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Impact of clinical exomes in neurodevelopmental and neurometabolic disorders☆

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ABSTRACT

Whole exome sequencing (WES) is well established in research and is now being introduced into clinically indicated diagnostics (so-called clinical exomes). We evaluated the diagnostic yield and clinical implications of WES in 72 patients from 60 families with undiagnosed neurodevelopmental disorders (NDD), neurometabolic disorders, and dystonias. Pathogenic or likely pathogenic variants leading to a molecular diagnosis could be identified in 21 of the 60 families (overall 35%, in 36% of patients with NDD, in 43% of patients with neurometabolic disorders, in 25% of patients with dystonias). In one family two coexisting autosomal recessive diseases caused by homozygous pathogenic variants in two different genes were diagnosed. In another family, a homozygous frameshift variant in *STRADA* was found to cause a severe NDD with early onset epilepsy, brain anomalies, hypotonia, heart defect, nephrocalcinosis, macrocephaly and distinctive facies so far designated as PMSE (polyhydramnios, megalencephaly, symptomatic epilepsy) syndrome. In 7 of the 21 families with a molecular diagnosis the pathogenic variants were only identified by clinical follow-up, manual reevaluation of the literature, a change of filter setting, and/or reconsideration of inheritance pattern. Most importantly, clinical implications included management changes in 8 cases and impact on family planning in 20 families with a molecular diagnosis. This study shows that reevaluation and follow-up can improve the diagnostic rate and that WES results have important implications on medical management and family planning. Furthermore, we could confirm *STRADA* as a gene associated with syndromic ID but find it questionable if the current designation as PMSE depicts the most important clinical features.

1. Introduction

Whole exome sequencing (WES) has proven to be a powerful tool to unravel the etiology of presumably monogenic diseases, in particular neurodevelopmental disorders (NDD), and to identify new disease or candidate genes. After having been tested in research, WES is now being introduced in clinically indicated diagnostics. For moderate to severe intellectual disability (ID) the identification of the underlying monogenic cause has been reported in 16% to 50% and most often consists of *de novo* heterozygous variants [1–3]; for patients with NDD or pediatric neurologic disorders, the yield of (likely) pathogenic findings ranges between 25 and 57%, settling at a level of 25 to 28% regarding large studies with broader inclusions (see Table 1). Recently, a high diagnostic rate of 68% (28/41) has been reported on investigation of 41 patients with ID and a broadly defined metabolic phenotype [4].

The benefit of a diagnosis for the assessment of the recurrence risk and for genetic counseling translating into informed decision making with regard to family planning, and possibly a prenatal diagnosis, has been known for a long time. Knowledge of a causal diagnosis may provide specific information on the disease course, facilitate the coping process, can give access to medical support and services, and helps to become involved in patient support groups [17]. Beyond these well-

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Table 1
Results of clinical exome studies in patients with neurodevelopmental disorders.

Reference	# subjects age	Phenotype	Diagnostic rate (%)	*Dn* mutation	Two or more diagnoses	Clinical implications by diagnosis	Clinical implications by incidental findings
De Ligt et al., 2012 [1]	100	Severe ID	16	81% (13/16)	0	n.d.	n.d.
Rauch et al., 2012 [2]	51	Severe non-syndromic ID	~50	~96%	0	n.d.	n.d.
Yang et al., 2013 [5]	250 89% ≤18 y	85% Neurol	25	53%	4 pts. (1.6%)	n.d.	12%
Hamdan et al., 2014 [3]	41	Moderate/ severe non-syndromic ID	29	100%	0	n.d.	n.d.
Srivastava et al., 2014 [6]	78 <18 y	NDD	41	59% (19/32)	1 pt. (1.3%)	All, management changes in 47%, impact on FP in 87%	n.d.
Lee et al., 2014 [7]	814 64% <18 y	Any, 37% DD,	26	50% (of trio-based diagnoses)	n.d.?	n.d.	Incidental findings in 5%
Yang et al., 2014 [8]	2.000 88% <18 y	Mostly NDD	25	51%	23 pts. (4.6%)	n.d.	4.6%
Wright et al., 2015 [9]	1.133 <18 y	87% DD/ID	27*	65%*	n.d.	n.d.	n.d.
Retterer et al., 2016 [10]	3.040 Any (mean 11.4 ± 13.2 y)	Any, 36% neurol/NDD	28.8	42.5%	28 pts. (± 1%)	n.d.	6%
Nolan & Carlson, 2016 [11]	50 <18 y	88% NDD	47	33%	0	In 78%, management changes in 52%, impact on FP in 48%	10%
Monroe et al., 2016 [12]	17	ID/NDD	29	n.d.	0	n.d.	n.d.
Tarailo-Graovac et al., 2016 [4]	41 90% <18 y	Neurometabolic disorders/ID + metabolic phenotype,	28/41	39% (11/28)	5/28 pts. (18%)	44% (18 pts)	2% (1/41)
Stark et al., 2016 [13]	80 ≤2 y	MCA + dysmorphism + other, 74% neurometabolic	57.5	36%	1 fam	Management changes in 32%, impact on FP in ≥62%	n.d.
Kuperberg et al., 2016 [14]	57 <18 y	NDD, Neurol	49	50%	0	All, changes in medic. in 5 pts	n.d.
Trujillano et al., 2017 [15]	1000 0–59 y 45% from cons. families	Any, 77% neurol/NDD	30.7	20%	3/307 pts. (1%)	n.d.	n.d.
Lisenka et al., 2017 [16]	150 <18 y	ID, Neurol	29.3	77% (34/44)	0	n.d.	n.d.

Legend: cons.: consanguineous, DD: developmental delay, *Dn*: *de novo*, fam: family, FP: family planning, ID: intellectual disability, n.d.: not documented, NDD: neurodevelopmental disorder, MCA: multiple congenital anomalies, neurol: neurologic disease, pts.: patients, y: years, * incl. CNVs.

known aspects of a causal diagnosis, there is growing evidence that a diagnosis influences the management of the disease, including surveillance for directly or indirectly related morbidities, and can pave the way to a targeted disease-modifying treatment [4,6,11,14].

We evaluated the diagnostic clues, the yield and the clinical implications of trio-based WES in a group of patients with presumably monogenic diseases, predominantly children with NDD, neurometabolic or movement disorders, following a phenotype-first approach and using a semi-automated bioinformatics pipeline. An illustrative case report of siblings with a *STRADA* associated NDD is included.

2. Patients and methods

2.1. Patients

WES was performed in a cohort of 72 patients from 60 families with undiagnosed, suspected genetic conditions. The patients were included between 1/2013 and 12/2015 after a phenotype-first approach, meaning that patients were thoroughly phenotypically characterized prior to WES and that the patient's phenotype was taken into consideration for the interpretation of WES data. The study cohort comprised 45 index patients with developmental delay (DD)/ ID and/or congenital malformations (NDD group) seen at the Institute of Human Genetics, eight patients with infantile dystonia (dystonia group), and seven patients with a neurometabolic disorder (neurometabolic group), seen at the Department of General Pediatrics, Division of Neuropediatrics and Metabolic Medicine, of Heidelberg University Hospital. The neurometabolic group includes one patient with clearly reduced concentration of 5-methyltetrahydrofolate in CSF (ZKJM003-014), four patients with abnormal glycosylation of alpha-1 antitrypsin and two patients with a general glycosylation deficiency (therefore presenting a presumed congenital disorder of glycosylation, CDG). Apart from continuously reduced serotonergic metabolites in CSF without clear pathophysiological significance in one of the patients with dystonia, there were no metabolic abnormalities observed among the eight patients of the dystonia group. For that reason, these patients have not been included in the neurometabolic group, although infantile dystonia can be caused by neurometabolic diseases. All patients were evaluated and phenotypically characterized by an experienced clinical geneticist and/or neuropediatrician. The evaluation included the medical history and family history of at least three generations and a physical, dysmorphological, and neurologic examination. Brain MRI was performed in patients with abnormal findings on neurologic examination in addition to DD/ID (*e.g.* focal neurologic deficits), or micro- or macrocephaly and in patients with a suspected genetic condition with expected brain phenotype. If clinically indicated examinations by other medical specialist (*e.g.* ophthalmologic evaluation) were performed. Clinical characteristics of the index patients are given in Table 2.

The patients had a mean age at diagnosis of 8.5 years compared to a mean age of 6.4 years at WES analysis regarding the patients in whom no diagnosis could be achieved. 50% of patients were males, and most were of German or Turkish origin (55% and 28%, respectively). 25% of families, mainly those of Turkish origin, reported consanguinity. 70% of index patients with known family history were sporadic cases, 30% had at least one affected sibling. Patients displayed a wide range of symptoms (Table 2), with 77% having DD/ID. Other common phenotypes were micro- or macrocephaly (53% and 12%, respectively), dysmorphic signs (40%), short stature (32%), epilepsy (28%), and