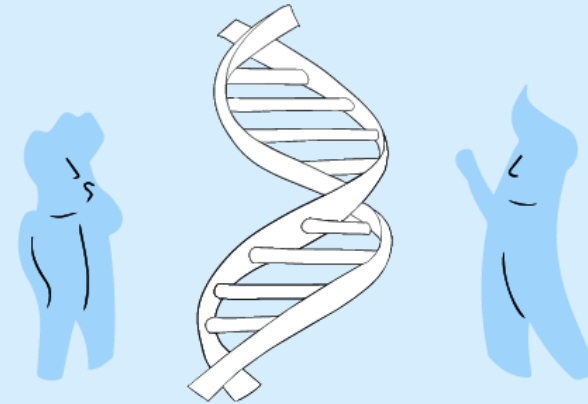


Kleefstra Syndrome Scientific Conference 2023

Moving towards the uptake and use of Artificial Intelligence
(AI) in research and clinical work



GenIDA participatory database

- GENetic forms of Intellectual Disability and Autism spectrum disorders -



Dr. Pauline Burger
Kleefstra Syndrome Scientific Conference
Ljubljana, June 1st 2023



AnDDI-Rares



GenIDA - GENetics of Intellectual Disabilities and Autism spectrum disorders

GenIDA is an **international participatory patient registry** on the manifestations (medical, behavioural, etc.) and natural history of **genetic forms of intellectual disability (ID) with or without ASD or epilepsy**

Purpose

Accelerate knowledge on genetic forms (~1500) of intellectual disability, autism and epilepsy **to improve patient care and families' information**

Who is concerned

> people with manifestations of ID and/or autism spectrum disorder (ASD) with a diagnosed genetic origin + their families
> doctors, researchers and other health professionals involved in the management and the care of the disease

TO LOG IN English

HOME PRESENTATION CONTACT

GENIDA

Genetic of Intellectual Disability and Autism Spectrum Disorders

Accelerate knowledge about genetic forms of Intellectual disability, autism and epilepsy by increasing participation:
- of people with autism, their families and the concerned associations.
- doctors, researchers and other professionals involved in the management of the disease

HELP US HELP YOU

1. For who?
One of your children, brothers, sisters or close relatives has been detected as having an intellectual disability (ID) and/or autism spectrum disorder (ASD) with a diagnosed genetic origin or You are at identified risk of a pathology such as Fxxtas or Valproate effect.

2. Why?
You wish to help to better know and understand the rare disease that concerns you in order to better treat it.

3. How?
You are willing to provide and update medical information about the affected person(s), data that will be anonymized.

SUBSCRIBE

1737 active users (>20% answers)

▶ EHMT1 (Kleefstra syndrome)	146	▶ 17q21.31 deletion (KdV syndrome)	203
▶ DDX3X	53	▶ 9q34.3 deletion (Kleefstra syndrome)	115
▶ ANKRD11 (KlB syndrome)	51	▶ Xq28 dup. (MECP2 dup. syndrome)	47
▶ KANSL1 (KdV syndrome)	48	▶ VALDEV project (non-genetic)	39
▶ MED13L	46	▶ 22q11.2 deletion (DiGeorge syndrome)	20

Search gene or genetic defect Example: KANSL1

GenIDA - GENetics of Intellectual Disabilities and Autism spectrum disorders

Initiated in 2016 by Jean-Louis Mandel (Kavli prize 2022 in neuroscience) and run by a project manager (Pauline Burger since Sept. 2020).

Was initially developed in collaboration with Radboud University Medical Centre, Nijmegen, The Netherlands (Pr Kleefstra, Dr Koolen, Dr Ockeloen, Pr de Vries) and collaborates with >200 professionals to develop new cohorts and to study the data collected to bring out new information of medical interest, allowing for better patient care.

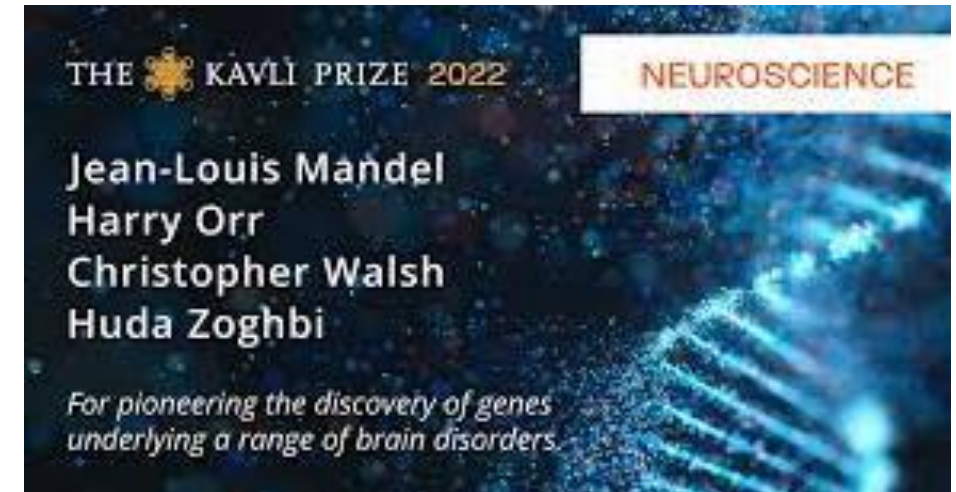
Collaborates with national and international patient/family associations

GenIDA's international Scientific Advisory Board meets annually at the conference of the European Society of Human Genetics (Next SAB: June 12th, 2023, Glasgow)

Is part of the French RaDiCo-Rare Disease Cohorts program (INSERM)

Ethical approval: project declared to the CNIL (n°1907912) and approved by the INSERM Ethical Evaluation Committee - CEEI-IRB (n°16-338)

Fundings: Unistra foundation, Fondation Jérôme Lejeune, GIS-Autisme, USIAS (University of Strasbourg Institute of Advanced Studies / IDEX)



GenIDA - GENetics of Intellectual Disabilities and Autism spectrum disorders

Main questionnaire

GenIDA questionnaire (20 Oct. 2016 release).

You answered to 0.0% of the questionnaire.

Open questions

1/46. What is the major problem that affects your relative's everyday life (quality of life)?
(Even if it seems unrelated to the genetic condition.)

2/46. What is the major behavioral / cognitive problem that affects your relative's and the family life?

3/46. Did your relative suffer a major medical problem or discomfort following specific medication?
(Specify drug and length of treatment.)

4/46. What are the major medical problems that occurred until now?
(Indicate at what age for each)

5/46. Please state your relative's strengths

Weight / Height

Pregnancy / Early life / Personal care

Intellectual disability and Autism aspects

Physical and neurological problems

Sensory problems

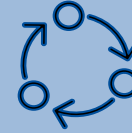
Other problems



Detailed health and behavioural data collection



Statistical data analysis and information synthesis



Data sharing with patients/families & professionals



Interaction between patients/families & professionals



Generation of novel and medically significant knowledge

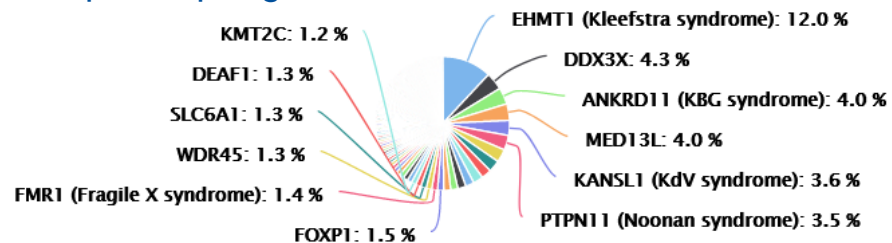
- Online questionnaire <https://genida.unistra.fr/>
- Available in French, English, Dutch, German, Portuguese, Italian, Spanish & Greek (soon : in Turkish, Romanian and Bulgarian)
- 46 major questions including 5 free text questions and 41 MCQs with sub-questions
- Medical information, behaviour, quality of life, adverse effects of treatment, etc.
- Completed and updated by the parents, possibly by the affected person
- Anonymised data

GenIDA - Cohorts

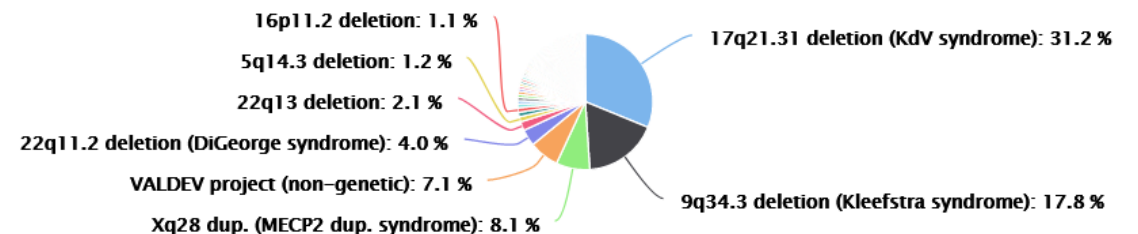
- ≥ 1800 participants having filled in the questionnaire
- > 60 nationalities represented
- ≥ 220 professionals
- approximate recruitment rate of 30 participants per month
- international participation across all cohorts

COHORT	GENE / GENETIC DEFECT	NB OF PART.	MAIN PROFESSIONALS AND ASSOCIATIONS INVOLVED
Koolen-de Vries syndrome	<i>KANSL1</i> & 17q21.31 del.	251	D. A. Koolen – Nijmegen, NL; KdVS Foundation, Kool Kid Alliance, KdVFrance
Kleefstra syndrome	<i>EHMT1</i> & 9q34.3 del.	207	T. Kleefstra, J. Kummeling – Nijmegen, NL; Kleefstra Syndrome Community, KS France, Idefine
Rasopathies	<i>PTPN11</i> , <i>BRAF</i> , <i>KRAS</i> , etc.	66	M. Patton – London, UK, B. Kerr – Manchester, UK, A. Verloes – Paris, FR; Noonan Syndrome Association UK, Association Française Syndrome de Costello et CFC
DDX3X	<i>DDX3X</i>	53	V. Ruault, D. Geneviève – Montpellier, FR, A.T. Morgan – Parkville, AU; Xtraordinaire, section DDX3X
KBG syndrome	<i>ANKRD11</i>	53	C. Ockeloën – Nijmegen, NL
MED13L	<i>MED13L</i>	46	J. Ghoumid, T. Smol, R. Caumes – Lille, FR; MED13L France
SETD5	<i>SETD5</i>	32	N. Chatron – Lyon, FR
Wiedemann-Steiner syndrome	<i>KMT2A</i>	32	B. Durand – Strasbourg, FR
DYRK1A syndrome	<i>DYRK1A</i>	32	A. Piton – Strasbourg, FR; DYRK1A UK Community
White-Suton syndrome	<i>POGZ</i>	30	L. Faivre – Dijon, FR; White Sutton France

Participation per gene:



Participation per genetic defect (CNV):



GenIDA – Kleefstra syndrome cohort

GenIDA - KS cohort (May 2023)



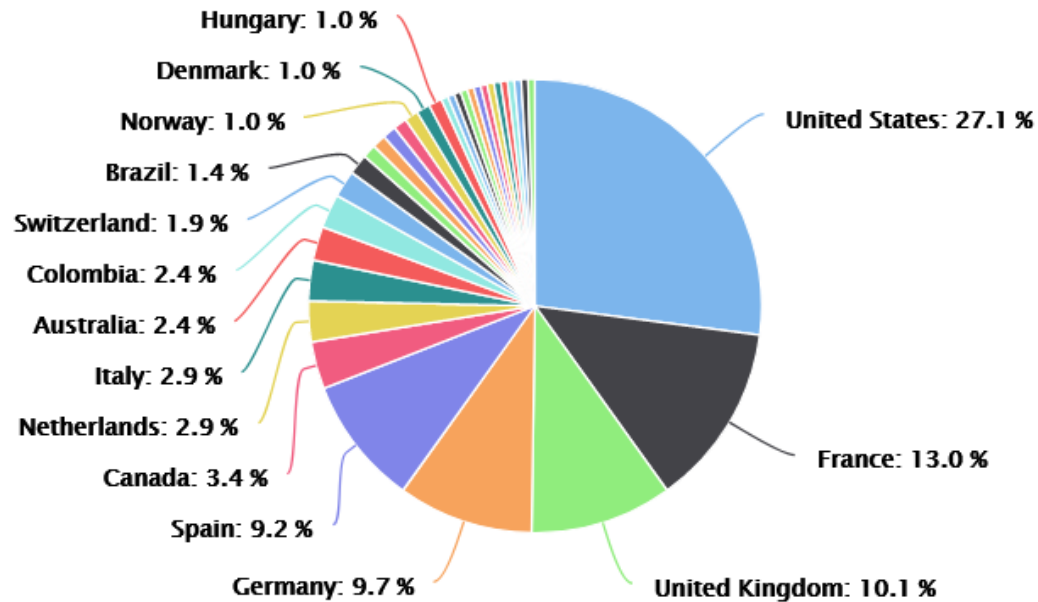
207 participants, including 110 women & 97 men



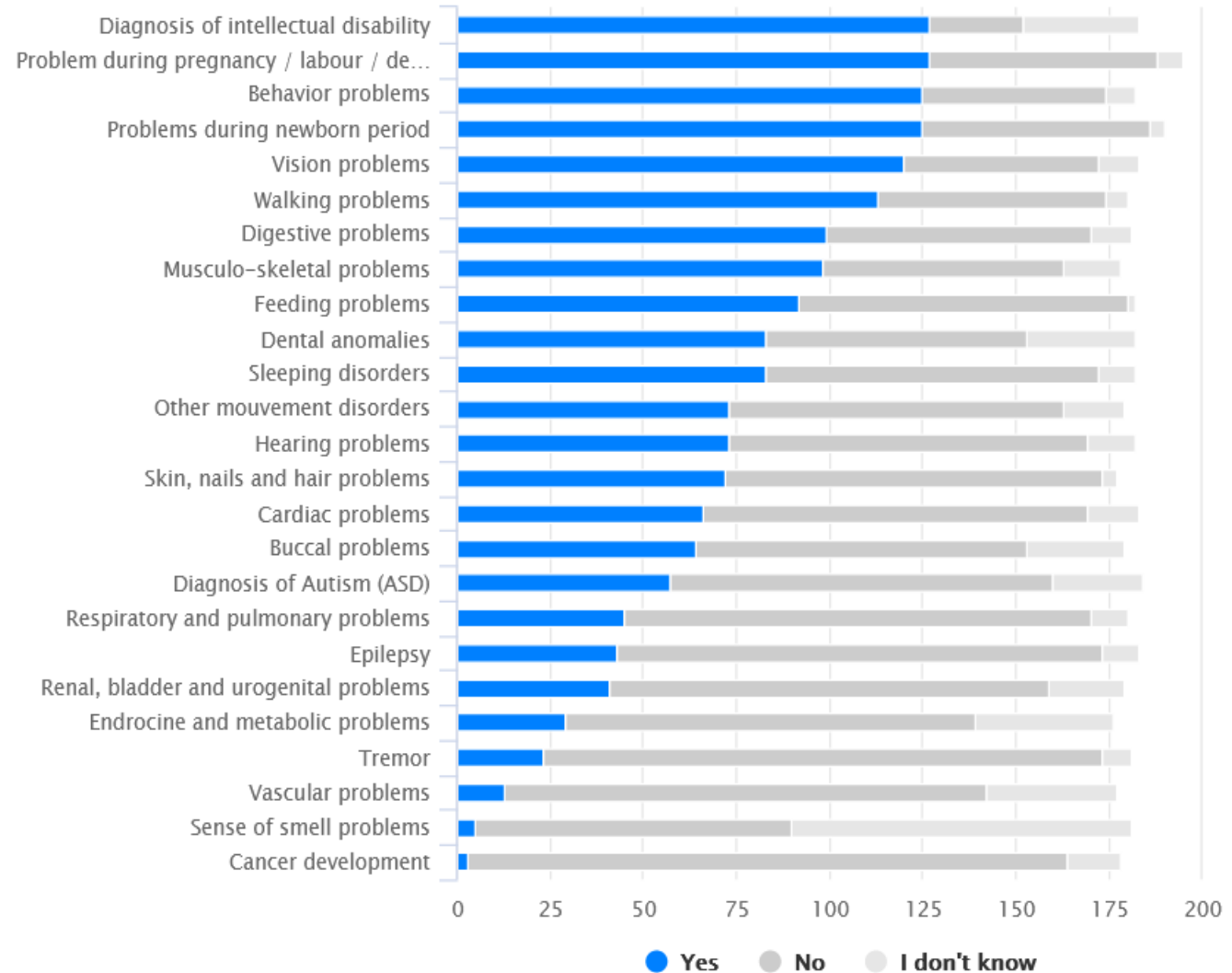
51 patients present the 9q34.3 deletion, & 78 carry a pathogenic variant in *EHMT1* (& 38% did not specify)

Mean age: 15 years

Country of origin:

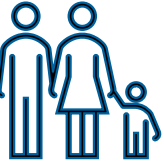


Kleefstra syndrome cohort – Overview May 2023



GenIDA - Recruitment of patients

Direct contact with national and international patient' associations (participation to family meetings, booth in the associative corner of some congresses, etc.)



Flyers available in English & French (paper versions) + Dutch, German, Portuguese, Italian, Spanish and Greek e-versions

Presentation of the registry
Facts and figures on GenIDA
Examples of data collected
Proofs of concept (KdVS and KS)
Presentation of collaborations
How and why to participate

Posters for clinicians' waiting rooms, and rare disease centres, etc.



Genida International Project



@GenIDaproject

Regular publications in French, English, Spanish: call for participation, results, etc.

> 1,3 K followers (FR, US, UK, Australia, The Netherlands, Canada, etc.)



Genida project

Videos in English and in French: presentation of the project, tutorial for participating

> 1550 viewings

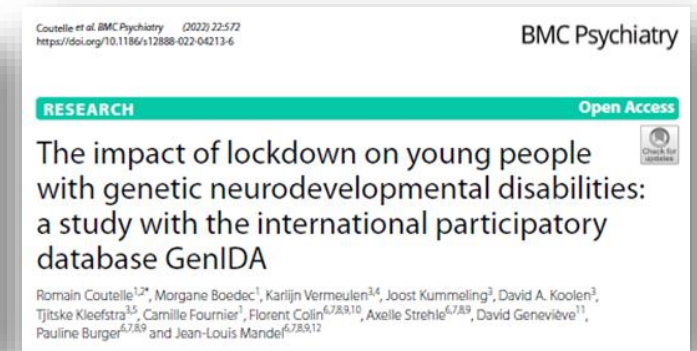
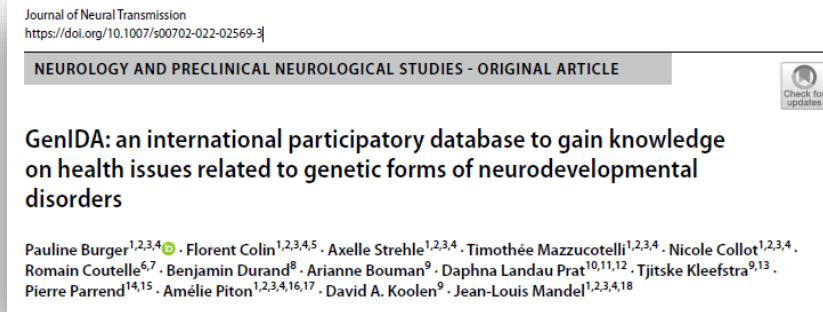
GenIDA – Participating professionals

Use GenIDA to:

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



Publications:



- Shalev et al. *Ocular manifestations in Koolen-de Vries syndrome – an international study*, **Canadian Journal of Ophthalmology**, under review
- Bouman et al. *Prevalence and radiological characteristics of scoliosis in Koolen-de Vries syndrome: An international retrospective cohort study*, **American Journal of Medical Genetics, A**, under review

Data collected to feed the drafting of national and international guidelines:

French guidelines: DYRK1A syndrome (2021), MED13L syndrome (2022), Koolen de Vries syndrome (*in prep.*), Wiedemann-Steiner syndrome (*in prep.*).

Professional clinical guidelines for Kleefstra syndrome (*in preparation*).



GenIDA - Koolen de Vries syndrome (KdVS)

Caused by the 17q21.31 deletion or by a pathogenic variant in *KANSL1*

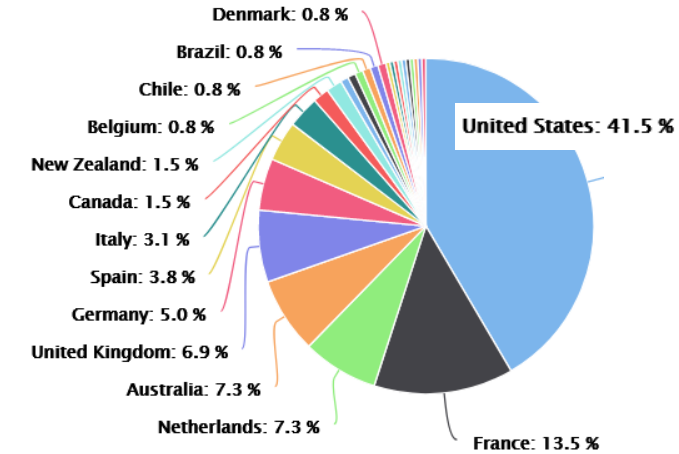
Main features: ID, hypotonia, suggestive facial features, variable frequency of epilepsy, congenital anomalies and various neuromuscular and orthopaedic manifestations

GenIDA - KdVS cohort (May 2022)

 **237 participants**, including  **121 women** &  **116 men**

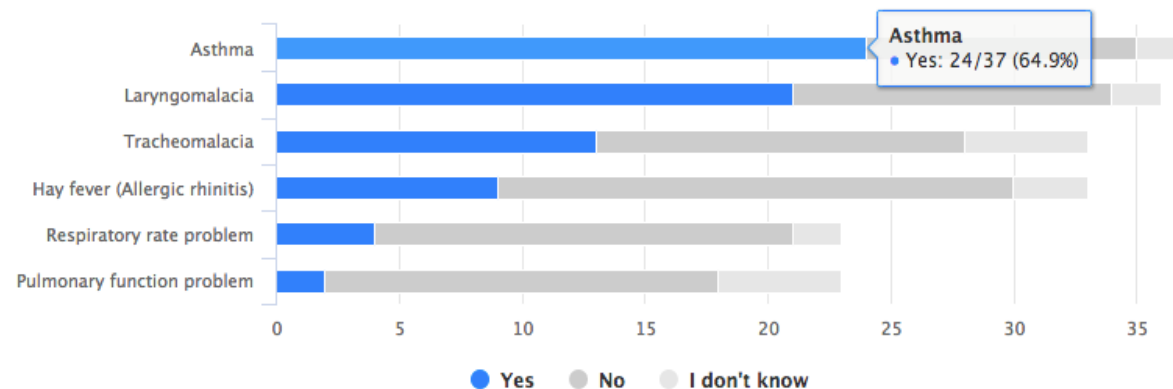
197 patients (83%) present the **17q21.31 deletion**, and **40** (17%) carry a **pathogenic variant in *KANSL1***

KdVS in GenIDA (May 2023):



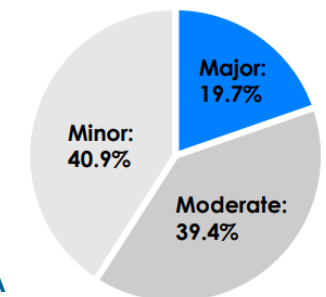
Respiratory problems briefly mentioned in the Unique guidelines and single mention of pneumonia in Koolen et al. 2016

No mention in OMIM, GeneReviews, or Zollino et al. 2015



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

Severity of respiratory problems reported in GenIDA



GenIDA – KdVS: Respiratory problems

No questions were initially asked about respiratory infections/pneumonia >> information reported by parents when answering open-ended questions:

Language variety for completion of the questionnaire!

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-occurring 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 [...].

Reported respiratory problems are new and medically significant information

→ **Important to understand the underlying mechanism in order to make recommendations for the prevention / treatment of these comorbidities.**

GenIDA – KdVS: Epilepsy

The frequency (40-50%) of epilepsy and age of onset are consistent with published data:



GenIDA provides detailed information on the types of epilepsy found in individuals with KdVS (absent in Zollino et al. 2015, Koolen et al. 2016).

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

Anti-epileptic drug	Drug use report	Good efficiency		Secondary effects	
		n/total	%	n/total	%
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	
Phénytoin	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

GenIDA - KdVS cohort (2020)

81 epileptic patients of which 14 reported no medication use (spontaneously resolved epilepsy or rare seizures) & 13 without information.

The two most commonly used anti-epileptics are Levetiracetam and Valproate, with a trend (to be verified) towards better efficacy and lower adverse effects for Valproate, a trend already observed by Myers et al. in 2017 in a smaller cohort.

collab. Dr N. Collot, expert physician in pharmacovigilance

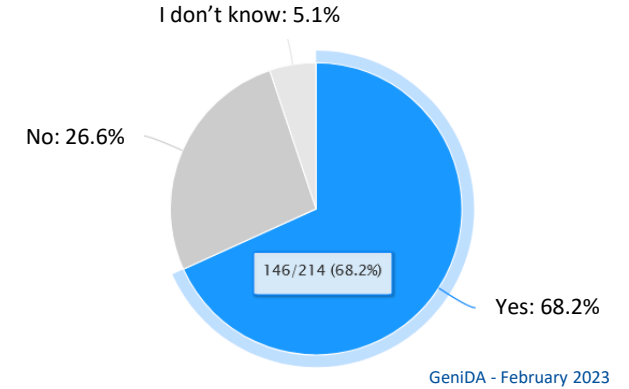
GenIDA – Ancillary research: Ophthalmological manifestations in KdVS



To deepen insight on known ophthalmological manifestations of KdVS (occurrence and frequency of ocular and oculofacial malformations) while uncovering novel ocular associations.



Call for participation and survey available in English and French



GenIDA (August 2021 – February 2022)



67 participants, including  **33 women** &  **34 men** – 53 participants (79.0%) were under 18y

International cross-sectional study:

- ocular survey (ocular symptoms, findings reported by an ophthalmologist, surgical interventions),
- medical records: ophthalmic exams, doctor visit summaries, test results, clinical photographs

Ocular abnormalities are a common finding in patients with KdVS

- common findings include amblyopia, strabismus, refractive errors, and upper eyelid ptosis,
- a possible association with rare **retinal disorders** (retinal pigment abnormalities, Sjögren's reticular dystrophy) was observed for the first time,
- a strong correlation of **nasolacrimal disorders** was described in KdVS for the first time, with a higher rate of congenital nasolacrimal duct obstruction as well as a more complex etiology

> Thorough ophthalmic evaluation is warranted in all KdVS patients for adequate treatment, vision preservation, and prevention of irreversible ocular and visual system insults (at initial diagnosis, or at 4-6 months of age for diagnosed newborns)

Acknowledgements

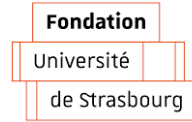
For more information and to access the data:

Contact: genida@igbmc.fr

Website: <https://genida.unistra.fr/>



- Fundings -



- Partners -



- Collaborators -

All the clinicians, researchers, etc. involved in the analysis of the GenIDA data

- Patients associations -

All the GenIDA participants - the patients and their families - and the patients' associations, as well as the rare diseases networks



Thank you for you attention