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2022-01

Aaltio , J , Hyttinen , V , Kortelainen , M , Frederix , G W J , Lönnqvist , T , Suomalainen , A & Isohanni , P 2022 , ' Cost-effectiveness of whole-exome sequencing in progressive neurological disorders of children ' , European Journal of Paediatric Neurology , vol. 36 , pp. 30-36 . https://doi.org/10.1016/j.ejpn.2021.11.006

http://hdl.handle.net/10138/348042
https://doi.org/10.1016/j.ejpn.2021.11.006

European Journal of Paediatric Neurology 36 (2022) 30–36

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Cost-effectiveness of whole-exome sequencing in progressive neurological disorders of children

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ARTICLE INFO

Article history:
Received 5 March 2021
Received in revised form
22 September 2021
Accepted 12 November 2021

Keywords:
Whole-exome sequencing
WES
Cost-effectiveness
Encephalopathy

ABSTRACT

Objectives: To clarify the diagnostic utility and the cost-effectiveness of whole-exome sequencing (WES) as a routine early-diagnostic tool in children with progressive neurological disorders.
Methods: Patients with infantile-onset severe neurological diseases or childhood-onset progressive neurological disorders were prospectively recruited to this WES study, in the pediatric neurology clinic at Helsinki University Hospital during 2016–2018. A total of 48 patients underwent a singleton WES. A control group of 49 children underwent traditional diagnostic examinations and were retrospectively collected from the hospital records. Their use of health care services, related to the diagnostic process, was gathered. Incremental cost-effectiveness ratio (ICER) per additional diagnosis was calculated from the health care provider perspective. Bootstrapping methods were used to estimate the uncertainty of cost-effectiveness outcomes.
Results: WES provided a better diagnostic yield (38%) than diagnostic pathway that did not prioritize WES in early diagnosis (25%). WES outperformed other diagnostic paths especially when made early, within one year of first admission (44%). Cost-effectiveness in our results are conservative, affected by WES costs during 2016–18.
Conclusions: WES is an efficient and cost-effective diagnostic tool that should be prioritized in early diagnostic path of children with progressive neurological disorders. The progressively decreasing price of the test improves cost-effectiveness further.

1. Introduction

The Online Mendelian Inheritance of Man database recognizes over 4000 clinical synopses with neurological involvement, out of which over 3000 with a confirmed molecular basis. The genetic complexity is significant: the same disease can be caused by variants in several different genes, for example Leigh disease [1] can be due to variants in more than 75 different genes, and even a single variant may cause variable symptoms in different patients such as in X-linked adrenoleukodystrophy [2]. The development of next-generation sequencing (NGS) methods for the human genome dramatically improved the diagnostic approaches [3], sometimes providing targeted approaches for treatment [4]. In addition, early genetic diagnosis provides tools for counseling [5] and guidance for reproductive planning [6].

Whole-exome sequencing (WES) provides data from protein-coding genes of the genome [7]. Sequence analysis of all the

Abbreviations: WES, Whole-Exome Sequencing; ICER, Incremental Cost-Effectiveness Ratio; NGS, Next-Generation Sequencing; WGS, Whole-Genome sequencing; HUS, Hospital District of Helsinki and Uusimaa; IQR, Interquartile Range; CI, Confidence Interval; SD, Standard Deviation.

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https://doi.org/10.1016/j.ejpn.2021.11.006

genes, instead of single candidate genes, reduces the time required for identification of gene defects exponentially, and enables discovery of novel disease-causing genes. Method development has also progressively reduced the costs of the analysis, making it feasible for routine diagnostics [7]. However, health care providers still may consider NGS methods expensive for clinical practice [8], which calls for cost-effectiveness studies to support decision-making.

The improved and efficient diagnostic yield as a consequence of NGS-analysis might result in better health outcomes or more efficient use of health care services [3]. A recent meta-analysis found that the pooled diagnostic utility, meaning the rate of definitive diagnoses achieved, for WES was 36% in children with suspected genetic diseases [9]. However, current studies on cost-effectiveness and economic outcomes of WES are limited to few studies [3]. In a diagnostic work up to reach a diagnosis, the largest cost drivers are found to be the costs of genetic tests and costs of WES [10], but if WES is used as a near first-line test in a selected cohort of patients, overall budget increase may not be required.

Here, we report diagnostic utility and cost-effectiveness of WES as a routine diagnostic tool in progressive neurological disorders of children.

2. Materials and methods

2.1. Study population and data collection

Patients with infantile-onset severe neurological disease or childhood-onset progressive neurological disorder were prospectively recruited to the WES study at Children's Hospital at Helsinki University Hospital, a tertiary care hospital, during the years 2016–2018. Exclusion criteria were non-progressive intellectual disability or autism spectrum disorder, family history of a known genetic disorder, or otherwise clinically identifiable genetic disorder. In total, 48 non-consanguineous pediatric patients underwent the singleton WES as a routine diagnostic test ("WES group"). Short clinical descriptions, including genetic testing before recruitment to the study, are presented in Appendix 1.

The control group included 49 children, who suffered from similar disorders as the WES group, but had often undergone some conventional diagnostic tests, such as metabolic investigations, Sanger sequencing, NGS gene panels, and karyotyping, but not WES. They were retrospectively collected from the hospital records, with earliest investigations for one patient starting in 2002. The data of study participants was collected until date of diagnosis or end of observation period in November 2018. Observation periods for the groups, 1315 days (median 897; IQR 373–1973) for prospective patients and 1453 days (median 1139; IQR 684–2200) for controls, did not differ significantly ($p = 0.4380$) from each other.

2.2. Patient cohort

The median age of study subjects was 2.4/0.9 years (range 0–16/0–17 years) at the beginning of the first diagnostic visit, and 63%/51% were male among WES group and control group, respectively (Table 1). There were statistically significant differences with residence district between WES and control groups ($p < 0.001$). The collection of data was more comprehensive concerning clinical visits for the control group, who were more likely to live in our hospital district.

Both patient cohorts consisted of heterogeneous phenotypes, with the majority affected by encephalopathy (54%/61%) and neuromuscular disorders (31%/29%). Additionally, patients undergoing WES were further characterized by how many years of investigations they had had in Children's Hospital before being recruited to this study. Patients getting WES during their first year of investigations (48%) constitute our early WES patient group.

The use of health care services related to the diagnostic path of study participants was gathered retrospectively from patient records. The data consisted of all diagnostic health care visits and investigations including hospitalizations, clinical visits, laboratory tests, imaging, and genetic testing. Only events considered relevant for the diagnostic process were included, and the events were reviewed individually by study physicians. In addition, gender and age at the first visit in the hospital, the date of diagnosis and timing of WES along the diagnostic path were recorded.

2.3. Whole-exome sequencing

WES was performed using exome capture by Agilent SureSelect V5 kit and Illumina MiSeq sequencing at the Finnish Institute of Molecular Medicine (FIMM) as described in Sainio et al. [11]. A customized exome analysis pipeline [11] was used to analyse the genetic data, and the gene findings were compared to phenotype with study physicians and thus to reach a definitive diagnosis. Sanger sequencing was used as an additional independent method to confirm findings and segregation in patient and family samples.

2.4. Diagnostic yield

Effectiveness outcome was diagnostic yield, which was calculated as a proportion of definitive diagnoses to the total number of patients in both groups. It was also calculated separately for the different time-subgroups.

2.5. Cost-effectiveness analysis

Economic analysis was performed from health care provider (hospital) perspective. Costs of laboratory tests, imaging and genetic tests were obtained from the hospital (Hospital District of Helsinki and Uusimaa, HUS) and diagnostic laboratory documentation (tests performed outside the hospital). Clinical visit costs were defined according to the hospital district's outpatient product costs for specialized somatic health care visits. The costs for hospitalization periods were determined from the estimates by Finnish National Institute for Health and Welfare for the unit costs of social and health care in 2011 [12]. The costs of non-WES diagnostic tests in 2019 were converted to 2018 prices in euros using the national health and social care price index by the Association of Finnish Local and Regional Authorities [13] and currency converter [14], or the current price was used, e.g. for diagnostic tests performed outside the hospital. WES price, including all technical and analytical costs including staff salaries, was estimated to be 1375€ per singleton WES according to the commercial price used in Helsinki hospital district's laboratory (HUSLAB) in November 2019.

Baseline characteristics of children in WES group and control group were compared by cross tabulation and chi-square and Fisher's exact tests. Continuous variables were analysed by Wilcoxon rank-sum test. Mean diagnostic costs per patient were calculated with standard deviations, medians and 95% confidence intervals (CI). In addition, mean costs per diagnosis were calculated by dividing total costs by the total number of diagnoses in the groups.

In the cost-effectiveness analysis incremental cost-effectiveness ratio (ICER = ΔCosts/(ΔDiagnostic yield)) per additional diagnosis was calculated by dividing the difference in mean costs per patient between WES and control groups by the difference in diagnostic yield (diagnosis rate) between the groups. Mean differences of the total costs per patient between WES and control groups were analysed using Wilcoxon rank-sum test. Bootstrapping simulation

Table 1
Demographics of participants.

	WES group (n = 48)	Control group (n = 49)	*p* value
Sex			0.254
Male (%)	30 (62)	25 (51)	
Female (%)	18 (38)	24 (49)	
Mean age at the first visit in hospital, years [SD]	5.4 [5]	3.7 [1]	0.0864
Living district			<0.001
HUS district (%)	26 (54)	43 (88)	
Other district (%)	22 (46)	6 (12)	
Diagnosis (%)	**18 (38)**	**12 (25)**	0.122
Time before WES[a]			
1 year (%)	23 (48)	*NA*	
>1–3 years (%)	10 (21)	*NA*	
>3–5 years (%)	7 (15)	*NA*	
> 5 years (%)	8 (16)	*NA*	

WES, whole-exome sequencing; HUS, Hospital district of Helsinki and Uusimaa; SD, standard deviation; NA, not available.
[a] From the first visit in hospital.

with 1000 replications was used to estimate the uncertainty of cost-effectiveness analysis. Bootstrapping resamples the data with replacement to building an empirical estimate e.g. of the mean costs or ICER of the sampling data ([15], p. 299). The early-WES subgroup was analysed separately. Since information on patient clinical visits was not comprehensive for the exome group and thus more favourable for the group, the additional analyses were done without clinical visit costs, with a third analysis with all study subjects.

Statistical significance was set at p-value <0.05. All analyses were made using Stata 15.1 (Stata, College Station, TX) except for bootstrap simulations, which were performed in Microsoft Excel.

2.6. Ethics

Ethical approval for the study was granted by the coordinating ethical committee of The Hospital District of Helsinki and Uusimaa. Informed consents were gathered from the parents of child participants.

3. Results

3.1. Diagnostic yield

Definitive diagnosis was obtained for 18/48 patients (38%) in the WES-group and for 12/49 patients (25%) in the control group (p = 0.122). The “early WES patients” had a slightly higher diagnostic yield with 10/23 patients diagnosed (43%).

3.2. Costs and cost-effectiveness

Mean cost per diagnosis was lower in the WES group (25,433€ vs. 40,467€). Mean costs per patient were 9537€ (range 3387–27,308€) in the WES group and 9910€ (2088–23,310€) in the control group (Table 2). WES yielded more definitive diagnoses with slightly lower costs and could therefore be considered dominant over standard care. However, the cost difference was not statistically significant (p = 0.5302).

Main cost drivers were genetic tests (32%, including the price of WES) and clinical visits (26%) in the WES group. In the control group, the largest cost drivers were clinical visits (33%) and genetic tests (26%). Control patients had on the average 3.0 genetic tests (range 0–7), whereas patients in the WES group had had 1.4 tests (range 0–8) before inclusion to the study. For patients that had WES done early after manifestation, the mean was 0.6 (range 0–3). Prior to the study, 40% of the patients in the WES group had been tested for chromosomal anomalies, 42% had at least one gene analysed by Sanger sequencing, and 19% had a gene panel analysis done (corresponding to 73%, 65%, and 31% for controls). In the WES group, the mean number of clinical visits were 4.9 (ranging 1–17) and in the control group, 6.5 visits (range 1-13) (p < 0.01).

Additional analyses (Table 3) were done without clinical visit costs. When only early WES-patients were included in the treatment group, WES was dominant, meaning potentially cost-effective, as WES had a greater diagnostic yield with lower costs (mean cost per diagnosis 5502€ vs. 6674€). The cost difference was not statistically significant (p = 0.3309).

A third analysis showed that mean costs per patient were slightly higher in the WES group than in the control group if clinical visit costs were not included. Still, cost-effectiveness analysis showed that WES yielded the incremental cost of 2847€ per one additional diagnosed patient.

4. Discussion

This study evaluates the diagnostic utility and cost-effectiveness of WES as a routine diagnostic tool in pediatric patients with progressive neurological disorders. Our results show that WES provides better diagnostic yield (37.5 vs. 24.5%) compared to conventional diagnostic path utilizing clinical diagnostic means complemented with gene panel testing. First-year “early-WES” was clearly most successful (43%). Our diagnostic yield in the WES group is in line with a recently published meta-analysis of children with suspected genetic diseases [9]. Considering patients that were recruited to the study even after three years of prior investigations (31%), who had been examined with a large set of standard diagnostic tools, WES resulted in previously unachievable diagnoses for four out of fifteen patients.

We chose to collect full costs of both WES and conventional diagnostic path, to elucidate the full costs related to the examinations. Previous studies have not used a similar control group of patients [16]. Many of the previous studies were modeled with diagnostic scenarios in the same study cohort [17–21] or using a hypothetical WES trajectory [22]. In addition, only a few studies were conducted in Europe [10,22]. Also, previous studies mainly investigated cost-effectiveness of WES in pediatric patients with any suspected monogenic disorders [6,19–21] or with specific disorders, such as epilepsy [17] or muscle disorders [18]. The finding that clinical visits and genetic tests were the main drivers of costs in both study groups are in line with previous studies, in pediatric cohorts [10] and mixed cohorts of children and adults [23] with complex neurological problems. Most of the previous studies have reached incremental cost savings per additional diagnosis when WES was used as a first-line test [18,19,21]. In a population-

Table 2
Cost drivers and mean costs per diagnosis and per patient in the WES and control groups.

	WES group (n = 48)	Control group (n = 49)	Difference
Total costs, € (%)	457,790 (100)	485,604 (100)	−27,814
WES (%)	66,000 (14)	*NA*	66,000
Genetics[a] (%)	79,849 (17)	126,656 (26)	−46,807
Imaging (%)	25,275 (6)	22,526 (5)	2749
Non-genetic laboratory tests (%)	67,274 (15)	87,243 (18)	−19,969
Hospitalization periods (%)	42,694 (9)	56,283 (11)	−13,589
Clinical visits (%)	119,661 (26)	158,567 (33)	−38,906
Other examinations[b] (%)	57,038 (13)	34,329 (7)	24,709
Total number of diagnoses (%)	18 (38)	12 (25)	6 (13)
Mean cost per diagnosis, €	25,433	40,467	−15,034
Mean cost per patient, € (SD, 95% CI)	9537 (4964; 8096–10,979)	9910 (4803; 8531–11,290)	−373 (SE 992; −2342–1596)
Median (IQR)	8945 (5771–11,560)	9615 (5926–12,200)	−670
ICER, €	***Dominant***		

WES, whole-exome sequencing; NA, not available; SE, standard error; CI, confidence interval; IQR, interquartile range.
[a] Genetics referring to all other genetic testing besides WES, including e.g. Sanger sequencing, molecular karyotypes, gene panels.
[b] Including e.g. electroencephalography (EEG) and electroneuromyography (ENMG) investigations and clinical exercise tests.

Table 3
Early WES patients and an additional analysis without clinical visit costs.

	WES group	Control group	Difference
	WES in 1 year (without clinical visit costs)		
	n = 23	n = 49	
Total number of diagnoses (%)	10 (43)	12 (25)	2 (19)
Mean cost per diagnosis, €	12,655	27,253	−14,598
Mean cost per patient, €	5502	6674	−1172
(SD, 95% CI)	(3047; 4185–6820)	(4413; 5407–7942)	(SE 1020; −3205–862)
Median (IQR)	5193 (2782–7095)	5832 (3605–7905)	−639
ICER, €	***Dominant***		
	WES (without clinical visit costs)		
	n=48	n=49	
Total number of diagnoses (%)	18 (38)	12 (25)	6 (13)
Mean cost per diagnosis, €	18,785	27,253	−8468
Mean cost per patient, €	7044	6674	370
(SD, 95% CI)	(4304; 5795–8294)	(4413; 5407–7942)	(SE 885; −1388–2128)
Median (IQR)	6230 (4305–7524)	5832 (3605–7905)	398
ICER, €	**2847**		
Bootstrapped ICER, € (95% CI)	3253 (−24,046–26,877)		

WES, whole-exome sequencing; SD, standard deviation; SE, standard error; CI, confidence interval; IQR, interquartile range; ICER, incremental cost-effectiveness ratio.

based study by Howell et al. [17] WES also yielded cost savings per additional diagnosis only when WES was targeted early and metabolic testing was limited compared to standard care without WES in patients with severe infantile epilepsies. In other pathways, including metabolic testing, repeated magnetic resonance imaging or skin and muscle biopsies before WES, the incremental cost per additional diagnosis was $3250–8559. One of the few European studies [22] evaluated that WES (trio) resulted in an ICER of 8950€ per additional diagnosis among children with complex pediatric neurological disorders. In our study, from the hospital perspective, singleton-WES yielded incremental cost of 2847€ per one additional diagnosis compared to traditional diagnostic path (without clinical visits), whereas WES performed during first year of investigations caused cost-savings.

Previously, health status or quality of life have been discussed not to necessarily be the only outcome measures in health economic evaluations of genetic testing, as genetic information itself is valued and can influence one's ability to make an informed decision [24]. However, there is no single threshold for interpreting the ICER result of our study, so cost-effectiveness depends on the payer's willingness to pay for one additional diagnosis. Further studies remain to be performed to estimate such willingness to pay and to outline whether payers are eager to reimburse on such outcome measures. The importance of genetic testing cannot be overemphasized, as it provides considerable personal benefit by ending diagnostic examinations, offering exact genetic diagnosis and counseling, providing prognosis, and sometimes directing therapy decisions.

The strength of this study is a prospective cohort study design, which allowed investigation of WES as a routine diagnostic tool. In addition, the study includes a retrospectively collected control group of patients who underwent traditional diagnostic tests. However, this study also has limitations. First, living district may present a selection bias and second, the sample size is relatively small. Diagnostic yield in different studies varies based on how well the original patient population was preselected, and directly affects cost-effectiveness. The diagnostic yield could have increased if trio-analysis had been implemented. However, in WES-studies often yields from 30 to 40% are achieved, pointing to the value of the diagnostic tool. In a benchmark meta-study of children with heterogeneous suspected genetic conditions, diagnostic yield for singleton-WES was found to be 26.5% (95% CI: 12.9–42.9) across studies, suggesting this range of yield to be characteristic for child manifestations [25]. Our study's sample size, limited due to

financial capacity to do WES, potentially also widened the confidence intervals of the bootstrapped results. Third, as the purpose of the study was to clarify the costs of early WES analysis, this sample is a selected subsample. Last, infantile encephalopathies and progressive neurological disorders of childhood are a clinically heterogeneous group of patients, and tour-de-force of examinations are often initiated to gain a specific diagnosis increasing the non-WES diagnostic costs. Similar cost-effectiveness studies for different kinds of patient groups would be informative.

The results are highly interesting, as our study group was clinically broadly defined – progressive neurological disorder of childhood – and genetically heterogeneous. We propose that WES could be used in first-line diagnosis of undefined progressive neurological disorders of children, as a third of such patients would obtain a diagnosis directly, and the care could be targeted based on the specific disease. The development in NGS methods and analysis, and progressively decreasing price of WES makes the method highly valuable in diagnostic path of children. In future studies, economic evaluations from the societal perspective including also costs after WES should be conducted; a recent paper [26] finds that diagnosis-related physician consultations do not decline after a negative WES. In addition, the cost-effectiveness should be studied based on other more generic effectiveness measures, such as quality adjusted life years (QALYs).

Conflicts of interest disclosures

The authors have no financial relationships relevant to this article to disclose.

Funding

This work was supported, as part of the Neurogenomics Finland consortia project, by the pHealth academy program of the Academy of Finland (sub grant number 292584). The funding source had no role in conducting this study.

Appendix 1. Exome cohort, patient phenotypes

	Patient id	Age at inclusion (years)	Sex	Number of tests performed before WES	Tests performed	Symptomatology/clinical diagnosis with HPO terms
Early WES	1	0.0	F	1	Molecular karyotype	Epileptic encephalopathy with neonatal onset
	2	0.2	M	2	Molecular karyotype, Sanger sequencing of ARPKD	Leukoencephalopathy, periventricular cysts, enlarged kidneys, hypertension, VSD, central sleep apnea, dysphagia with neonatal onset
	3	0.2	F	1	Molecular karyotype	Encephalopathy, neonatal hypotonia, and epilepsy with neonatal onset
	4	0.5	F	0		Nystagmus, muscular hypotonia, and vitamin B12 deficiency with infantile onset
	5	0.7	M	2	Molecular karyotype, Sanger sequencing of PPT1	Microcephaly, epilepsy, global developmental delay, CNS hypomyelination, and hypoplasia of the corpus callosum
	6	1.1	M	2	Molecular karyotype, gene panel	Encephalopathy and dystonia with pons and nucleus dentatus signal intensity with antenatal onset
	7	1.1	F	0		Global developmental delay, epilepsy, leukoencephalopathy, progressive microcephaly, nystagmus with infantile onset
	8	1.5	M	0		Spastic paraparesis with infantile onset
	9	2.2	F	3	Karyotype, molecular karyotype, Sanger sequencing of FMR1	Vomiting, growth delay, global developmental delay, and infantile lactic acidosis with antenatal onset
	10	2.6	M	0		Paroxysmal dystonia, delayed speech and language development, global developmental delay, and fatigue with infantile onset
	11	3.3	M	0		Generalized myoclonic seizures, global developmental delay and cerebellar vermis abnormality with infantile onset
	12	4.4	F	2	Molecular karyotype, gene panel	Fatigable weakness with infantile onset
	13	6.9	M	0		Sensorimotor polyneuropathy affectings arms more than legs, motor delay, and exercise intolerance
	14	11.4	F	0		Sensorimotor axonal polyneuropathy with juvenile onset
	15	12.0	F	0		Peripheral axonal neuropathy with childhood onset
	16	12.7	M	0		Progressive spasticity with infantile onset
	17	13.0	M	0		Peripheral axonal neuropathy with childhood onset
	18	13.6	M	0		Exercise-induced myalgia in calves with juvenile onset
	19	13.6	F	0		Progressive tremor with childhood onset
	20	13.7	F	1	Gene panel	Progressive dyskinesia with juvenile onset
	21	13.9	F	0		Peripheral axonal neuropathy with childhood onset
	22	14.5	M	0		Paroxysmal vertigo, diplopia, dysartria, and dyskinesia with juvenile onset
	23	15.9	M	0		Paroxysmal dyskinesia and migraine with juvenile onset
	24	1.6	M	4	Molecular karyotype, gene panels x2, Sanger sequencing of NKH2, NKH3	Agenesis of corpus callosum, delayed myelination, microcephaly, epilepsy, global developmental delay, vocal cord paresis with antenatal onset
	25	1.9	F	3	Molecular karyotype, MLPA, Sanger sequencing of DM1	Muscular hypotonia since birth and global developmental delay with infantile onset
	26	2.3	M	4	Molecular karyotype, gene panel, Sanger sequencing of SMA, DM1	Encephalopathy and central hypotonia; regression, cerebellar atrophy, thalamus and nucleus dentatus signal abnormality with infantile onset

(*continued*)

Patient id	Age at inclusion (years)	Sex	Number of tests performed before WES	Tests performed	Symptomatology/clinical diagnosis with HPO terms
27	2.6	M	1	Molecular karyotype	Infantile muscular hypotonia, hearing impairment, encephalopathy, autistic behavior, and global developmental delay with congenital/infantile onset
28	2.9	M	1	Sanger sequencing of DM1	Infantile muscular hypotonia, global developmental delay, and autistic behavior with infantile onset
29	3.4	F	4	Karyotype, molecular karyotype, MLPA, Sanger sequencing of HPRT1	Global developmental delay, ataxia, dystonia, fasciculations, hypoplasia of the corpus callosum, and delayed myelination with infantile onset
30	3.5	M	1	Gene panel	Epileptic encephalopathy with infantile onset
31	4.8	F	3	Karyotype, molecular karyotype, Sanger sequencing of DM1	Growth delay, feeding difficulties, global developmental delay, lower limb spasticity, and CNS hypomyelination with antenatal/infantile onset
32	4.9	M	1	Molecular karyotype	Spastic paraparesis and global developmental delay
33	5.1	M	2	Karyotype, molecular karyotype	Severe dystonia with swallowing difficulty and epilepsy with antenatal/infantile onset
34	5.2	M	3	Gene panel, Sanger sequencing of SMA, DM1	Myopathy and flexion contracture with congenital/infantile onset
35	5.3	M	0		Generalized muscle weakness, respiratory insufficiency due to muscle weakness with childhood onset
36	6.1	M	5	Karyotype, molecular karyotype, mitochondrial sequence x2, Sanger sequencing x1	Encephalopathy and sensorineural hearing impairment with antenatal onset
37	6.9	M	8	Karyotype x2, molecular karyotype, FISH, VGH, MLPA, Sanger sequencing of RB1	Intellectual disability, epilepsy, ventricular septal defect, retinoblastoma, and central sleep apnea with infantile onset
38	8.8	F	3	Molecular karyotype, gene panel, Sanger sequencing DYT gene	Severe dystonia with infantile onset
39	11.7	F	0		Progressive spastic paraparesis and intellectual disability with infantile onset
40	13.3	M	1	Sanger sequencing of PRRT2	Exercise intolerance and myopathy with childhood onset
41	13.4	M	0		Hemiplegic migraine with childhood onset
42	14.2	M	1	Sanger sequencing DYT11	Progressive dyskinesia with juvenile onset
43	14.6	M	0		Severe tremor and migraine with aura with infantile onset
44	15.3	M	2	Sanger sequencing of PMP22, HNPP	Neuropathy with juvenile onset
45	15.4	M	2	Karyotype, Sanger sequencing of FMR1	Peripheral axonal neuropathy with juvenile onset
46	15.8	F	2	Gene panel, Sanger sequencing of CPT2	Exercise-induced myalgia with juvenile onset
47	16.3	M	2	Mitochondrial sequencing, Sanger sequencing of EPM1	Cerebral ischemia causing hemiparesis, epilepsy requiring surgery, hypothyroidism, ataxia, and myoclonus with neonatal/childhood onset
48	17.3	F	0		Spastic paraplegia with childhood onset

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