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RESEARCH ARTICLE

Frequency of genetic variants associated with epilepsy in pediatric patients

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Abstract

Introduction: Epilepsy in pediatric patients is a relatively frequent condition in our population, which may have genetic origin. In this study, we determined the frequency of genetic variants associated with epilepsy in patients of the medical genetics service of the Dr. Hugo Mendoza Pediatric Hospital in the period August 2018 - August 2021. **Results**: In a sample of 154 patients, a total of 107 cases, the most frequent variants associated with epilepsy were identified and characterized according to age, sex, inheritance pattern and zygosity. The pathologies associated with each variant of the study participants were also identified. **Conclusion**: The most frequent age at which a genetic variant was found was 3 years. The female sex was identified as the most frequent, and the autosomal dominant inheritance pattern presented the highest number of cases, followed by the autosomal recessive pattern, and finally the X-linked patterns; dominant and recessive.

INTRODUCTION

Epilepsy is a disease of the central nervous system characterized by recurrent seizures, in brief episodes and crises, triggered by abnormal electrical discharges of a group of hyperexcitable neurons, affecting a part of the body (partial), or the whole body (generalized), is a chronic disease, which affects about 50 million people worldwide [1].

The development of genetic technology has led to the identification of an increasing number of genes associated with epilepsy [2]. These discoveries provide the basis for including genetic testing in clinical practice and improving the diagnosis and treatment of epilepsy. In the databases [OMIM, HGMD, EpilepsyGene and recent publications in PubMed], there are 977 genes that are associated with epilepsy.

Advances in genomic techniques, especially the development of next-generation sequencing, have increased our knowledge about genetic changes occurring throughout the human genome, allowing rapid and efficient discovery of genes implicated in many diseases. Epilepsies can result from primary genetic abnormalities or secondary to well-defined structural or metabolic disorders, some of which also have genetic causes. It is estimated that almost half of the epilepsies have a genetic basis [3].

Gene identification from sequencing-based studies has been limited mainly to rare and monogenic forms of epilepsy, and much of the attention has been focused on a group of severe diseases. Epileptic encephalopathies usually begin early in life and are characterized by intractable seizures and mild disability. It is known that one in 2,000 infants will develop severe epilepsy that will begin before the age of 18 months. The incidence of these groups is not well established, but they are recognized as the most common and least severe forms of epilepsy. Each account for 20% to 40% of epilepsies [4]. Epi-

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lepsy is a condition with variable clinical pictures, within which the identification of genetic variants associated with specific disorders helps us in the management of these patients, especially in drug-resistant presentations of the disease. Several scientific studies have demonstrated the benefits of identifying the etiological genetic cause of epilepsy, from the diagnostic, therapeutic and prognostic point of view [5].

Epilepsy is one of the most common neurological disorders in pediatric patients with other underlying neurological defects, occurring in 4 to 10 cases per 1,000 people. About 5 million cases of epilepsy are diagnosed annually worldwide [1]. Epilepsy is characterized by the occurrence of a synchronous and excessive discharge of a group of neurons sensitive to excitatory stimuli, and is evidenced by spontaneous and recurrent seizures, which may present with motor, sensory, cognitive, psychic and even autonomic signs and symptoms. It is estimated that 40% of epilepsies have a genetic origin, and that 20-30% of all patients diagnosed as epileptic are drug-resistant. This research seeks to identify genetic variants associated with susceptibility to epilepsy in patients of the medical genetics service of the Dr. Hugo Mendoza Pediatric Hospital, and to become a point of reference in fields such as clinical neurology, neurosciences and scientific research in the Dominican Republic.

This is a condition that is difficult to treat, given the high rate of drug resistance that we currently have, so it is essential that the latest molecular genetic diagnostic technologies, such as Next Generation Sequencing (NGS), are introduced into routine clinical practice. These technologies help us to differentiate the cause of epilepsy, from a disorder of genetic origin, to a syndrome of organic origin, caused by trauma, tumors, cerebrovascular events, etc. In this study, we evaluate the most frequent genetic variants associated with epilepsies in patients of the Pediatric Hospital from August 2018 to August 2021.

MATERIALS AND METHODS

A descriptive, cross-sectional study was conducted with retrospective collection of information to determine the frequency of genetic variants associated with epilepsy in patients at the Dr. Hugo Mendoza Pediatric Hospital in the Villa Mella sector, Santo Domingo City, Dominican Republic. The study period covered from August 2018 to August 2021.

The general objective of this work is to determine the frequency of genetic variants associated with epilepsy in our population. Specifically, we wish to identify the most frequent age and sex of the genetic variants associated with epilepsy (See Supplementary Table 2). The inheritance pattern of the genetic variants associated with epilepsy is also determined. Likewise, the molecular diagnosis and the zygosity of the genetic variants found are established.

The dependent variable used was the classification of the variable found, of nominal type, taking into consideration the inheritance pattern and the clinical consequence (see supplementary table 1). The independent variants used were: age, sex, inheritance pattern, zygosity and genetic diagnosis.

The population consisted of 154 patients treated for epilepsy in the hospital, being the sample the group of patients who met the inclusion criteria, with a total of 107 patients who underwent molecular genetic studies, treated for epilepsy in that institution. Data collection was performed through the us of collection forms, including clinical history number, genetic variant, age, sex, inheritance pattern, zygosity and genetic diagnosis (see annex 1).

Inclusion and exclusion criteria

All pediatric patients seen for epilepsy, and who underwent molecular genetic studies, in the Medical Genetics service of the hospital in the established period were included. We excluded all pediatric patients treated for epilepsy who, for various reasons, did not undergo molecular studies or who had incomplete records.

Ethical aspects involved in the research The information collected in this research complied with all the institutional ethical parameters, such as: not obtaining information beyond that necessary for the study, including: the patient's name, origin, other comorbidities, etc.

RESULTS

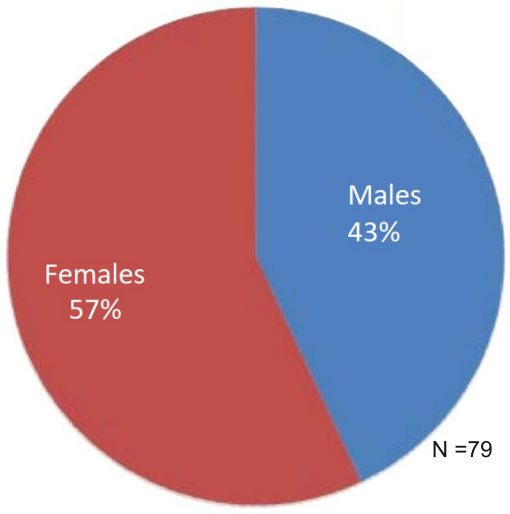
A total of 107 cases were observed with the highest frequency between the ages of 3 to 4 years, followed by the group of 0 to 2 years. The lowest number of cases was found in the 15 to 16 years age group (Table 1).

Table 1. Distribution according to age of genetic variants associated with epilepsy.

Age	Frequency	Percentage
0-2	24	22%
3-4	31	29%
5-6	14	13%
7-8	8	7%
9-10	12	11%
11-12	5	5%
13-14	5	5%
15-16	3	3%
17-18	5	5%
Total	107	100%

Source: Dr. Hugo Mendoza Pediatric Hospital.

Graphic 2. Sex distribution of genetic variants associated with epilepsy.



Source: Dr. Hugo Mendoza Pediatric Hospital.

Table 2. Distribution according to inheritance patterns of genetic variants associated with epilepsy.

Inheritance pattern	Frequency	Percentage
Autosomal dominant	103	90%
Autosomal recessive	5	4%
X-linked recessive	3	3%
X-linked dominant	3	3%
Total	114*	100%

Note: In each case, multiple genetic variants associated with epilepsy were identified. Source: Dr. Hugo Mendoza Pediatric Hospital.

Most cases were identified in the female sex, with a total of 57% (Figure 1). The phenotypic inheritance pattern for the variants associated with epilepsy was autosomal dominant with 90% of the cases, followed by 4% of variants with autosomal recessive inheritance pattern, and X-linked cases, both with 3% of the cases (Table 2). Likewise, zygosity was evaluated, documenting 92% heterozygous variants, 7% homozygous variants and 1% hemizygous variants (Table 3).

The top three genes identified in our population (ARHGEF15, SCN1A, FASN) corresponded to 30% of all identified variables (Table 4), and together, most of the affected genes were associated with early infantile epileptic encephalopathy.

DISCUSSION

During the period from August 2018 - August 2021, in the medical genetics service of the Dr. Hugo Mendoza Pediatric Hospital, a total of 2,016 patients were attended, this being our universe, of which 154 patients were attended for presenting epilepsy, selecting them as our population, from the latter a sample of 107 patients was taken, which molecular genetic studies were performed, and only 79 patients turned out to have one or more genetic variants associated with epilepsy, and 28 of them, did not present any variant.

It is evident that the economic situation of our country is an important barrier so that 47 patients treated for epilepsy did not undergo molecular studies, which reveals the deficit with an important group of patients not diagnosed from the genetic point of view.

Table 3. Zygosity distribution of genetic variants associated with epilepsy.

Zygosity	Frequency	Percentage
Heterozygous	105	92%
Homozygous	8	7%
Hemizygous	1	1%
Total	114	100%

Note: Each case could have more than one variant. Source: Dr. Hugo Mendoza Pediatric Hospital.

Table 4. Distribution according to genetic diagnoses of variants associated with epilepsy.

Gene	Diagnosis	Num. of variants
ARHGEF15	Early childhood epileptic encephalopathy	8
SCN1A	Genetic epilepsy with febrile seizures	7
FASN	Early infantile epileptic encephalopathy	6
KCNT1	Frontal lobe nocturnal epilepsy	4
RELN	Lateral temporal lobe epilepsy	4
SCN8A	Early infantile epileptic encephalopathy	4
SCN9A	Genetic epilepsy with febrile seizures	4
DEPDC5	Familial focal epilepsy with variable foci	3
NPRL3	Familial focal epilepsy with variable foci	3
SCN2A	Benign familial infantile neonatal seizures	3
SCN3A	Developmental and epileptic encephalopathy	3
SPTAN1	Developmental and epileptic encephalopathy	3
CACNA1A	Developmental and epileptic encephalopathy	2
CHD2	Early infantile epileptic encephalopathy	2
CHRNA2	Nocturnal frontal lobe epilepsy	2
CHRNA4	Nocturnal frontal lobe epilepsy	2
CUX2	Epileptic and developmental encephalopathy	2
EEF1A2	Developmental and epileptic encephalopathy.	2
FGF12	Developmental and epileptic encephalopathy.	2
GABRB3	Early infantile epileptic encephalopathy.	2
KANSL1	Koolen De Vries syndrome	2
KCNQ3	Benign familial neonatal neonatal seizures	2
SETD2	Luscan-Lumish syndrome	2
SLC1A2	Developmental and epileptic encephalopathy	2
MECP2	Rett syndrome	2
MTOR	Smith-Kingsmore syndrome	2
WWOX	Developmental and epileptic encephalopathy	2
CDK13	CDK13-related disorder	1
CDKL5	Early infantile epileptic encephalopathy/West syndrome.	1
ATP1A2	Early infantile epileptic encephalopathy.	1
ATP6AP2	Intellectual disability with epilepsy	1
CYFIP2	Developmental and epileptic encephalopathy.	1
DYNC1H1	Early infantile epileptic encephalopathy	1
EHMT1	Kleefstra syndrome	1
FARS2	Early infantile epileptic encephalopathy	1
FRRS1L	Developmental and epileptic encephalopathy	1
GABRA1	Early infantile epileptic encephalopathy	1
GCDH	Glutaric acidemia type 1	1
GFAP	Alexander disease	1
HCN1	Early infantile epileptic encephalopathy	1
HRAS	Costello syndrome	1
JMJD1C	Rett syndrome	1
KCNMA1	Generalized epilepsy and paroxysmal dyskinesia	1
KCTD7	Progressive myoclonic epilepsy	1
LGI1	Lateral temporal lobe epilepsy	1
NEDD4L	Early infantile epileptic encephalopathy	1
NRXN1	Pitt-Hopkins syndrome	1
PACS2	Developmental and epileptic encephalopathy	1
POLG	Alpers-Huttenlocher syndrome	1
RAI1	Smith-Magenis syndrome	1
RBFOX3	Idiopathic generalized epilepsy	1
ROGDI	Kohlschutter syndrome	1
RYR3	Early infantile epileptic encephalopathy	1
SLC6A1	Myoclonic-atonic epilepsy	1
SMARCD1	Coffin-Siris syndrome type 1	1
TCF4	Pitt-Hopkins syndrome	1
TSC2	Tuberous sclerosis type 2	1
WDR45	Early infantile epileptic encephalopathy	1
SLC9A6	Christianson syndrome	1
Total		114

Source: Dr. Hugo Mendoza Pediatric Hospital

The data were organized in decreasing order using the number of cases, by means of a frequency table. We analyzed the number of times a variant was presented in relation to the total number of cases presented. With the analysis of these 114 cases we determined the most frequent genetic variants associated with epilepsy in our population, which corresponded to ARHGEF15, followed by the SCN1A variant, continuing with the FASN variant, and finally the variants KCNT1, RELN, SCN8A and SCN9A.

Our results can be contrasted with the studies performed by Dongfang Zou,† Lin Wang † and collaborators, published in the BRAIN journal of the University of Oxford, in 2021, where their most frequent genetic variant was SCN1A, with a total of 10 patients out of 95 cases.

These findings are directly close to the results of our study, since SCN1A, presented 7 cases out of 79 studied. In spite of not having an identical sampling, but a similar one, the same differs from our research, in that the most frequent affected gene is ARHGEF15, presenting 8 cases out of 79 studied.

Regarding the age group of these patients, 33 cases corresponded to patients between 3 and 4 years of age, of which 16 patients corresponded to the age of 3 years, the latter being the most frequent.

When comparing again with the study of Dongfang Zou, et. al., we see that the most frequent age was 4.3 years, which is close to our study, since the most frequent age at which the variants associated with epilepsy were presented was 3 years of age, thus showing, as a possible diagnostic target, these age intervals to initiate molecular research.

Of the total number of cases of genetic variants associated with epilepsy, our results showed that the female sex, with a total of 45 patients, was the most frequent, compared to the male sex, which only presented 34 patients.

Analyzing the publication in the journal Frontiers in Molecular Neuroscience. Tiejia Jiang, Jia Gao and collaborators, in the year 2021, who studied 221 patients of which 96 were female and 125 were male, the same with a larger sampling than in our study, determined that the male sex was more frequent.

Our findings can also be placed in contrast with the one published in the Canadian Journal of Neurological Sciences where So Lee, Natalya Karp and collaborators in the year 2021, studied 105 children, of which 55 patients were male and 50 female patients with a variety of seizures, where despite having a difference of 3 patients with respect to our research, they reflect a greater number of patients in the male sex, than in the female sex.

The inheritance patterns of the most frequent genetic variants associated with epilepsy were analyzed, and we determined that the autosomal dominant inheritance pattern was presented, followed by the autosomal recessive pattern and finally the X-linked inheritance patterns; recessive and dominant. It should be noted that the sample size is a fundamental axis to validate the frequency of these inheritance patterns with respect to other investigations.

In this sense, the study of Dongfang Zou, et. al. entitled "Genome sequencing of 320 Chinese children with epilepsy", which resulted to have autosomal dominant inheritance pattern in 68 cases out of 107 studied, with autosomal recessive in 27 cases, X-linked dominant in 10 cases and X-linked recessive in 2 cases, we can observe that the autosomal dominant pattern is the most frequent.

Our research was able to establish the zygosity of the variants associated with epilepsy, in such sense our findings were consistent with patients in heterozygous state, presenting a total of 105 cases of variants, the homozygous with 8 cases, and finally the hemizygous with 1 case.

In the journal Epilepsia, official journal of the International League Against Epilepsy. Krishna R Veeramah, Laurel Johnstone et al. In 2013, they concluded that 70% of their patients presented heterozygosity and 30% homozygosity. This differs from our study, where 92% of the variants correspond to heterozygosis and 7% to homozygosis, in addition to the fact that they did not present hemizygotes, which represent 1% respectively in our research.

In this study we identified a set of pathologies and we were able to obtain diagnoses of variants associated with epilepsy and we observed a large number of variants that are associa-

ted with the same pathology (See Table 5) such as: ARHGEF15, CUX2, ATP1A2, CHD2, DYNC1H1, FARS2, FASN, FGF12, GABRA1, GABRB3, HCN1, NEDD4L, RYR3, SCN3A, SCN8A. All of these are associated with early infantile epileptic encephalopathy.

Developmental and epileptic encephalopathies were found to have variants such as: WWOX SCN3A, FGF12, CUX2, CACNA1A, CYFIP2, FRRS1L, PACS2, SLC1A2, SPTAN1, WDR45.

We can compare our results with those of the study published in the journal NEUROL, I. Herrera-Peco, V. Fernández-Millares and collaborators, in 2009. Where temporal lobe epilepsy was the most frequent, however, its variants found differ from those reported in our study. In our research within lobar epilepsies we identified CHRNA4, CHRNA2, both associated with frontal lobe nocturnal epilepsy, as well as the variants LGI1, RELN associated with lateral temporal lobe epilepsy.

We found in our findings different variants of familial, focal and febrile inheritance such as; DEPDC5, NPRL3 both associated to familial focal epilepsy with variable foci and focal epilepsy with variable foci, and within the neonatal ones KCNQ3, SCN2A, both variants associated to benign familial infantile neonatal seizures, and in turn the variants SCN1A, SCN9A associated to genetic epilepsy with febrile seizures.

In the framework of study of myoclonic epilepsies we found the variants SLC6A1 associated with myoclonic-atonic epilepsy and KCTD7 associated with progressive myoclonic epilepsy, contrasting with the study published in the BRAIN journal of the University of Oxford. Dongfang Zou, † Lin Wang † and coworkers, which reported epilepsy with myoclonic-atonic seizures associated with the ITPR1 variant and early myoclonic encephalopathy associated with the EEF1A2 variant.

Such as the study published in The American Journal of Human Genetics, where the Epi25 Collaborative group found rare epileptic syndromes, different from the variants in our study, which were: NRXN1, TCF4 both associated with Pitt-Hopkins syndrome, EHMT1 associated with Kleefstra syndrome and SMARCD1 associated with Coffin-Siris syndrome type 1.

Our findings also reported the variants; GCDH associated with glutaric acidemia type 1, GFAP associated with Alexander disease, HRAS Costello syndrome. In turn the variants, KANSL1 Koolen de Vries syndrome, KCNMA1 associated with generalized epilepsy and paroxysmal dyskinesia and SLC9A6 associated with Christianson syndrome.

Other variants associated with genetic syndromes were also identified, such as: CDK13 associated with CDK13-related disorder, MTOR associated with Smith-Kingsmore syndrome, ATP6AP2 Intellectual disability with epilepsy. The CDKL5 variant associated with West syndrome was also identified.

We identified genetic variants associated with pathologies such as Rett syndrome, Alpers-Huttenlocher syndrome, Smith-Magenis syndrome, idiopathic generalized epilepsy, Kohlschutter syndrome, Luscan-Lumish syndrome and tuberous sclerosis type 2.

Our diagnoses differ broadly with the results of the study published by Dongfang Zou, et. al, where they identified diagnoses and variants associated with epilepsy such as: West syndrome associated with PAFAH1B1, UBA5, SUOX, DCX, DEPDC5, GNAO1, HCN1, KCNH1, KCNQ2, PRKCG, TSC2, WDR45 and WWOX variants. They also identified the diagnoses of tuberous sclerosis associated with TSC1 and TSC2 variants, Dravet syndrome associated with SCN1A variant, Ohtahara syndrome associated with ABAT, CDKL5, GNAO1, KCNT1, STXBP1 variants, among other variants. However, in the comparison with our study, their research only coincided in the diagnosis of tuberous sclerosis associated with the TSC2 variant.

CONCLUSIONS

After performing the data collection, tabulation, analysis and discussion of the results, we proceed to present the following conclusions:

The highest frequency determined of genetic variants associated with epilepsy by the medical genetics service of the Dr. Hugo Mendoza Pediatric Hospital in the period August 2018 - August 2021, corresponds to the ARHGEF15 variant.

According to the patients studied, the most frequent age at which a genetic variant associated with epilepsy was presented was at 3 years of age.

After analyzing the percentage of males and females studied in this research, it was identified that the female sex is the most frequent.

Our research showed that the autosomal dominant inheritance pattern presented the highest number of cases, followed by the autosomal recessive pattern, and finally the X-linked patterns; dominant and recessive.

Once the zygosity of the epilepsy-associated variants in our study was established, it was shown that heterozygous patients had the highest number of cases, followed by homozygotes and then hemizygotes. At the end of our research, we identified the epileptic syndromes and the genetic syndromes associated with epilepsy of each variant in the patients studied.

Recommendations

Our recommendations are:

- To the health institutions of the Dominican Republic, we urge them to continue to deepen this study, and thus improve the care of patients with epilepsy.

- We recommend the Dr. Hugo Mendoza Pediatric Hospital to continue promoting research in medical genetics and in patients with epilepsy.

- We emphasize the importance of raising awareness so that research in medical genetics continues to be strengthened in students and professors of the medical schools of the Dominican Republic.

- Encourage the medical population in general, about the importance of these studies, both in the diagnosis, prognosis and monitoring of patients with epilepsy.

Contributions

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