GENIDA
AIDEZ-NOUS À VOUS AIDER

GENIDA

GENetic forms of Intellectual Disability and Autism spectrum disorders

Dr. Pauline Burger & Pr. Jean Louis Mandel

ERN ITHACA Board Meeting
December 11, 2020

1. The GenIDA project

GENetics of Intellectual Disabilities and Autism spectrum disorders

What ?

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

Why ?

Accelerate knowledge on genetic forms (~1000) of intellectual disability, autism and epilepsy **to improve management**

Who may be concerned ?

> people with manifestations of ID and/or autism spectrum disorder (ASD) with a diagnosed genetic origin (or foetal exposure to Valproate/Depakine)

> doctors, researchers and other professionals involved in the management and the care of the disease.

1. The GenIDA project

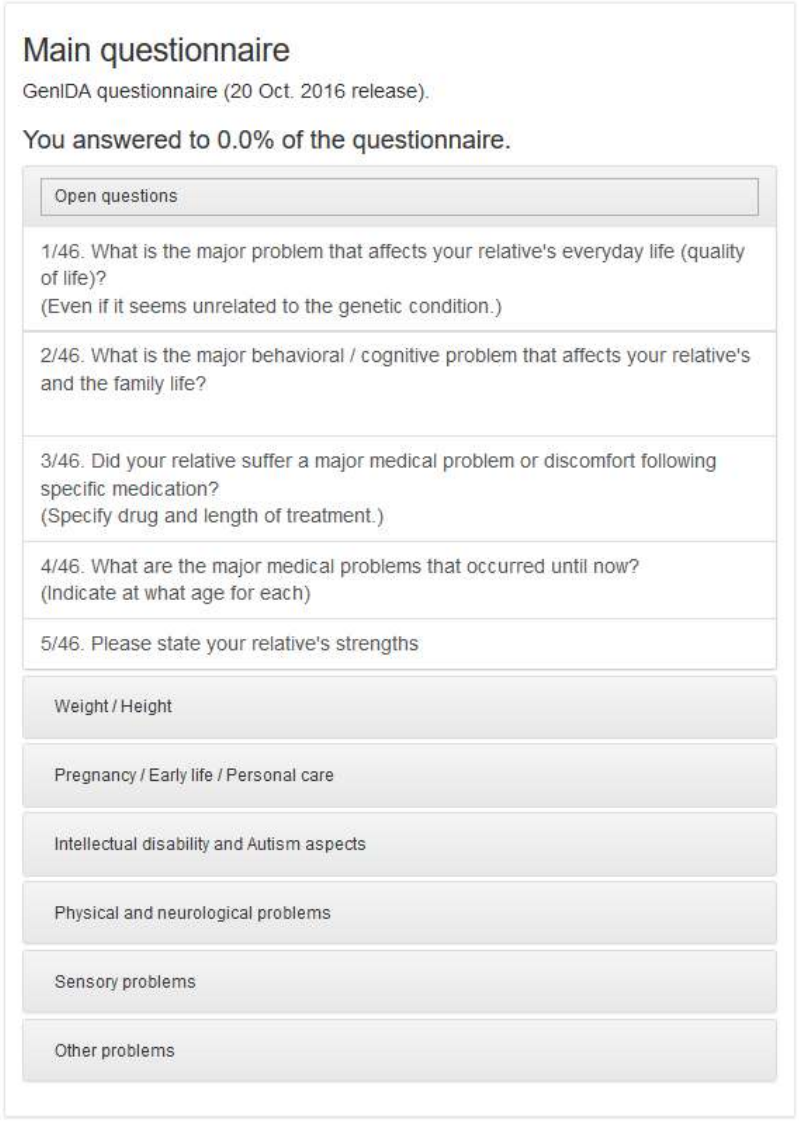
GENetics of Intellectual Disabilities and Autism spectrum disorders

- Initiated in 2016 by Prof. Jean-Louis Mandel and Dr Florent Colin (project leader), Dr Pauline Burger (project leader since September 2020)
- Funding: USIAS (University of Strasbourg Institute of Advanced Studies/IDEX), Fonds Roche pour la médecine personnalisée/Fondation Unistra, Fondation Jérôme Lejeune, GIS-Autisme
- Project declared to the CNIL (n°1907912) and approved by the INSERM Ethical Evaluation Committee - CEEI-IRB (n°16-338)
- Is one of the 13 cohorts selected in the RaDiCo (Rare Disease Cohorts) program
- Close collaboration with D. Koolen and T. Kleefstra, Radboud University, Nijmegen, The Netherlands
  Other collaborations in development
  Meeting of the International Scientific Board at the annual conference of the *European Society of Human Genetics*
- Partnership with patient/family associations

2ème conseil scientifique de GenIDA, ESHG Copenhague, Juin 2017

1. The GenIDA project

GENetics of Intellectual Disabilities and Autism spectrum disorders



How ?

- Online questionnaire https://genida.unistra.fr/
- French, English, Dutch, German, Portuguese
- 46 major questions including 5 free text and the other MCQs with sub-questions
- Medical information, behaviour, quality of life, adverse effects of treatment, etc.
- Informed and updated by the parents, possibly by the affected person.
- Anonymised data.

2. The GenIDA project

Today

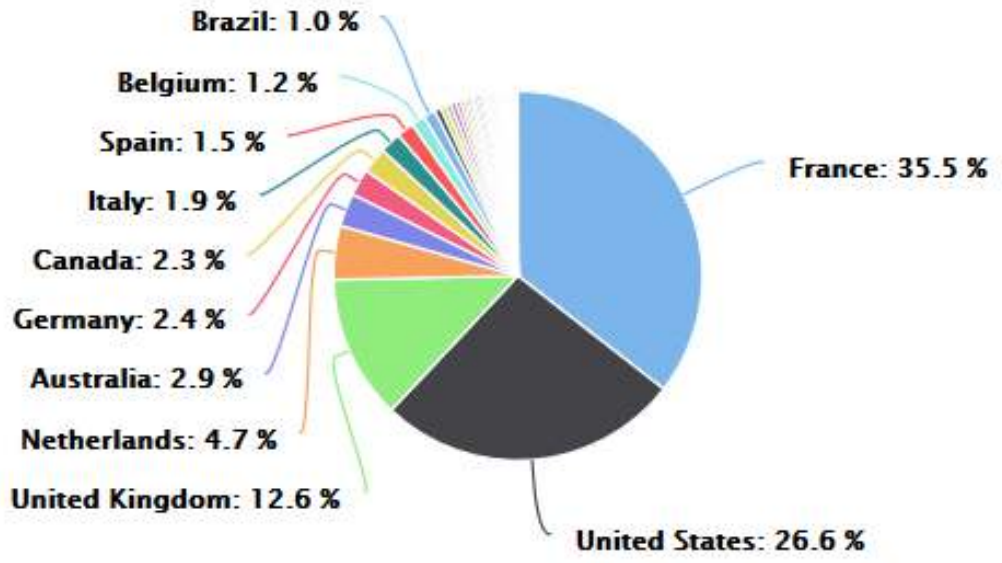
Today

- 991 active participants (parent of an affected individual with a diagnosed gene defect or CNV, who has filled the questionnaire on behalf of the patient, with at least 20% of questions answered*)
- 146 professionals

- 646 listed genes
- 129 listed CNVs

> frequent updates

Patients' countries of origin

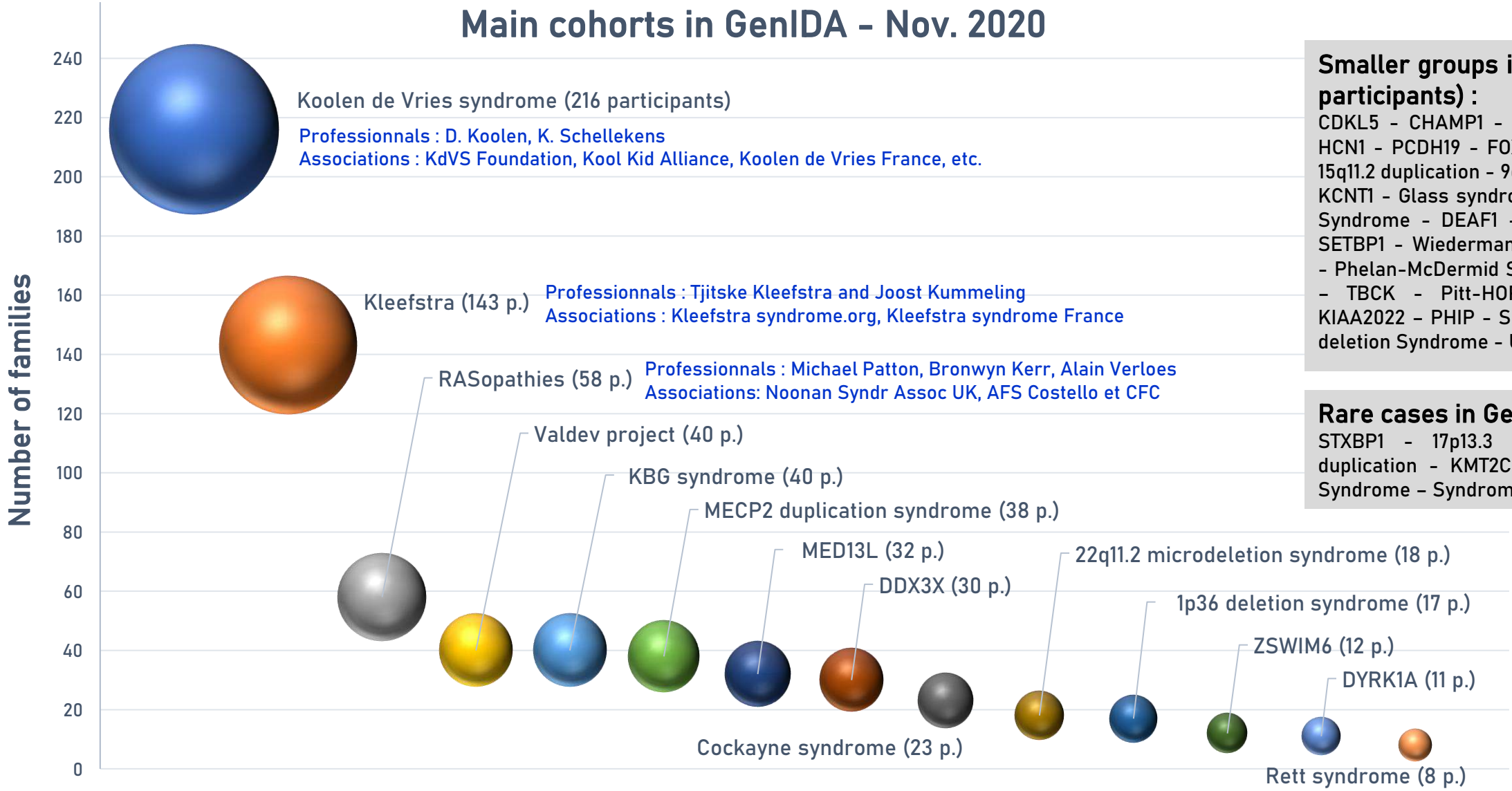


44% of registered parent participants are not considered active (did not complete the questionnaire or only answered a few questions).
> The ergonomics of the website is being improved

* ~90% of them have filled > 50% of questions, 60% have completed the questionnaire

2. The GenIDA project

Today



Smaller groups in GenIDA (2 to 6 participants) :

CDKL5 - CHAMP1 - FOXG1 - GATAD2B - HCN1 - PCDH19 - FOXP1 / 3q13 deletion - 15q11.2 duplication - 9q33.3p34.11 - GRIN2B KCNT1 - Glass syndrome - TRIP12 - Down Syndrome - DEAF1 - DHX30 - KCNQ2 - SETBP1 - Wiedermann-Steiner Syndrome - Phelan-McDermid Syndrome - SYNGAP1 – TBCK - Pitt-HOPKINS Syndrome - KIAA2022 – PHIP - SETD5 – TRIO - 16p11.2 deletion Syndrome - USP7 - SLC6A1

Rare cases in GenIDA :

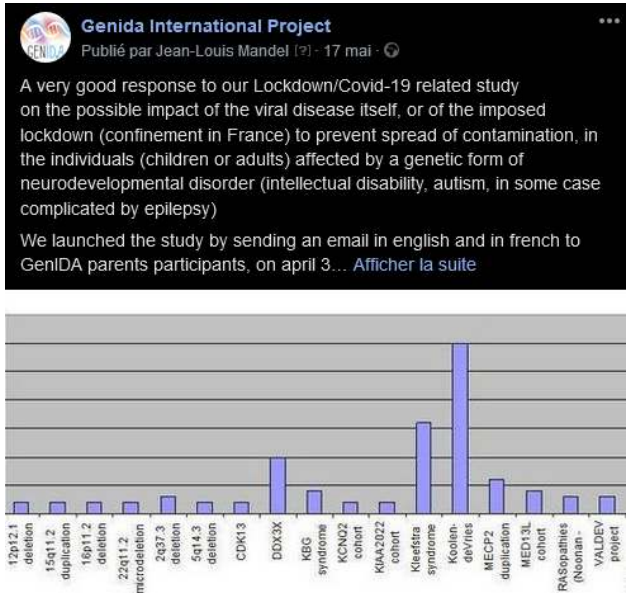
STXBP1 - 17p13.3 triplication - 1q21.1 duplication - KMT2C - MYT1L - 48,XXXY Syndrome – Syndrome du Cri du chat

3. Social networks

Facebook - Genida International Project

@GenIDAproject

Results of the lockdown study



Creation of the Youtube channel

15 publications since January 2020 in English and French
845 followers (compared with 638 in mid-June 2019)
> FR 247, US 236, UK 84, Australia 31, Netherlands 27, Canada 21, Germany 19
… a total of 790 likes + comments and shares

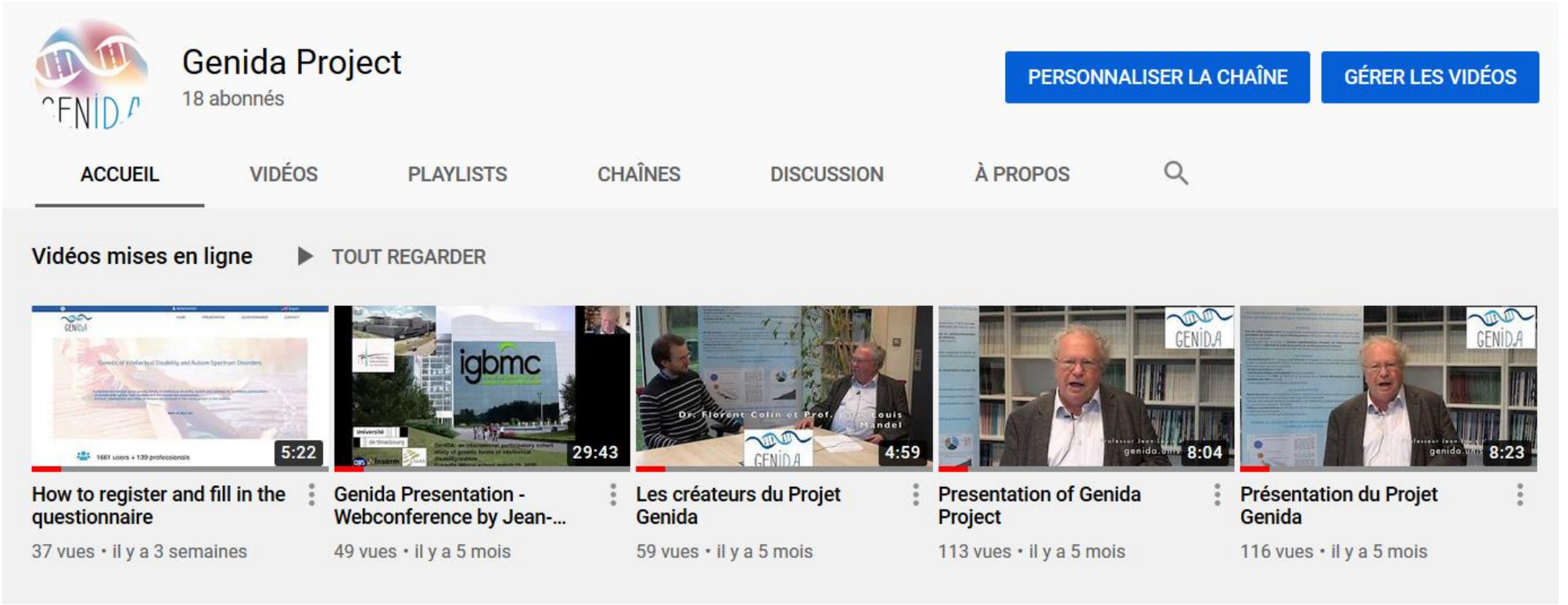
3. Social networks

Youtube - Genida Project

Youtube channel « Genida project » created in May 2020 (thanks to our colleague, Prof R. Welter, University of Strasbourg)

5 videos: 3 in English and 2 in French, 21 followers, **> 400 views**

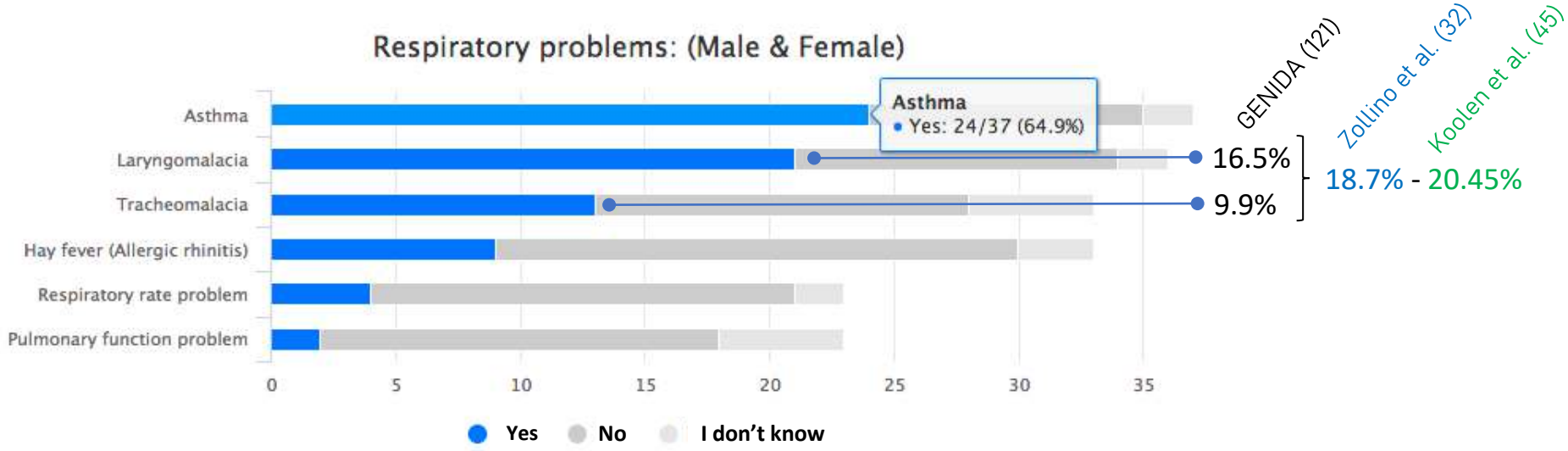
Pr Richard Welter



4. Proof of concept

Koolen de Vries Syndrome (KdVS) - Unexpected events: Pneumonia and Asthma

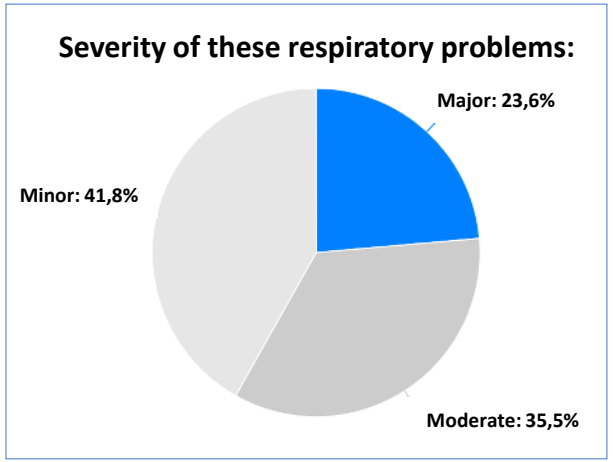
- No mention of asthma, pneumonia, croup or stridor in text in OMIM
- No mention of pulmonary problems in GeneReviews (briefly mentioned in Unique Guidelines)
- Zollino *et al.* 2015 : no mention of lung or any respiratory problems
- Koolen *et al.* 2016 : one mention of pneumonia in the text



GENIDA (121) | Zollino et al. (32) | Koolen et al. (45)

16.5% | 18.7% - 20.45%

9.9%



➡ **Asthma is one of the most commonly reported co-morbidities in GENIDA (for KdVS).**

➡ **Respiratory problems are considered a major problem by many families.**

4. Proof of concept

Koolen de Vries Syndrome (KdVS) - Unexpected events: Pneumonia and Asthma

There were no questions on respiratory infections/pneumonia >> information reported by the parents answering the open-ended questions:

Asthma

m 2.0 RSV virus turned into bronchiolitis/pneumonia and hospitalized for a week at 3 months old. Dx Restrictive Airway Disease (asthma for babies)
f 6.5 ASTHMA AGE 1
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 10.4 … asthma (infant), repeated pneumonias, Otitis media (birth), …
m 12.9 4. Pulmonology Asthma w/ acute exacerbation, Obstructive Sleep Apnea and re-occuring bacterial and viral Pneumonia
f 17.0 Outgrew asthma by age 5
f 18.2 Fl a de l'épilepsie, des problèmes respiratoires (bronchites, laryngites, pneumonie, asthme)
m 27.4 Tumor behind eye age 3. Premature birth. Low birth weight. Jaundice at birth. Allergies. . Lazy eye. Asthma. Hashimoto disease

m 29.4 Ages 2-9 - severe asthma with 2x daily home breathing treatments, several hospitalizations

f 35.3 Asthma, chronic bronchiolitis, chronic croup (in other words, she is often struggling to breathe)

Pneumonia

m 2.0 RSV virus turned into bronchiolitis/pneumonia and hospitalized for a week at 3 months old. Dx Restrictive Airway Disease (asthma for babies)
f 6.9 Laryngomalacia (0-2 years old) Croup/bronchitis/pneumonia (0-ongoing in 2018)
f 7.7 1-5 years old: Immune problems. She seemed to catch every sickness she was exposed to, and had recurring bouts of pneumonia, a few which ended up with her in the hospital.
m 8.0 Many bouts of aspiration pneumonia. Always hospitalised for severe croup requiring nebuliser adrenaline and other medications
m 8.0 Repetitive pneumonia
f 8.3 Last year a pneumonia with hospitalization. With six years of age.
f 10.0 Until the age of 6 she had several pneumonias and bronchial problems. She has recovered and is without problems now
m 10.4 … asthma (infant), repeated pneumonias, Otitis media (birth), …
m 11.0 re-occuring Pneumonia
m 12.9 4. Pulmonology Asthma w/ acute exacerbation, Obstructive Sleep Apnea and re-occuring bacterial and viral Pneumonia
f 18.2 Fl a de l'épilepsie, des problèmes respiratoires (bronchites, laryngites, pneumonie, asthme)
f 24.4 RECURRING COLDS AND CHEST INFECTIONS ONE OF WHICH LED TO PNEUMONIA UNTIL APPROX 10 YEARS OLD

Richness of open-ended answers

Reported respiratory problems are new and medically significant information (related to tracheo / laryngo malacia ?).

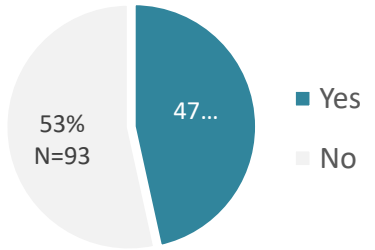
Once the mechanism is better known, guidelines can be proposed for prevention / treatment.

4. Proof of concept

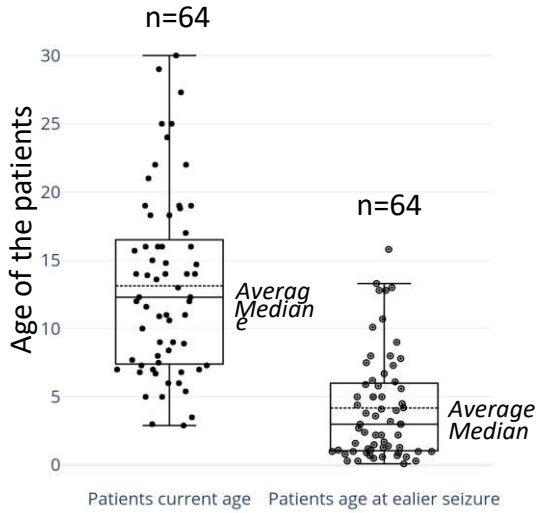
Koolen de Vries Syndrome (KdVS) - Epilepsy as reported by families

Frequency, type of epilepsy and age at onset are coherent with previously published data (Myers et al. 2017).
We can report on the frequency of use of various antiepileptic drugs, their **perceived efficacy** and associated **adverse events**.
The two mostly used anti-epileptic drugs were Levetiracetam and Valproate, with a trend to better efficacy and lower adverse events for Valproate. Oxcarbazepine although less used, appears with a good profile. **Open text answers are a rich source of observations on responses to these drugs.**

Proportion of epileptic patients (n=174)

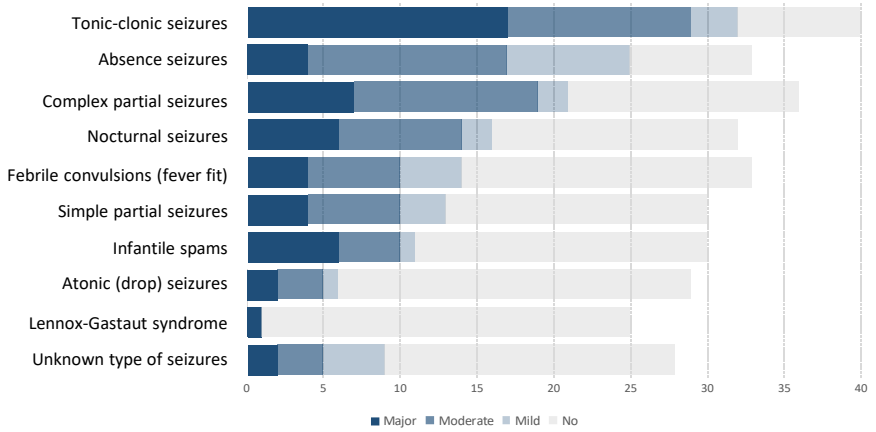


Age of onset, from 64 well described patients



Subtype of epilepsy and perceived severity

(only the last answer available for a given patient is currently considered ; "I don't know" answers are excluded).



f 13.8 K. was put on **Keppra** after suffering her first seizure at 12 y (focal onset seizure, which developed into a generalized tonic clinic seizure). **Keppra** was effective at holding off seizure activity, however, she developed a pervasive stutter! .... we switched her to **Clobazam** . The stuttering stopped, but we encountered massive weight gain in a short period of time. We weaned her off and she is now taking **Zonegran** and doing great, she has lost some of the weight she gained previously

f 19.2 la **micropakine** lui a fait prendre plus de 10 kg en un an. Le médecin a alors prescrit du **Keppra** qui a eu des effets secondaires sur ses muqueuses labiales dès le début du traitement. Ce traitement a été arrêté ... Prend maintenant de l'**Epitomax**.

m 11.2 Taking **Keppra** for seizures was difficult. J. behavior was modified negatively....

Antiepileptic drugs used, reported efficacy and secondary events. *Drugs used >5 times: > 80% efficacy; >40% reported adverse*

	Used	Good efficiency reported	Significant secondary events
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 (0%)
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
Benzodiazepine			
Clobazam	7	6/7 (86%)	4/7 (57%)
Diazepam	4	4/4	1/4
Midazolam	4	3/3	0/3
Clonazepam	2	1/2	1/2
Lorazepam	2	2/2	1/2
Other			
Ketogenic diet	3	1/3	0/3

Data completed by recontacting families for additional information. 17 out of 81 patients excluded as parents did not specify treatment, or reported epilepsy as a sporadic event or that resolved on its own.

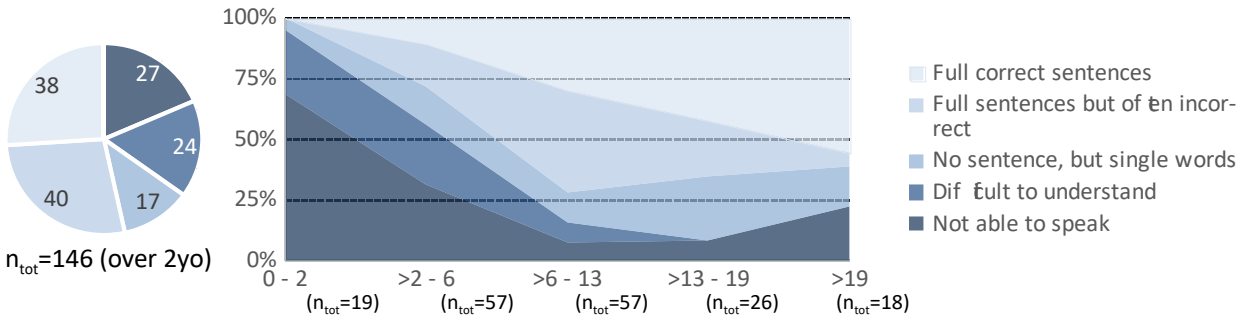
4. Proof of concept

Cognitive abilities

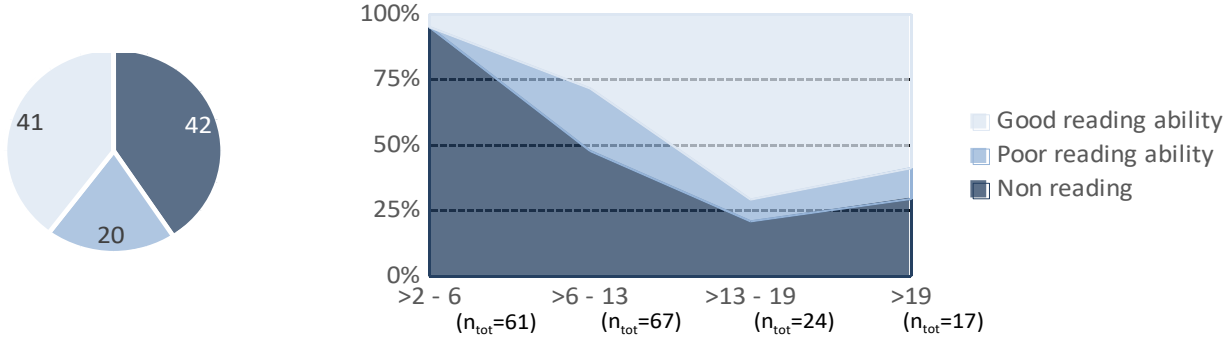
As the cohorts include patients of different ages we can reconstruct longitudinal evolution (A and B for speech/language, and reading) : Data show a **clear delay in speech and reading abilities**, but they tend to improve over time in a majority of KdVS patients. Speech/language and reading ability appear acquired by about 50% of adolescents, as perceived by parents. Speech a/dyspraxia (reflected by impaired understandability) appears a problem as noted previously by Morgan et al (2018), underlying importance of early speech/language therapy. The delay or impairment in these cognitive acquisitions appear greater in KS patients, and less severe in KBG syndrome patients (not shown, except for age at first words and understandability).

Speech and reading abilities of KdVS patients:

Speech ability reported for children 2yo and older.



Reading ability reported for children 6yo and older.



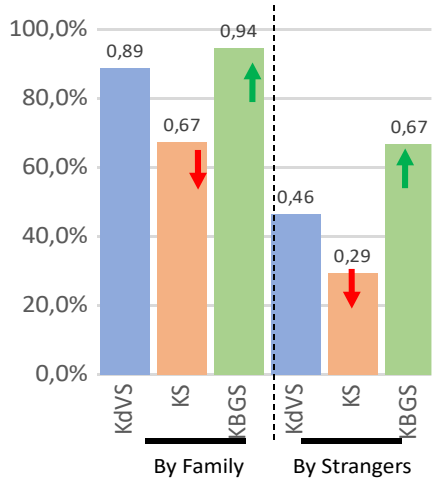
Speech ability in KdV (KdVS), Kleefstra (KS) and KBG syndromes (KBGS):

Reported age at first word (in years)

KdVS patients (>6yo): 97
KS patients (>6yo): 58
KBGS patients (>6yo): 18

	KdVS	KS	KBGS
Average	**2.2 yo**	**2.4 yo**	**1.5 yo**
Median	2.0 yo	2.3 yo	1.5 yo
Upper quartile	3.0 yo	3.0 yo	2.0 yo
Lower quartile	1.1 yo	1.7 yo	1.0 yo
n_{tot} of answers	**n=110**	**n=54**	**n=29**

Reported understandability (patients ≥6yo)



Conclusion

Our data show the willingness of parents to participate in studies dealing with rare diseases affecting their child.

The data entered by parents appear generally reliable. They are valuable and bring new knowledge for rare NDDs such as Koolen-deVries, Kleefstra or KBG Syndrome, and **suggest topics for further targeted clinical studies**.

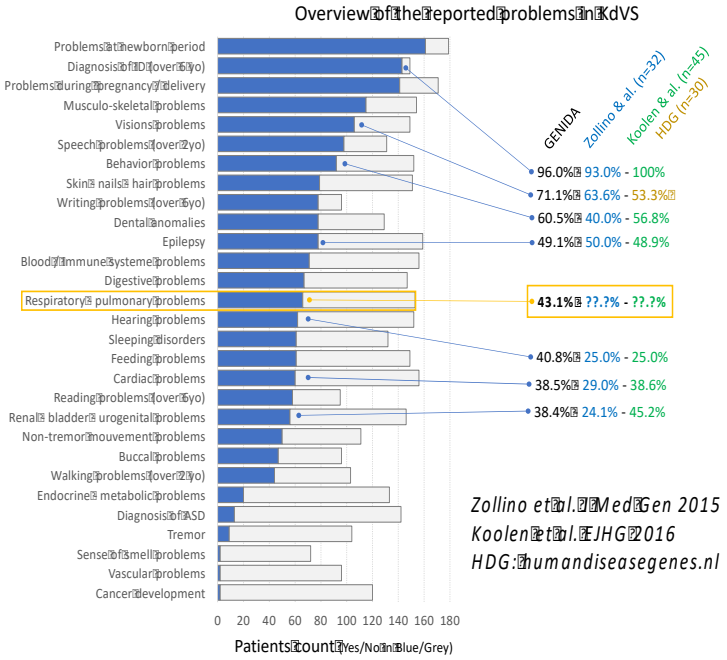
Additionel presentations of results: the overview for a given condition, comparison of behavior problems in 3 syndromes

⇒ **For each cohort** an **overview** is automatically generated that presents the frequency of reported problems covering a wide range of comorbidities

⇒ **Behavioral problems**: explored through 13 sub-questions: here comparison between KdVS, Kleefstra and KBG syndromes for 4 sub-questions. A **lower frequency of behavioral problems was reported for KdVS** (56%, compared to KS and KBGS, 73 and 79%).

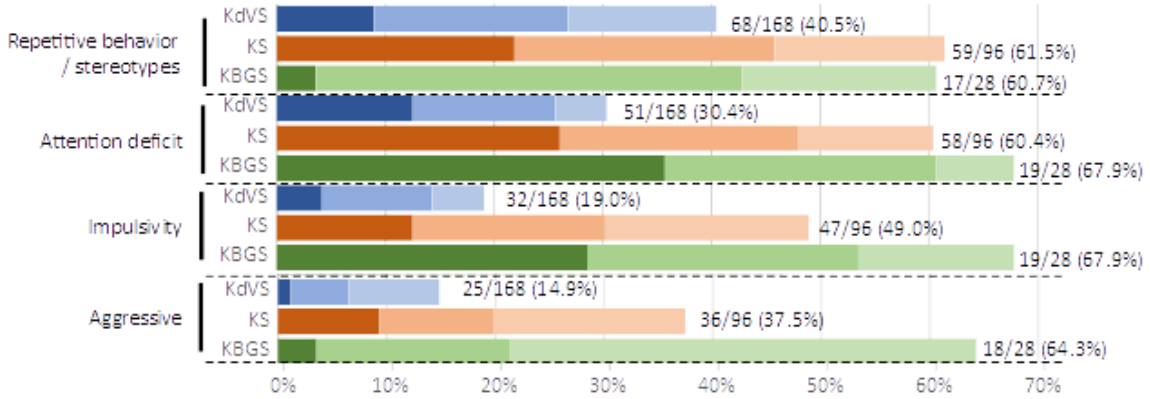
⇒ **KS scores highest for repetitive behavior/stereotypes**, while **KBG scores highest for attention deficit, impulsivity and aggressiveness**, and **KdVS scores lowest on all 4 items**

Respiratory problems: an **unexpected high frequency of respiratory problems** was reported, including **asthma** and **infections,** including reports of **repeated pneumonia** (from open text answers), mostly between infancy and about 10y. Our search for explanations did not identify a clear cause yet, although parents reported non specific immunodeficiency, hypotonia, reflux, and tracheo-laryngo malacia may also be possible contributing causes.



Zollino et al. Med Gen 2015
Koolen et al. EJHG 2016
HDG: humandiseasegenes.nl

Overview of the reported medical problems in patients with KdVS, from the online GENIDA survey (32 questions) ranked in absolute number of reported cases, and compared for some items, with previous publications (Zollino 2015, Koolen 2016)



Frequencies of reported behavior problems and their perceived severity in Koolen-deVries (KdVS), Kleefstra (KS) and KBG syndromes (KBGS). KdVS data are in grades of blue (from major to moderate and mild), KS data are in grades of red and KBGS data are in grades of green. Out of n=13 parameters.

ERN ITHACA & GenIDA

GENIDA
Aidez-nous à vous aider

⟷

ITHACA

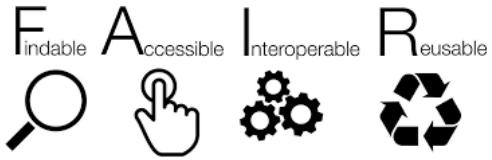
WP 6: *Interaction with other registries and biobanks*

→ […] aims to create a federation of individual registries in a network built around ITHACA's Central Registry, which will be able to integrate queries encompassing these external registries.

Our 2 objectives are :

- to strengthen our recruitment capabilities at the European level

- to implement interoperability of the GenIDA project with ILIAD in line with the FAIR principles



Europe / FAIR data : https://fr.wikipedia.org

GENIDA

ERN ITHACA & GenIDA

Strengthening of our recruitment capabilities at the European level

- Improve the ergonomics of our website
- Widen the accessibility of the website and the questionnaire
  → **increase the number of translations available**, targeting the main EU languages
- the **communication towards targeted families, associations and professionals** members and referent centres members of ITHACA.

Currently under progress :

- the GenIDA website and database are being refined by Cigest IT company (registration, etc.)
- working on the Italian and Spanish versions of the questionnaire (translated versions of the website will be available in a second time, once online)
- active recruitment of participating families *via* social networks and associations throughout Europe ; direct implication of professionals in the recruitment process

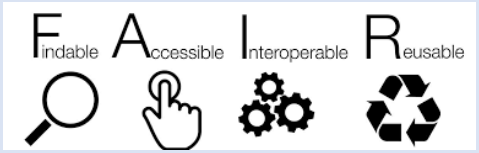
Europe : https://fr.wikipedia.org

ERN ITHACA & GenIDA

Implementation of the interoperability of GenIDA with IILIAD

Upgrading of GENIDA's current architecture while at the same time

- ensuring that no patient is duplicated between GENIDA and other databases while guaranteeing our users' disidentification
- streamlining access to our clinical data for ITHACA healthcare professionals by upgrading the CERBERUS Access Control System
- allowing for optimal reuse by indexing our clinical data on the Human Phenotype Ontology, according to the FAIR principles.



Collaboration:

umcg

Pr Morris Swertz,
Groningen Genomics Coordination Center,
University Medical Center Groningen, The Netherlands

⟷

Cigest

FAIR data : https://fr.wikipedia.org

GENIDA

GENIDA
AIDEZ-NOUS À VOUS AIDER

Thank you for your attention !

burgerp@igbmc.fr ; genida@igbmc.fr