Molecular Genetics and Metabolism Reports 29 (2021) 100812

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

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

Julian Delanne [a,b], Ange-Line Bruel [a,c], Frédéric Huet [d], Sébastien Moutton [a,b], Sophie Nambot [a,b], Margot Grisval [d], Nada Houcinat [b], Paul Kuentz [a,c,e], Arthur Sorlin [a,b,c], Patrick Callier [a,f], Nolwenn Jean-Marcais [b], Anne-Laure Mosca-Boidron [f], Frédéric Tran Mau-Them [a,c], Anne-Sophie Denommé-Pichon [a,c], Antonio Vitobello [a,c], Daphné Lehalle [b], Salima El Chehadeh [b], Christine Francannet [g], Marine Lebrun [h], Laetitia Lambert [i], Marie-Line Jacquemont [j], Marion Gerard-Blanluet [k], Jean-Luc Alessandri [l], Marjolaine Willems [m], Julien Thevenon [a,b,c], Mondher Chouchane [d], Véronique Darmency [d], Clémence Fatus-Fauconnier [d], Sébastien Gay [n], Marie Bournez [d], Alice Masurel [b], Vanessa Leguy [d], Yannis Duffourd [a,c], Christophe Philippe [a,c], François Feillet [m], Laurence Faivre [a,b,c,1], Christel Thauvin-Robinet [a,c,o,*,1]

[a] INSERM – University of Bourgogne Franche-Comté, UMR 1231 GAD Team, Genetics of Developmental Disorders, FHU TRANSLAD, CHU Dijon Bourgogne, France
[b] CHU Dijon, Centre de référence maladies rares Anomalies du Développement et Syndromes Malformatifs, Centre de Génétique, FHU TRANSLAD, CHU Dijon Bourgogne, France
[c] Unité Fonctionnelle d'Innovation diagnostique dans les maladies rares, Laboratoire de Génétique chromosomique moléculaire, CHU Dijon Bourgogne, France
[d] Centre de Compétence Maladies Héréditaires du Métabolisme, CHU Dijon Bourgogne, France
[e] Biologie moléculaire, CHU Besançon, Besançon, France
[f] Laboratoire de cytogénétique et génétique moléculaire, CHU Dijon Bourgogne, France
[g] Service de Génétique Médicale, Centre de Référence Déficiences Intellectuelles de causes rares, CHU Clermont Ferrand, France
[h] Laboratoire de génétique, CHU de Saint-Etienne, Saint-Etienne, France
[i] Service de Génétique Clinique, CHRU Nancy, France
[j] Unité de Génétique Médicale, Pole Femme-Mère-Enfant, Groupe Hospitalier Sud Réunion, CHU de La Réunion, La Réunion, France
[k] APHP, Department of Genetics, Robert Debré Hospital, Paris, France,
[l] Service de Réanimation Néonatale, Pole Femme-Mère-Enfant, CH Felix Guyon, CHU de La Réunion, Saint-Denis, La Réunion, France
[m] Department of Medical Genetics, Reference Center for Rare Diseases, Developmental Disorders and Multiple Congenital Anomalies, Arnaud de Villeneuve Hospital, Montpellier, France
[n] Service de Pédiatrie, CH William Morey, Chalon-Sur-Saône, France
[o] Centre de référence maladies rares Déficiences Intellectuelles de causes rares, Centre de Génétique, FHU TRANSLAD, CHU Dijon Bourgogne, France

ARTICLE INFO

*Keywords:*
Inherited metabolic disorders
Exome sequencing
Intellectual disability
Developmental delay
Genotype first

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.

* Corresponding author at: Centre de Génétique, Hôpital d'Enfants, CHU Dijon Bourgogne, France.
*E-mail address:* christel.thauvin@chu-dijon.fr (C. Thauvin-Robinet).
[1] These authors equally contributed to the work.

https://doi.org/10.1016/j.ymgmr.2021.100812
Received 29 July 2021; Received in revised form 7 October 2021; Accepted 9 October 2021

## 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 unspecific 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 (*DNML1, ADCK3, ALDH18A1, ST3GAL5, SLC13A5, SLC6A1, NGLY1, PIGN*), although two of them display non-specific elevated lactates (*DNML1, 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, PIGN*) (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 unspecific 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 unspecific 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.

**Table 1**
Summary of the clinical and genetic features of the 21 individuals with IMD diagnosed using ES.

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Disorders of mitochondrial DNA maintenance and replication | ***DNM1L*** | Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1 (MIM # 614388) | Mitochondrial/ peroxisomal fission | 1 | 10.5 years | ID, microcephaly, ataxic gait, seizures, insensitivity to pain | Normal carbohydrate deficient transferrin, array-CGH, telomeric MLPA, DM1/DM2 amplification, *MECP2*, *FOXG1*, 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*** | Coenzyme Q10 deficiency, primary, 4 (MIM # 612016) | Coenzyme Q10 metabolism | 2 | 7 years | Cerebellar ataxia, motor delay | Normal albumin, total cholesterol, array-CGH | Solo | NM_020247.4:c.638G > A<br>NM_020247.4:c.1471 T > A | p.Arg213Gln<br>p.Trp491Arg | IV<br>III | None | Coenzyme Q10 |
| | | | | | 3 years | Status epilepticus, global DD, walking disability | Normal plasmatic ammonia, aminoacid chromatography, carnitine level, blood/CSF glucose level, CPK, carbohydrate deficient transferrin, urinary organic acid chromatography, muscle mitochondrial respiratory chain, array-CGH, *POLG* sequencing Moderate elevated lactates | Solo | NM_020247.4:c.811C > T<br>NM_020247.4:c.1625_1626del | p.Arg271Cys<br>p.Ile542Argfs*31 | III<br>IV | None | Ketogenic diet Coenzyme Q10 |
| Disorders of amino acid metabolism | ***ALDH18A1*** | Spastic paraplegia 9B, 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<br>NM_002860.3:c.177del | p.Arg425Cys<br>p.Lys59Asnfs*9 | V<br>IV | None | NA* |
| Disorders of organelle biogenesis, dynamics and interactions | ***PPT1*** | Ceroid lipofuscinosis, neuronal, 1 (MIM # 256730) | Catabolism of lipid-modified proteins | 2 | 5 years | Progressive myoclonic encephalopathy | Normal tripeptidyl peptidase I and palmitoyl-protein thioesterase 1 in leucocytes,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<br>NM_000310.3:c.471del | p.Val181Met<br>p.His158Thrfs*10 | V<br>IV | – | – |

(*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) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2 years | Microcephaly, global DD, neurological regression, myoclonic epilepsy | Normal plasmatic lactate, pyruvate, ammonia, phytanic, pristanic and pipecolic acids, guanidoacetate aminoacid chromatography, very long chain fatty acid tests, lymphocyte vacuoles, blood/CSF glucose level, CPK, uric acid, carbohydrate deficient transferrin, urinary organic acid chromatography, lysosomal storage disease explorations, array-CGH, FRAXA Skin biopsy: autofluorescent ceroid lipopigments | Solo | chr1:40558255-40562842del hmz | NA | V | Leucocyte enzyme deficiency | – |
| | ***CLN3*** | Ceroid lipofuscinosis, neuronal, 3 (MIM # 204200) | N-glycosylation | 2 | 44 years | Microcephaly, retinitis pigmentosa, late onset cerebellar ataxia with cerebellar atrophy, axonal and myelinic neuropathy | Normal total cholesterol, alpha foetopreotein, vitamin E, CPK, plasmatic aminoacid chromatography, carbohydrate deficient transferrin, very long chain fatty acid tests, urinary organic acid chromatography, muscle mitochondrial respiratory chain, mitochondrial DNA, *LAMP2* and *ASPM* sequencing | Solo | NM_000086.2:c.883G > A<br>chr16:28497282_28498403del | p.Glu295Lys<br>NA | V<br>V | None | – |
| | | | | | 10 years | Retinitis pigmentosa, seizures | – | Solo | chr16:28495668_28498500del hmz | NA | V | NA | – |
| | ***HEXA*** | Tay-Sachs Disease (MIM # 272800) | GM2-gangliosidosis | 1 | 4,5 years | Epileptic encephalopathy | Normal albumin, alpha foetopreotein, vitamins E, B1 and B2, CPK, ammonia, plasmatic aminoacid chromatography, very long chain fatty acid tests | Solo | NM_000520.4:c.533G > A hmz | p.Arg178His | V | Leucocyte enzyme deficiency | – |

(*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) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neurotransmitter disorders | ***NPC1*** | Niemann-Pick disease, type C1 (MIM # 257220) | Regulation of intracellular cholesterol trafficking | 1 | Fetus (33 WG) | Hydrops, hepatosplenomegaly | Moderate elevated lactate<br>Normal array-CGH, prenatal explorations for lysosomal storage disease | Solo | NM_000271.4:c.2819C > T hmz | p.Ser940Leu | V | microvacuolization in some macrophage cells in fetal spleen slides | NA* |
| | ***ST3GAL5*** | Salt and pepper developmental regression syndrome (MIM # 609056) | GM3 synthase deficiency | 2 | 6 years | Epileptic encephalopathy, deafness, microcephaly | Normal plasmatic lactate, pyruvate, ammonia, aminoacid chromatography, acylcarnitine profile, CPK, copper level and ceruloplasmin, urinary organic acid chromatography, oligosaccharides, AICAR-SAICAR, array-CGH, FRAXA, *MECP2*, *FOXG1*, and UBE3A sequencing | Solo | NM_003896.3:c.740G > A hmz | p.Gly247Asp | V | None | – |
| | | | | | 7.5 years | ID, seizures, stature and weight delay, cerebral atrophy | Normal plasmatic aminoacid chromatography, very long chain fatty acid tests, acylcarnitine profile, CPK, copper level and ceruloplasmin, urinary organic acid chromatography, AICAR-SAICAR, array-CGH, | Solo | NM_003896.3:c.740G > A hmz | p.Gly247Asp | V | None | – |
| | ***MAN2B1*** | Mannosidosis, alpha-, types I and II (MIM # 248500) | N-glycosylation | 2 | 8 years | ID, marfanoid habitus, deafness, dysmorphism | Normal array-CGH | Solo | NM_000528.3:c.2402dup<br>NM_000528.3:c.1645-1G > A | p. Ser802Glnfs*129<br>p.? | IV<br>IV | Mannose-rich oligosaccharidiuria and leucocyte alpha-mannosidase deficiency | – |
| | | | | | 8.5 years | Deafness, learning disabilities, abnormal teeth enamel, dysmorphism | Normal array-CGH, *GJB2* sequencing | Solo | NM_000528.3:c.418C > T<br>NM_000528.3:c.2864_2879del | p.Arg140*<br>p. Thr955Serfs*73 | IV<br>IV | Mannose-rich oligosaccharidiuria and leucocyte alpha-mannosidase deficiency | – |
| | ***SLC2A1 / GLUT1*** | GLUT1 deficiency syndrome 1, infantile onset, severe (MIM # 606777) | Cerebral glucose transport | 1 | 1 year | Global DD, infantile spasms, microcephaly (< − 3 SD), hypotonia | Normal array-CGH, *MECP2, CDKL15,* and *FOXG1* sequencing | Solo | NM_006516.2:c.102 T > G | p.Asn34Lys | IV | Abnormal blood/ CSF glucose level | Ketogenic diet |
| | ***SLC13A5*** | Developmental and epileptic encephalopathy 25, with amelogenesis | Cerebral citrate transport | 1 | 4 years | Early epileptic encephalopathy, global DD | – | Solo | NM_177550.3:c.1463 T > C hmz | p.Leu488Pro | IV | None | Citrate |

(*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) | Variant(s) (protein) | ACMG variant classification | Biochemical markers performed after ES results for reverse phenotyping | Specific treatments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | imperfecta (MIM # 615905) | | | | | | | | | | | |
| | ***SLC6A1*** | Myoclonic-atonic epilepsy (MIM# 616421) | GABA transport | 2 | 2 years | Global DD, hand stereotypies, seizures with abnormal EEG pattern | Normal array-CGH and SNRPN methylation, targeted panel sequencing (9 genes implicated in encephalopathy) | Solo | NM_003042.3:c.801delC | p.Ile268Serfs*36 | IV | None | – |
| | | | | | 17 years | Learning disabilities, marfanoid habitus | Normal standard chromosomal analysis, plasmatic and urinary homocysteine | Trio | NM_003042.3:c.1377C > A | p.Ser459Arg | IV | None | – |
| | ***SPR*** | Dystonia, dopa-responsive, due to sepiapterin reductase deficiency (MIM # 612716) | NADPH-dependent reduction of various carbonyl substances | 1 | 5 years | Microcephaly, global DD, abnormal movements, | Normal plasmatic lactate, pyruvate, ammonia, aminoacid 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 | Solo | NM_003124.4: c.18_19insGGGCGGGCTG hmz | p.Arg7Glyfs*37 | IV | Elevated lactates, abnormal CSF neurotransmittor profile | L-DOPA |
| Congenital disorder of glycosylation | ***NGLY1*** | Congenital disorder of deglycosylation (MIM # 615273) | Protein deglycosylation | 1 | 5.5 years | Epileptic encephalopathy, severe global DD, dyskinesia, (alacrimia)*** | 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_001145293.1: c.1427_1434del NM_001145293.1:c.931G > A | p. His476Leufs*14 p.Glu311Lys | IV III | 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) | Variant(s) (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 phoshokinase; 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 adénine dinucléotide 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.

## Acknowledgements

We thank the families for taking part in the study. We thank the University of Burgundy Centre de Calcul (CCuB) for technical support and management of the informatics platform, and the Centre de Ressources Biologique (CRB) of Dijon University Hospital. Most authors of this publication are members of the European Reference Network for Developmental Anomalies and Intellectual Disability (ERN-ITHACA). This work was supported by grants from Dijon University Hospital, the ISITE-BFC (PIA ANR) and the European Union through the FEDER programs. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100812.

## 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. Ezgu, 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. Heptinstall, 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. Bélanger, 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. Sherr, J.B. Moeschler, A.L. Gropman, 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. Donley, 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. Med. Genet. 16 (2014) 922–931.
[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. Med. Genet. 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. Hayeems, K.M. Boycott, Genome-wide sequencing technologies: a primer for paediatricians, Paediatr. Child Health 23 (2018) 191–197.
[18] J. Thevenon, Y. Duffourd, A. Masurel-Paulet, M. Lefebvre, F. Feillet, S. El Chehadeh-Djebbar, J. St-Onge, A. Steinmetz, F. Huet, M. Chouchane, V. Darmency-Stamboul, P. Callier, C. Thauvin-Robinet, L. Faivre, J.B. Rivière, 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. Vabres, N. Houcinat, E. Tisserant, F. Feillet, A. Bruel, V. Quéré, C. Philippe, A. Sorlin, F.T. Mau-Them, A. Vitobello, J. Costa, A. Boughalem, D. Trost, L. Faivre, 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 Molecular 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. Beaufrere, 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) 2509–2512.
[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.L. Alessandri, C.T. Gordon, M.L. Jacquemont, et al., Recessive loss of function PIGN alleles, including an intragenic deletion with founder effect in La Réunion Island, in patients with fryns 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. Ellegård, 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. Kucinska-Chahwan, T. Roszkowski, M. Geremek, 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-congenital disorder of glycosylation with a novel splice site mutation and an extended phenotype, Am. J. Med. Genet. A 179 (2019) 480–485.
[29] 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.
[30] 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.