Evaluation of the etiology of epilepsy and/or developmental delay in children presenting to a pediatric neurology clinic with next generation sequencing: A single center experience

Kava H.*, Alanay Y., Yeşilyurt A., Isik U.*

Acibadem University, School of Medicine, Department of Pediatrics, Division of Pediatric Neurology*

Acibadem University, School of Medicine, Depatment of Pediatrics, Division of Pediatric Genetics

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ABSTRACT

Children with epilepsy have a variety of developmental disorders like global developmental delay, intellectual disability, autism spectrum disorder and attention deficit hyperactivity disorder. (1) In the last decade, with the invention of next generation sequencing (NGS) , many genes related to epilepsy and DD have been identified. With a better understanding of the pathogenesis and cellular electrophysiology of genetic epilepsies, more treatment options are likely to emerge. (2)

OBJECTIVES

In this study we aimed to understand the genetic etiology in children presenting with epilepsy and/or developmental delay by using NGS.

MATERIALS & METHODS

We included children presenting to our pediatric neurology clinic with the diagnosis of epilepsy and/or developmental delay between January 2019 and December 2021. The patients were evaluated with the NGS (whole exome sequencing-WES or whole genome sequencing-WGS or both) in our genetic laboratory. Sociodemographic, clinical, EEG and MRI findings were retrospectively examined and the results of the genetic tests were evaluated according to the recent genetics literature.

RESULTS

A total of 90 patients were included in the study. Fifty one patients (56.6%) were male and 39 (43.3%) were female. The age range of the patients at the time of admission to our clinic ranges from 13 days to 16 years. The mean age of patients was 3,98 years and median age was 2.70 years. Nine patients (10%) had only epilepsy, 53 patients (58.8%) had both developmental delay (DD) and epilepsy, 28 patients (31.1%) had only DD. Sixty patients had only WES, 12 patients had only WGS, 18 patients had both WES and microarray. Twenty (33.3%) out of 60 patients who had WES had pathogenic or likely pathogenic variants (P/LP), 15 (25%) had variant of unknown significance (VUS). Five (41.6%) out of 12 patients who had WGS had P/LP variants and 6 (50%) had VUS. Eleven (61.1%) out of 18 patients who had WES and microarray had P/LP variants, 2 (11.1%) had VUS. Twelve patients (13.3%) had a diagnosis with a known specific treatment.

Pathogenic/Likely pathogenic variants	
Epilepsy	PRRT2 (2), KCNQ2, SCN2A
Epilepsy and DD	SCN1A (2), del. 22q11, ASH1L, ABCC8, del. 2q37 dup. 3q26, GNB1, PACS2, PPT1,PNPO, PLA2G6 (2), WWOX,KCNQ2,GFAP, [ALDH7A1, SLC22A5], NAGA, CUX1
DD	[BCL11A, SCN8A], del. 3q13, BCL11B, ERCC6, ECEL1, KDM6A, TCF20, DHCR7, GCDH, ZEB2, SOX5, PANK2, PIK3R2, KIF1A

CONCLUSIONS

NGS helps to diagnose children with epilepsy and/or DD precisely and also provides a correct prognosis, specific treatment methods and multidisciplinary approach. It also provides the chance of preimplantation methods to the families and a communication network for rare diseases.

REFERENCES

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CONTACT

Isik U. MD ugur.isik@acibadem.com

Kava H. MD handan.kava@acibadem.com

Patients who had a diagnosis with a known specific treatment					
P	S	Gene	Related Disorder	Phenotype	Treatment
P11	E	SCN1A	Dravet syndrome	DD, epilepsy (4 months), ADHD	VPA, TPM
P41	E	SCN1A	Dravet syndrome	Epilepsy (7 months), ID, ADHD	LEV, TPM, PB, STP, FFA
P27	K	SLC2A1	GLUT1DS1	Epilepsy (4 months), spasticity, DD	KD, LEV, CLB
P35	E	ALDH7A1; SLC22A5; MTHFR	EPD; CDSP; MTHFR deficiency	Epilepsy (birth), dysmorphism, DD	TPM, PB, folic acid, L-carnitine, P5P
P25	E	PNPO	PNPOD	Epilepsy (birth), hypotonia	P5P, VPA
P10	E	FOLR1	NCFTD	Epilepsy (5 years), DD	CZP, TPM, folinic acid
P33	K	KCNQ2	DEE 7	Epilepsy (3 days),DD, hypotonia	VGB, CBZ
P4	E	KCNQ2	DEE 7	Epilepsy (3 days)	PB, CBZ
P5	E	SCN2A	BFIS, 3	Epilepsy (1 month)	LEV,CBZ
P63	E	SCN8A	CIAT	DD, ADHD, dysmorphism	-
P2	E	PRRT2	BFIS, 2	Epilepsy (5 months)	OXC
P3	E	PRRT2	BFIS, 2	Epilepsy (3 months)	PB

ADHD: Attention deficit hyperactivity disorder DD:Developmental delay ID: Intellectuel disability GLUT1DS1: GLUT1 deficiency syndrome 1, infantile onset, severe EPD: Epilepsy, pyridoxine-dependent CDSP: Carnitine deficiency, systemic primary PNPOD: Pyridoxamine 5'-phosphate oxidase deficiency NCTFD: Neurodegeneration due to cerebral folate transport deficiency DEE: Developmental and epileptic encephalopathy CIAT: Cognitive impairment with or without cerebelllar ataxia BFIS: Seizures, benign familial infantile, VPA: Valproic acid, TPM:Topiramate, LEV:Levatirecetam CBZ: Carbamazepine, OXC:Okscarbazepine KD: Ketogenic diet PB:Phenobarbital STP:Stiripentol CLB: Clobazam FFA: Fenfluramine CZP:Clonazepam VGB: Vigabatrin P5P: pyridoxal 5 phosphate