The diagnostic rate of inherited metabolic disorders by exome sequencing in a cohort of 547 individuals with developmental disorders

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ABSTRACT

Considering that some Inherited Metabolic Disorders (IMDs) can be diagnosed in patients with no distinctive clinical features of IMDs, we aimed to evaluate the power of exome sequencing (ES) to diagnose IMDs within a cohort of 547 patients with unspecific developmental disorders (DD). IMDs were diagnosed in 12% of individuals with causative diagnosis (177/547). There are clear benefits of using ES in DD to diagnose IMD, particularly in cases where biochemical studies are unavailable.

Synopsis: Exome sequencing and diagnostic rate of Inherited Metabolic Disorders in individuals with developmental disorders.

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1. Introduction

Inherited Metabolic Disorders (IMDs), which affect 1/500 live-born infants, harbor a great phenotypical and genetic heterogeneity [1,2]. When an IMD is suspected without any obvious clinical diagnosis, a first-line biochemical screening is generally proposed (lactate and pyruvate levels, plasma amino acids, urine organic acids, acylcarnitines, ketone bodies and very long chain fatty acids). Usually, these initial results drive specific secondary investigations, mainly based on enzymatic studies and/or targeted genetic analyses. This strategy offers an overall diagnostic yield around 50%, when clinical features are highly suggestive of IMDs (i.e. encephalopathy, coma, hypotonia or organomegaly) and are associated with biological marker elevation [3,4].

Exome/genome sequencing (ES/GS) has revolutionized translational research and diagnosis in rare diseases in a diagnostic genotype-first approach, followed by reverse phenotyping [5]. Harboring a high diagnostic yield (40–70%) in suspected IMDs [6], ES has also appeared efficient in individuals with intellectual disability (ID) and unexplained metabolic anomalies (diagnostic yield 68%) [7]. Some authors therefore suggested updating the diagnosis strategy for IMDs in different steps, bringing together first-line biochemical screening and targeted next-generation panels [4]. For years, biochemical screening has been indicated in first-line etiological investigations for individuals with global developmental delay (DD) or ID [8,9]. However, in isolated ID, the diagnostic yield of first-line biochemical screening is extremely low, around 1%, increasing to 5% in the presence of specific neurological features [10]. ES now appears to be one of the most cost-effective and powerful tools for the diagnosis of ID, with a mean diagnostic yield of 36% [5,11–16]. It has dramatically improved the diagnosis of uninformative or atypical phenotypes and has led to the discovery of hundreds of unknown genes [17].

Here, we aim to evaluate the power of ES to diagnose IMDs in a cohort of 547 patients with non-specific developmental disorders.

2. Patients and methods

Over a five-year period (2015–2019), we recruited 547 individuals affected with a wide variety of developmental disorders. The local ethics committee approved the study (DC 2011-1322). They presented with multiple congenital anomalies or syndromic ID (56%), non-syndromic ID (20%), seizures or epileptic encephalopathy (9%), abnormal neurologic features without seizure (5%) or other presentations (10%). Seventeen were the offspring of consanguineous parents. The majority of patients had solo or trio ES after different genetic tests selected according to their phenotype, particularly array-CGH. A minority of patients had ES as a first diagnostic test.

ES was performed from DNA obtained from blood samples. A solo strategy was used in 506/547 individuals (92%), following protocols previously described [5,18,19] and American College of Medical Genetics and Genomics guidelines [20]. All candidate or pathogenic variants were verified by a second genetic technique, as well as familial segregation. If available, biomarkers were retrospectively checked to confirm ES results.

3. Results

In the overall cohort, 177/547 individuals (32%) had a positive diagnosis identified by ES [5]. Within this cohort, 21/177 individuals (12%) were diagnosed with 15 different IMDs (Table 1). No dual diagnosis was found. Therefore, the diagnostic yield for IMDs included 3.8% of the total cohort. Nineteen of these 21 individuals were live-born (9 males and 10 females), ranging from 6 days to 44 years of age. Two were fetuses (1 male and 1 female), aged 27 and 33 weeks of gestation, presenting multiple congenital anomalies. Ten individuals had disorders of organelle biogenesis, dynamics and interactions, five neurotransmitter disorders, two congenital disorders of glycosylation (CDG), two disorders of mitochondrial cofactor biosynthesis, one disorder of mitochondrial DNA maintenance and replication, and one disorder of amino acid metabolism (Table 1). Five individuals have already been published in the literature [21–24]. Eight of the 17 IMDs did not have known specific biomarkers (DNM1L, ADCK3, ALDH18A1, ST3GAL5, SLC13A5, SLC6A1, NGLY1, PNGN), although two of them display non-specific elevated lactates (DNM1L, ADCK3). Within this cohort, two treatable diseases were diagnosed, leading to a direct benefit for the affected individuals (GLUT1, SPR) (details in supplemental data).

Twelve of the of these 21 individuals (57%) benefited of variable biochemical investigation. Eighteen were alive when the ES results were returned to the physicians. Specific treatments or diet were given to 5/18 individuals (28%).

4. Discussion

ES identified a diagnosis of IMDs in 3.6% of cohort of individuals with non-specific developmental disorders, accounting for 12% of the causal diagnoses. Panel and ES showed similar results (13%) in a smaller cohort of individuals with childhood epilepsy [25]. However, considering the prevalence of IMD (1 in 500 live born infants), this rate appears low because most individuals affected with IMDs did not present developmental disorders.

In 11/19 live-born individuals, the presence of seizures associated with DD/ID (DNM1L, CLN3, COQ8A, PPT1, ST3GAL5, SLC2A1, SLC13A5, SLC6A1, NGLY1, 10 individuals), or abnormal movements (SPR, 1 individual), could have led to informative biochemical screening. However, in the majority of individuals, no specific biochemical biomarker could have led to the diagnosis of the IMD (DNM1L, COQ8A, ST3GAL5, SLC13A5, SLC6A1, NGLY1, PNGN) (8/12 individuals). Indeed, ES made it possible to obtain an early diagnosis for non-specific IMD phenotypes, which is of particular interest seeing as certain of these diseases are treatable. In addition, obtaining a diagnosis is particularly important for genetic counseling and prenatal diagnosis, especially since most IMDs follow an autosomal recessive inheritance, and the risk of recurrence in siblings is 25%. Parents may therefore be eligible for early prenatal diagnosis or even preimplantation diagnosis.

The literature already reports the unexpected diagnosis of IMDs using non-targeted tests such as ES. For example, the diagnosis of PGM1-CDG was reported in a 13-year-old girl with short stature and cleft palate, who died of sudden cardiac arrest, which revealed severe cardiomyopathy [26]. ES made it also possible to diagnose IMDs in fetuses with uninformative symptoms. For example, ES performed the diagnosis of glutaric acidemia type 2 in a fetus with enlarged hyperechoic kidneys [27] and of COG8-CDG in a fetus with facial dysmorphism, Dandy-Walker malformation and arthrogryposis multiplex congenita [28]. In our series, ES identified extreme fetal presentations of IMDs that would not have been suspected clinically [22]. ALDH18A1 pathogenic variants are usually associated with autosomal recessive spastic paraplegia 9B (MIM # 616586) and NPC1 pathogenic variants with Niemann-Pick disease type C1 (MIM # 257220).

In addition to the clinical analysis focused on OMIM-morbid genes, ES is a well-known powerful tool for the discovery of new genes in a translational research setting [31]. In our series, ES identified the first individual affected by an autosomal recessive epileptic encephalopathy with early seizures linked to SLC13A5 variants (MIM # 615905) [29]. In the specific case of IMDs, the identification of novel causal genes can also uncover new metabolic pathways. This could also lead to the development of new therapeutic approaches or the use of well-known therapeutics through drug repositioning [30].

Overall, this study demonstrates that ES is a powerful tool that can be used for the earlier diagnosis of IMDs, especially in the case of uninformative developmental disorders without specific biomarkers. This implicates a result delivery time compatible with patient care. When biochemical confirmation is available, it should be proposed as part of reverse phenotyping.
| Class of IMDs | Gene name | OMIM-related disease (MIM number) | Biochemical Pathway / Mechanism | Number of index cases diagnosed | Age at ES | Clinical presentation | Biochemical and genetic investigations performed prior to ES | Solo/ES | Variant(s) (cDNA or CNV) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments |
|--------------|-----------|----------------------------------|---------------------------------|-------------------------------|-----------|----------------------|-----------------------------------------------------------|---------|---------------------|----------------------|----------------------------|---------------------------------------------------------------|-------------------|
| Disorders of mitochondrial DNA maintenance and replication | DNM1 | Disordered growth, ataxia, deafness, hypomyelination, neonatal death (MIM # 604476) | Mitochondrial/ peroxisomal fission | 1 | 0.5 years | ID, microcephaly, ataxic gait, seizures, insensitivity to pain | Normal carbohydrate deficient transferrin, array-CGH, telomeric MLPA, DM1/DM2 amplification, MECP2, FOXL1, targeted gene panel sequencing (9 genes implicated in encephalopathy) | Solo | NM_005690.4:c.1085G > A | p.Gly362Asp | V | None | – |
| Disorders of mitochondrial cofactor biosynthesis | COQ8A / ADCK3 | Mitochondrial ubiquinol cytochrome c reductase deficiency, primary, 4 (MIM # 612906) | Coenzyme Q10 metabolism | 2 | 3 years | Status epilepticus, global DD, walking disability | Normal albumin, total cholesterol, array-CGH | Solo | NM_020247.4:c.638G > A | p.Arg213Gln | IV | None | Coenzyme Q10 |
| Disorders of amino acid metabolism | ALDH1A1 | Spastic paraplegia IB, autosomal recessive (MIM # 616586) | Biosynthesis of proline, ornithine, and arginine | 1 | Foetus (27 WG) | Corpus callosum agenesis, hypoplastic cerebellum IUGR short long bones and ribs, cutis laxa | Normal standard chromosomal analysis, array-CGH | Solo | NM_002860.3:c.1273C > T | p.Arg425Cys | V | None | NA* |
| Disorders of organelle biogenesis, dynamics and interactions | PPT1 | Cerebral lipofuscinosis, neuronal 1 (MIM # 256730) | Catabolism of lipid-modified proteins | 2 | 5 years | Progressive myoclonic encephalopathy | Normal tripeptidyl peptidase 1 and palmitoyl-protein thioesterase 1 in leukocytes, standard chromosomal analysis, array-CGH, telomeric MLPA, SNRPN methylation, ARX duplication, MECP2, CDKL5, CLN5, CLN6 and CLN8 sequencing Skin biopsy: autofluorescent ceroid lipopigments | Solo | NM_000310.3:c.541G > A | p.Val181Met | IV | – | – | (continued on next page)
| Class of IMDs | Gene name | OMIM-related disease (MIM number) | Biochemical Pathway / Mechanism | Number of index cases diagnosed | Age at ES | Clinical presentation | Biochemical and genetic investigations performed prior to ES | Solo/trio ES | Variant(s) (cDNA or CNV) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments |
|----------------|------------|----------------------------------|----------------------------------|-----------------------------|-----------|----------------------|-------------------------------------------------------------|-----------|------------------------|-------------------|-----------------------------|-------------------------------------------------------------|------------------|
| **CLN3**       | Ceroid lipofuscinosis, neuronal, 3 (MIM # 204200) | N-glycosylation                   | 2                               | 2 years                     | Microcephaly, global DD, neurological regression, myoclonic epilepsy | chr1:40558255-40562842del chr1:40562842del chr1:40562842del | NA | V Leucocyte enzyme deficiency | – |
| **HEXA**       | Tay-Sachs Disease (MIM # 272800) | GM2-gangliosidosis               | 1                               | 4.5 years                   | Retinitis pigmentosa, seizures | chr16:28495668_28498500del chr16:28495668_28498500del chr16:28495668_28498500del | NA | V NA None | – |
| Class of IMDs | Gene name | OMIM-related disease (MIM number) | Biochemical Pathway / Mechanism | Number of index cases diagnosed | Age at ES | Clinical presentation | Biochemical and genetic investigations performed prior to ES | Solo/ trio ES | Variant(s) (cDNA or CNV) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments |
|--------------|-----------|---------------------------------|--------------------------------|-------------------------------|-----------|----------------------|-------------------------------------------------|----------------|-------------------------|----------------------|---------------------------|-------------------------------------------------|----------------------|
| Niemann-Pick disease, type C1 (MIM # 257220) | NPC1 | Regulation of intracellular cholesterol trafficking | 1 | Fetus (33 WG) | Hydrops, hepatosplenomegaly | Moderate elevated lactate | Normal array-CGH, prenatal explorations for lysosomal storage disease | Solo NM_000271.4:c.2819C > T hmrz | p.Ser940Leu | V | microvacuolization in some macrophage cells in fetal spleen slides | NA* |
| Salt and pepper developmental regression syndrome (MIM # 609056) | ST3GAL5 | GM3 synthase deficiency | 2 | 6 years | Epileptic encephalopathy, deafness, microcephaly | | | | | | |
| Mannosidosis, alpha-, types I and II (MIM # 248500) | MAN2B1 | N-glycosylation | 2 | 7.5 years | ID, seizures, stature and weight delay, cerebral atrophy | acylcarnitine profile, CPK, copper level and ceruloplasmin, urinary organic acid chromatography, AICAR-SAICAR, array-CGH | Solo NM_003986.3:c.740G > A hmrz | p.Gly247Asp | V | None | – |
| GLUT1 deficiency syndrome 1, infantile onset, severe (MIM # 600777) | SLC2A1 / GLUT1 | Cerebral glucose transport | 1 | 8 years | ID, marfanoid habitus, deafness, dysmorphism | Normal array-CGH | Solo NM_000528.3:c.2402dup | p.Asn34Lys | IV | | | |
| Neurotransmitter disorders | SLC13A5 | Cerebral citrate transport | 1 | 4 years | Early epileptic encephalopathy, global DD | | | | | | | | |

(continued on next page)
| Class of IMDs | Gene name | OMIM-related disease (MIM number) | Biochemical Pathway / Mechanism | Number of index cases diagnosed | Age at ES | Clinical presentation | Biochemical and genetic investigations performed prior to ES | Solo/ trio ES | Variant(s) (cDNA or CNV) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES | Specific treatments |
|--------------|-----------|-----------------------------------|---------------------------------|-------------------------------|----------|---------------------|----------------------------------------------------------|-------------|------------------------|---------------------|---------------------------|--------------------------------|---------------------|
| imperfecta (MIM # 615905) | SLC6A1 | Myoclonic-atonic epilepsy (MIM# 616421) | GABA transport | 2 years | Global DD, hand stereotypes, seizures with abnormal EEG pattern | Normal array-CGH and SNRPN methylation, targeted panel sequencing (9 genes implicated in encephalopathy) Normal standard chromosomal analysis, plasmatic and urinary homocysteine Normal plasmatic lactate, pyruvate, ammonia, aminocacid chromatography, very long chain fatty acid tests, acylcarnitine profile, blood/CSF lactate level, CPK, carbohydrate deficient transferrin, urinary organic acid chromatography, array-CGH, FRAXA, SMN1 deletion, SNRPN methylation and DM1 amplification analyses Mitochondrial respiratory chain in muscle and fibroblasts Normal plasmatic ammonia, guanidoacetate, aminoacid chromatography, very long chain fatty acid tests, copper level blood/CSF glucose level, CPK, AICAR/SAICAR, urinary copper level and organic acid chromatography, lysosomal storage disease explorations, standard | Solo | NM_003042.3:c.801delC | p.Ile268Serfs*36 | IV | None | Elevated lactates, abnormal CSF neurotransmitter profile |
| SPR | Dystonia, dopa-responsive, due to sepiapterin reductase deficiency (MIM # 612716) | | | | Learning disabilities, marfanoid habitus | | | | Trio | NM_003042.3:c.1377C > A | p.Ser459Arg | IV | None | | |
| Congenital disorder of glycosylation | NGLY1 | Congenital disorder of deglycosylation (MIM # 615273) | Protein deglycosylation | 1.5 years | Epileptic encephalopathy, severe global DD, dyskinesia, (alacrimia)*** | | | | Solo | NM_001145293.1: c.1427_1434del | | IV | None | | | | | (continued on next page)
Table 1 (continued)

| Class of IMDs | Gene name | OMIM-related disease (MIM number) | Biochemical Pathway / Mechanism | Number of index cases diagnosed | Age at ES | Clinical presentation | Biochemical and genetic investigations performed prior to ES | Solo/trio ES | Variant(s) (cDNA or CNV) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments chromosomal analysis, array-CGH, ARX duplication and SNRPN methylation analysis, STXBP1 targeted gene panel sequencing 220 genes implicated in intellectual disability) |
|---------------|-----------|----------------------------------|---------------------------------|--------------------------------|-----------|----------------------|------------------------------------------------------------|------------|-----------------------------------|-----------------------------|---------------------------------------------------------------|---------------------------------------------------------------------|
| PIGN          | Multiple congenital anomalies-hypotonia-seizures syndrome 1 (MIM # 614080) | Glycosylphosphatidylinositol anchor biosynthesis | 1 6 days Congenital bilateral cataract, club feet, cleft lip and palate, congenital cardiopathy | – Solo chr18:59819883_59824941del hmz | NA V None NA** | | | |

ACMG: american college of medical genetics; AICAR/SAICAR: aminoimidazole carboxamide ribotide / succinylaminoimidazole-carboxamide riboside; CSF: cerebrospinal fluid; CGH: comparative genomic hybridization CNV: copy number variation; CPK: creatine phosphokinase; DD: developmental delay; DM1/DM2: dytrophic myotony types 1 and 2; cDNA: complementary DNA; ES: exome sequencing; GABA: gamma-aminobutyric acid; ID: intellectual disability; hmz: homozygous; IMD: inherited metabolic disorders; WG: weeks of gestation; IUGR: intrauterine growth retardation; MIM: mendelian inheritance in man; MLPA: multiplex ligation-dependent probe amplification; NA: not available; NADPH: nicotinamide adenine dinucleotide phosphate; OMIM: online mendelian inheritance in man; SD: standard deviation; *foetal case; ** death at 8 days of life, *** noted in reverse phenotyping.
Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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References

[1] J.-M. Saudubray, A. Garcia-Cazorla, An overview of inborn errors of metabolism affecting the brain: from neurodevelopment to neurodegenerative disorders, Dialogues Clin. Neurosci. 20 (2018) 301–325.
[2] F. Ega, Inborn errors of metabolism, Adv. Clin. Chem. 73 (2016) 195–250.
[3] M. Tarailo-Graovac, W.W. Wasserman, C.D.M. Van Karnebeek, Impact of next-generation sequencing on diagnosis and management of neurometabolic disorders: current advances and future perspectives, Expert. Rev. Mol. Diagn. 17 (2017) 307–309.
[4] A. Ghosh, H. Schlecht, L.E. Hepkinson, et al., Diagnosing childhood-onset inborn errors of metabolism by next-generation sequencing, Arch. Dis. Child. 102 (2017) 1019–1029.
[5] S. Nambot, J. Thevenon, P. Kuentz, et al., Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: substantial interest of prospective annual reanalysis, Genet Med. 20 (2018) 645–654.
[6] C.F. Wright, D.R. FitzPatrick, H.V. Firth, Paediatric genomics: diagnosing rare disease in children, Nat. Rev. Genet. 19 (2018) 253–268.
[7] M. Tarailo-Graovac, C. Shyr, C.J. Ross, et al., Exome sequencing and the management of neurometabolic disorders, N. Engl. J. Med. 374 (2016) 2246–2255.
[8] S.A. Belanger, J. Caron, Evaluation of the child with global developmental delay and intellectual disability, Paediatr. Child Health 23 (2018) 403–419.
[9] D.J. Michelson, M.I. Shevell, E.H. Serr, J.B. Moeschler, A.L. Groppman, S. Ashwal, Evidence report: genetic and metabolic testing on children with global developmental delay: report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, Neurology 77 (2011) 1629–1635.
[10] M. Shevell, S. Ashwal, D. Dooley, et al., Practice parameter: evaluation of the child with global developmental delay: report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, Neurology 60 (2003) 367–380.
[11] Deciphering Developmental Disorders Study, Large-scale discovery of novel genetic causes of developmental disorders, Nature 519 (2015) 223–228.
[12] A. Iglesias, K. Anyane-Yeboa, J. Wynn, et al., The usefulness of whole-exome sequencing in routine clinical practice, Genet. Med. Off. J. Am. Coll. Genet. Med. 16 (2014) 922–951.
[13] G.R. Monroe, G.W. Frederix, S.M.C. Savelberg, et al., Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability, Genet. Med. Off. J. Am. Coll. Genet. Med. 18 (2016) 949–956.
[14] M.M. Clark, Z. Stark, L. Farnaes, T.Y. Tan, S.M. White, D. Dimmock, S. F. Kingsmore, Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases, NPJ Genom Med. 3 (2018) 16.
[15] L.E.L.M. Vissers, C. Gilissen, J.A. Veltman, Genetic studies in intellectual disability and related disorders, Nat. Rev. Genet. 17 (2016) 9–18.
[16] Y. Yang, D.M. Muzny, F. Xia, et al., Molecular findings among patients referred for clinical whole-exome sequencing, JAMA 312 (2014) 1870–1879.
[17] R.Z. Hayemms, K.M. Boycott, Genome-wide sequencing technologies: a primer for paediatricians, Paediatr. Child Health 23 (2018) 191–197.
[18] J. Thevenon, Y. Duffourd, A. Manuel-Paulet, M. Lefebvre, F. Feillet, S. El Chehadah-Djebbar, J. St-Onge, A. Steinmetz, F. Huet, M. Chouchane, V. Darmency-Stamboul, P. Callier, C. Thauvin-Robinet, L. Faire, J.B. Riviere, Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test, Clin. Genet. 89 (2016) 700–707.
[19] P. Garret, C. Bris, V. Procaccio, P.A. Bonneau, P. Vanbers, N. Houcinat, E. Tisserant, F. Feillet, A. Bruel, V. Quéré, C. Philippe, A. Sorlin, F.T. Mau-Them, A. Vitolo, J. Costa, A. Boughalem, D. Trost, L. Faire, C. Thauvin-Robinet, Y. Duffourd, Deciphering exome sequencing data: bringing mitochondrial DNA variants to light, Hum. Mutat. 40 (2019) 2430–2443.
[20] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W.W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H.L. Rehm, Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Medical Pathology, Genet Med. 17 (2015) 405–424.
[21] J. Thevenon, M. Milh, F. Feillet, et al., Mutations in SLC13A5 cause autosomal-recessive epileptic encephalopathy with seizure onset in the first days of life, Am. J. Hum. Genet. 95 (2014) 113–120.
[22] M. Lefebvre, A.-M. Beaurefere, C. Francannet, et al., Extending the ALDH18A1 clinical spectrum to severe autosomal recessive fetal cutis laxa with corpus callosum agenesis, Am. J. Med. Genet. A 176 (2018) 2509–2515.
[23] D. Lehalle, R. Colombo, M. O’Grady, et al., Hearing impairment as an early sign of alpha-mannosidosis in children with a mild phenotype: report of seven new cases, Am. J. Med. Genet. A 179 (2019) 1756–1763.
[24] J.J. Alessandri, C.T. Gordon, M.L. Jacobson, et al., Recessive loss of function PGH alleles, including an intragenic deletion with founder effect in La Réunion Island, in patients with frisyn syndrome, Eur. J. Hum. Genet. 26 (2018) 340–349.
[25] G. Costain, D. Cordeiro, D. Matviychuk, S. Mercimek-Andrews, Clinical application of targeted next-generation sequencing panels and whole exome sequencing in childhood epilepsy, Neuroscience 418 (2019) 291–310.
[26] E. Fernlund, O. Andersson, R. Elgerd, et al., The congenital disorder of glycosylation in PGM1 (PGM1-CDG) can cause severe cardiomyopathy and unexpected sudden cardiac death in childhood, Forensic Sci. Int. Genet. 43 (2019), 102111.
[27] A.M. Cukincha-Chabwan, T. Rozkowski, M. Gersonk, et al., Prenatal diagnosis of glutaric acidemia type 2 with the use of exome sequencing - an up-to-date review and new case report, Ginekol. Pol. 92 (2021) 51–56.
[28] V. Arora, R.D. Puri, P. Bhai, et al., The first case of antenatal presentation in COG8-related disorder, J. Inherit. Metab. Dis. 41 (2018) 1385–1387.
[29] Y. Yang, D.M. Muzny, F. Xia, et al., Molecular findings among patients referred for clinical whole-exome sequencing, JAMA 312 (2014) 1870–1879.
[30] A.-L. Bruel, S. Nambot, V. Quéré, et al., Increased diagnostic and new genes identification outcome using research reanalysis of singleton exome sequencing, Eur. J. Hum. Genet. 27 (2019) 1519–1531.
[31] E. Graham, J. Lee, M. Price, et al., Integration of genomics and metabolomics for prioritization of rare disease variants: a 2018 literature review, J. Inherit. Metab. Dis. 41 (2018) 435–445.