



## Pan-european landscape of research into neurodevelopmental copy number variants: A survey by the MINDDS consortium

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### ABSTRACT

**Background:** Several rare copy number variants have been identified to confer risk for neurodevelopmental disorders (NDD-CNVs), and increasingly NDD-CNVs are being identified in patients. There is a clinical need to understand the phenotypes of NDD-CNVs. However due to rarity of NDD-CNVs in the population, within individual countries there is a limited number of NDD-CNV carriers who can participate in research. The pan-european MINDDS (Maximizing Impact of Research in Neurodevelopmental Disorders) consortium was established in part to address this issue.

**Methodology:** A survey was developed to scope out the current landscape of NDD-CNV research across member countries of the MINDDS consortium, and to identify clinical cohorts with potential for future research.

**Results:** 36 centres from across 16 countries completed the survey. We provide a list of centres who can be contacted for future collaborations. 3844 NDD-CNV carriers were identified across clinical and research centres spanning a range of medical specialties, including psychiatry, paediatrics, medical genetics. A broad range of phenotypic data was available; including medical history, developmental history, family history and anthropometric data. In 12/16 countries, over 75% of NDD-CNV carriers could be recontacted for future studies.

**Conclusion:** This survey has highlighted the potential within Europe for large multi-centre studies of NDD-CNV carriers, to improve knowledge of the complex relationship between NDD-CNV and clinical phenotype. The MINDDS consortium is in a position to facilitate collaboration, data-sharing and knowledge exchange on NDD-CNV phenotypes across Europe.

### 1. Introduction

Advances in genetic technologies in the past decade have led to the discovery of new pathogenic genetic variants which are making significant contributions to the way we understand neuropsychiatric disorders. Discovery of copy number variants (CNVs) in the human genome allows us to study patients with a shared genetic aetiology, thus

employing a “genotype-first approach” rather than a classical “phenotype-first approach” as has been traditionally done in psychiatry (Lord and Veenstra-VanderWeele, 2016). CNVs include microdeletions and microduplications of DNA of multiple sizes (Grayton et al., 2012). These structural chromosomal modifications can be limited to a single gene or include many genes and can occur either *de novo* or be inherited. CNVs significantly contribute to inter-individual variation and while some are

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benign, others predispose to diseases (Bijlsma et al., 2009; Männik et al., 2015; Sebat et al., 2004; Watson et al., 2014). Some pathogenic CNVs tend to be highly variable in penetrance and expressivity. A number of rare CNVs have been associated with increased risk for neurodevelopmental disorders (NDD-CNVs). The term NDD encompasses a range of disorders including autism spectrum disorder (ASD), developmental disorder/intellectual disability (DD/ID), attention deficit/hyperactivity disorder (ADHD), and schizophrenia (SCZ). NDDs occur in about 4% of the population and tend to impact individuals throughout their life-span (Mitchell, 2011). Studying CNVs offers unique opportunities to elucidate the genetic basis of NDDs (Doherty and Owen, 2014; Gudmundsson et al., 2019; Kirov et al., 2014; Marshall et al., 2017; Owen, 2014; Sanders et al., 2015).

An increasing number of recent studies indicate that NDDs share genetic mechanisms, and suggest that NDD-CNVs have a pleiotropic effect on clinical phenotypes and potentially impact convergent underlying brain pathways (de la Torre-Ubieta et al., 2016; Gudmundsson et al., 2019). 22q11.2 deletion syndrome (22q11.2DS) is an example of a NDD-CNV with pleiotropic effects across the lifespan. Individuals with 22q11.2DS may present with congenital abnormalities, immunological dysfunction, epilepsy and seizures, intellectual disability, development coordination disorder, ADHD, ASD, anxiety disorder and sleep disturbances in childhood as well as high risk of schizophrenia and Parkinson's disease in adulthood (Bassett et al., 2005; Bassett et al., 1998; Boot et al., 2018; Cunningham et al., 2018; Eaton et al., 2019; Jonas et al., 2014; McDonald-McGinn et al., 2015; Moulding et al., 2020; Murphy et al., 1999; Niarchou et al., 2014; Schneider et al., 2014), and there is a high degree of co-occurrence of neurodevelopmental and psychiatric symptoms, neurological traits and sleep disturbances in 22q11.2DS (Cunningham et al., 2018; Cunningham et al., 2020; Eaton et al., 2019; McDonald-McGinn et al., 2015; Moulding et al., 2020; Mullen et al., 2013; Niarchou et al., 2014). Multimorbidity carries a great burden both for the affected individual, their families and wider society, and current clinical care focuses mainly on treatment of presenting symptoms, rather than targeting the underlying neuropathology. Understanding the pathophysiological mechanisms of NDD-CNVs is crucial for the development of improved and tailored treatments. Furthermore, better understanding of the relationship between behavioral phenotype and underlying genetic factors will inform optimal genetic counselling and clinical care.

Progress with research into NDD-CNVs is however hampered by the fact that patients with these variants are rare posing challenges for researchers to bring together samples that are sufficiently powered to address important research questions. The pleiotropic effects of NDD-CNVs indicate that wide-ranging assessments should be conducted to capture the complex phenotypic presentation of these patients (Chawner et al., 2019), which should ideally go beyond clinical records to include other informative measures such as neurocognitive skills (Chawner et al., 2017; D'Angelo et al., 2016; Vorstman et al., 2015), motor function (Cunningham et al., 2019, 2020), physical health problems such as seizures (Eaton et al., 2019), sleep disturbances (Moulding et al., 2020) and brain imaging (Maillard et al., 2015; Sun et al., 2020; van der Meer et al., 2020). It is therefore important for clinicians and researchers to join efforts to gather large datasets in order to draw valid conclusions. The MINDDs (Maximizing Impact of Research in Neurodevelopmental Disorders) consortium was established in part to address this issue.

The MINDDs consortium is a 4 year EU-funded COST action pan-European collaborative network established in 2017 (CA16210), <https://mindds.eu/>. This consortium aims to maximize research impact of the study of rare individuals with NDD-CNVs to gain better understanding, and contribute towards improved diagnosis and new treatments. MINDDs has five working groups (WGs) that focus on: (1) patient cohort framework; (2) clinical phenotyping, (3) emerging technologies, (4) databases and informatics; (5) and integration and convergence. It has brought together clinicians, researchers, and patient organizations from 30 EU countries and COST member/co-operating states to design

and develop an approach for transnational patient recruitment with standardized protocols, incorporating regulatory, legal and ethical requirements.

The MINDDs Consortium includes 2 executive full members and 2 substitute members for each of the 30 countries involved in the Action: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Malta, Montenegro, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Spain, Sweden, Switzerland, Turkey, United Kingdom and the Republic of North Macedonia.

WG2 of the MINDDs action focuses on deep clinical phenotyping and harmonizing standardized assessment tools for NDD-CNV research. As one of its goals, WG2 aims to review current methodologies and survey common research practices across COST participating countries and international partners. As part of this effort, WG2 aims to gain a clearer picture of the research into NDD-CNVs conducted in COST member and co-operating states; in order to provide a basis for large-scale multi-centre research collaborations. This is important as currently most published NDD-CNV research is still based on one-site studies and therefore relatively in small scale. Large international networks such as MINDDs are needed to be able to fully capture the variable complex and overlapping phenotypes of NDD-CNVs.

## 2. Methods

A survey was developed by MINDDs WG2 with the aim of gaining a clearer picture of the NDD-CNV research, more specifically about NDD-CNV projects that respondents may have conducted or have been involved with. Furthermore, respondents were asked about clinical cohorts they had access to and which offered a potential for new research.

MINDDs focused on NDD-CNVs based on their prevalence as well as robustness of evidence of association with NDDs (Brunetti-Pierri et al., 2008; Dolcetti et al., 2013; Hoeffding et al., 2017; Kushima et al., 2017; McDonald-McGinn et al., 2015; Niarchou et al., 2019; Ye et al., 2012). These included deletions and duplications at the following loci: 1q21.1, 2p16.3 (*NRXN1*), 3q29, 7q11.23, 9q34.3 (Kleefstra Syndrome), 15q11.2, 15q11-13, 15q13.3, 16p11.2 (breakpoint 4–5), 16p11.2 distal, 16p13.11, 17q12, 22q11.2 (Velo-Cardio-Facial Syndrome), 22q13.3 (Phelan-McDermid Syndrome). The survey was designed to take 30 min to complete.

The survey was developed by WG2 of the MINDDs consortium via several stages of stakeholder engagement in the MINDDs consortium (Fig. 1). Initially, WG2 held a meeting of the MINDDs consortium in which a scoping exercise was undertaken whereby clinical and research stakeholders from member countries provided open-ended information about NDD-CNV research and clinical cohorts within their country. This scoping exercise identified the key questions to take forward by WG2 to develop into a survey. The wording of the survey questions was reviewed by WG2 clinical and researcher members to ensure the survey was accessible and was interpreted consistently across countries. WG2 members then piloted the survey with clinical and research colleagues to demonstrate feasibility. The survey was then finalized at a WG2 meeting. Through this process it became clear that the survey had to be appropriate both for research studies and clinical cohorts where there was potential for research.

The survey asked respondents for contact details for their research and/or clinical centre and for the frequency of NDD-CNV carriers, by variant, whereby (a) research data was available (b) clinically identified individuals where there was potential for research. Further questions were asked regarding the range of phenotypic measures collected, the extent to which individuals could be re-contacted, the age category of individuals, the referral pathway by which patients were ascertained and the method of genetic testing used (See Appendix 1).

The representatives of each country identified locally the research and clinical centres the survey should be distribute. We did not aim to capture all research and clinical centres within each country, rather the



Fig. 1. Development of the survey.

aim was to capture data from centres that indicated interest in future research and collaboration via the MINDDS consortium.

The survey was launched in May 2019 and was distributed to the MINDDS consortium executive members from each country. Data collection ended in December 2019. Following guidance from Cardiff University ethics committee, the survey was developed in agreement with GDPR legislation (further details in [Appendix 1](#)).

### 3. Results

38 countries are eligible to be part of COST actions including MINDDS, and at the time of the survey 30 countries were engaged in the MINDDS consortium. Of these 30 countries, a total of 23 countries (77% of MINDDS countries) responded to the survey. Out of the 23, 16 were able to provide full responses on the majority of questions, which was the inclusion criteria for the study. Barriers for the 7 countries where it was not possible to complete the survey in full, included lack of access to centralized healthcare data on genetic testing, and/or lack of routine genetic testing in the country. 2 of these 7 countries (Bosnia & Herzegovina and North Macedonia) did provide preliminary information, and indicated potential for research in their countries. Within the 16 countries that were able to provide full information, we received 9 responses from Turkey, 4 from Croatia, 4 from UK, 3 from Netherlands, 3 from Poland, 2 from Portugal, 2 from Romania, and 1 each from Belgium, Bulgaria, Ireland, Israel, Denmark, Montenegro, Norway, Serbia, and Switzerland ([Fig. 1](#)). This resulted in responses from 36 centres across MINDDS countries (see [Appendix 2](#) for details and contact information). Responses were received from individuals from a range of professional

backgrounds ([Fig. 2](#)). [Fig. 3](#) shows that there is an overlap in the specialties studying/providing care for patients with NDD-CNVs across countries that completed our survey. Responses came from medical geneticists in 10 countries, academic and clinical researchers in 10 countries, psychiatrists/psychologists in 5 countries, and pediatricians in 3 countries.

#### 3.1. Number of CNV carriers

13 countries (81%) reported on-going studies into NDD-CNVs. Most are involved in 22q11.2DS (9/13), with other NDD-CNVs studied including 22q11 duplication (3/13), 16p11.2 deletion and duplication (2/13), *NRXN1* deletion (1/13), 1q21.1 deletion (1/13), and Kleeftstra syndrome (1/13). Some of the research groups focused on investigating NDD-CNVs which can be found in ASD (1/13) or during postnatal diagnostics (1/13). Three countries did not report current research regarding NDD-CNVs; patients in these countries are diagnosed for clinical purposes with the potential for future research and collaboration. In addition, although not all centres within countries are currently involved in research, some have the potential to do so. [Table 1](#) provides a summary of the approximate numbers of individuals with NDD-CNV available for research based on our survey. Across MINDDS countries, 3844 NDD-CNV carriers were identified.

Across Europe, testing for NDD-CNVs takes place across the lifespan spanning from prenatal testing (50%, 8/16) to childhood (94%, 15/16), adolescence (69%, 11/16) and adulthood (75%, 12/16). Initial referral reasons for CNV testing varied and included neurodevelopmental delay in 14 countries (87%), neuropsychiatric issues in 11 countries (69%),

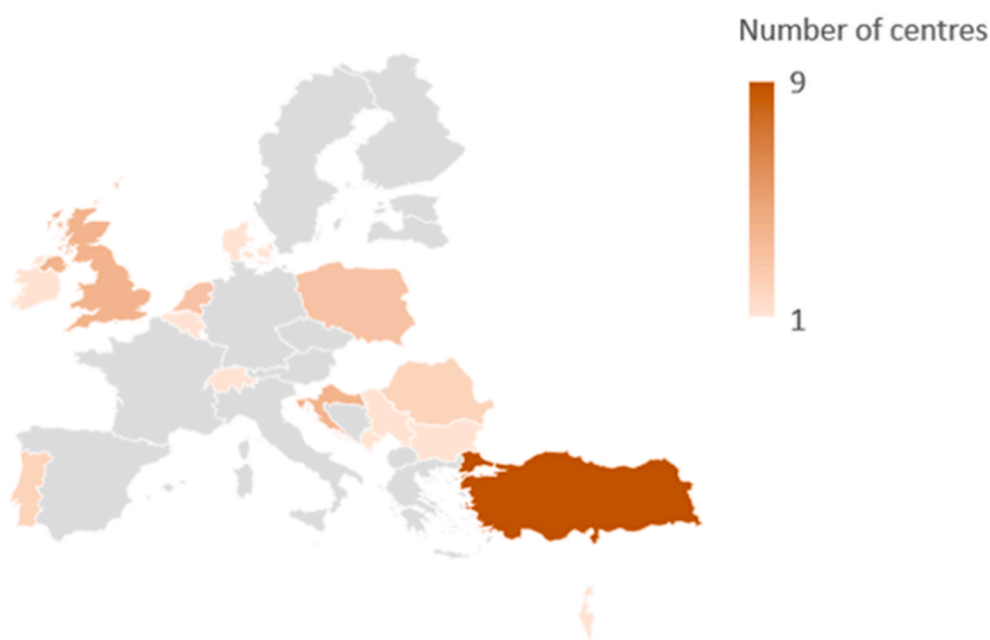
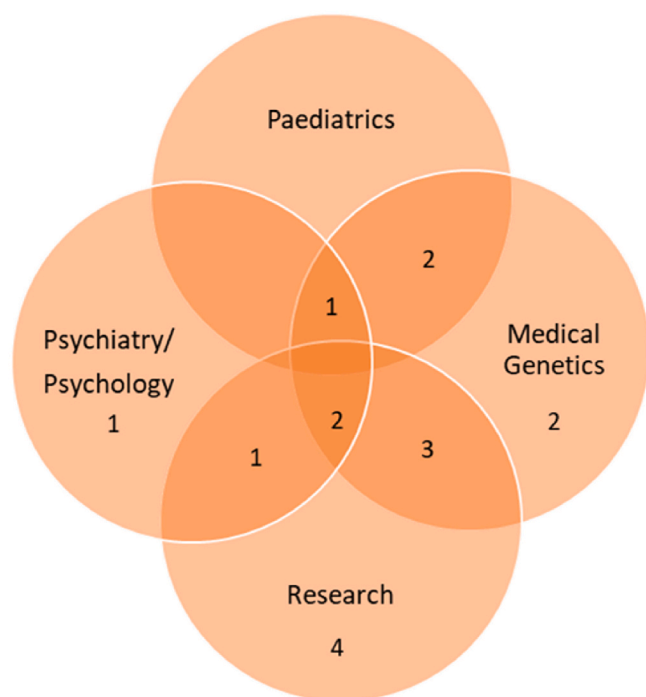


Fig. 2. MINDDS countries that took part in survey.



**Fig. 3.** Overlap in professional background of respondents; numbers refer to countries.

**Table 1**

Approximate numbers of NDD-CNV carriers reported among professionals within MINDDS countries.

CNV	Clinicians	Researchers	Both	Total
1q21.1del	14	52	37	103
1q21.1dup	4	57	18	79
NRXN1del	7	105	59	171
NRXN1dup	0	2	5	7
3q29del	2	10	11	23
3q29dup	2	2	7	11
7q11.23del	13	6	179	198
7q11.23dup	1	5	17	23
9q34.3del	5	29	28	62
9q34.3dup	0	4	2	6
15q11.2del	16	106	148	270
15q11.2dup	14	32	34	80
15q11-13del	10	7	284	301
15q11-13dup	1	6	32	39
15q11.3del	7	44	61	112
15q11.3dup	9	94	17	120
16p11.2del	8	115	191	314
16p11.2dup	1	56	171	228
16p11.2distaldel	2	5	17	24
16p11.2distaldup	1	2	18	21
16p13.11del	4	9	38	51
16p13.11dup	9	14	28	51
17q12del	0	2	17	19
17q12dup	5	6	27	38
22q11.2del	58	354	788	1200
22q11.2dup	6	57	116	179
22q13.3del	7	3	98	108
22q13.3dup	1	1	4	6
<b>TOTAL</b>	<b>207</b>	<b>1185</b>	<b>2452</b>	<b>3844</b>

congenital malformations in 11 countries (69%), and potential familial inheritance in 8 countries (50%).

### 3.2. Summary of current data available from sites

A broad range of methods have been used for NDD-CNV screening

across Europe. Most of the countries (88%, 14/16) reported use of microarray (CGH), followed by the FISH method (63%, 10/16), while lower frequencies were observed for whole genome sequencing (38%, 6/16) and exome sequencing (38%, 6/16).

MINDDS members were asked to report the range of phenotypic data available. All countries reported availability of medical history, developmental history, family history and anthropometric data. The majority (94%, 15/16) also reported data on educational history, neuropsychological evaluations including IQ testing, as well as treatment and intervention history. 63% (10/16) reported availability of psychiatric data. Regarding biological data, all countries had DNA samples available within their cohorts; whilst only 13% (2/16) had original blood samples available, 13% (2/16) had RNA samples available, 6% (1/16) had iPSC cells, 6% (1/16) EBV cell lines, 6% (1/16) amniotic cells, and 6% (1/16) fetal material. Regarding neurophysiological data, 75% (12/16) of the countries reported MRI (structural and/or functional), 69% (11/16) EEG, 6% (1/16) MEG, 56% (9/16) audiological testing, 31% (5/16) eye-tracking, and 12.5% (2/16) wearables data available.

One of the major challenges in future studies and collaborations is the possibility to re-contact the patients with NDD-CNVs. 4 countries reported that all participants could be re-contacted, 8 countries reported that 75% of participants could be re-contacted, 3 countries reported that 50% could be re-contacted, and 1 country reported that 25% could be re-contacted.

## 4. Discussion

We developed a survey which aimed to capture the landscape of clinical and research cohorts of patients with NDD-CNVs across Europe, to inform the potential of conducting large scale research studies. We did not set out to capture every diagnosed NDD-CNV carrier in Europe, rather this survey aimed to capture information from research and clinical centres where there would be potential and enthusiasm for contributing to future collaborative research on NDD-CNV carriers. Through the MINDDS consortium, 36 clinical and research centres across 16 countries completed the survey. Appendix 2 provides a useful resource to the European research community in developing new international collaborations focused on NDD-CNVs. The majority of respondents were working in the field of medical/clinical genetics, psychology/psychiatry and pediatrics, mostly in a position as both clinician and researcher. 3844 NDD-CNV carriers were identified across Europe, and centres provided information indicating availability of a range of genetic and phenotypic data, as well as the extent to which participants could be re-contacted and data shared. This survey represents a first step to a pan-European approach to understanding the clinical phenotype of NDD-CNV carriers.

Results of the survey provided a broad perspective of the current situation regarding clinical and research practice within MINDDS consortium. Firstly, we queried the professional backgrounds of the respondents. We found that the majority were medical geneticists, who tended to combine clinical (psychiatrists, psychologists, pediatricians) and research duties. In a few countries we received reports from only academic researchers, and in one from clinician only. This could indicate a need for greater awareness and education of clinicians regarding contribution of CNVs in NDDs. For example, few recent papers addressed this issue with topics related to increasing genetic knowledge in psychiatrists (Grimm et al., 2020; Nurnberger et al., 2018), and particularly regarding CNVs (Sullivan and Owen, 2020). Increased awareness of the contribution of rare genetic conditions to clinical diagnosis in fields such as psychiatry/psychology, pediatrics, cardiology, neurology and occupational therapy, should improve building a multidisciplinary clinical network in providing a diagnosis on time, as well as specific care and treatment for patients with NDD-CNVs. Furthermore, most of the countries (14/16) reported that the main referral reason for NDD-CNV testing was neurodevelopmental delay. Neuropsychiatric symptoms and congenital malformations were reasons



for testing in 11 countries, while family history was reported as indication for testing in 8 of the countries. These results are similar to the findings for the most common indications for testing for 22q11.2 deletion syndrome (Swillen and McDonald-McGinn, 2015). Referral reasons varied across Europe, possibly reflecting differing clinical and research practices. This points to a need for the development of European clinical guidelines to underpin referral procedures and to increase awareness of these conditions in NDDs.

In addition, children were the most tested group in all countries, while adolescents and adults were tested less frequently, potentially reflecting current bias in referral for genetic testing. It may also reflect the fact that the largest group of responders to our study were pediatricians, who may have greater awareness of NDD-CNVs. Nonetheless, our findings are in accordance with phenotypic studies which indicate that diagnosis of clinical symptoms occurs most frequently in the post-natal or early childhood period (Swillen and McDonald-McGinn, 2015).

Finally, the results of our survey provide a perspective of ongoing NDD-CNV research, availability of biological and phenotype data, as well as numbers of NDD-CNV carriers in countries which are less research intensive or have conducted no research in this field. One of the aims of the overall COST initiative is to stimulate research in countries that have been historically less research intensive. There is great potential to achieve this in MINDDS as many NDD-CNV clinical cohorts which offer potential for research in currently less research-intensive countries are accessible via the MINDDS consortium. In fact, approximate numbers of NDD-CNV carriers presented in Table 1 revealed great potential for extension of collaborations in on-going research fields as well as for new collaborations. According to the literature, there are currently two international consortiums focusing on ND-CNV, related to 22q11.2 deletion syndrome and 16p11.2 deletion and duplication (D'Angelo et al., 2016; Gur et al., 2017; Schneider et al., 2014). Numbers of European carriers identified in our survey are larger than cohorts of European carriers in existing consortiums; 16p11.2 duplication, MINDDS total = 228 vs European carriers in existing consortiums total = 127; 16p11.2 deletion, MINDDS total = 314 vs European carriers in existing consortiums total = 222; 22q11.2 deletion, MINDDS total = 1200 vs European carriers in existing consortiums total = 976 (D'Angelo et al., 2016; Gur et al., 2017; Schneider et al., 2014). Our survey indicates there is huge potential for large-scale study of NDD-CNV carriers from Europe, as some, but not all are involved in current consortiums, indicating potential for collaborations that increases diversity and sample size of cohorts in Europe. Regarding other NDD-CNVs, numbers are higher compared to individual study cohorts (Al Shehhi et al., 2019; Bernier et al., 2016; Chawner et al., 2019). There is a broad range of phenotypic data that is collected across the countries including clinical, neuroimaging, and electrophysiological data. All countries reported to have medical history, developmental history, family history and anthropometric data, majority have cognitive data, while psychiatric data are less present. One of the reasons could be lack of knowledge and involvement of psychiatrists in NDD-CNV research, which again highlights a need for further genetic education.

As far as we know, this survey is the first of its kind to capture the potential for NDD-CNV research across Europe. However, the survey findings should be considered in light of some limitations. Specifically, some of the sites that responded focused on the study or treatment of a limited range of CNVs. This may be attributable to a specific research focus or the clinic's scope for diagnosing rare genomic disorders (such as 22q11.2 deletion and 7q11.23 deletion), leading to ascertainment bias. In addition, it should be noted that our survey focused on well-characterized pathogenic CNVs in NDDs, however, although there is increasing research evidence for the role of non-coding CNVs in NDDs, these, were not covered by this survey. However, the MINDDS consortium provides a framework for collaboration that can be applied to newly discovered variants in the future. Furthermore, not every country in the MINDDS network completed the survey, and in our results, we highlighted some of the barriers (in some countries) in completing the

survey, often due to lack of access to centralized records. Lack of responses from some countries indicate that not all countries may have the resources or infrastructures to currently contribute to collaborative studies or would require additional resources to participate in international research networks. However, it is encouraging that the survey was completed by many countries classified by COST as Inclusiveness Target Countries which are currently not research-intensive. This demonstrates great potential for future European research networks that are more inclusive of a wider range of countries, and therefore more likely to capture how the phenotype of NDD-CNVs is expressed across a range of cultural, ethnic and socioeconomic settings. Moreover, our study highlights interest for building larger multi-centre studies on NDD-CNVs including countries which are traditionally less research-intensive. International consortiums have the potential to provide platforms for facilitating the research potential of countries that have been traditionally less research-intensive, leading to large highly-powered research programmes that have greater representation of the diversity of patients as well as the talent of researchers that exists across Europe. Networks like MINDDS represent a framework for establishing such a converging research platform which will (a) contribute to and increase/improve our knowledge and understanding of the link between CNV and NDD phenotypes; (b) improve care and quality of life for CNV carriers and their families.

An important step in delivering a pan-European study will be the harmonization of previously collected data and standardizing phenotypic protocols for future data collection. This will require the consideration of several issues including (a) developing a protocol that is feasible across a range of clinical and research centres with varying constraints on resources and contact time with patients, (b) creating protocols that can be delivered in a range of languages and are appropriate across the cultural diversity in Europe, and (c) developing databases and data collection procedures suitable for large scale multi-site studies involving potentially sensitive data. Within MINDDS, a training school was conducted to start to discuss and address some of these issues (<https://mindds.eu/activities/training-schools/skopje/>). As mentioned before, there have been some initial collaborative efforts for the 22q11.2 Deletion and 16p11.2 Deletion and Duplication NDD-CNVs, but arguably these collaborations have not involved a diverse range of European countries (D'Angelo et al., 2016; Gur et al., 2017), and have been limited to categorical psychiatric diagnoses and IQ scores. There is a need for international studies to create standardized protocols that go beyond diagnoses and capture dimensional endophenotypes across the full range of NDD-CNVs (Chawner et al., 2019, 2020).

In conclusion, this survey within the MINDDS consortium has established great potential for large multi-centre studies of NDD-CNV carriers in Europe. The MINDDS consortium is strongly positioned to contribute to collaborations and exchange of knowledge and information across Europe. The development of new pan-European studies will contribute to and improve knowledge of the complex relationship between NDD-CNV and clinical phenotype, resulting in improved care, counselling and quality of life for NDD-CNV carriers and their families across Europe.

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## CRediT authorship contribution statement

**Samuel J.R.A. Chawner:** Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Marina Mihaljevic:** Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing. **Sinead Morrison:** Methodology, Investigation, Resources, Writing -

review & editing, Project administration. **Hale Yapici Eser:** Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing. **Anne M. Maillard:** Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing. **Beata Nowakowska:** Methodology, Investigation, Resources, Writing - review & editing, Funding acquisition. **Marianne B.M. van den Bree:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Funding acquisition. **Ann Swillen:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision, Funding acquisition.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmg.2020.104093>.

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