GenIDA

Platform for participatory clinical research on genetic forms of intellectual disability, autism and epilepsy

https://genida.unistra.fr/

Intellectual disability (ID) with or without manifestations of autism spectrum disorders (ASD) and/or epilepsy affects 1-2% of the population, and it is estimated that more than 50% of these cases have a single genetic cause (mutation in a gene, chromosomal abnormality or copy number variation / CNV).

Our understanding of the genetic causes of neurodevelopmental disorders (NDDs) has improved tremendously over the past decade, especially with the use of high-throughput sequencing since 2012.

More than 1000 genes and recurrent chromosomal abnormalities are involved in these genetic forms of ID or ASD, which often remain insufficiently described in terms of clinical spectrum, associated medical problems and natural history, due to their rarity and the often limited number of patients observed.

For instance, it required 10 years of diagnostic and phenotypic study of families affected by Fragile X syndrome worldwide (1991-2001)[1] to establish, from only 5 initial cases, that male carriers of the Fragile X premutation can present with a late-onset neurodegenerative disorder[2], and a further 3 years were needed to collect data to estimate the age-related penetrance of the disease[3].

In such a context, how can patient cohorts be efficiently constructed to obtain sufficient and complete data to identify information of medical interest to families and professionals?

[1]Rousseau et al. 1991, [2]Hagerman et al. 2001, [3]Jacquemont et al. 2004

GenIDA

GenIDA* is an **international participatory database** initiated in 2016, with the aim of **better characterising the clinical manifestations and natural histories of these genetic forms of ID and/or ASD**.

The aim of this project is to **accelerate knowledge about these rare diseases** by **strengthening the participation of affected individuals, their families and the associations concerned** in order to **create international cohorts of patients of sufficient size** so that doctors, researchers and other professionals can **extract new medically significant data** to improve the care of affected individuals.

GenIDA also enables longitudinal studies to be carried out, in particular to monitor the evolution of cognitive skills and possible behavioural problems in people with the disease.

Collection of health and behavioural data

Statistical analysis of data and synthesis of information

Sharing data with patients/families & professionals

Promoting interaction between patients / families & professionals

Generating new and medically meaningful data

In order to do this, patients and their families are asked to answer a structured questionnaire currently available in 7 languages covering physical, medical, cognitive and behavioural aspects of the disease.

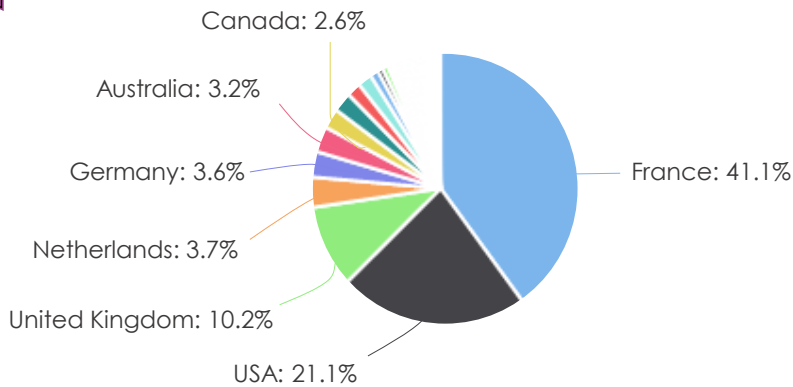
*__Gen__etics of __I__ntellectual __D__isability and __A__utism Spectrum Disorders

GenIDA, March 2023

> 1760 completed patient records

& > 200 professionals (clinicians, geneticists, etc.) registered

> 60 nationalities represented:



Selected cohorts in GenIDA:

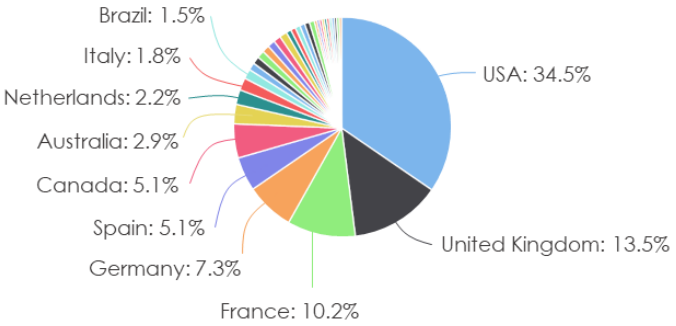
Cohort	Gene / genetic defect	Nb of participants
Koolen-de Vries syndrome	*KANSL1* & 17q21.31 deletion	251
Kleefstra syndrome	*EHMT1* & 9q34.3 deletion	193
Rasopathies	*PTPN11*, *BRAF*, *KRAS*, etc.	66
DDX3X	*DDX3X*	53
KBG syndrome	*ANKRD11*	53
MED13L	*MED13L*	46
Wiedemann-Steiner syndrome	*KMT2A*	32
DYRK1A syndrome	*DYRK1A*	32
White-Sutton syndrome	*POGZ*	29

Type of data collected

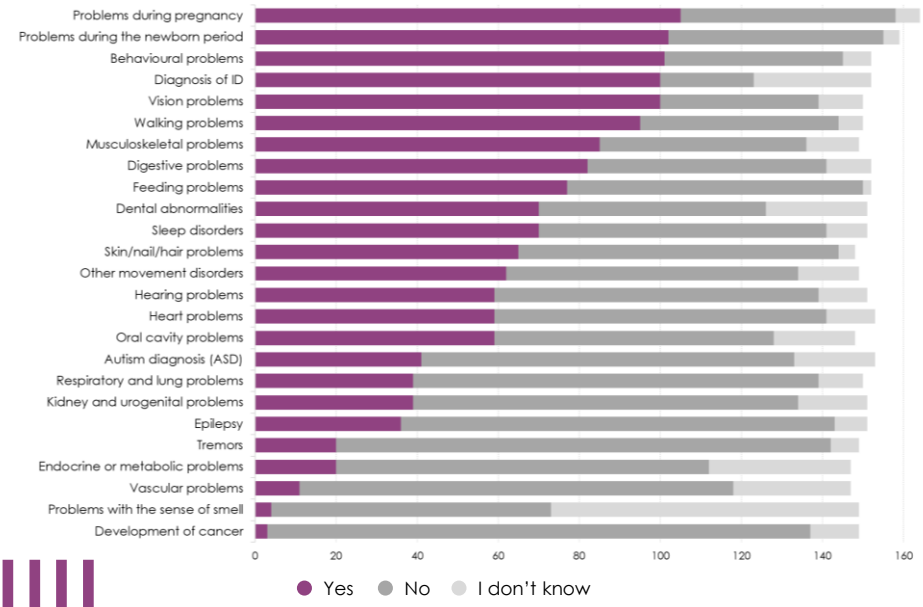
An overview of the data is automatically generated for each cohort (updated every 24 hours).

GenIDA - Kleefstra syndrome cohort (May 2022)

174 participants, including **90 women** & **84 men**



Overview:



Validation of the GenIDA approach

The GenIDA data generally confirm the information reported in the literature, but also allow new observations.

Koolen-de Vries syndrome (**KdVS**) is caused by the 17q21.31 deletion or by a pathogenic variant of the *KANSL1* gene[4,5,6]. The main features are intellectual disability, hypotonia, suggestive facial features, variable frequency of epilepsy, congenital anomalies and various neuromuscular and orthopaedic manifestations.

GenIDA - KdVS cohort (May 2022)

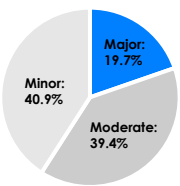
235 participants, including **120 women** & **115 men**

195 patients (83%) have the **17q21.31 deletion**, and **40** (17%) carry a **pathogenic *KANSL1* variant**.

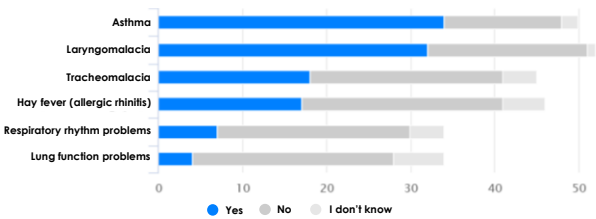
KdVS / Respiratory problems - New observations:

Respiratory problems briefly mentioned in Unique guidelines and one mention of pneumonia in Koolen et al. 2016[6]; no mention in OMIM, GeneReviews, or Zollino et al. 2015[7].

Severity of respiratory problems reported in GenIDA



Respiratory problems (male & female)



Asthma and pneumonia or other respiratory infections are among the most reported comorbidities for KdVS in GenIDA and these problems are considered major by many families.

[4]Koolen et al. 2006, [5]Koolen et al. 2012, [6]Koolen et al. 2016, [7]Zollino et al. 2015

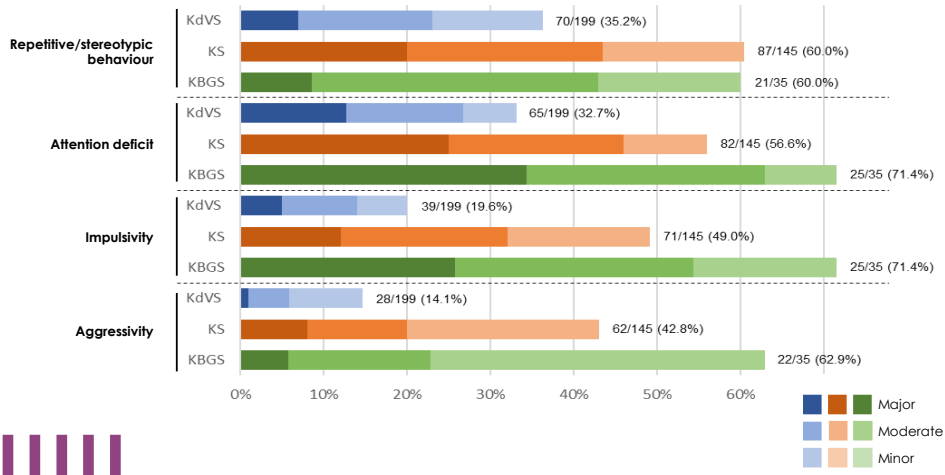
Richness of open-ended answers from families:

f	10.0	Until the age of 6 she had several pneumonias and bronchial problems. She has recovered and is without problems now
m	8.0	Repetitive pneumonia
m	8.0	He had asthma triggered by respiratory infections from birth to around 9 years old. This subsided as he got older and is now completely gone.
m	11.0	Re-occuring pneumonia
f	4.5	Inflammation des bronches peut être due à un reflux
f	1.0	Classée comme asthme du nourrisson après 3 épisodes de bronchiolite. Traitement au flixotide d'octobre à mars
f	21.0	Système respiratoire fragile avec bronchite et laryngites
m	3.3	Broncopneumopatia cronica, ricoverata 10/12/2010 per 13 giorni in rianimazione per insufficienza respiratoria. Successivamente bronchiti ricorrenti [...].

Koolen-de Vries, Kleefstra (KS) and KBG (KBGS) syndromes - Behavioural problems

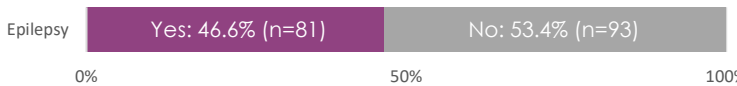
A lower frequency of behavioural problems was reported in GenIDA for KdVS (54%), compared to KS (70%) and KBGS (80%).

The KS had the highest score for repetitive/stereotypic behaviour, while the KBGS had the highest scores for attention deficit, impulsivity and aggressivity:



KdVS / Epilepsy (study conducted in collaboration with Dr Nicole Collot, expert physician in pharmacovigilance):

The frequency, type of epilepsy and age of onset are consistent with previously published data[8]:



Study of **the frequency of use of different anti-epileptic drugs, their perceived efficacy and associated side effects**:

	Drug use report	Good efficiency		Secondary effects	
		n/total	%	n/total	%
Anti-epileptic drugs					
Levetiracetam	30	20/30	67%	14/30*	47%
Valproate	24	20/24	83%	10/24	42%
Oxcarbazepine	13	11/13	85%	1/13	8%
Topiramate	6	3/6	50%	2/6	27%
Carbamazepine	5	2/5	40%	3/5*	60%
Lamotrigine	5	4/5	80%	0/5	
Zonisamide	4	4/4		0/4	
Phenobarbital	3	2/3		0/3	
Lacosamide	2	2/2		0/2	
Phenytoin	2	2/2		0/2	
ACTH	1	0/1		1/1	
Vigabatrin	1	1/1		0/1	
Benzodiazepines					
Clobazam	7	6/7	86%	4/7	57%
Diazepam	4	4/4		1/4*	
Midazolam	3	3/3		0/3	
Clonazepam	2	1/2		1/2*	
Lorazepam	2	2/2		1/2	
Others	6	2/6		0/6	

* Major adverse effects reported

The two most commonly used anti-epileptic drugs are Levetiracetam and Valproate, with a trend (to be verified) towards better efficacy and lower adverse effects for Valproate.
Oxcarbazepine, although less used, seems to have a good profile.

[8]Myers et al. 2017

Collaborations

GenIDA was initially developed in collaboration with Radboud University Medical Centre, Nijmegen, The Netherlands (Pr Tjitske Kleefstra, Dr David A. Koolen, Dr Charlotte Ockeloen, Pr Bert B. A. de Vries).

GenIDA collaborates with many professionals in order to develop new cohorts and to study the data thus collected in order to bring out new information of medical interest, allowing for better patient care (non-exhaustive list):

- Murdoch Children's Research Institute, Melbourne, Australia (Pr. Angela T. Morgan);
- Royal Manchester Children's Hospital, Manchester, UK (Pr. Bronwyn Kerr);
- St Georges Hospital Medical School, London, UK (Pr. Michael Patton);
- The Goldschleger Eye Institute, Dept of Ophthalmology, Sheba Medical Center, Tel Aviv University, Israel (Dr. Daphna Landau Prat);
- Dijon University Hospital (Pr Laurence Faivre-Olivier);
- Lille University Hospital (Pr Jamal Ghoumid, Dr Thomas Smol, Dr Roseline Caumes);
- Hospices Civils de Lyon (Dr Nicolas Chatron);
- Montpellier University Hospital (Pr David Geneviève, Dr Valentin Ruault);
- APHP, Paris (Pr Alain Verloes);
- Strasbourg University Hospital (Dr Amélie Piton, Dr Romain Coutelle, Dr Anne de Saint-Martin, Dr Elise Schaefer, etc.).

2nd GenIDA Scientific Advisory Board, ESHG Copenhagen, June 2017

Families, professionals, you want to participate?

It is easy > go to **https://genida.unistra.fr/**
from a computer or a tablet

The registration procedure and access to the GenIDA study are presented in this video: https://youtu.be/-8eJD9Chbe4

Families, create your personal space and read the consent form to be able to participate in the GenIDA study by providing and regularly updating medical and quality of life information about the patient.

Consent to be given at the time of registration.
Your data are anonymised and hosted securely.
Project declared to the French Commission on Information Technology and Liberties (n°1907912) and approved by the Ethical Evaluation Committee of INSERM - CEEI-IRB (n°16-338).

What is the benefit to the participating families?

As soon as the number of participants in a cohort is sufficient, we make the anonymised results of our analyses available.
The larger the number of participants, the better the quality and usefulness of the results for families and professionals (doctors, researchers, etc.).

You can download a single PDF containing all your answers, which can be added to the patient's medical file.

Professionals (medical and paramedical), create your profile and select your cohort(s) of interest in order to participate in the GenIDA study and access the medical data collected.

Access to the visualization of the results of our statistical analyses, according to your cohorts of interest.

More complete access to anonymised patient records upon request.

Secure data storage and exchange in compliance with the GDPR and French regulations.

Use GenIDA to:

- generate new and medically significant knowledge that can be translated into improved patient management (scientific publications, recommendations / guidelines, etc.);
- submit additional specific questions to subsets of patients;
- recruit patients for ethically approved research projects or clinical studies (subject to approval by GenIDA's Scientific Advisory Board).

Bibliography:

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• *Coutelle, Boedec, […], Geneviève, Burger & Mandel (2022). The impact of lockdown on young people with genetic neurodevelopmental disabilities: A study with the international participatory database GenIDA.* ***BMC Psychiatry****, 22:572*

• *Burger, Colin, […], Piton, Koolen & Mandel (2022). GenIDA: an international participatory database to gain knowledge on health issues related to genetic forms of neurodevelopmental disorders.* ***Journal of Neural Transmission,*** *doi.org/10.1007/s00702-022-02569-3*

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Our partners

French rare diseases networks

Our partners

Our institutional partners

French and international patient associations (non-exhaustive list)

Contact us

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Genida International Project

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