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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

GenIDA: an international participatory database to gain knowledge on health issues related to genetic forms of neurodevelopmental disorders

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Abstract

Intellectual disability with or without manifestations of autism and/or epilepsy affects 1–2% of the population, and it is estimated that more than 30–50% of these cases have a single genetic cause. More than 1000 genes and recurrent chromosomal abnormalities are involved in these genetic forms of neurodevelopmental disorders, which often remain insufficiently described in terms of clinical spectrum, associated medical problems, etc., due to their rarity and the often-limited number of patients' phenotypes reported. GenIDA is an international online participatory database that aims to better characterise the clinical manifestations and natural histories of these rare diseases. Clinical information is reported by parents of affected individuals using a structured questionnaire exploring physical parameters, cognitive and behavioural aspects, the presence or absence of neurological disorders or problems affecting major physiological functions, as well as autonomy and quality of life. This strengthens the implication in research of the concerned families. GenIDA aims to construct international cohorts of significant size of individuals affected by a given condition. As of July 2022, GenIDA counts some 1545 documented patient records from over 60 nationalities and collaborates with clinicians and researchers around the world who have access to the anonymized data collected to generate new, medically meaningful information to improve patient care. We present the GenIDA database here, together with an overview of the possibilities it offers to affected individuals, their families, and professionals in charge of the management of genetic forms of neurodevelopmental disorders. Finally, case studies of cohorts will illustrate the usefulness of GenIDA.

Keywords Intellectual disability · Participative study · Rare diseases · Cohorts · Comorbidities

Introduction

Neurodevelopmental disorders (NDDs) are developmental impairments in one or more cognitive skills that manifest early in a child's development, typically before primary school entry. These include intellectual disability (ID), autism spectrum disorders (ASD), communication disorders, specific learning disorders (commonly referred to as "dys" disorders: dyslexia, dyspraxia, etc.), motor disorders (developmental coordination disorder) and attention deficit disorder with or without hyperactivity (ADHD) (American Psychiatric Association 2013). NDDs are frequently associated with each other, but also with other psychiatric or neurological manifestations (such as behavioural disorders, epilepsy) and other non-neurological comorbidities (INSERM 2016; Hansen et al. 2018; Des Portes 2020). ID, classically characterised by an intelligence quotient (IQ) below 70, combines deficits in intellectual functions, such as reasoning, planning, or abstract thinking, with impairments in adaptive functioning. The latter lead to an inability of the individual to meet developmental and socio-cultural requirements for personal independency and social responsibility, and thus limit functioning in one or more areas of daily life (communication, social participation, etc.) (American Psychiatric Association 2013). ID affects about 1–2% of children and young adults (0.4–0.5% for the most severe forms of ID) (Maulik et al. 2011). In 30–40% of cases, ID

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as defined above is accompanied by ASD (Boulanger 2016; Bertelli et al. 2020). Similarly, it is estimated that up to one-third of people with a diagnosis of ASD have an associated ID (INSERM 2016; Rosen et al. 2018; Christensen et al. 2018). Beyond ASD, people with ID are at risk for somatic and psychiatric comorbidities that have a significant impact on their health, such as epilepsy, motor disorders or disorders affecting other physiological functions (INSERM 2016). It has been estimated that nearly 40% of people with ID also present behavioural disorders (Munir et al. 2008). The prevalence of these disorders is 3–5 times higher in these individuals compared to the general population (Tsakanikos and McCarthy 2013; INSERM 2016; Bertelli et al. 2020). Common health problems (feeding difficulties, sleep disorders, vision, or hearing problems) can also have significant consequences for their quality of life. Indeed, while more frequent in people with ID than in the general population, such problems are generally less well detected and managed because of the difficulties affected individuals have in expressing themselves in this regard (INSERM 2016; Ba et al. 2020). It thus appears necessary to better characterise and understand NDDs and the associated comorbidities, the consequences, and the impact they have on the persons concerned.

Our understanding of the genetic causes of NDDs and their diagnosis has improved tremendously over the past decade, especially thanks to improved molecular genetic techniques such as high-throughput sequencing (Next Generation Sequencing or NGS) targeting either panels of known ID genes or the whole exome (Whole Exome Sequencing or WES), or Comparative Genomic Hybridization (CGH array) (Cooper et al. 2011; Mefford et al. 2012; Redin et al. 2014; Zarrei et al. 2015). These techniques enable the identification of a causative genetic abnormality in 50–60% of cases of severe ID (Vissers et al. 2016) or around 30% of conclusive molecular diagnosis for mild to severe NDDs (van der Sanden et al. 2022). This may be an aneuploidy, e.g., an abnormal number of chromosomes, such as trisomy 21, by far the most frequent specific cause of ID. This may also be an abnormality affecting a chromosome segment (deletion or duplication of this segment, implying that carriers, instead of having two copies of this segment, have only one (deletion), or three copies (duplication)). Such chromosomal rearrangements leading to losses or gains of chromosomal material are called Copy Number Variant (CNV) and when they show frequent recurrence, are at the origin of recognizable syndromes, such as Prader-Willi syndrome (OMIM # 176270), which is characterized by hypotonia and feeding difficulties at birth, followed by early obesity associated with hyperphagia (Driscoll et al. 1998). Another striking example are the recurrent deletion or duplication at chromosome 16p11.2 initially described as associated with autism in 2008 and later shown to also cause mirror extreme Body Mass Index (BMI) phenotypes, i.e., obesity in the case of a deletion, and abnormally low BMI in the case of the duplication (Jacquemont et al. 2011). Finally, ID can be caused by the presence of mutations affecting a single gene. This type of genetic abnormality is cumulatively the most important cause of ID. Genes involved in such monogenic forms of ID are far from being all known and the list is still growing (Vissers et al. 2016; Turro et al. 2020; Kaplanis et al. 2020). The SysID database, recently replaced by SysNDD (https://sysndd.dbmr.unibe.ch/), counted at the time of its last update (November 18, 2021), 1534 "primary ID genes," i.e., genes for which causal monogenic variants have been identified in a sufficient number of unrelated patients and/or for which there is sufficient clinical information (Kochinke et al. 2016).

Issue

These genes and recurrent chromosomal abnormalities correspond to as many distinct rare diseases, which often remain insufficiently described in terms of clinical spectrum, associated medical problems and patients' natural history (evolution of the pathology over the course of a lifetime) due to their very recent identification.

In fact, if pathologies recently discovered thanks to the progress of molecular genetics are often poorly known and insufficiently described, this can be also true for diseases that have been identified for several decades. For instance, it required 10 years of diagnostic and phenotypic study of families affected by Fragile X syndrome worldwide (1991–2001) to establish, from only 5 initial cases, that male carriers of the Fragile X premutation can present with a late-onset neurodegenerative disorder, and a further 3 years were needed to collect data to estimate the age-related penetrance of the disease (Rousseau et al. 1991; Hagerman et al. 2001; Jacquemont et al. 2004). One can also cite the KBG syndrome (OMIM #148050), first described in 1975, and for which, only 45 patients were identified until 2006 (Hermann et al. 1975; Brancati et al. 2006). In many cases of specific genetic forms of NDDs, the few clinical publications devoted to these conditions are based on the observation of a small number of patients, often insufficient to define an effective management of these pathologies. As these disorders are individually rare or very rare, and very diverse, it is extremely difficult for geneticists or other academic specialists who do not regularly follow the affected children and adults to build up consequent cohorts of clinically well-characterized patients, and even more so, specific databases.

These limitations in the study of genetic forms of NDDs invite the evolution of research, taking into account the recommendations for research issued by the French group of experts gathered by INSERM (French Institut National de

la Santé et de la Recherche Médicale) in the framework of the collective expertise procedure concerning intellectual disabilities (INSERM 2016). These recommendations call for future studies in the field of ID to be conducted according to the quality standards of scientific research, favouring longitudinal studies that allow for the follow-up of cohorts of national or even international scope to collect structured data sets available to researchers. Because of the increase in the life expectancy of people with ID with or without ASD, experts also recommend broader coverage of all age groups, and the collection in new studies of information on the evolution of these disorders in adulthood and in older people (Ayanouglou 2012; INSERM 2016). These recommendations are in line with practical guidelines issued at the international level to assess and manage intellectual disability (Kishore et al. 2019).

To overcome the gap of knowledge about the clinical, cognitive, and behavioural manifestations associated with each of these numerous genetic disorders, and to favour more inclusive research, it is essential to have cohorts well-defined in terms of the genetic origin of the ID, age, and sex of the affected individuals, built with the participation of those directly concerned, namely, people with ID and their relatives/caregivers. Those cohorts should also allow longitudinal follow-up of the affected persons to better understand the developmental characteristics and natural history of these disorders.

Such databases and cohorts exist for some relatively common conditions, such as Fragile X (FORWARD—Fragile X Online Registry With Accessible Research Database: https://fragilex.org/our-research/projects/forward-registry-database/; Sherman et al. 2017; Berry-Kravis et al. 2021) or Rett syndrome (https://www.rettsyndrome.org/research/our-research/natural-history-study/, Buchanan et al. 2022), often maintained by researchers and supported by patients' organizations. More recently, numerous patients/families' groups of varying size have been initiated on social networks with support from experts, but only a limited number are collecting formalized medical data. Very few recent initiatives collect medical and longitudinal data on various diseases through a participatory online approach. The Human Disease Genes (HDG; https://www.humandiseasegenes.nl/) website series represents a systematic international approach that records detailed information on the clinical phenotype of novel genetic variants in the human genome, including unpublished clinical information captured through an online questionnaire by clinicians after informed consent (Dingemans et al. 2021). The online patient community PatientsLikeMe (www.patientslikeme.com) has currently a very limited recruitment on genetic forms of ID (PatientsLikeMe). WaihonaPedia (www.waihonapedia.org), a platform allowing the connection and exchanges between affected individuals and their families, caregivers, doctors and therapists, started with a *TCF4*-cohort (de Winter et al. 2016) and focuses currently on 21 genetic forms of ID (WaihonaPedia). The Simons Foundation Autism Research Initiative (SFARI) initially launched the SPARK (Simons Foundation Powering Autism Research for Knowledge, sparkforautism.org) program online targeting individuals living in the U.S. with a professional diagnosis of ASD, that combined parental responses to an online questionnaire and professionally conducted phone interviews (Feliciano et al. 2018; SPARK). The subsequent Simons Searchlight research program (www.simonssearchlight.org) further dives into these rare genetic NDDs by collecting detailed, standardised medical histories and blood samples and sharing them with many investigators (Simons Searchlight). Primarily aimed at English speakers, it currently offers study participation in Spanish, French and Dutch. For instance, the neurobehavioural phenotype of 28 individuals with de novo pathogenic/likely pathogenic variants in *SLC6A1* was recently refined (Kahen et al. 2021). If the types and frequency of clinical features reported (including hypotonia, ID/developmental delay, language disorder/speech delay, seizures, ASD, high pain tolerance, and sleep issues) are consistent with previous observations, it was also possible to clarify the strengths and weaknesses of these patients, and more specifically the specific areas of relative strength (socialisation and life skills) and weakness (communication and motor skills) by means of standardised behavioural measures (Vineland Adaptive Behaviour Scales—VABS, Child Behavior Checklist).

Considering the ever-growing list of genes or recurrent CNV involved in ID, and within the existing databases landscape, GenIDA was designed to better characterise the many genetic forms of ID with or without manifestation of ASD or epilepsy, corresponding to an equivalent number of rare and distinct disorders, in terms of spectrum of clinical features, co-morbidities and progression over time (natural history). It involves parents/caregivers who have the motivation and the knowledge about the manifestations of the condition. GenIDA's participatory approach, as well as the nature of the variables collected, will be presented through the examples of 3 case studies initiated from the answers provided by parents/caregivers in the database.

GenIDA

The GenIDA[1] project (https://genida.unistra.fr) is an example of a novel approach of participatory research targeting genetic forms of ID, that will bring new insights to their phenotypic description and natural history delineation. This international participatory database was developed

[1] Genetics of Intellectual Disability and Autism spectrum disorders.

and launched online in November 2016, with the aim of better characterising these rare forms of ID and/or ASD of genetic origin, via the direct insight of affected individuals and their families that are asked to answer a structured questionnaire. GenIDA enables longitudinal studies to be carried out, to monitor the evolution of cognitive skills and possible behavioural problems in affected people in ecological conditions as the information are reported by the parents.

The longitudinality of the study lies in the fact there is no minimum age requirement or age limit for enrolment of individuals with these forms of ID in the database. Natural history is mainly obtained from the answers by parents of patients of different ages and not by following patients in GenIDA for a long time.

However, the participating families are encouraged to regularly update the data on their affected family member. Such an update is recommended annually, but because of the voluntary nature of participation in this study, it can be more or less frequent. Thus, we observe that this data update is generally directly concomitant with the occurrence of a new event in the life of the persons concerned (appearance of a new symptom or comorbidity, adverse effects resulting from medication, etc.). Data update reminders are frequently posted on GenIDA's Facebook page (www.facebook.com/GenIDAproject/), and the message is also conveyed by patient organizations (via their own newsletters, their social networks or at their information meetings).

The answers are strictly anonymous, and the questionnaire can be completed in several rounds. As the aim of GenIDA is to better characterise rare forms of ID and/or ASD of genetic origin in terms of associated comorbidities and symptomatology, having identified a causal gene, or CNV is the only condition for participating in the study. Such massive data collection right at the source (i.e., the affected person and her/his family) will greatly contribute to accelerate the knowledge about these rare diseases. It also allows the affected individuals, their families and the relevant patients' associations to be involved in the construction of international cohorts of sufficient size from which physicians, researchers and other professionals can extract new medically significant data to improve the care of people with the disease.

The project was developed in collaboration with RaDiCo (https://www.radico.fr/en/accueil), the French rare disease cohort program (RaDiCo—Rare Disease Cohorts) and specialists in information security and database management from the ICube laboratory in Strasbourg (P.P.). Potential risks regarding data storage, security, confidentiality, type of data requested, or website structure have been considered during the development of this database and are detailed in the validated research protocol of the project (available upon request) submitted to INSERM.

The questionnaire

The GenIDA questionnaire, designed to be understandable to non-healthcare or research professionals, is currently available in 7 languages (French, English, Dutch, German, Spanish, Italian, and Portuguese). Its design beneficiated from input, or even translation, from representatives of some patients' associations. It currently includes 5 free text qualitative questions, 5 numerical questions (weight, height, head circumference, Apgar score, age at developmental milestones), as well as 36 multiple choice questions (MCQs) with their 92 sub-questions. Each of these MCQs also contains a free text field allowing to give complementary information (e.g., on clinical manifestations, treatment). The MCQs notably investigate cognitive aspects (e.g., diagnosis and degree of ID, spoken language competency, etc.), behavioural aspects including ASD, neurological manifestations (epilepsy, motor defects) and core physiological functions (cardiac, renal, endocrinal, etc.). The open text questions address perceptions of manifestations that most affect the health, behaviour, and quality of life of the person with NDD, as well as potential adverse effects of medications administered as part of targeted or symptomatic treatments for comorbidities. We avoided mandatory responses for the clinical questionnaire by allowing participants to skip questions, to answer the questionnaire out of order, and in multiple rounds to reduce potential caregiver burden and maximize participation. Questions about dysmorphology were intentionally omitted.

The questionnaire was designed by GenIDA to be understandable by lay people and submitted to an international advisory board made up of clinicians, researchers, as well as concerned parents and representatives of patients' associations. By "lay people", we mean parents/caregivers who do not belong to the medical or the scientific research world and who are, therefore, not necessarily familiar with the medical lexicon, but who are nevertheless sufficiently aware of the pathology and its comorbidities to be able to participate in our study. In more than 91% of cases, one or both parents of the affected person answered the questionnaire. Translations, especially of medical terms and NDD-specific lexical fields, were carefully proofread by a native speaker of the language in comparison with the English version of the questionnaire.

An online visualization system generates informative real-time numerical graphs of medical and behavioural manifestations and cognitive abilities for each genetic form of NDD for which there are sufficient participating families (these data are updated every 24 h). We have designed an access control system to fine-tune the access of participating families and association members to

disease-specific questionnaires and to specific aggregated data analyses, depending on the size of the cohort (Parrend et al. 2018). Additional numerical, textual, and genetic data may go through a curation step when needed for a specific study. Interested clinicians and researchers, in particular those who wish to collaborate on data analysis, can have access upon request to de-identified statistical data and textual answers.

A database for families

The "participatory" nature of GenIDA comes from the observation that parents / caregivers of people with disabilities are generally the most knowledgeable about the manifestations of their disorders. They are indeed the more susceptible to observe the day-to-day development of their relative and to describe the problems affecting their health and quality of life as stated by (Kishore et al. 2019).

Indeed, families are perfectly able to describe the manifestations of the disease and their effects on the quality of life or autonomy of their affected relative, but above all, they can reveal aspects of the pathology that had been underestimated until then. They are, moreover, particularly motivated to make progress in knowledge, as shown by the impressive growth of patient and family associations and groups for rare diseases, especially on social networks. They are, therefore, the most eager for answers to their questions about the future of the affected person: *will she learn to speak, to write?*, *will she be autonomous?*, *if she suffers epilepsy, will it be treatable?*, *will it decrease with age?*, *are there any regression episodes to be feared?*, etc. The objective is to collect data corresponding to each dysfunctional gene or chromosomal abnormality, and through their analysis, to produce new knowledge that is meaningful for the medical follow-up of affected individuals and their families. It is hoped that the collected data will allow for an improvement of the management of the care of these pathologies and of information to concerned families.

To take part in the study, family members (most often one of the parents) of a person with a genetic form of ID must create a personal space as *participant* by providing a functional email. They must then give consent to participate in the GenIDA study by producing and regularly updating medical and quality of life information about their affected relative. Mandatory information is collected about the *participant* (username; email address; password; her/his relationship with the affected person: parents, grandparents, siblings, referent/guardian). Information collected about the affected individual during the online registration procedure encompass pseudonym, month and year of birth, sex, and name of gene or CNV stated as causal after genetic diagnosis without required specification of the exact mutation(s) or duplication/deletion borders as the latter would be potentially identifying information. The information about affected individuals undergoes curation and validation steps by the GenIDA administrator that occasionally includes, in case of inconsistency or error, directly re-contacting caregivers by mail for edition.

At any time during the completion of the questionnaire, the participant can download and print for personal use a PDF file summarizing all the questions with his or her answers precisely dated. This document constitutes a useful compilation of health and quality of life data that can be attached to the affected person's health record. This document can also be used as a memory aid to check whether the answers given to the GenIDA questionnaire need to be updated.

Cohort-specific statistical data based on MCQs are available directly on the GenIDA website to concerned participating families when the cohort size is more than 10. Anonymized results from the analysis of cohort-specific responses collected can also be shared with relevant stakeholders at association events (family gatherings, general assemblies, etc.), or relayed via social networks or patient group websites.

A database for professionals

The statistical data specific to each cohort, already mentioned above, as well as the free text answers, are also accessible to medical and paramedical professionals involved in the management and care of this type of genetic disorders (doctors, clinicians, researchers, etc.). To access the de-identified data collected, these professionals must register on the GenIDA platform via a separate registration form. This registration allows these specialists to express their interest in the project and in particular cohorts, and even to become more actively involved in the project. Professionals can participate in the recruitment of families affected by specific pathogenic genes, syndromes or CNVs. An example of the joint involvement of an associative partner and clinicians in recruiting participants is the MED13L cohort, which has experienced active and steady growth since the first enrolment in September 2017 through the combined efforts of the French association (Association MED13L Syndrome, www.med13lsyndrome.eu) and clinicians from the Lille University Hospital Center, France (Dr. T. Smol, Dr. J. Ghoumid, and Dr. R. Caumes). This cohort counts 44 participants as of July 2022, of which 47% are French families. We have noted an increase in enrolment in this cohort systematically after each intervention by these clinicians during which they presented results from GenIDA.

Professionals can also participate in the analysis of data related to these genes, syndromes or CNVs, and can, in

Table 1 Major cohorts in GenIDA (as of July 2022)

Cohort	Gene/genetic defect (OMIM number)	Number of participants (GenIDA, as of July 2022)
Koolen-de Vries syndrome	17q21.31 deletion (OMIM #610443) or *KANSL1* pathogenic variants* (OMIM #612452)	241
Kleefstra syndrome	9q34.3 deletion (OMIM #610253) or *EHMT1* pathogenic variants* (OMIM #607001)	185
RASopathies	*PTPN11* (OMIM #176876), *BRAF* (OMIM #164757) and *SOS1* (OMIM #182530) pathogenic variants* mainly	61
KBG syndrome	16q24.2 / 16q24.2q24.3 deletion (OMIM #148050) or *ANKRD11* pathogenic variants* (OMIM #611192)	48
DDX3X	*DDX3X* pathogenic variants* (OMIM # 300160)	47
MED13L syndrome	*MED13L* pathogenic variants* (OMIM #608771)	45

*(including likely pathogenic variants)

this way, generate new and medically significant knowledge that can translate into improved patient care and contribute to the drafting of scientific publications, care management recommendations in the form of guidelines, etc. In particular, the data collected by GenIDA were made available to clinicians in charge of writing the PNDS, i.e., the French diagnostic and care management protocols, for Koolen-de Vries, MED13L and Wiedemann-Steiner syndromes (all scheduled for publication in the near future). At the international level, data on Kleefstra syndrome are currently being reviewed by the team of Dr. T. Kleefstra (Radboud university medical centre in Nijmegen, The Netherlands) for use in the development of *Professional clinical guideline for Kleefstra syndrome*.

Professionals can also investigate certain aspects of a disease of interest by submitting additional questions to the families concerned, or recruit families for clinical studies and/or research projects. To do so, they must contact the GenIDA team, which, after consultation and subject to the approval of its scientific advisory committee, will relay the information to the families concerned. The search for additional information can be done in the form of a new specific questionnaire developed by the professional in consultation with the GenIDA team and posted on the platform, or simply relayed by GenIDA to the families concerned by email (especially if the request involves sending medical documents: imaging, etc.).

GenIDA satisfies ethical requirements (see "Compliance with Ethical Standards" paragraph), and the authorisations obtained allow for this type of incidental study without seeking specific legal authorisation again as participants are asked to give their informed consent before accessing any questionnaire (general questionnaire, Covid-19 questionnaire, etc.).

GenIDA nowadays (July 2022)

Registry recruitment was launched in November 2015 for a 1-year beta test, during which time volunteer families were included to test the website's functionality and merge after consenting their data into the Syndrome Monitor database (unpublished) developed at Radboud University Medical Centre, Nijmegen, The Netherlands (the latter survey covered 36 of the 46 major questions of the GenIDA survey). Open recruitment was conducted exclusively on the GenIDA website after November 2016.

Since then, information about GenIDA has been presented at several national and international medical conferences and the study has been regularly publicized via social media, support groups and at patient family meetings in France, and abroad (including mainly the Netherlands, the UK, Australia and the US). GenIDA received the active support of many professionals and patients' associations for the recruitment of patients, and as of July 2022, the database has recruited over 1545 caregivers from over 60 nationalities who have completed at least 20% of the questionnaire (past this threshold, the average answer rate is in fact exceeding 80% for over 83% of the participants (Colin et al. under revision)). The recruitment rate is 30 participants on average per month. The database contains over 75 000 answers. The main countries of origin of participants were France (41.1%), followed by the United States (20.8%), the United Kingdom (10.2%), the Netherlands (3.7%), Germany (3.6%), and Australia (3.1%). We have data on 47 specific genes or CNVs for which at least 5 patients are documented in the database.

The most numerous cohorts in GenIDA are presented in Table 1; a variety of new cohorts have also been created

Table 2 Selected cohorts created in GenIDA in the last 2 years, reporting their respective number of participants (as of July 2022)

Cohort	Gene/genetic defect (OMIM number)	Number of participants (GenIDA, as of July 2022)
Wiedemann-Steiner syndrome	*KMT2A* pathogenic variants* (OMIM #605130)	29
SETD5 cohort	*SETD5* pathogenic variants* (OMIM #615761)	28
Phelan-McDermid syndrome	22q13.3 deletion (OMIM #606232) or *SHANK3* pathogenic variants* (OMIM #606230)	25
DYRK1A syndrome	*DYRK1A* pathogenic variants* (OMIM #614104)	24
White Sutton syndrome	*POGZ* pathogenic variants* (OMIM #616364)	20
Coffin-Siris syndrome	*ARID1A* (OMIM #603024), *ARID1B* (OMIM #614556), *ARID2* (OMIM #609539), and *SMARCA4* (OMIM #603254) pathogenic variants* mainly	18

*(including likely pathogenic variants)

over the past year and already have an interesting participation rate (Table 2).

Case studies

Koolen-de Vries syndrome

Koolen-de Vries syndrome (KdVS) is caused by the 17q21.31 deletion or by pathogenic variants in *KANSL1* (Koolen et al. 2006, 2012, 2016). The detailed phenotypic features were described from two cohorts totalling 77 patients (17 individuals with a pathogenic *KANSL1* variant) (Zollino et al. 2015; Koolen et al. 2016). Clinical data from 170 individuals with KdVS (probably partly overlapping with the former cohorts) are now available in the HDG website series (https://www.humandiseasegenes.nl/kansl1/graph-and-chart), but do not include longitudinal information (Human Disease Genes). The main features of KdVS are neonatal hypotonia, developmental delay, intellectual disability, facial dysmorphism, epilepsy, congenital anomalies of the heart and urogenital tract and various orthopaedic manifestations. The accumulation of information on the natural history of the condition and the broadening of the spectrum of clinical elements assessed using the GenIDA platform offer the possibility to improve the clinical management of patients by health professionals and caregivers.

In a forthcoming study, the GenIDA data on 237 individuals with KdVS are reported (Colin et al. under revision). The phenotypic characterisation of the syndrome is consistent with previous reports and there are no significant differences between patients with a 17q21.31 microdeletion and those with a pathogenic variant in *KANSL1*. Interestingly, the data analysis also revealed a previously unreported susceptibility of these patients to respiratory problems (including recurrent pneumonia, and childhood asthma). The frequency of epilepsy reported in GenIDA is consistent with data from the medical literature (Myers et al. 2017), but GenIDA data analysis provided further information on the nature of the seizures associated with KdVS, as well as information on the efficacy and possible adverse effects of the anti-epileptic treatments used to treat these disorders. With regard to cognitive abilities, the data show a clear delay in the speech and reading abilities of KdVS patients, but these tend to improve over time in a majority of them, since according to parental perception, these abilities seem to be acquired by about 45% of adolescents. Verbal dyspraxia (reflected by reduced understanding of the affected person by family members and strangers) is a major problem, as previously reported (Morgan et al. 2018), which highlights the importance of early speech and language therapy.

Comparison of the KdVS data to the overall GenIDA data shows clinical features that are significantly more frequent in KdVS and that may require extra attention. This type of comparison demonstrates an interesting potential for GenIDA, because many clinical features in individuals with NDDs are relatively unspecific, such as hypotonia, or sleep problems. It also confirms previous observations, notably about the gentle nature children / young adults with KdVS, although behaviour problems including repetitive behaviour/stereotypes, attention deficit, anxiety, obsessive behaviour, and hyperactivity are also reported. However, those behavioural problems appear statistically less frequent in the KdVS cohort compared to Kleefstra syndrome, which scores higher for repetitive/stereotypic behaviour, and KBG syndrome, which scores higher for attention deficit, impulsivity and aggressiveness.

It is also worth noting that two incidental studies, conducted by international collaborators and using the GenIDA platform to rapidly reach concerned people with KdVS likely to participate, have emerged from the study of these data:

(i) The first one conducted under the direction of Dr. D. A. Koolen by the team at Radboud University Medical Centre in Nijmegen, The Netherlands, examines the prevalence, clinical and radiological characteris-

tics of musculoskeletal problems, notably scoliosis, in people with KdVS, as GenIDA results indicated the occurrence of scoliosis and abnormal thoracic kyphosis in more than 27% of these individuals, compared with a prevalence of 2–4% in the general population (Horne et al. 2014). Spinal radiographs, MRIs, and corresponding radiological reports for scoliosis and additional abnormalities of 54 individuals with KdVS were reviewed in this international retrospective study to assess the occurrence of scoliosis-related clinical conditions and to raise awareness for early detection and adequate therapy. This retrospective cohort study showed that scoliosis is common among the respondents (56%) with a clear increase of the prevalence with age. Systematic screening with coronal and sagittal radiographs of the standing spine is, therefore, recommended before the onset of the growth spurt and at age 18 years (Bouman et al. in preparation).

(ii) Following the analysis of data collected for this syndrome in GenIDA, another study focusing on the ophthalmological manifestations of KdVS was conducted by Dr. D. Landau Prat and Dr. D. Shalev, MDs (The Goldschleger Eye Institute, Department of Ophthalmology, Sheba Medical Center affiliated to the Sackler school of medicine, Tel Aviv University, Israel). Indeed, while ocular manifestations, including strabismus, hyperopia, and ptosis, have been reported in KdVS, detailed data remained restricted. Families of individuals with KdVS already included in GenIDA were recontacted for inclusion in this study, which aimed to deepen insight on known ophthalmological manifestations (occurrence and frequency of ocular and oculofacial malformations) while uncovering novel ocular associations. Participants were asked to answer to a specific questionnaire regarding ocular and adnexal issues and to transmit ophthalmological data, such as clinical visits reports and test results, as well as clinical photos of their ocular area to examine eyelid abnormalities. This specific questionnaire distributed by GenIDA to all participants in the cohort was available in English and French from August 2021 to January 2022: a total of 67 families, one-third of which were from Europe, took part in this study. The study's findings indicated that KdVS is associated with various ophthalmic findings, such as amblyopia, strabismus, refractive errors, and upper eyelid ptosis. Retinal abnormalities and nasolacrimal disorders were described for the first time in KdVS (Shalev et al. submitted). Thorough ophthalmic assessment is, therefore, recommended for all KdVS individuals.

These examples demonstrate that GenIDA is valuable in extracting new and medically meaningful information to complement data from clinical studies, which are often performed on smaller numbers of patients.

Study of the impact of the 1st Covid-19 related lockdown

Given the particular sanitary situation in 2020, GenIDA has opened an online investigation into the consequences of Covid-19-related lockdown on people with genetic NDDs. For this purpose, a targeted questionnaire was developed during the first Covid-19-related lockdown (spring 2020) in collaboration with Dr. R. Coutelle, child psychiatrist, University Hospital, Strasbourg, France, including questions on diagnosis, lifestyle and questions regarding behaviour, diet, and sleep, in the 6-month period before lockdown and during lockdown. Participants were also asked to evaluate the intensity of these problems by severity level and could freely comment on the medical and/or quality of life problems they had encountered during this lockdown. This questionnaire was rapidly implemented on the GenIDA platform, and the call for participation in this study was disseminated to the GenIDA community, i.e., participating families and related patient associations and Facebook groups by email and posts on social networks. More than 200 questionnaires were completed in some 5 weeks (30.04.2020–09.06.2020). After data curation, a total of 199 files of participants (144 children and 45 adults) with NDDs (ID: 79.4%, and/or ASD: 21.6%) of various genetic origins, from some 15 different nationalities mainly from Europe and North America, were included (Coutelle et al. 2022). The apparently small overlap between ID and ASD is due to a bias, namely, that once a diagnosis has been made (ID or ASD), formal investigations are usually stopped outside of strict research protocols (Myers et al. 2020).

The average duration of lockdown at the time of the survey was 57 days. No difference in the frequency and intensity of eating and sleep disorders was evidenced before and during lockdown. A decrease in sociability scores with both familiar and unfamiliar children and with adults during lockdown was observed. For persons with behavioural problems at both periods, relatives reported an increase in aggressivity, self-aggressivity, depressiveness, stereotypies, and restricted interests during lockdown, all of which might be interpreted as consequences of a lack of stimulation or a reaction to unexpected changes in daily habits (including notably therapy and/or education cessation during lockdown).

These results show the interest of GenIDA for longitudinal follow-up of people with NDDs of genetic origin, and demonstrate the plasticity of the database, which allows for the rapid implementation of new specific online

questionnaires and the ability to quickly mobilize a large number of participants for a new study.

Neurocognitive and neurobehavioural characterization of the DYRK1A and Wiedemann–Steiner syndromes

DYRK1A and Wiedemann–Steiner (WSS) syndromes are among the most common monogenic forms of NDD, caused by pathogenic variants in the *DYRK1A* and *KMT2A* genes, respectively (McRae et al. 2017), and are associated with both ID and ASD. While the clinical phenotypes of these two syndromes have been widely described (van Bon et al. 2016; Sheppard et al. 2021), their behavioural and neurocognitive profiles have not been systematically assessed using standardised tools. To address this, we combine a clinical study carried out using adapted and validated tools (DYRK1A syndrome: $n=14$ and WSS: $n=21$), and information reported by participating families in GenIDA (DYRK1A syndrome: $n=20$ and WSS: $n=20$) to characterize patients' adaptive behavioural profiles, autistic features, ADHD symptomatology, anxiety disorders, maladaptive behaviours, and sensory disorders. Significantly higher, but also more heterogeneous, adaptive functioning was reported in the WSS group compared to the DYRK1A syndrome group from the clinical study. A diagnosis of ASD was established for 57% of individuals with DYRK1A syndrome compared to only 24% of those with WSS. Severe communication and speech impairments are observed in people with DYRK1A syndrome, which is confirmed by the GenIDA data, which also show higher comprehension skills than language and communication skills. Their use of various means of alternative communication—gestures, sounds, pictures, sign language—was reported in both the clinical study and in GenIDA. The clinical exploration of behavioural phenotypes revealed the importance of anxiety symptomatology and signs of ADHD in patients with WSS, also reported in GenIDA. This study, describing the behavioural and neurocognitive profiles of individuals with WSS and DYRK1A syndrome, highlighted some important specificities to be addressed in patients' management (Durand et al. 2022).

This project demonstrates the opportunity that GenIDA offers to study specific aspects of smaller cohorts in depth and even to compare NDDs with each other. The results also demonstrate the complementarity and the consistency of retrospective clinical studies, and the data collected through parent/caregiver testimonies in GenIDA.

It is also important to note that the announcement of the initiation of this study to the respective patients' associations, allowed the recruitment of new participants to GenIDA. Indeed, the prospect of having their data analysed by clinicians, in a relatively short time frame, quickly mobilized new participants who saw a concrete perspective to their investment of time in answering the questionnaire (so did the announcement of the preparation of French guidelines for WSS as well).

GenIDA's limitations

The GenIDA questionnaire may appear rather lengthy and requires that caregivers, when a patient is already a few years old, go back to his or her medical record to report accurate information. This is tedious to some caregivers and may account for low answer rate by some participants. They are, therefore, regularly reminded that it is possible to fill in the questionnaire in several rounds without this affecting the interest of their participation in the study, since each answer is recorded and dated precisely, and that they are asked to specify the age of the patient corresponding to each answer given. On the other hand, there is a lack of ergonomics in the software tool, which is currently being revised according to the feedback received from GenIDA's users.

It is also necessary to consider the access to a personal computer (or tablet) not always democratized according to the countries or social categories, and the capacity of each one to use or not such an electronic device more or less easily. We noted that a certain number of older caregivers (often grandparents of patients) required more assistance to access the questionnaire or to download the summary of their answers in PDF format than those of a more recent generation. The GenIDA project also faces the limitations inherent in questionnaire studies, including recall bias, missing answers, and variable personal interpretation of questions by respondents.

Two major biases of GenIDA from a purely genetic perspective are (1) genes with multiple associated syndromes (e.g., depending on the type of mutation), (2) inherited genetic forms of NDDs in which the parents of the individual concerned are themselves more or less severely affected and will, therefore, tend to respond less. GenIDA is, therefore, more suitable for genetic forms of NDDs occurring de novo, or for recessive ones.

Conclusions

The participatory and empowering approach on which GenIDA relies is original and innovative given the direct involvement of families, who become actors in the research. GenIDA allows, in the context of rare or even very rare diseases, such as genetic forms of ID, to efficiently build well-defined cohorts of persons with a given condition, of sufficient size to obtain quality data to better understand the developmental characteristics of these disorders. Because of its properties and the variables studied,

GenIDA is particularly well suited to longitudinal studies that will help to clarify the natural history of these rare genetic diseases.

Our experience with Koolen–deVries syndrome but also with smaller cohorts (DYRK1A and Wiedeman–Steiner syndromes) shows the power and potential of a participative approach and the willingness of caregivers to participate in studies dealing with rare diseases affecting their relative as they are truly "experts" on the disorder. By reporting their observations anonymously, they provide researchers with valuable data, which can after statistical analysis bring useful new knowledge in rare genetic NDDs, and may help to identify new aspects that have been overlooked by clinicians in previous publications. GenIDA syndrome-specific results are so far consistent with previous data published in the medical literature, while providing greater phenotypic richness regarding the conditions studied, for instance concerning previously under- or over-estimated susceptibility to certain comorbidities or informing on perceived efficacy and/or adverse effects of specific treatments. To date, GenIDA has documented some 35 genes/CNVs (cohort size ≥ 10) responsible for ID, but our goal is to increase the number of participating families internationally to open new fields of investigation of other genes and to improve the knowledge of genetic NDDs, providing new and useful data for affected individuals and families concerned, as well as for professionals involved in the care of these patients. Interoperability with existing registries dedicated to rare diseases, and in particular to specific forms of ID, is planned to be implemented in the near future and should eventually allow the development of collaborative projects on a European scale, combining "participatory" data with clinical data.

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Data availability statement Data specific to a patient cohort in GenIDA are accessible in processed form via the visualization tab (https://genida.unistra.fr/visualizations/), item by item, on the website to any person registered in GenIDA in the said cohort (https://genida.unistra.fr/register/) as soon as the threshold of 10 completed files for the said condition is reached (defined for statistical analysis).

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval GenIDA satisfies all ethical requirements: the research is carried out in accordance with the provisions of the French Data Protection Act (French law of 6 January 1978, amended by the law of 6 August 2004 on the protection of individuals regarding the processing of personal data), and complies with the General Data Protection Regulation 2016/679 (GDPR). The study has been declared to the French Commission on Information Technology and Liberties on 27/11/2015, number 1907912v0. It has been reviewed and approved by the Ethics Evaluation Committee of INSERM—Institut National de la Santé Et de la Recherche Médicale—(IORG0003254, FWA00005831), the Institutional Review Board (IRB00003888) of the French Institute of Medical Research and Health on 15/11/2016, number 16–338, and on 04/09/2019, number 16–338 bis. Participants are asked to read the information note and to give their informed consent before accessing any questionnaire on the GenIDA website (general questionnaire, Covid-19 related lockdown questionnaire, etc.). This consent form details the terms and conditions of participation in the GenIDA research. It specifies that participation is free and that the agreement to participate can be withdrawn at any time, without justification of any kind, simply by logging back into one's account on the GenIDA website. Hence, informed consent is obtained from all participants to the GenIDA studies, i.e., either the subject him/herself or his/her relative responding to the study on behalf of the person with ID (parent or legal guardian(s)).

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