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GENES AND SPEECH

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Tento článek si můžete v českém jazyce přečíst zde.

Abstract

The human genome contains approximately 20,000 protein-coding genes, of which more than 15,000 (3/4) are expressed, among others, in the central nervous system. Variants that damage the function of these genes (called pathogenic variants) can lead to various forms of neurodevelopmental disorders (NDD), including speech and language disorders. These can occur alone or in various combinations. In this review article, we provide information on the possibilities, limits and importance of genetic testing in patients with NDD.

Keywords

neurodevelopmental disorders, speech and language disorders, genomic variants, genetic testing

Introduction

Clinical genetics deals with the study and detection of pathogenic genomic variants that can have a negative impact on human health, and their intergenerational transmission. The human genome contains approximately 20,000 protein-coding genes and a number of regulatory regions. Genomic variants leading to malfunction of these genome regions can have various health consequences. Changes in the function of genes involved in the development and function of the central nervous system (CNS), of which there are more than 15,000 according to the Human Protein Atlas, can result in a variety of Neuro-Developmental Disorders (NDDs).

NDDs are defined as disorders that have their basis during embryonic development and usually manifest in childhood. They are a phenotypically and etiologically heterogeneous group of deficits that *"produce impairments of personal, social,*

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academic, or occupational functioning" (MeSH descriptors, 2024). In addition to disorders of Intellectual Development (ID), Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD), this broad group also includes, according to ICD-11, Developmental Learning Disorder, Tic Disorders or developmental speech or language disorders. These include developmental Speech Sound Disorder (SSD), better known in Czech terminology as *dyslalia*, Developmental Language Disorder (DLD) also known as developmental dysphasia or Developmental Speech Fluency Disorder presenting as stuttering and cluttering. According to a more recent concept, NDDs also cover schizophrenia and bipolar disorder (Morris-Rosendahl & Crocq, 2020) and could also be taken to include Developmental and Epileptic Encephalopathy (DEE).

The etiology of NDDs is predominantly genetic, the heritability coefficient (i.e. the share of genetic influences in all forming factors) is estimated to range between 0.5 and 0.9. However, when searching for the etiology of NDDs, we need to take into account the influence of other than genetic factors. Damage to the developing CNS by external influences during pregnancy, peripartum or early postnatally may also play a role. The perceived percentage of risk factors in NDD etiology is evolving as knowledge improves, in favour of genetic factors, though external factors are not negligible in their etiology, especially in genetically predisposed individuals. Moreover, even today we find a significant portion of disorders, particularly the less severe ones, still being classified as disorders with unknown/unexplained etiology. In these cases, an important role seems to be played by multifactorial inheritance, i.e. a combination of low-penetrant genomic variants and exposure to less significant external risk factors that may have eluded attention (Ropers, 2010; Wiśniowiecka-Kowalnik & Nowakowska, 2019).

Epidemiology of NDDs

The cumulative occurrence frequency of NDDs in the global population is not precisely mapped. However, estimates are available from various studies, which mostly relate to particular NDDs, and fail to note that NDDs often cluster within a complex of disabilities (Table 1). According to various studies, the prevalence of ID is 1–3%, of ASD 1–2.2% and of ADHD 2–7%. The total prevalence of developmental speech or language disorder is unknown, but estimates range from 6–15% (Table 2). How many people actually suffer from NDDs cannot be obtained from these data, as most people have more than one NDD and the cumulative prevalence cannot be the simple sum of the above figures. A conservative estimate posits around 4% of the European population, and if we include a broader range of disorders, this could be up to 10% of the population (Mezinska et al., 2021; Mitani et al., 2021).

NDD	Comorbid NDDs (in %)			
	ID	ASD	Epilepsy	ADHD
ID	x	40[1]	20–30[2]	8–14[3]
ASD	31[4]–70[5]	x	5–46[6]	~45[7]
Epilepsy	26–32[6]	5–21[6]	x	28–70[6]

Table 1: ***Estimated frequency of comorbidities among NDDs. Sources: [1] La Malfa et al., 2004, [2] van Ool et al., 2016, [3] Hässler et Thome, 2012, [4] Wiśniowiecka-Kowalnik & Nowakowska, 2019, [5] Fombonne, 2002, [6] Nickels et al., 2016, [7] Gordon-Lipkin et al., 2018.***

Estimated incidence in the population (%)	
ID[1]	1–3
ASD[2]	1–2.2
ADHD[3]	2–7
Epilepsy[4]	0.5–1
DLD[5]	6–15

Table 2: ***Estimated prevalence of NDDs and epilepsy in the population. Sources: [1] Ropers, 2008; de Vries et al., 2005; Marrus et Hall, 2017, [2] Baron-Cohen et al., 2009; Kim et al., 2014, [3] Nickels et al., 2016, [4] Kršek, 2010; Beghi 2020, [5] ICD-11***

NDDs and their Etiology from the Point of View of Clinical Geneticists

The classification of NDDs has been undergoing constant revision over the years, one of the likely reasons being a progressively more profound understanding of their causes.

NDDs can theoretically occur in isolation. In these cases, the patient would suffer from only one of the disorders, e.g. Expressive Developmental Dysphasia or cluttering. However, NDDs usually occur in combination, as symptoms of more complex involvement (Table 1), but with a common cause. In this case, we are talking about a "syndrome", as defined in Wikipedia: *"A syndrome is a set of medical signs and symptoms which are correlated with each other and often associated with a particular disease or disorder. The word derives from the Greek σύνδρομον, meaning 'concurrence'."*

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At this point, however, we encounter potential misunderstandings between clinical geneticists and other specialists, as syndromic impairment is perceived differently by geneticists and is related to the historical need to diagnose with the most accurate description of the phenotype, encompassing dysmorphic features ("minor anomaly" such as hypertelorism) and associated malformations ("major anomaly" such as congenital heart disease). This is mainly due to the fact that in the past, clinical genetics as a discipline was dominated by dysmorphological analysis, and the feasibility of confirming our assumptions at the molecular level was very limited or non-existent (Hennekam et al., 2013). In the past, the syndromes described often had a very specific facial phenotype and a number of distinctive symptoms (consider the well-known Down syndrome, but also Rett syndrome, Fragile X syndrome and others). Children with NDDs who did not have a sufficiently specific phenotype were usually categorized as having "cerebral palsy", "mild brain dysfunction" and the like. The syndromological approach of clinical geneticists persists even today, when the scope for molecular diagnostics has reached a very high level, and careful evaluation of the phenotype, including dysmorphic features, is important for reverse phenotyping and correlation of the variants obtained with the phenotype (Hurst & Robin, 2020).

This different approach implies that whereas from the point of view of neurologists, psychologists, psychiatrists or clinical speech therapists the child's disability may be complex (syndromic), since the child has more than one NDD, from the point of view of genetics it may be a non-syndromic disability, as the child does not show dysmorphic features or associated malformations. This alternate viewpoint has to be mentioned, in order to avoid future misunderstandings between clinical geneticists, parents and other specialists (Figure 1). It should be added that even from our point of view, "non-syndromic" NDDs can have a genetic cause in the form of a highly penetrant pathogenic variant in a single gene. Many tens to lower hundreds of such genes are already known, and their number is still growing thanks to Massively Parallel Sequencing methods (Vissers et al., 2016). Last but not least, the clinical geneticist's approach to a patient with NDDs is focused, among other things, on what is – for us – a key question: "What is the probability of proving an unambiguous genetic cause?" (highly penetrant pathogenic genomic variants). There are several reasons for this approach. The probability of detection of a highly penetrant pathogenic genomic variant determines the choice of molecular-genetic examination methods, the method of communication with the child's parents, the likelihood of comorbidities, the likelihood of recurrence of the disease in the family, the risk to relatives and the chances of effective therapy.

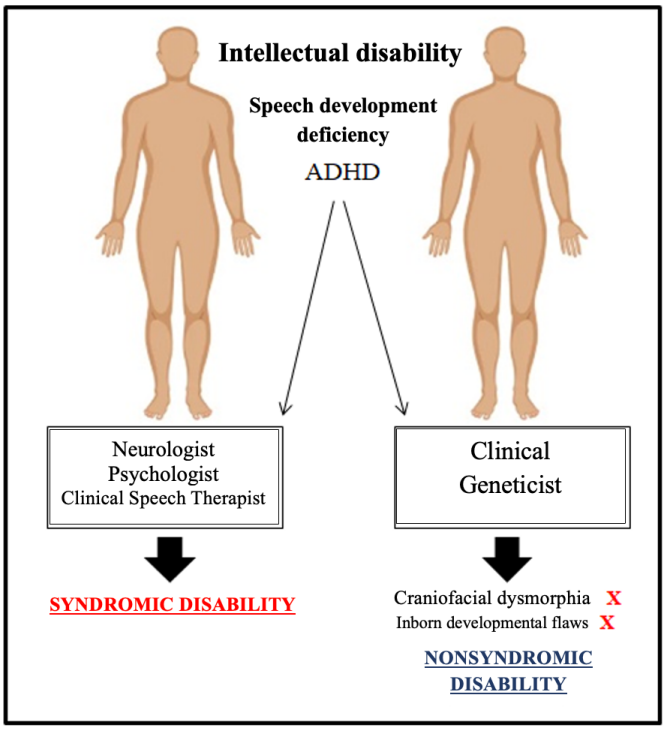


Figure 1: ***Syndromic disability from the perspective of geneticists vs. other specialists. If significant dysmorphic features and developmental defects are not present, the geneticist evaluates complex NDDs as non-syndromic.***

Variants in the Human Genome as a Cause of NDDs and Methods of their Detection

Genomic variants can be roughly divided into Copy Number Variants (CNVs[3]), including microscopically detectable aneuploidies, deletions, duplications, and unbalanced larger-scale translocations, Single Nucleotide Variants (SNVs[4]), including single or multiple nucleotide insertions/deletions (ins/del variants), and expansions of repetitive sequences, usually triplets. The clinical consequences then depend on the type and degree of impairment of the expression of the affected gene or genes, and are not always predictable, nor always known at all. For example, according to the OMIM (Online Mendelian

[3] Copy Number Variants – the multiplication (duplication) or loss (deletion) of a larger part of genetic information.

[4] Single Nucleotide Variant – the substitution of one nucleotide for another, deletion of one nucleotide or insertion of one nucleotide.

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Inheritance in Men) database, we currently know the associated phenotype for only about 8000 genes; for the others the consequence of their damage to human health is not sufficiently researched and substantiated, although a negative effect is assumed (Amberger et al., 2009).

Methods for detecting variants in the human genome have undergone intensive development over the last 50 years, and with their development, the clarification of rare diseases, whether general (Figure 2) or specifically those associated with NDDs (Figure 3), is increasing. Table 3 shows the currently most widely used methods. The appropriate method of analysis is chosen by a clinical geneticist after a comprehensive evaluation of the patient. The choice of method depends on the expected type of causal pathogenic variant, which can sometimes (but not always) be predicted according to the patient's clinical picture. Depending on the evaluation of the patient's clinical picture, we can choose a targeted examination to detect a specific pathogenic variant (e.g. if the phenotype clearly corresponds to Fragile X syndrome, Down syndrome, etc.). In the case of a non-specific phenotype we opt for whole-genome analyses. At present, the method of first choice at our department is typically exome sequencing (ES) in "short read" quality, which detects both SNVs, albeit less reliably, and CNVs and some triplet expansions.

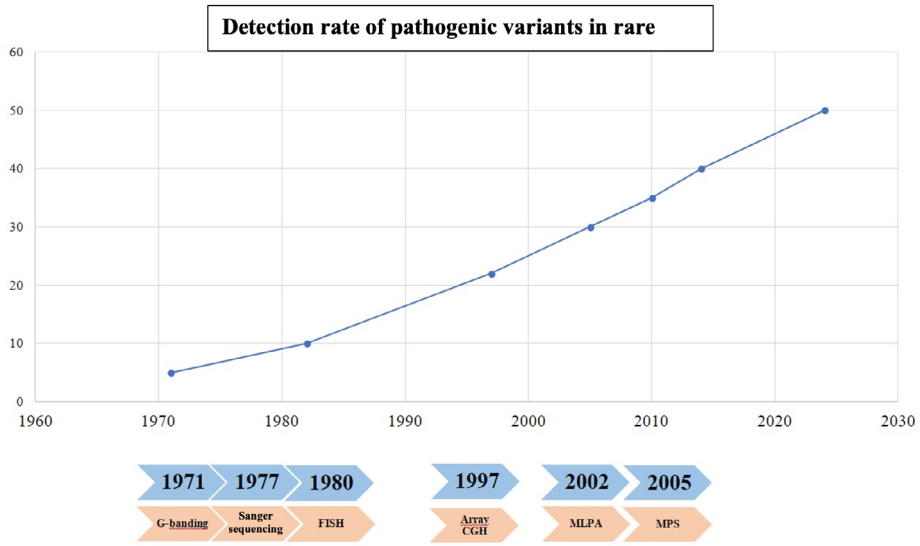


Figure 2: ***Development of methods for detecting genomic variants and % of solved cases of rare diseases from 1970 to the present. FISH – Fluorescence In Situ Hybridization, arrayCGH – Comparative Genomic Hybridization on a chip, MLPA – Multiplex Ligation-dependent Probe Amplification, MPS – Massively Parallel Sequencing.***

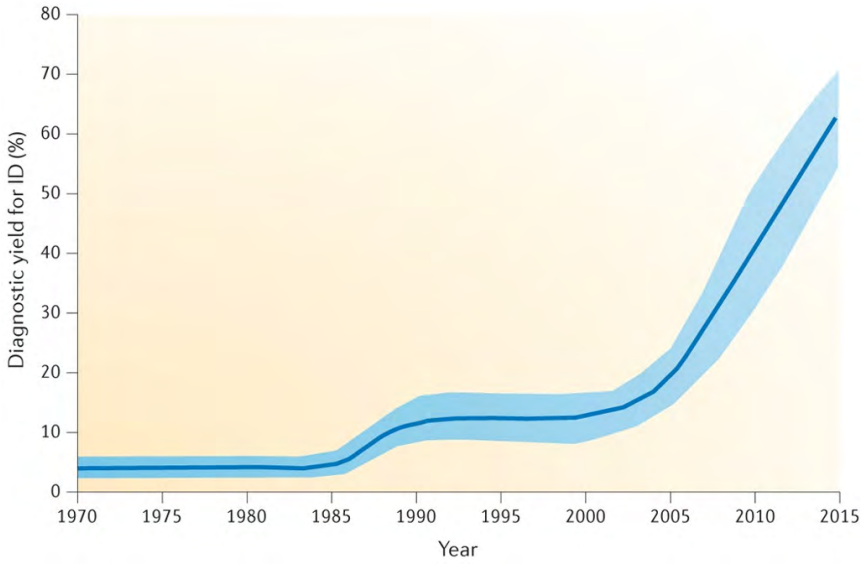


Figure 3: ***Development of knowledge about genetic causes of NDDs over time. Adapted from Vissers et al., 2016.***

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Method	Detectable variants
Targeted methods	
Fluorescence *In Situ* Hybridization (FISH)[1]	CNV (microdeletions, microduplications), mosaics, marker chromosomes
Multiplex Ligation-dependent Probe Amplification (MLPA)[2]	Intragenic CNV
Sanger sequencing[3]	Single nucleotide variants (SNVs)
Modified PCR[4]	(Tri)nucleotide repeats
Whole-genome methods	
Karyotyping using G-banding[5]	CNV (aneuploidy, larger CNV), translocation, inversion, marker chromosomes
Comparative Genomic Hybridization on chips (aCGH)[6]	CNV (microdeletion, microduplication)
SNP-based array (SNPa)[7]	CNV, homozygosity regions
Whole-exome (WES)/whole-genome (WGS) sequencing[8]	SNV, CNV, trinucleotide repeats

Table 3: ***An overview of the most commonly used targeted and whole-genome laboratory methods used to identify genomic variants. [1] Pinkel et al., 1986, [2] Schouten et al., 2002, [3] Sanger et al., 1977, [4] Tassone, 2015, [5] Sanchez et al. 1973, [6] Solinas-Toldo et al., 1997; Pinkel et al., 1998, [7] Gijsbers et al., 2009, [8] van Dijk et al., 2014.***

Copy Number Variants

In terms of genomic variants, the longest-known in NDD etiology is aneuploidy, i.e. CNV, where the entire chromosome is missing or excessive. Most of these CNVs are lethal, prenatally or early postnatally. In those that may not be prenatally lethal (Table 4), we encounter various manifestations from the NDD spectrum, typically with a whole complex of adversities, both in the sense of a combination of different NDDs and in the sense of the presence of malformations and dysmorphic features. If these are not detected during pregnancy screening, they are diagnosed immediately after birth, with the exception of some sex chromosome aneuploidies, which may be clinically inconspicuous until puberty or even throughout life. From the diagnostic point of view, aneuploidy occurring in mosaics is also problematic, as it may also concern chromosomes other than those listed in Table 4, but this is beyond the scope of this paper. The method of choice in case of suspected aneuploidy is QF-PCR (Quantitative Fluorescence Polymerase Chain Reaction) for rapid detection and confirmation of the suspicion, followed by karyotyping to clarify its nature (free trisomy vs. translocation form – this is important for the further reproductive prognosis of the parents, not for the prognosis of the child).

Syndrome	ORPHA code	Estimated prevalence[1]	ID (%)[2]	ASD (%)	Epilepsy (%)
Down sy.	870	1/400–3000	80–99	40[3]	1–13[4]
Edwards sy.	3380	1/6000–8000	80–99	NA	65.5
Patau sy.	3378	1/8000–15000	80–99	NA	80–99[2]
Turner sy.	881	1/5000	<1	<1[2]	<1[2]

Table 4: ***Overview of aneuploidies associated with NDDs. [1] Name and prevalence according to OrphaNet (www.orpha.net). Frequency of NDDs in individual syndromes: [2] According to the Genetic and Rare Diseases Information Center (GARD); [3] According to Wester Oxelgren et al., 2017; [4] According to Rahman & Fatema, 2019; [5] According to Verrotti et al., 2015. Frequency of <1% indicates the population probability of the occurrence of a given NDD. Sy. – syndrome, NA – Data Not Available.***

A specific group of genomic variants detectable by karyotyping consists of larger-scale unbalanced translocations, deletions, duplications and marker chromosomes, which are often unique (non-recurrent) and whose prognosis is uncertain because many dozens of genes are affected. However, association with NDDs is the rule for these types of genomic variants.

Another group of genomic variants, which have been progressively described thanks to the introduction of FISH (Fluorescence *In Situ* Hybridization), MLPA (Multiplex Ligation-dependent Probe Amplification) and arrayCGH (Comparative Genomic Hybridization on chips), are CNVs responsible for microdeletion or microduplication syndromes. Compared to the previous group, these syndromes are often recurrent due to the specific genome architectonics at fault points and their prognosis is somewhat more predictable. Once again, NDDs practically always accompany phenotypic expression. As with aneuploidies, in most cases, patients also have a number of other problems, such as smaller stature, failure to thrive, visual disturbances, hearing disorders and various malformations (most often heart or cleft defects). An overview of the most well-known recurrent syndromes is given in Table 5.

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Syndrome[1]	ORPHA code	Estimated prevalence[1]	ID (%)[2]	ASD (%)[2]	Epilepsy (%)[2]	ADHD (%)[2]
22q11.2 deletion sy.	567	1/2000–4000	30–79	5–29	5–29	30–79
1p36 deletion sy.	1606	1/5000–10000	80–99	30–79	30–79	<1
Angelman sy.	72	1/10000–20000	80–99	<1	80–99	<1
Prader-Willi sy.	739	1/15000–30000	30–79	1–4	1–4	30–79
Smith-Magenis sy.	819	1/15000–25000	80–99	<1	5–19	80–99
Koolen-De Vries sy.	96169	1/55000	80–99	<1	30–79	<1
22q13.3 Monosomy	48652	NA	5–29	30–79	5–29	<1
Miller-Dieker sy.	531	1/100000	100	<1	80–90	<1

Table 5: ***Examples of recurrent microdeletion and microduplication syndromes associated with NDDs. [1] Syndrome name and prevalence according to OrphaNet. Sy. – syndrome, NA – Data Not Available. [2] Frequency of NDDs for the respective syndromes according to GARD. Frequency of <1% indicates the population probability of the occurrence of a given NDD.***

Thanks to genome-wide methods, a number of recurrent CNVs have been described, which probably have only the character of "susceptibility" (a risk factor) and only contribute to the resulting phenotype. The interpretation of the influence of these variants is not so clear, as they are often inherited from an unaffected parent and it is not clear to what extent they contribute to the phenotype of the patient with NDDs. There is speculation about incomplete penetrance, variable expressivity, but also about the so-called second hit model, which assumes that a worse affected individual from the family carries other variants which, in combination with the detected CNV, leads to their more severe disability (Girirajan & Eichler, 2010). Currently, the term "High Frequency, Low Penetrant" (HFLP) is being introduced for these variants, as they are often detected even in healthy populations. Examples of known recurrent CNVs that have incomplete penetrance and some are more of the "susceptible" character, rather than clearly pathogenic in status, are shown in Table 6.

Syndrome[1]	ORPHA code[1]	Estimated prevalence[1]	Association with NDDs[1]
1q21.1 Microduplication	250994	<1/1000000	ID, ASD, ADHD
15q11.2 Microdeletion	261183	NA	ASD, ADHD, Epilepsy
15q13.3 Microdeletion	199318	NA	ID, ASD, Epilepsy
16p11.2 Distal Microdeletion	261222	NA	ID, ASD
16p11.2p12.2 Microduplication	261204	<1/1000000	ID, ASD
17q12 Microdeletion	261265	<1/1000000	ID, ASD
17q12 Microduplication	261272	<1/1000000	ID, ASD, Epilepsy
22q11.2 Microduplication	1727	NA	ID

Table 6: ***Examples of recurrent microdeletions and microduplications that have incomplete penetrance and variable expressivity (HFLP) but may be associated with NDDs. (1) Data from OrphaNet. NA – Data Not Available.***

Expansion of Triplet Repeats

Genomic variants from this category play a minor role in the etiology of NDDs. They play a larger role in the etiology of neurodegenerative diseases, typically manifested in adulthood. Their detection is not easy due to their molecular nature and it is usually necessary to use targeted testing, as whole-genome methods are not optimized for their detection. Of this group, a patient with Fragile X chromosome syndrome is the most likely to appear in a clinical speech therapist's outpatient clinic, a patient with a severe form of myotonic dystrophy 1, less so. In any case, being a monogenic disease type, these are assigned to Table 7.

Single Nucleotide Variants

Findings about SNVs playing a role in the etiology of NDDs grew very slowly before the era of genome-wide methods, but after their advent, and introduction into practice, a significant speeding-up can be seen. Prior to the introduction of Massively Parallel Sequencing (MPS) methods, clinical geneticists, working with other specialists, were able to clinically diagnose well-defined, known and common syndromes associated with NDDs. The molecular basis of these syndromes could then usually, but not always, be identified using targeted methods (Sanger sequencing, MLPA, etc., see above). Without access to the laboratory method, the diagnosis was made only clinically, and in some patients confirmed or re-evaluated years later, based on new analyses. A significant shift in the diagnosis of genetic causes of monogenic and especially non-syndromic NDDs occurred after the introduction of MPS methods, which enabled identification of not only (but especially) *de novo* pathogenic variants in patients who did not have a phenotype fitting the defined syndrome. These patients may show isolated severe NDDs or complex NDDs, yet may or may not exhibit dysmorphic features, and may or may not have associated developmental defects. The contribution of *de novo* SNVs to the etiology of NDDs with a known monogenic genetic cause is

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significant. It is estimated at 15–25% for ASD (Ramaswami & Geschwind, 2018), for ID at more than 70% (Bowling et al., 2017) and for severe epilepsy and DEE at more than 80% (Staněk et al., 2018). An overview of common and relatively well-known monogenic syndromes associated with NDDs, which could be diagnosed at the molecular level even before the MPS era, is shown in Table 7. At present, many hundreds of such diseases are defined and it would not be useful to list them here. The data can be found in databases such as OMIM or OrphaNet.

Basic information about the syndrome[1]				Combined NDDs %[2]			
Syndrome name	ORPHA code	Gene	Estimated prevalence	ID	ASD	Epilepsy	ADHD
Fragile X sy.	908	*FMR1*	1/2400–1/6000	80–99	5–29	5–29	30–79
Myotonic dystrophy Type 1	273	*DMPK*	1–5/10000	30–79	5–29	NA	NA
Rett sy.	778	*MECP2*	1/9000–30000	80–99	1	30–79	<1
Phenylketonuria	79254	*PAH*	1/15000	30–79	<1	1	1
Tuberous sclerosis	805	*TSC1, TSC2*	1/11300–25000	30–79	30–79	30–79	5–29
Sotos sy.	821	*NSD1*	1–9/100000	30–79	5–29	1	1–4
Smith-Lemlius-Opitz sy.	818	*DHCR7*	1/20000–40000	80–99	30–79	5–29	30–79
Dravet syndrome	33069	*SCN1A*	<1/40000	30–79	30–79	30–79	<1
Atypical Rett sy.	3095	*CDKL5, FOXG1, NTNG1, MECP2*	1/45000	30–79	<1	30–79	<1
Mowat-Wilson sy.	2152	*ZEB2*	1/50000–70000	1–4	<1	30–79	<1
Costello sy.	3071	*HRAS*	1/250000–300000	30–79	<1	<1	<1

Table 7: ***Examples of more common monogenic syndromes with a specific phenotype and associated NDDs, the molecular diagnosis of which was possible in the Czech Republic before the introduction of MPS methods (unpublished data). [1] Data from the OrphaNet database; [2] data from the GARD database. Sy. – syndrome, NA – Data Not Available.***

What are the Limits of Genetic Diagnosis of NDDs

Although knowledge about genomic variants and their clinical impacts has been rapidly growing in the last decade and despite the fact that whole-genome analyses, including ES, are now routinely available, the probability of detecting a causal genomic variant in patients with NDDs is still relatively low (although significantly higher than it was some 15 years ago). The probability of proving a causal variant correlates, among other things, with the severity of the affliction – the more severe and complex the phenotype, the greater the probability of detecting a pathogenic variant with high penetrance. Nevertheless, even in strictly selected cohorts, the success rate is around 50% (Vissers et al., 2016) and lower in less strictly selected cohorts. One of the problems faced is limited detection of some types of variants (see above) and the other, probably more significant, is limited interpretation. The human genome is huge, there are many variants at different levels, and the impact of all of them is far from fully explored. The situation is a little easier in CNVs of a larger scale, where the pathogenic effect is rather likely, although size is not always decisive, and even CNVs of a larger extent may have reduced penetration.

The situation is a bit more complicated in the case of monogenic NDDs. The main limitations in the diagnosis of SNV include the inability to detect or correctly interpret variants lying in non-coding regions of genes (so-called intron variants), while variants lying in coding regions (in exons) are not fully explored. A clinically significant variant may thus escape attention. We also come up against the fact that there is no clear association with phenotype for many genes, so although these genes are expressed in the CNS and we detect the variant in them, we are often not sure whether it causes NDDs in the patient.

The most problematic NDDs are the multifactorially preconditioned. In these cases, current genetics does not suffice, and although a lot of effort is focused on genome analyses and calculations of "polygenic risk scores", these approaches cannot yet be used in routine practice.

How to Proceed if NDDs are Suspected

First of all, it should be said that there is no universal guide. Given the heterogeneity of the difficulties and the individual factors that affect the course and prognosis of the NDDs, such a catch-all guide is not possible. One approach applies to newborns and infants with a significantly high-risk pre- and perinatal history or developmental defects, who are often under the care of specialists, including geneticists, from birth. A different approach applies to seemingly physiologically normal newborns and small infants who are "merely" referred to the care of general practitioners. In their cases, the first signs of NDDs are to be noted by the general practitioner during preventive examinations, focused, among other things, on proper psychomotor development. A child suspected to have NDDs should then be referred to appropriate specialists. Genetic testing makes sense especially for more severe combined NDDs, which are more likely to prove a highly penetrant causal pathogenic genomic variant, but it is also possible

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to refer patients with a milder form of NDDs – whether a sporadic or familial occurrence. For these, there is a lesser chance of proving underlying cause, but there is still the possibility of detecting genetic risk factors from HFLP groups.

Of course, clinical geneticists will find it helpful if such a child is first examined by a neurologist, and preferably by a psychologist, before visiting the genetic clinic. This allows us to better choose the method of examination and also to better evaluate data from the ES by entering more accurate HPO terms. There is also the question of scheduling the genetic testing. In the case of most non-syndromic monogenic and multifactorial NDDs, which are the most common, there is probably no risk in delay (although there may be a risk of epilepsy as a common comorbidity). In these cases, genetic diagnosis should be performed only when the family is ready for it and when they feel that it can be of some benefit for them (see below).

How Genetic Diagnostics can Harm a Patient and their Family

The referring specialists take little account of the fact that genetic diagnosis represents considerable stress and anxiety for the family as they await the outcome. We should thus always consider what, and if any, benefit the diagnosis will bring and whether it is not better to postpone it in some cases. However, the decision-making process is usually complicated – on the one hand, there is the desire of the referring specialists to find out what the problem is and try to help the child (and save the child from more invasive examinations), on the other hand, a number of genetically determined diseases are associated with a very consequential prognosis and parents (with access to the Internet) know this very well and come to genetic consultations expecting the worst. Another problem arises when the genetic cause is confirmed, since there is practically no scope for causal therapy. For parents, this news takes away the hope that their child will recover, and they feel considerable stress and sometimes defeatism. Another problem may lie in the fact that many patients with genetically determined diseases are assessed by field workers unfamiliar with the disease. A situation may then arise where a problem that is not related to the genetic diagnosis and has another (solvable) cause is attributed to the syndrome, without further necessary examinations, which can even endanger our patients. Last but not least, a diagnosis of a genetic disease can have a negative effect on family cohesion, especially if the causal genomic variant is inherited from one parent.

Why Genetic Diagnosis Makes Sense

Despite all the limits, risks and psychosocial aspects that genetic testing entails, knowing the cause of problems can also be beneficial to the family. First of all, there is the reproductive prognosis for the patient, their parents, siblings, as well as the wider family. If we know the genetic basis of the disease (causal genomic variant), we are able to determine this risk (Figure 4), offer targeted testing to relevant relatives and offer preimplantation testing or prenatal diagnosis. Although we face a number of problems in this field (most often ethical and psychological), this is one of the areas where the family can benefit from diagnostics. Another possible benefit is that of more targeted therapy. Although most genetically determined NDDs are not curable, many of them have well-described procedures for symptomatic therapy, including measures focused on speech and language development disorders in specific syndromes. Another benefit is the possibility of preventing associated complications (e.g. known risk during anaesthesia in patients with certain syndromes) or their early detection and management (e.g. hypocalcemia in patients with Di-George syndrome). Knowing the cause of NDDs in the child will also help parents better understand what happened and take away the feeling of guilt that they did something wrong. Parents often look for an explanation for the child's disadvantaged condition in their own behaviour before conception (e.g. the father smoked), during pregnancy (e.g. the mother took paracetamol once for a temperature), or blame it on, say, some vaccination, or a minor head injury that they "allowed to happen". Last but not least, knowledge of the cause will allow parents to join patient support organizations that bring together patients with the same diagnosis and exchange practical experience with child care. Proving a genetic cause can also make it easier for the family to access the subsidies and allowances needed for (often expensive) care.

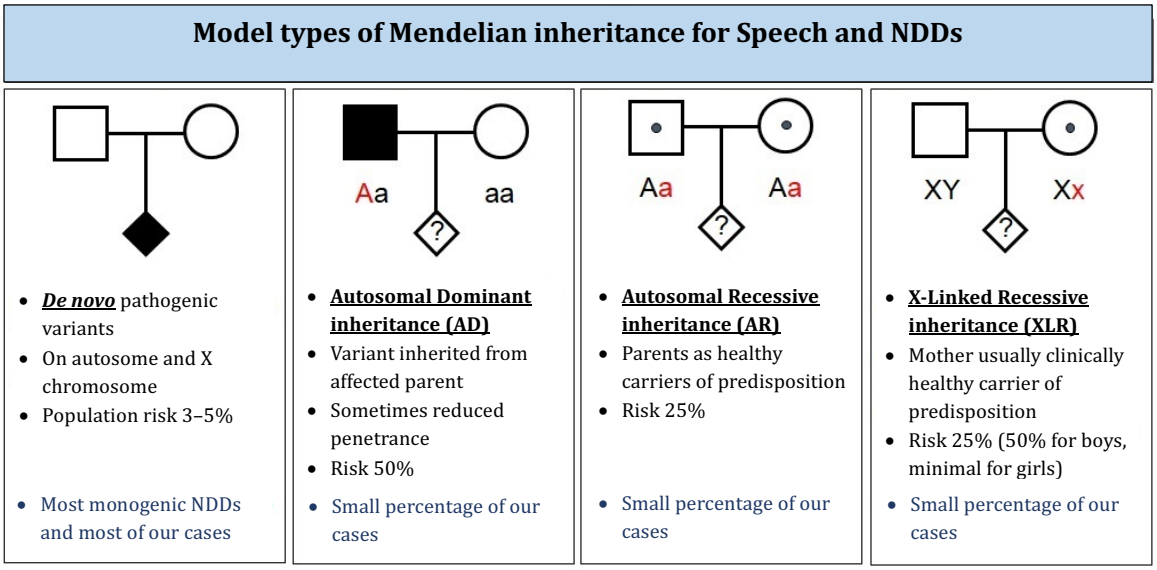


Figure 4: ***Model examples of NDDs inheritance, source: ÚBLG FNM, unpublished data. The 'mutant' allele is marked in red, the 'wild type' allele without the mutation in black.***

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Conclusion

Although NDDs show a high heritability coefficient and whole-genome analyses are currently widely available, genetic testing is not a panacea and the genetic cause (pathogenic variants) is currently detected in approximately 50% of cases. In addition, identifying a genetic cause can cause stress and discomfort for the family. On the other hand, there are also benefits for the patient and their family in the form of hope for targeted therapy and determination of the reproductive prognosis. However, it is clearly true that the family should not be forced into a diagnosis by a specialist if they themselves do not want it. Yet it is also true that if the family does welcome a diagnosis, any specialist, including clinical speech therapists, can refer the patient to the clinical genetics department.

It is therefore not a mistake to ask patients with NDDs (or their parents) whether they have already undergone genetic testing and whether they would care to have it done.

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