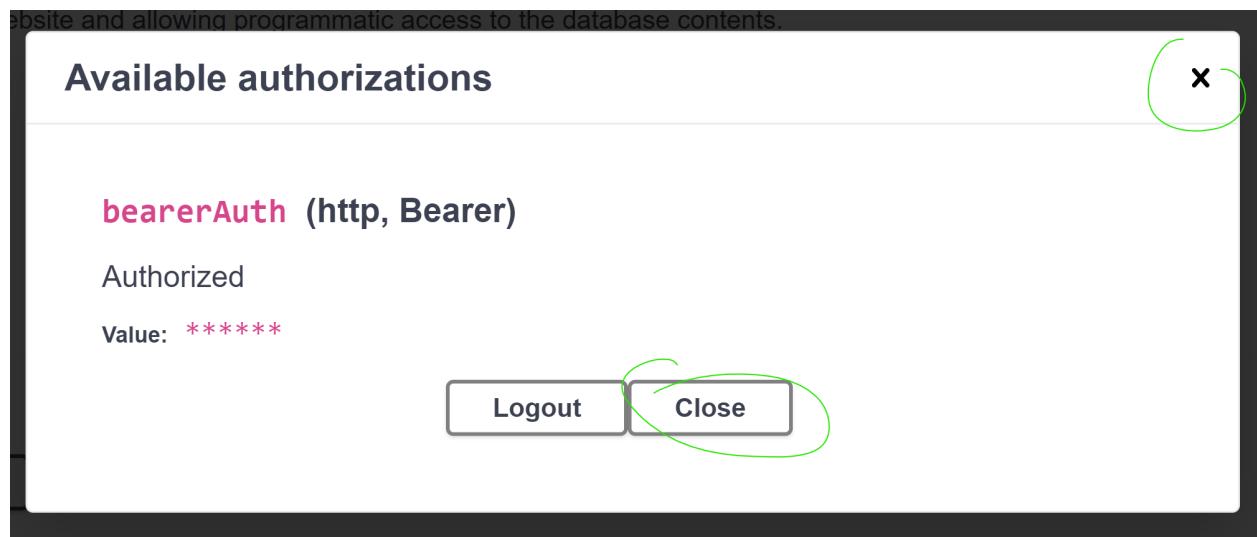


Figure 43: Authorize modal logged in

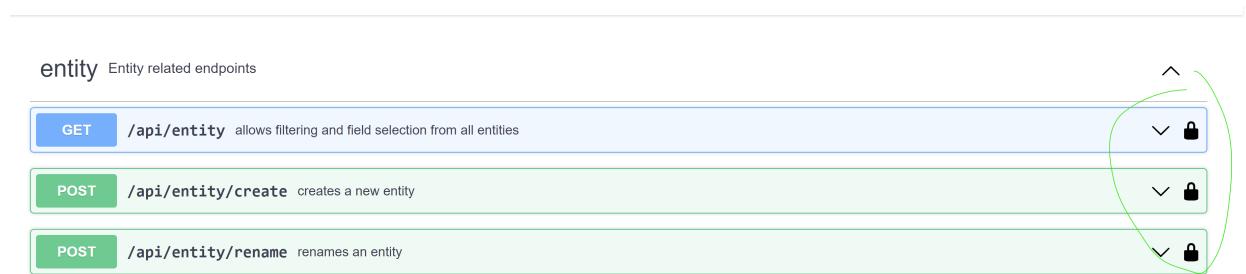


Figure 44: API logged in

SysNDD currently uses the open-source MySQL 8.0<sup>33</sup> relational database management system (RDBMS).

The design of our DB schema can be viewed in DB DESIGNER<sup>34</sup>:

SysNDD DB schema<sup>35</sup>

As of 2022-06-07 the database schema looks like this:

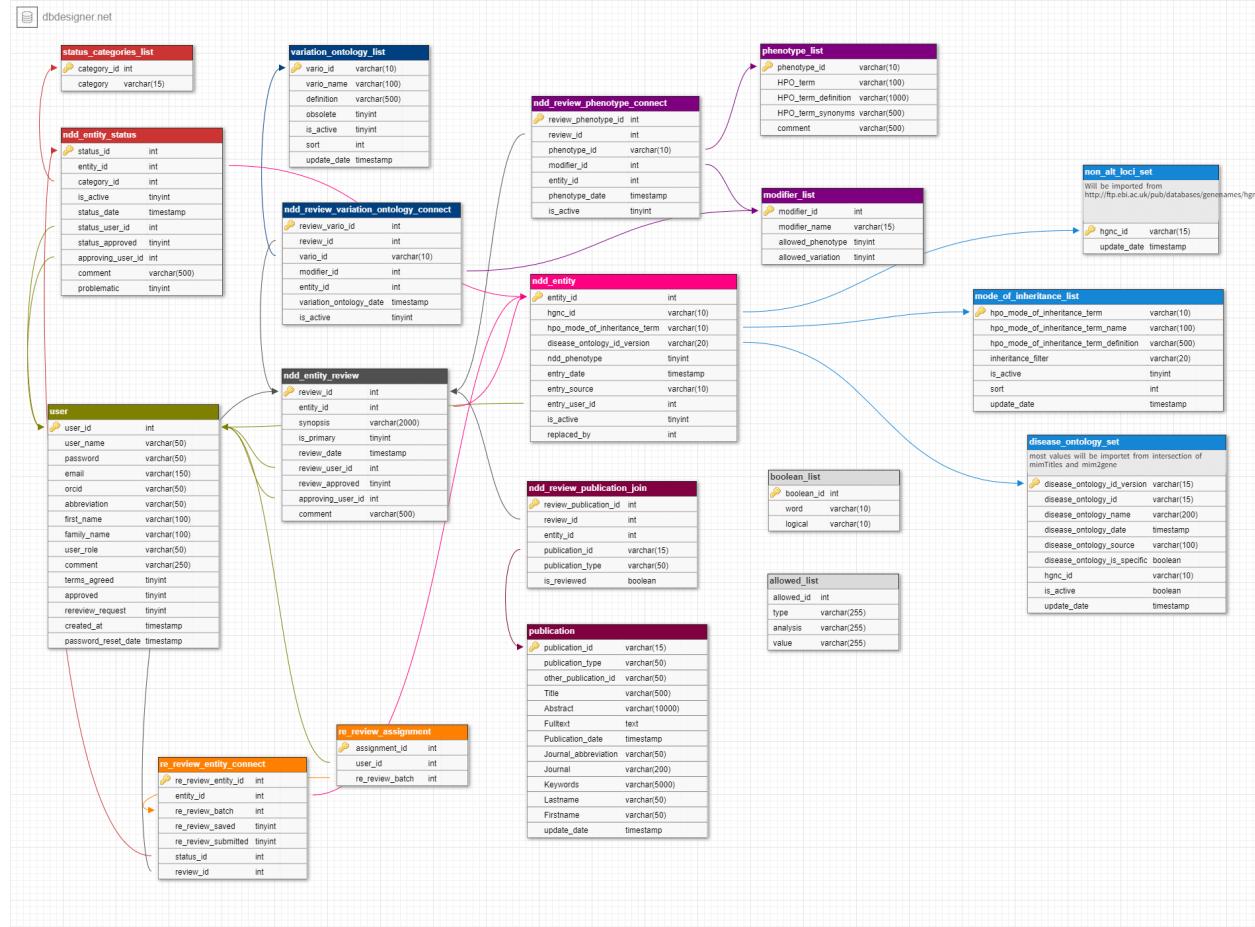


Figure 45: SysNDD MySQL database

The database runs in a docker container using the official mysql docker image<sup>36</sup> (version 8.0.29).

## 5 Curation criteria

### 5.1 Definitions

Intellectual disability (ID) and neurodevelopmental disorders (NDDs) are defined in the scope of SysNDD as follows:

<sup>33</sup><https://dev.mysql.com/doc/relnotes/mysql/8.0/en/>

<sup>34</sup><https://www.dbdesigner.net/>

<sup>35</sup><https://dbdesigner.page.link/3Morx9HZxzqt4R379>

<sup>36</sup>[https://hub.docker.com/\\_/mysql](https://hub.docker.com/_/mysql)

- Early onset neurodevelopmental delay and cognitive impairment (severe ID to learning difficulties)
- Regression/ neurodegeneration in the first years of life with or without prior developmental delay
- Disorders with cognitive impairment in a significant (ca. >10%) fraction of individuals

## 5.2 NDD Definitive entities

Inclusion criteria for Category 1 (“Definitive”):

1. Publication required (no grey literature like conference abstracts or personal communication; manuscripts on preprint servers can be considered individually but only entered through their DOI in the comment field until published with PMID, when they should be updated)

**AND**

2. Clear-cut frequency (no further criteria needed)

- $\geq 10$  cases with *de novo* variants
- $\geq 5$  autosomal-recessive families
- $\geq 3$  families with X-chromosomal variants

**OR**

3. Cumulative evidence

- 1 strong frequency criterium

**PLUS**

- 1 strong genetic or 1 strong clinical criterium

**OR**

- 2 further strong (genetic and/or clinical) criteria in case of only 2 families with recessive inheritance

**OR**

- $\geq$  two moderate criteria

### 5.2.1 Strong criteria

Strong frequency criteria:

- $\geq 3$  patients with *de novo* variant
- $\geq 2$  families with bi-allelic truncating variants
- $\geq (2\text{-})3$  families with bi-allelic missense variants
- $\geq 2$  families with X-chromosomal variants

Strong genetic criteria:

- recurrence of a variant
- clustering of variants

- *de novo* truncating variants in a gene intolerant to loss-of-function variants (gnomAD constraint score)

Strong clinical criteria:

- Homogeneous phenotype
- Presence of specific/distinct clinical aspects (e.g., recognizable facial gestalt; rare specific malformations; pattern of multiple malformation; characteristic MRI anomalies; specific metabolic/enzymatic anomalies)

### **5.2.2 Moderate criteria**

- Multigenerational segregation of variants
- Functional tests
- Gene involved in a pathway/complex where variants in other subunits are associated with a similar phenotype
- *De novo* missense variants in a gene intolerant to missense variants (gnomAD constraint scores)

### **5.2.3 Possible negative criteria**

These should be included into consideration in borderline cases.

- Age of first publication(s) without further confirmatory reports in the meantime
- Publication quality and journal or genetics expertise “doubtful”
- New evidence against gene and/or variants: e.g., constraint scores, frequencies in gnomAD

## **5.3 NDD Moderate and Limited entities**

These categories include the previous category of “candidate genes” and are now split into criteria for entity categories 2 (“Moderate”) and 3 (“Limited”):

1. Must be published (no private, in-house candidate lists)

**AND**

2. ID indicated, but criteria not sufficient for category 1, examples:

a. Limited genetic evidence

- < 3 cases with *de novo*, different variants and non-specific NDD phenotype
- 1 recessive family with truncating variant or <= 2 recessive families with missense variants (category 2 or 3 depending on number of affected and tested individuals per family, functional evidence and homogeneity of phenotype etc.)
- candidate gene from translocation or larger deletion
- reports of enzymatically confirmed patients with specific metabolic disorders but without genetic mutation confirmed

b. Limited clinical evidence

- not much evidence for ID, e.g. reported as ADHD or ASD or neurological disorder without clearly reported low IQ and ID
- known disorder, but only single patients reported with ID
- motor developmental delay without evidence for cognitive impairment

- clear neurodegenerative course without ID or cognitive delay present in the first years
- lethal before ID might be evident, although e.g. brain malformations or metabolic abnormalities might point to ID
- ID reported in other, similar disorders caused by mutations in the same pathway/complex but not (yet) in association with this particular gene (e.g. Fanconi anemia)

**c. Limited combined genetic and clinical evidence**

- Gene enriched for *de novo* or rare deleterious variants in large NDD cohorts or meta-studies, no further details

**5.3.1 Exclusion criteria**

1. Published as candidate gene only based on function or experimental results but without variants reported in humans

**AND/OR**

2. Only 1 *de novo* case from longer ago without further evidence and gene tolerant towards missense and/or loss-of-function variants according to gnomAD constraint scores

**AND/OR**

3. Only 1 sporadic case with bi-allelic variants and without any further supporting evidence such as segregation in other family members, functional tests, similar phenotypes in other patients with variants in genes from the same pathway, etc.

**5.3.2 When to choose category 2 (“Moderate”)?**

Too good for category 3 (“Limited”) but not good enough for category 1 (“Definitive”)

Examples:

- Recurrent *de novo* variant in 2 individuals with a similar phenotype
- Bi-allelic or X-chromosomal truncating variant segregating in  $\geq$  two generations of a large family
- Convincing functional evidence
- 1-2 patients with convincing variants in a gene which is in the same complex/pathway with other known disease genes and phenotype fits (e.g. CDG syndrome)

**5.3.3 Special case: non-NDD entities**

Some genes are associated with multiple entities. Among these entities there might be some without ID as a clinical feature. These non-NDD entities will be included in SysNDD but they will not be classified to any of the categories. Instead, they are tagged with “n.a.” (not applicable).

## 6 Re-review instructions

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The goal of the SysNDD “Re-Review” effort is to update and standardize the SysID entities collected during the past years to enable better integration into and inter-operability international with gene curations.

### 6.1 Re-review tool usage

We created Reviewer status accounts for participating scientists.

#### 6.1.1 Login

You can log into your account by pointing your browser to <https://sysnnd.dbmr.unibe.ch/> and then clicking the “Login“ link on the right side of the menu:

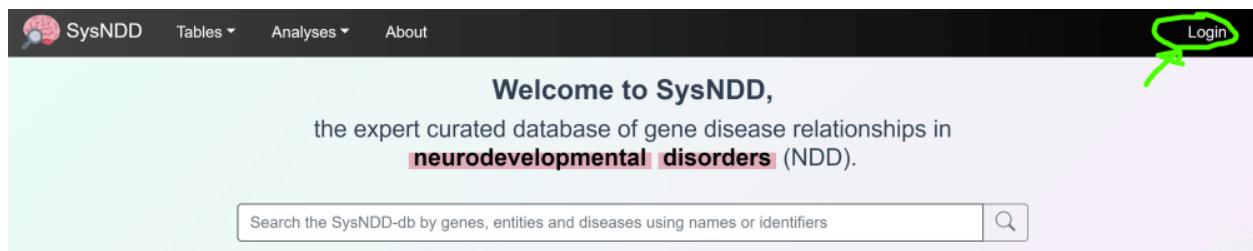


Figure 46: Login menu

On the Login page enter your credentials and press the Login button:

After successful login, you will be redirected to the start page and the navigation bar will show new links depending on your account privileges:

Your login token (JWT; JSON Web Token) is valid for 1 hour, after which you will be logged out. You can however always refresh the time by clicking the link in the user menu. The website will warn you at 5, 3 and 1 minutes before log out.

#### 6.1.2 Review page

Click the “Review” link to your personal “Re-Review” site:

The “Re-Review” page is structured as a table enriched with information and controls.

These show you the number of entities assigned to your account

- (1) your account information status specific controls (e.g. switching to “Curator” mode, applying for a new batch of entities)
- (2) menu items to filter/ navigate the table
- (3) and finally, the table with the entity information and
- (4) controls to review and change the information:

By clicking the action buttons, you can open 3 different windows to change the entities review:

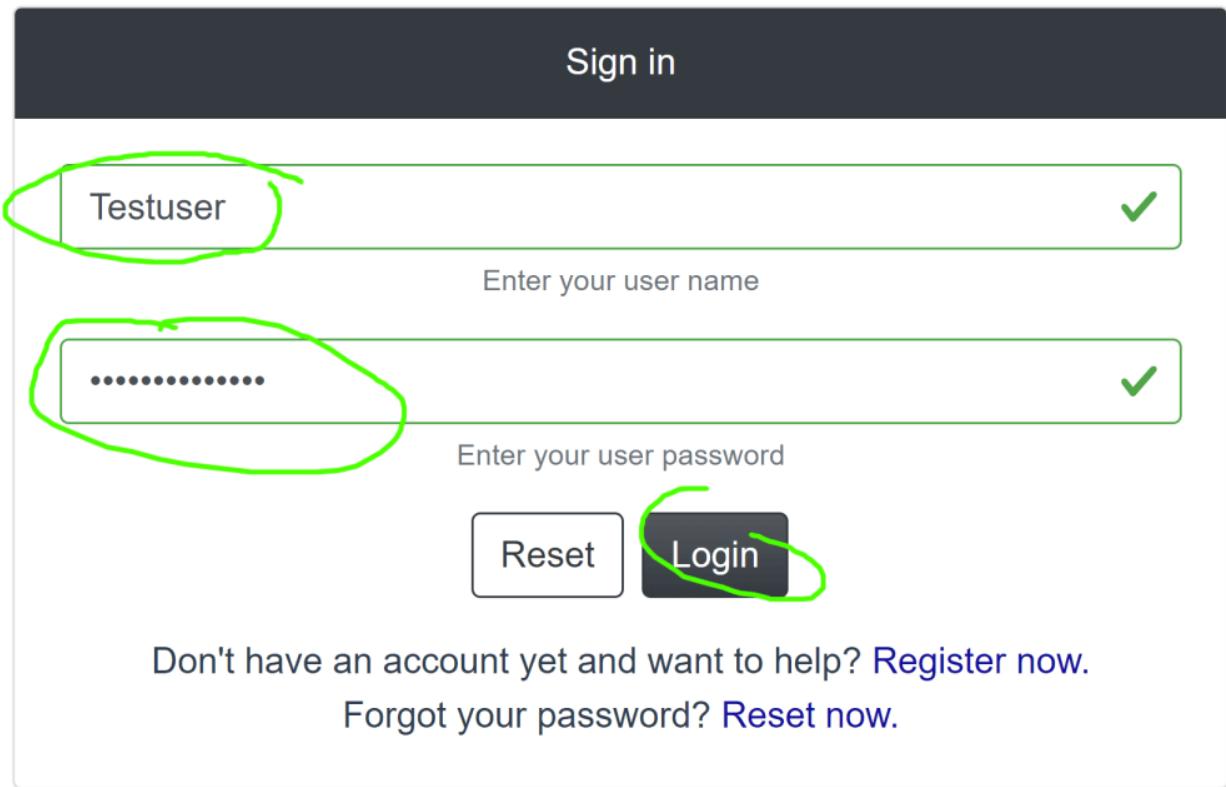


Figure 47: Login page

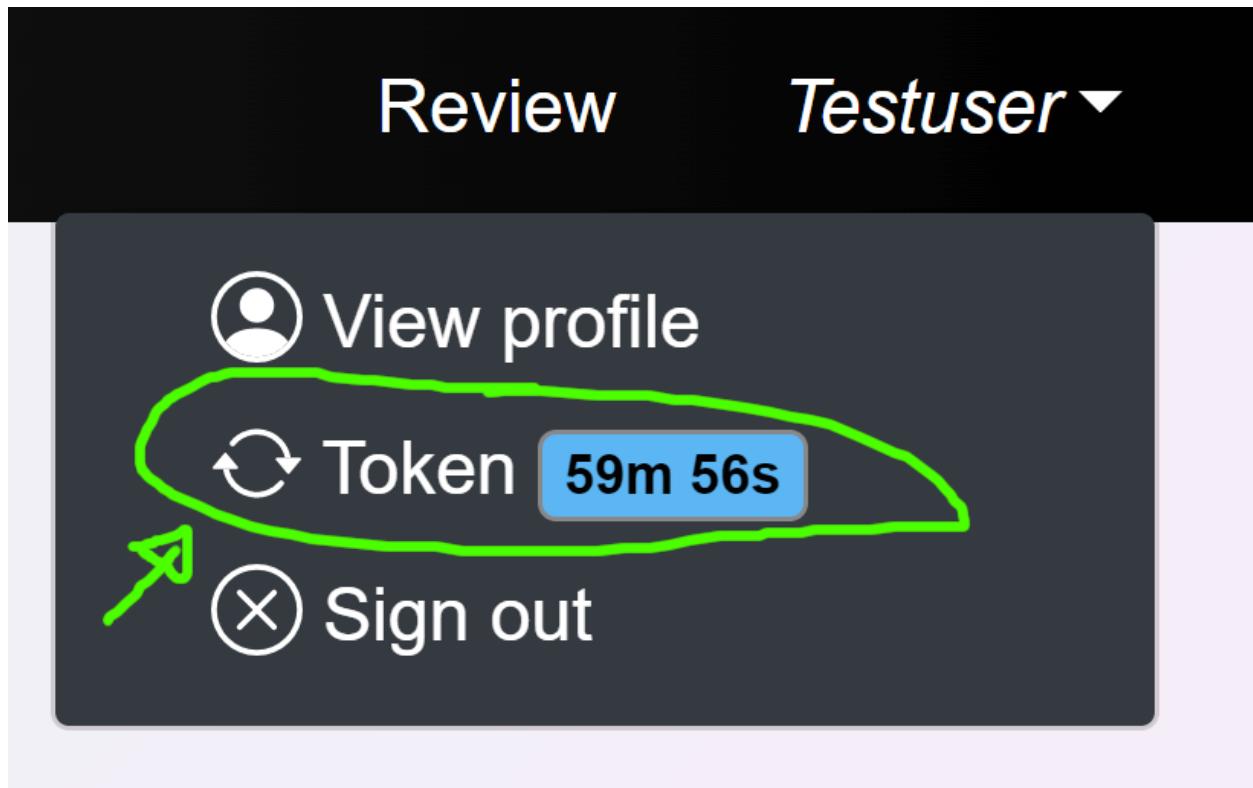


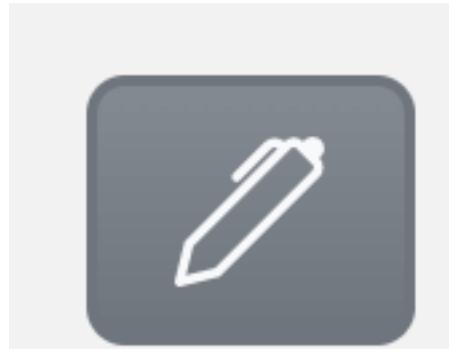
Figure 48: Login token menu



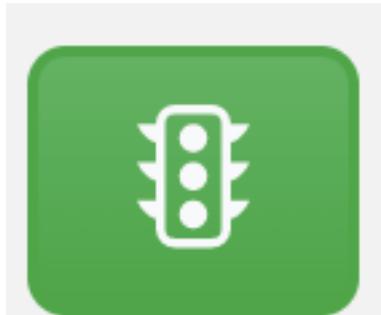
Figure 49: Review page menu

Re-review table					
Entities: 29					
Entity	Gene	Disease	Inheritance	NDD	Actions
sysnnd:49	AP3B1	Hermansky-Pudlak syndrome 2	AR	✓	
sysnnd:50	AP4B1	Spastic paraplegia 47, autosomal	AR	✓	
sysnnd:51	AP4E1	Spastic paraplegia 51, autosomal	AR	✓	
sysnnd:52	AP4S1	Spastic paraplegia 52, autosomal	AR	✓	
sysnnd:53	APTX	Ataxia, early-onset, with oculomotor apraxia	AR	✓	
sysnnd:54	ARFGEF2	Periventricular heterotopia with intellectual disability	AR	✓	
sysnnd:55	ARHGEF6	intellectual disability	XR	✓	
sysnnd:56	ARID1A	Coffin-Siris syndrome 2	AD	✓	
sysnnd:57	ARID1B	Coffin-Siris syndrome 1	AD	✓	
sysnnd:58	ARL13B	Joubert syndrome 8	AR	✓	

Figure 50: Review page



(1) entities review ( )



(2) the status ( )



(3) and to submit your work ( )

### 6.1.3 New Review edit

In this window you have:

- the possibility to change/adapt or completely rewrite the current synopsis (1),
- add, or remove phenotype associations (2),
- add or remove publications from the review by PMID (3)
- and add/ edit fitting GeneReviews articles by PMID (4).
- Finally, you can add a comment to your review for the Curator later approving this entities changes (5) and
- save your review (6).

By clicking on the little question marks you can show help messages for each item:

These help instructions are:

**Synopsis:** Short summary for this disease entity. Please include information on: a) approximate number of patients described in literature, b) nature of reported variants, b) severity of intellectual disability, c) further phenotypic aspects (if possible with frequencies) d) any valuable further information (e.g. genotype-phenotype correlations).

Examples:

*de novo* truncating or missense variants in > 20 individuals: variable ID (mild to severe), 50% short stature and microcephaly, 30% seizures, non-specific facial dysmorphism, variable cardiac and renal anomalies in some

bi-allelic truncating variants in 7 individuals from 3 families: severe ID, microcephaly, seizures in 3/7, MRI anomalies

**Phenotypes:** Add or remove associated phenotypes. Only phenotypes that occur in 20% or more of affected individuals should be included. Please also include information on severity of ID where available and applicable.

**Publications:** No complete catalogue of entity-related literature required! If information in the clinical synopsis is not only based on OMIM entries, please include PMID of the article(s) used as a source for the clinical synopsis.

**GeneReviews:** Please add PMID for GeneReview article if available for this entity.

**Comment:** Additionally add information about your review potentially helpful to the curator approving the entity later.

Modify review for entity: sysnnd:49

**Synopsis** 0

multi system disorder, albinism, bleeding diathesis, pulmonary fibrosis, granulomatous colitis, platelet and T-lymphocyte dysfunction and neutropenia, mild ID in some patients

**1**

**Phenotypes** 0

present: Abnormality of the eye x present: Intellectual disability x rare: Intellectual disability, mild x present: Abnormality of blood and blood-forming tissues x  
present: Abnormality of the immune system x

**2**

**Variation ontology**

present: variation x

**3**

**Publications** 0

Enter PMIDs separated by comma or semicolon  Add

**4**

**Genereviews** 0

Enter PMIDs separated by comma or semicolon  PMID:20301464 x Add

**5**

**Comment**

Additional comments to this entity relevant for the curator.

**6**

Review by: Christiane Curator

Cancel Save review

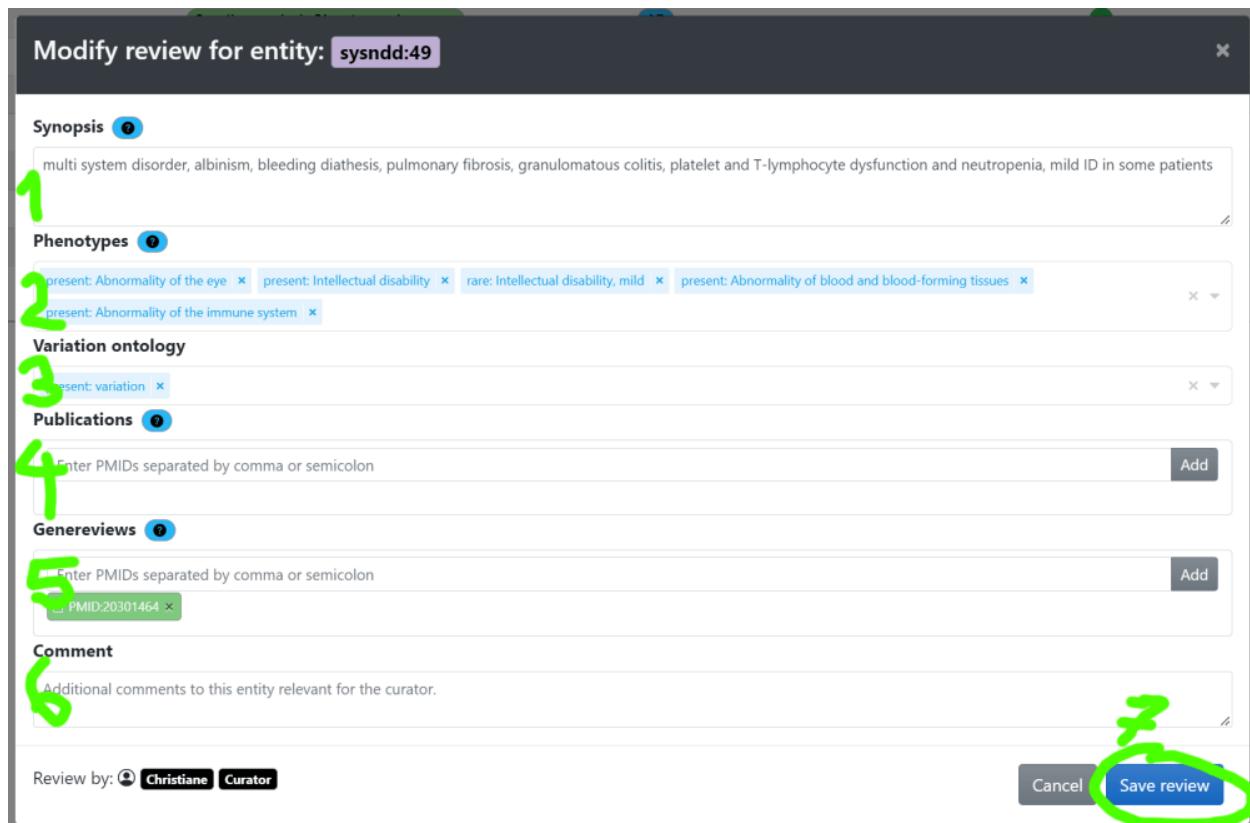


Figure 51: Review page

#### 6.1.4 New Status edit

In this window you can propose

- to change the entities association confidence category (1),
- suggest its overall removal (2),
- add a comment for your change suggestions for the curators to better understand the proposal (3) and
- save your work (4):

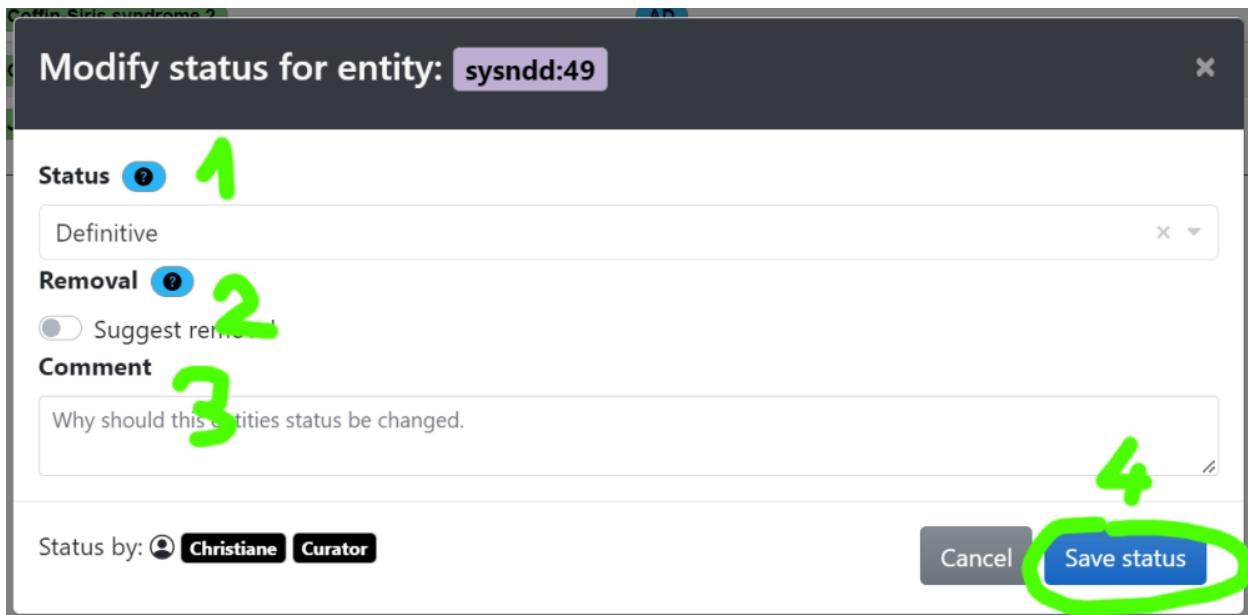


Figure 52: Submit re-review modal

#### 6.1.5 Submit Re-review

The last action window is just to confirm that you are satisfied with your work and would like to submit it for curation:

After clicking this button, the entity will disappear from your list. And you can proceed with the remaining entries until no entity is left in your list.

## 6.2 Re-review curation

### 6.2.1 Definitive association status

1. Check if category 1 ("Definitive") is correct or shift status to category 2 ("Moderate") or 3 ("Limited"), where appropriate
2. Check and revise gene-related entities regarding diseases/inheritance patterns (ID and non-ID disorders) -> non-ID disorders will not go into any of the categories but will be tagged with "n.a." (not applicable)
3. Check and revise associated phenotypes: select HPO terms from the list, only use HPO term if this specific aspect is present in approximately  $\geq 20\%$  of patients. Please also check and revise severity of ID using HPO terms. If ID is very variable, select all appropriate ID terms (e.g. severe, moderate, mild, borderline)

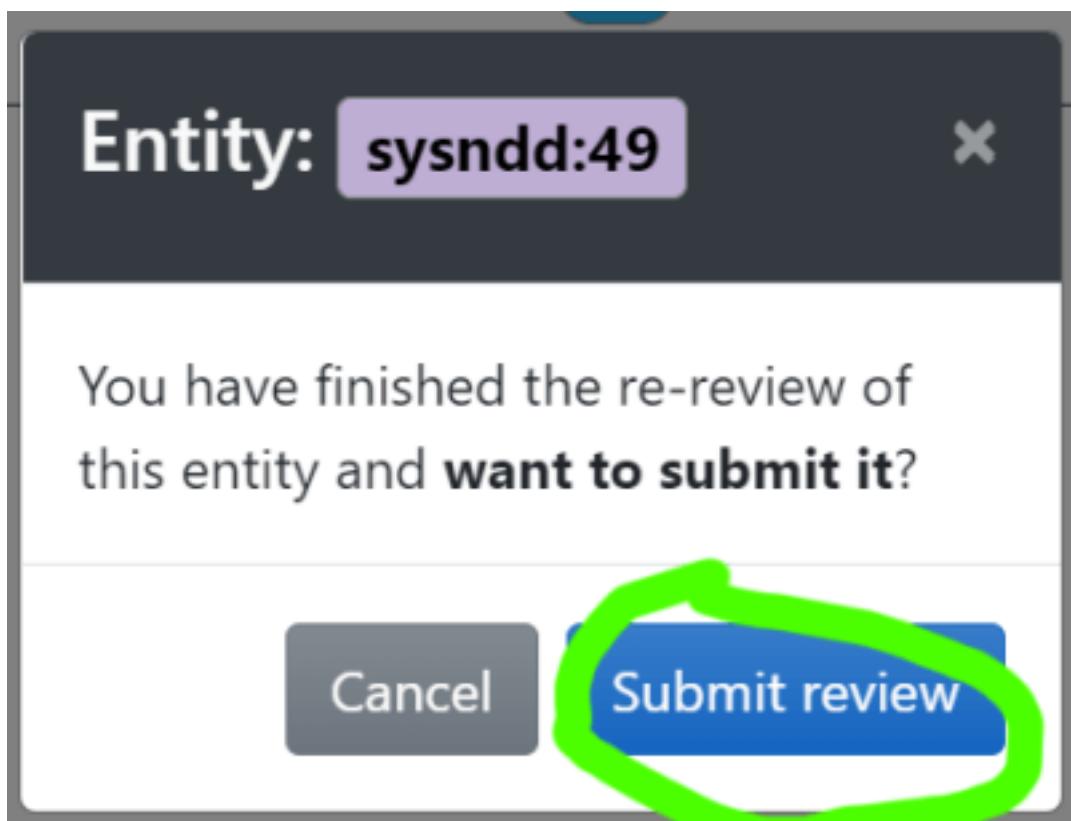


Figure 53: Submit re-review modal

4. Check references (OMIM, PMID, GeneReviews). References do not have to be complete but should be sufficient to give a good impression on the mutational and clinical spectrum. Add references where it would add to the picture.
5. Check and revise clinical synopsis: it does not have to contain everything that is known but should give a short and comprehensive picture on:
  - which data the gene and disease category were chosen on and
  - the molecular and clinical picture.

Please include information on:

- a) approximate number of patients described in literature,
- b) nature of reported variants,
- c) severity of intellectual disability,
- d) further phenotypic aspects (if possible with frequencies),
- e) any valuable further information (e.g. genotype-phenotype correlations)

Examples:

*de novo* truncating or missense variants in > 20 individuals: variable ID (mild to severe), 50% short stature and microcephaly, 30% seizures, non-specific facial dysmorphism, variable cardiac and renal anomalies in some

bi-allelic truncating variants in 7 individuals from 3 families: severe ID, microcephaly, seizures in 3/7, MRI anomalies

### 6.2.2 Moderate and Limited association status

- Check if inclusion criteria for candidate genes are still fulfilled or if it should be deleted from the list (“Refuted”)
- Check if candidate status is still correct and sort it into Category 2 (“Moderate”) and 3 (“Limited”) (or reclassify to 1 (“Definitive”), if applicable)
- Check, if associated phenotype still fits
- Check, if references are correct, if there is any new published information and modify clinical synopsis where appropriate
- Clinical synopsis can be very short for candidate genes
- no associated phenotypes (HPO terms) and frequencies are needed for candidate genes, but could be helpful

Examples:

*de novo* missense variants in 2 individuals: autism, ID in 50%

bi-allelic missense variant in 2 affected individuals from 1 family: moderate ID, MRI anomalies

### 6.2.3 Refuted association status

- Check if there is current evidence against this gene association (e.g. few truncating variants described in old publications before gnomAD constrain scores and the gene now has a pLI of 0; genes reported in a family with later report of another cause etc.)

## References

Korinna Kochinke, Christiane Zweier, Bonnie Nijhof, Michaela Fenckova, Pavel Cizek, Frank Honti, Shivakumar Keerthikumar, Merel A. W. Oortveld, Tjitske Kleefstra, Jamie M. Kramer, Caleb Webber, Martijn A. Huynen, and Annette Schenck. Systematic Phenomics Analysis Deconvolutes Genes Mutated in Intellectual Disability into Biologically Coherent Modules. *American Journal of Human Genetics*, 98(1):149–164, January 2016. ISSN 1537-6605. doi: 10.1016/j.ajhg.2015.11.024.