GenIDA participatory database
- GENetic forms of Intellectual Disability and Autism spectrum disorders -

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

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

Participation per gene:

- KMT2C: 1.2%
- DEAF1: 1.3%
- SLC6A1: 1.3%
- WDR55: 1.3%
- FMR1 (Fragile X syndrome): 1.4%
- FOXQ1: 1.5%
- EHMT1 (Kleefstra syndrome): 12.0%
- DDX3X: 4.3%
- ANKRD11 (KBG syndrome): 4.0%
- MED13L: 4.0%
- KANSL1 (KvdV syndrome): 3.6%
- PTPN11 (Noonan syndrome): 3.5%

Participation per genetic defect (CNV):

- 16p11.2 deletion: 1.1%
- 5q14.3 deletion: 1.2%
- 22q13 deletion: 2.1%
- 22q11.2 deletion (DiGeorge syndrome): 4.0%
- VALDEV project (non-genetic): 7.1%
- Xq28 dup. (MECP2 dup. syndrome): 8.1%
- 17q21.31 deletion (KvdV syndrome): 31.2%
- 9q34.3 deletion (Kleefstra syndrome): 17.8%
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:

- United States: 27.1%
- France: 13.0%
- United Kingdom: 10.1%
- Germany: 9.7%
- Spain: 9.2%
- Netherlands: 2.9%
- Italy: 2.9%
- Australia: 2.4%
- Brazil: 1.4%
- Switzerland: 1.9%
- Colombia: 2.4%
- Denmark: 1.0%
- Hungary: 1.0%

Kleefstra syndrome cohort – Overview May 2023

- Diagnosis of intellectual disability
- Problem during pregnancy / labour / delivery
- Behavior problems
- Problems during newborn period
- Vision problems
- Walking problems
- Digestive problems
- Musculo-skeletal problems
- Feeding problems
- Dental anomalies
- Sleeping disorders
- Other movement disorders
- Hearing problems
- Skin, nails and hair problems
- Cardiac problems
- Buccal problems
- Diagnosis of Autism (ASD)
- Respiratory and pulmonary problems
- Epilepsy
- Renal, bladder and urogenital problems
- Endocrine and metabolic problems
- Tremor
- Vascular problems
- Sense of smell problems
- Cancer development

Mean age: 15 years

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)
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  @GenIDApject

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
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:

- 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

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.

Colin*, Burger* et al. GenIDA, an international participatory study of medical and natural history data in genetic forms of neurodevelopmental disorders: novel observations in 237 patients with Koolen-de Vries syndrome, Genetics in medicine, 2023
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!

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

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.

Colin*, Burger* et al. GenIDA, an international participatory study of medical and natural history data in genetic forms of neurodevelopmental disorders: novel observations in 237 patients with Koolen-de Vries syndrome, Genetics in medicine, 2023
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:

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.

* Major adverse effects reported

collab. Dr N. Collot, expert physician in pharmacovigilance

Colin*, Burger* et al. GenIDA, an international participatory study of medical and natural history data in genetic forms of neurodevelopmental disorders: novel observations in 237 patients with Koolen-de Vries syndrome, Genetics in medicine, 2023
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

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)

Shalev et al. Ocular manifestations in Koolen-de Vries syndrome – an international study, Canadian Journal of Ophthalmology, under review
Acknowledgements

For more information and to access the data:

Contact: genida@igbmc.fr
Website: https://genida.unistra.fr/

- Fundings -
- Partners -
- Patients associations -

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

Thank you for your attention