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Is the Genetics Primary Underlying Factor in Epilepsy and Autism Spectrum Disorders in Childhood?

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Abstract

Background: Among all epilepsies only a small proportion is defined to be mono-genetic. However, recent studies have helped to create effective technologies for genome analysis to identify de novo genetic mutations, particularly those associated with genes critical to neuronal functions and metabolism.

Material and Methods: In this study, three patients with epilepsy those have underlying genetical defects were presented. *SCN1A*, *CHD2*, *BRCA2* and *KIF1A* genes of all exon regions in the genomic DNA sample isolated from patients' peripheral blood has been studied using the MiSeq system with a new generation of sequence analysis method.

Results: In our first case with epilepsy, the variant c.2415 + 1G> A detected heterozygously in the *SCN1A* gene causes the degradation of the highly conserved donor site in intron 13. In our second case with epilepsy; the variant c.1651T> G (p.Ser551Ala) detected heterozygously in the *SCN1A* gene causes the Serine amino acid at position 551 to be converted to Alanine and variant c.1719G> A (p.Thr573 =) detected heterozygously in the *CHD2* gene causes a synonymous variant. In our third case with developmental delayed, autism spectrum disorder (ASD) and febrile convulsion; the variant c.4139_4140dup p. (Lys1381Leufs * 8), which is heterozygous in the *BRCA2* gene, causes an early stop codon and variant c.3869T> C p (Ile1290Thr), which is detected heterozygously in the *KIF1A* gene, causes Threonine conversion of Isoleucine amino acid at position 1290.

Conclusion: Epileptic syndromes are highly seemed to be in relation with *SCN1A, CHD2, K1F1A* genes. Also the gene sequencing of these patients shows a correlation between some gene mutations with ASD. In order to determine whether this mutations, which has been confirmed by Sanger sequencing, is hereditary or de novo, it is recommended that family studies should be conducted with Sanger sequencing in future studies. Genetic counseling should be recommended to epileptic syndromes and ASD of childhood.

Keywords: Epilepsy • Autism Spectrum Disorder (ASD) • Genetics Counselling • Childhood

Introduction

Recent studies have helped to create effective technologies for genome analysis to identify de novo genetic mutations, particularly those associated with genes critical to neuronal functions and metabolism. Thus, it was possible to identify more recent cases. These studies have demostrated important data on the etiology and causative mechanisms of epilepsy, mental insufficiency and autism spectrum disorders [1]. Data from the literature indicate that 20% of children with epilepsy are mistakenly diagnosed with autism spectrum disorder [2]. In some cases, the negative effects of persistent seizures on the brain parenchyma may be a factor for additional brain functional disorders; many other seizures, ASD, and mental disability are accompanied by an underlying brain abnormality [3].

New technologies such as high-throughput genotyping and sequencing have made remarkable progress in defining the genetic etiology of childhood epilepsy. In this study variants detected heterozygously in *SCN1A, CHD2, BRCA2 and KIF1A* genes were important in terms of showing the underlying epileptic status in the patients in our study. Types of seizures associated with *SCN1A* include a spectrum ranging from simple febrile seizures with autosomal dominant inheritance and generalized epilepsy with febrile seizures, dravet syndrome and generalized tonic-clonic seizures with resistant child age epilepsy [4]. Pathogenic variants in the *CHD2* gene are associated with "Autosomal Dominant Childhood Epileptic Encephalopathy". Affected individuals have cognitive impairment and intellectual disability. Pathogenic germline variants in the *BRCA2* gene are associated with "Autosomal Dominant Familial Breast / Ovarian Cancer Type 2". Patients with de novo variants of the *KIF1A* gene were defined as mild to severe global growth retardation and mental failure.

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Case presentations

Our first case is 8 years old, female, Turkish origin and her parents are first degree relatives. Standard karyotypes as well as *SCN1A* gene mutation analysis were negative in all first degree relatives of the patient in her family. The female patient was born at term after a normal pregnancy from healthy first degree consanguineous and healthy parents. She has a healthy 10 years old brother. In her 4th month of life she had her first convulsion which was iniated in right arm with high frequency cry. She attended a special education school for behavioral and motor development due to psychomotor delay from the age of 2 years. Our patient's speaking skills were insufficient to express herself. WISC has a severe MRI with a full-scale IQ of 40. She also exhibited behavioral problems requiring pharmacological treatment. She had epilepsy with severe convulsions that require antiepileptic drugs. Electroencephalogram showed severe epileptic pattern in this patient. He had normal vision and hearing and no dysmorphic features. A brain computed tomography scan was performed and it was normal. Variants for case 1 displayed in (Figure 1).

The second case is 7 years old, female, Turkish origin and her parents

Gene (transcript)	Nucleotide Transformation	Aminocyte Transformation	Genetype	DbSNP ID	Variant Classification	Transcript
SCN1A	c.2415+1G>A	-	Heterozygous (OD)	-	Pathogenic	(AB093548)

Figure 1. Variants Associated with Disease for case 1

Gene (transcript)	Nucleotide Transformation	Aminocyte Transformation	Genetype	DbSNP ID	Variant Classificition	Transcript
SCN1A	c.1651T>G	(p.Ser551Ala)	Heterozygous (OD)	-	VUS	(NM_001202435.2, sequencing)
CHD2	c.1719G>A	(p.Thr573=)	Heterozygous (OD)	-	VUS	(NM_001271.3,sequencing)

Figure 2. Variants Associated with Disease for case 2

Gene (transcript)	Nucleotide Transformation	Aminocyte Transformation	Gene type	DbSNP ID	Variant Classificition	Transcript
BRCA2	c.4139_4140dup	(p. Lys1381Leufs*8)	Heterozygous (OD)	-	Pathogenic	(NM_000059.3, sequencing)
KIF1A	c.3869T>C	(p. Ile1290Thr)	Heterozygous (OD)	-	VUS	(NM_001244008.1,sequencing)
SCN1A	c.5701G>A	(p. Val1901Ile)	Heterozygous (OD)	-	VUS	(AB093548.1, sequencing)

Figure 3. Variants Associated with Disease for case 3

are first degree relatives. Standard karyotypes as well as *SCN1A* and *CHD2* gene mutation analysis were negative in all first degree relatives of the patient in her family. The female patient was born at term after a normal pregnancy from healthy first degree consanguineous and healthy parents. She has a healthy 4 years old sister. She had epilepsy with severe convulsions that require antiepileptic drugs since 8 months of age. Electroencephalogram showed severe epileptic pattern in this patient. He had normal vision and hearing and no dysmorphic features. A magnetic resonance scan was performed and it was normal. Variants for case 2 displayed in (Figure 2).

The third case is 6 years old, male, Turkish origin and her parents aren't relatives. Standard karyotypes as well as *SCN1A, K1F1A* and *BRCA2* gene mutation analysis were negative in all first degree relatives of the patient in her family. The famale patient was born at term after a normal pregnancy from healthy nonconsanguineous and healthy parents.He had epilepsy with severe convulsions that require antiepileptic drugs since 2.5 years of age. Electroencephalogram showed severe epileptic pattern in this patient. He attended a special education school for behavioral and motor development due to psychomotor delay from the age of 2 years. Our patient's speaking skills were insufficient to express himself. WISC has a severe MRI with a full-scale IQ of 44. He had normal vision and hearing and no dysmorphic features. A magnetic resonance scan was performed and it was normal. Variants for case 3 displayed in (Figure 3).

Material and Methods

Method

Next Generation DNA Sequence Analysis (NGS)

Platform used: In the study; the 60MB exomes in humans (targeting 99% of the regions covering CCDS, RefSeq and gene code databases) were enriched using the Enriched "Agilent Sure Select Human All Exon V6" kit. The enriched library was sequenced with an average of 100X coverage on the Illumina next generation sequencing platform. Typically, 97% of the sequenced regions are> 10X.

Bioinformatics Analysis: In-house

Reference sequence: Bioinformatic analyzes were performed using the *GRCh37 / hg19* genome alignment, and regions with low coverage and variants with artifacts were excluded.

Reference databases: ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/). The Human Gene Mutation Database (HGMD) (http://www.hgmd.cf) .ac.uk / ac / index.php), CentoMD® (https://www.centogene.com/digital-services/mutation-database-centomd.html), ExAc database (http://exac.broadinstitute.org) /)

Filters used: All disease-related variants reported in HGMD®, ClinVar or CentoMD® were considered in the evaluation, as well as variants with a small allele frequency (MAF) of less than 1% considered in the ExAc database. Intornic regions within +/- 20 bases of coding exons were also analyzed. When evaluating the variants, all possible inheritance patterns, as well as family history and clinical information, are considered. All identified variants are evaluated for pathogenicity and causality and are classified according to the following system. All variants related to the patient's phenotype have been reported, with the exception of benign or possibly benign variations.

All Exom Sequence Methods: The coding regions, exons, of the genes are sequenced by the next generation sequencing method. It is estimated that approximately 2% of the genome is composed of exomes and 85% of them are disease-causing. The consensus coding regions of the fragmented genomic DNA are prepared for processing on the NextSeq platform (Illumina) using approximately 340,000 probes. Finally, the data from the NextSeq platform is subjected to the bioinformatics process, which consists of steps such as detection of base sequences, filtering of poor quality and erroneous

readings, and anotation of variants. For clinical evaluation, all disease-causing variants specified in the HGMD and ClinVar databases are evaluated. Variants affecting protein function are primarily examined and reported in relation to their phenotype.

All Exom Sequence Restrictions: New generation sequencing technologies, including the whole exom sequencing method, have a false positive rate of 5-10%. Accordingly, clinically important variants obtained by next-generation sequencing are verified by the Sanger sequencing method to determine if the variant is true positive. The Sanger sequencing system at our University Genome Center is optimized for validation and interpretation of these variants.

Test results; clinical findings are interpreted in the context of family history and other laboratory data, and only variations in genes associated with the patient's clinical findings are reported. If the data is incomplete or incorrect, there is a possibility that the results may be misinterpreted. However, sparse polymorphisms may cause positive results. Reported variants do not necessarily relate to all symptoms of the patient. More clinical findings are important for a more accurate evaluation. Different tests may be considered where the results do not match the clinical findings. Filtration of the found variants can be performed in the light of further clinical findings.

Results

The variant c.2415 + 1G> A detected heterozygously in the *SCN1A* gene causes the highly conserved donor site in intron 13 to be disrupted in our first case validation analysis. According to Human Gene Mutation Database (HGMD) Professional 2018.4 data. It has been reported to be related to Dravet Syndrome. It is classified as a pathogen change (Class I) AC according to American College of Medical Genetics and Genomics (ACMG) criteria.

The variant c.1651T> G (p.Ser551Ala) detected heterozygously in the SCN1A gene causes the Serine amino acid at position 551 to be converted to Alanine in our second case validation analysis. According to ACMG criteria, it is classified as a change with unknown clinical effect (Class III) '. The variant c.1719G> A (p.Thr573 =) detected heterozygously in the *CHD2* gene causes a synonymous variant. This change is close to the highly conserved donor splice site of exon 14. In silico analysis programmes, splicing mechanism is predicted to be affected. This change confirmed by Sanger sequencing; ClinVar is listed as potentially pathogenic (clinical tests, variation ID: 374747). According to ACMG criteria, it is classified as a change with unknown clinical effect (Class III) '.

The variant c.4139_4140 dup p. (Lys1381Leufs * 8), which is heterozygous in the *BRCA2* gene, causes an early stop codon in our third case validation analysis . This change confirmed by Sanger sequencing. According to HGMD Professional 2018.4 data. It is classified as pathogen change (ClassI) AC according to ACMG criteria. The variant c.3869T> C p (Ile1290Thr), which is detected heterozygously in the KIF1A gene, causes Threonine conversion of Isoleucine amino acid at position 1290. According to ACMG criteria, it is classified as a change with unknown clinical effect (Class III) '. The variant c.5701G> A p (Val1901Ile), which is detected heterozygously in the *SCN1A* gene, causes the Valine amino acid at position 1901 to convert to Isoleucine. According to ACMG criteria, it is classified as change with unknown clinical effect (Class III) '.

Discussion

Types of seizures associated with *SCN1A* include a spectrum ranging from simple febrile seizures with autosomal dominant inheritance and generalized epilepsy with febrile seizures, dravet syndrome and generalized tonic-clonic seizures with resistant child age epilepsy [5]. A Phenotypes with persistent seizures, including Dravet syndrome, are often associated with progressive dementia. Less common phenotypes include myoclonic-astatic epilepsy, Lennox-Gastaut syndrome, infantile spasms, and vaccine-induced encephalopathy and seizures. The phenotype of *SCN1A*-related seizure disorders may vary even within the same family [6,7]. Some pediatric genetic epilepsies are given in (Table 1) with their underlying defective gene and locusus.

Pathogenic variants in the *CHD2* gene are associated with "Autosomal Dominant Childhood Epileptic Encephalopathy". Epileptic encephalopathy (EEOC) in childhood is characterized by the onset of multiple seizure types in the first few years of life and is associated with poor prognosis. Affected individuals have cognitive impairment and intellectual disability [8].

Table 1. Genes and loci for pediatric genetic epilepsies

Syndrome	Genes and loci
Genetic epilepsy with febrile seizures plus	*SCN1A, SCN2A, SCN1B, GABRD, GABRG2, PCDH19*
Febrile seizures	8q13–q21 (FEB1), 19p (FEB2), 2q23–q24 (FEB3), 5q14–q15 (FEB4), 6q22–q24 (FEB5), 18p11 (FEB6)
West syndrome and early infantile epileptic encephalopathy with suppression	*ARX, CDKL5, STXBP1*
Other early-onset epilepsies (inllectual disability and ASD)	*PLCB1, PCDH19, KCTD7, BCKDK, SYN1, GRIN2B, GRIN2A, TNK2, KCNQ2*
Severe myoclonic epilepsy of infancy and related syndromes	*SCN1A, SCN2A, GABRG2*
Benign familial infantile seizures)	*PRRT2, ATP1A2*
Familial infantile myoclonic epilepsy	*TBC1D24*
Malignant migrating partial seizures of infancy	*KCNT1*
Benign familial neonatal convulsions	*KCNQ2, KCNQ3*
Juvenile myoclonic epilepsy	*EFHC1, GABRA1*
Benign familial neonatal–infantile seizures	*SCN2A*
Childhood absence epilepsy	*GABRG2, GABRA1* (childhood absence epilepsy with juvenile myoclonic epilepsy), *SLC2A1*
Familial lateral temporal lobe epilepsy	*LGI1*
Familial focal epilepsy with variable foci	*DEPDC5*
Epilepsy + paroxysmal exercise-induced dyskinesia	*SLC2A1*
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4, CHRNA2, CHRNB2, KCNT1*

*Adapted from ref (8-pandolfo2013). ASD, autism spectrum disorder

Pathogenic germline variants in the *BRCA2* gene are associated with "Autosomal Dominant Familial Breast / Ovarian Cancer Type 2". Hereditary breast and ovarian cancer associated with *BRCA1* and *BRCA2* is characterized by increased risk for other types of cancer in women and men: breast cancer (38-84%), ovarian cancer (16.5% - 27%), and to a lesser extent prostate cancer (%) 15), pancreatic cancer (2% to 7%) and an increased risk of melanoma, especially for people with *BRCA2* pathogenic variants, have been reported [9].

Pathogenic variants in the *KIF1A* gene are associated with " Autosomal Dominant Mental Retardation type 9, Autosomal Recessive Hereditary Sensory Neuropathy Type IIC and Hereditary Spastic Paraplegia Type 30 ". Patients with de novo variants of the *KIF1A* gene were defined as mild to severe global growth retardation and mental failure. Additional variable features include delay in tongue development, optic nerve atrophy, microcephaly, seizures, progressive spastic paraparesis, peripheral neuropathy, and cerebral and / or cerebellar atrophy. Although the disease is progressive, the severity of symptoms varies between affected individuals [10].

Conclusion

Epileptic syndromes are highly seem to be in relation with *SCN1A, CHD2, K1F1A* genes. *BRCA1* gene mutations previously shown to be highly related with breast cancer, ovarian cancer and to a lesser extent prostate cancer, pancreatic cancer and an increased risk of melanoma; is also classified to be a pathogenic change in our validation analysis of third case. *BRCA1* gene mutations and epilepsy relation need to be worked much in future studies to identify whether it's a true positivity of not. Also the gene sequencing of this patient shows a correlation between some gene mutations with ASD. In order to determine whether this mutations, which has been confirmed by Sanger sequencing, is hereditary or de novo, it is recommended that family studies should be conducted with Sanger sequencing in future studies. Genetic counselling should be recommended to epileptic syndromes and ASD of childhood.

Declarations

Ethics approval and consent to participate: have been taken from Bruni University Medicine School Ethical Committie.

Consent for publication: have been taken from the patients' parents. Patient's parents gave informed written consent for their personal or clinical details along with any identifying images to be published in this study.

Availability of data and material statement: Not applicable

Competing interests: None decelerated

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