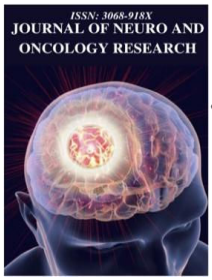

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Research Article

A Study of the Clinical and Genetic Aspects of Familial Epilepsy

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Abstract

Epilepsies are very ancient diseases and the most widespread neurological diseases in the world. They are common conditions that constitute a heterogeneous group from an etiological perspective and, to this day, represent a source of tension between magical and scientific concepts, between superstitious beliefs and rational explanations. Most cases are multifactorial pathologies whose determinism involves environmental and genetic factors, which depend on the epilepsy group considered. The lack of genetic data on this disease in Lubumbashi prompted us to conduct a study on the clinical and genetic aspects of familial epilepsy in Lubumbashi. This study included patients aged 40 years or less who were diagnosed with epilepsy and had a family history of the disease. We performed a stratified probabilistic sampling, which allowed us to collect 72 families. In the first phase, these families were subjected to a cross-sectional analytical study, which led us to find a prevalence of 11.23% for familial epilepsy in Lubumbashi, with a mean patient age of 15.24 years ± 11.03 years and a sex ratio of 1.32 favoring the male sex. Generalized seizures were present in 70.83% of cases and absence seizures in 8.33%. The EEG showed paroxysmal grapho-elements in 35.75% and was normal in 27.78%. Epilepsy was transmitted in an autosomal dominant manner in 41.67% and in a recessive manner in 33.33% and no cases of consanguinity were noted. Five families were subjected to a second phase, a matched case-control study with whole-exome sequencing, which allowed us to highlight genetic variants/mutations. The sequencing data from our study indicated that genetic variants with good phenotype-genetic concordance according to ACMD criteria in cases of idiopathic epilepsy with generalized tonic-clonic seizures are: ATP2B1, SCN3A. The genetic mutations in cases of absence seizures are: CACNA1, NPRL2.

Keywords: Clinical; Genetic; Familial Epilepsy; Lubumbashi

Introduction

State of the Art

Epilepsies, old and widespread neurological diseases, are frequent conditions that constitute a heterogeneous group in terms of etiology. Most cases are multifactorial pathologies in which environmental and genetic factors are involved, depending on the group of epilepsies considered. This makes these diseases a source of tension between magical and scientific conceptions, between superstitious beliefs and rational explanations [1,2].

Incidence and Prevalence

The annual incidence of epilepsy is estimated at about 50 new cases per 100,000 inhabitants/year in industrialized countries,

while in developing countries, this figure is higher, ranging from 100 to 190 new cases per 100,000 inhabitants/year [3]. Among the reasons that can explain this difference in incidence are the high risk of cerebral infections (neurocysticercosis, meningitis and malaria), obstetric complications and malnutrition [4]. The average incidence of epilepsy in the Arab world, was estimated through a study at about 56 new cases/100,000 inhabitants/year.[5].

According to worldwide studies, the average prevalence of epilepsy is estimated at about 8.2 per 1000 in the overall population [6, 7]. However, this could be an underestimation, as some studies in developing countries (Colombia, Ecuador, India, Liberia, Nigeria, Panama, United Republic of Tanzania and Venezuela) suggest a higher prevalence, greater than 10 per 1000 [8-10].

A multicenter cross-sectional study was conducted in 2012 in Algeria to determine the national prevalence of epilepsy. This study included 8,046 subjects over the age of two months, distributed across five regions of the country (Algiers, Sétif, Sidi Belabes, El Oued and Laghouat). Sixty-seven patients were identified as having active epilepsy, giving a crude prevalence ratio of 8.32 per 1000 (95% CI: 6.34-10.3) and an age-adjusted ratio of 8.9 per 1000. The highest ratio (16.92 per 1000) was noted in the 10-19 year age group [11].

Idiopathic Generalized Epilepsies (IGE) are a common group of epilepsies with a good prognosis, representing 15 to 20% of epilepsy cases. They are characterized by generalized epileptic seizures, including absence seizures, myoclonic seizures, generalized tonic-clonic seizures and myoclonic-tonic-clonic seizures. An EEG can show paroxysmal figures such as generalized spikes/polyspikes-slow waves [12].

In his study on the etiologies of epilepsies in the neurology department of the Marrakech CHU, M. Boanimbek Bakoume Bernard Baudouin (2015) found that generalized onset seizures were present in 80 patients in his study and accounted for 26.67% of seizures. Tonic-clonic seizures were the most common type of generalized seizure, representing 57.5% of generalized seizures. Myoclonias were present in 16 patients (20% of generalized seizures), while absence seizures were present in 14 of his patients (17.5%). Atonic seizures were found in 4 patients (5% of generalized seizures) [13].

Generally, IGEs include four syndromes: Childhood-Onset Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) and epilepsy with Generalized Tonic-Clonic Seizures only (GTCA) [14].

Genetic Aspect

There is a broad consensus that the majority of otherwise unexplained epilepsies are due at least in part to genetic factors. As a result, genetic testing for patients with epilepsy has also evolved to include many clinically available testing options, including genome-wide comparative genomic hybridization/Chromosomal Microarray (CGH/CMA), Multigene Panel (MGP), Exome Sequencing (ES) and Genome Sequencing (GS). These tests are used to determine copy number and sequence variants involving epilepsy-related genes [15].

Already in his time, Szepetowski (2000) had shown that the etiologies of epilepsies and epileptic seizures were varied and resulted from a combination of genetic or acquired factors. In those that are genetically determined, exogenous factors favor the expression of the disease [16]. Similarly, genetic factors govern the epileptogenic potential of structural lesions of the central nervous system and thus the essential etiological factor of idiopathic epilepsy syndromes is a genetic predisposition. In this context, Elsa Rossignol (2019) showed in her study that epilepsy was an etiologically heterogeneous condition, so it was essential for her to better understand the epileptogenic cellular and physiological mechanisms that underlie the various early-onset epilepsy syndromes refractory to current treatments, which remain poorly understood, in order to develop new therapeutic approaches [17].

The studies of Sheidley BR, et al. and Truty R, et al., showed a growth in cases of genetic epilepsies for which a specific treatment or a change in management is indicated [18,19]. Advances in genetic testing over the past decade have led to a rapid increase in the understanding of the genetic basis of epilepsy. Although the first epilepsy-associated genes were identified in 1995, until the past decade, few causal or susceptibility variants had been confirmed. The emergence of tables and New-Generation Sequencing (NGS) technologies has led to the identification of hundreds of epilepsy-associated variants and genes.

In Algeria, in her work on the search for genetic vulnerability variants to epilepsy in Algerian families, Amina Chentouf showed

that among sixty-five epileptic families, the average age of onset of the disease was 9.5 ± 6.1 years, with a slight male predominance (sex ratio: 1.35) [20]. Generalized seizures were slightly more frequent than focal seizures (50% vs. 40%), with a parental consanguinity rate of 50%. A phenotypic concordance was observed in 2/3 of the families. Based on the pedigree analysis, epilepsy was transmitted in an Autosomal Dominant (AD) mode in 29 families (44.6%) and in an Autosomal Recessive (AR) mode in 23 families (35.4%). Genetic analyses identified mutations of the EPM1 gene in patients with progressive myoclonic epilepsy and a mutation of the RELN gene in individuals with temporal lobe epilepsy.

Despite new exploration techniques, the etiology of epilepsies remains unknown in nearly 2/3 of cases [3,21]. Over the past three decades, several case-control studies aimed at identifying risk factors associated with epilepsy have been conducted (Edwards T, et al. [8]. Although these studies have identified a series of factors, the results were very heterogeneous, ranging from perinatal complications to head trauma, including strokes, brain tumors and central nervous system infections [22,23].

The studies by Marini C, et al. and Vadlamudi L, et al., showed that genetic factors play important roles in the pathogenesis of IGE with complex transmission [24,25]. Similarly, Sheidley BR, et al., 2018 and Truty R, et al., showed in their study a growth in cases of genetic epilepsies for which a specific treatment or a change in management is indicated [18,19].

Advances in genetic testing over the past decade have led to a rapid increase in the understanding of the genetic basis of epilepsy. Although the first epilepsy-associated genes were identified in 1995, until the past decade, few causal or susceptibility variants had been confirmed. The emergence of tables and New-Generation Sequencing (NGS) technologies has led to the identification of hundreds of epilepsy-associated variants and genes.

For their part, Weber YG, et al. and Liu XR, et al., 2021were able to identify several genes in their studies on idiopathic epilepsies, including CACNA1H, CACNB4, CASR, EFHC1, GABRA1, GABRB3, GABRG2, HCN2, ICK, KCNMA1, SLC2A1 and SLC12A5 (OMIM, https://www.omim.org/), which represent a small proportion (2 to 8%) of IGEs. With the application of whole-exome sequencing, an increasing number of genes and variants have been identified in patients with IGE [26,27].

Problem Statement A multicenter cross-sectional study was conducted in 2012 in Algeria to determine the national prevalence of epilepsy. This study included 8,046 subjects over the age of two months, distributed across five regions of the country (Algiers, Sétif, Sidi Belabes, El Oued and Laghouat). Sixty-seven patients were identified as having active epilepsy, giving a crude prevalence ratio of 8.32 per 1000 (95% CI: 6.34-10.3) and an age-adjusted ratio of 8.9 per 1000. The highest ratio (16.92 per 1000) was noted in the 10-19 year age group [11].

In his study in Pointe Noire on the Clinical, Etiological and Therapeutic aspects of Infant and Child Epilepsy, Sounga Bandzouzi et al. (2021) [28] found that thirty-two (82.1%) of infants and children had idiopathic generalized epilepsy, of which 28 (87.5%) had epilepsy with generalized tonic-clonic seizures and four (12.5%) had absence epilepsy. Of the seven infants and children with focal epilepsy, five (71.4%) had epilepsy with centro-temporal spikes (EPCT), while epilepsy with frontal seizures was observed in two participants (28.6%).

Ntenga P, et al., in their studies on epilepsy and the school attendance rate in Congolese children, showed that in 41% of cases, children living with epilepsy had a family history of epilepsy and that their average age was 9.6 ± 3.9 years, with an average age of seizure onset of 5.8 ± 3.0 years. This percentage of family history of epilepsy, i.e., 41% of cases, could have a genetic character in Lubumbashi [29].

In a study by Zhi-Jian, et al., on trio-based whole-exome sequencing, performed on 60 cases with Idiopathic Generalized Epilepsy (IGE), the pathogenicity of candidate genetic variants was evaluated according to the American College of Medical Genetics and Genomics (ACMG) criteria and the clinical causality was evaluated by the concordance between the observed phenotype and the reported phenotype [30]. Seven candidate variants were detected in seven unrelated IGE cases (11.7%, 7/60). According to ACMG, a de novo SLC2A1 variant (c.376C>T/p.Arg126Cys) identified in infantile absence epilepsy was evaluated as pathogenic with clinical concordance. Six variants were evaluated as being of uncertain significance by ACMG but then considered causal after evaluation of clinical concordance. These variants included the hemizygous CLCN4 variant (c.2044G>A/p.Glu682Lys) and the heterozygous IQSEC2 variant (c.4315C>T/p.Pro1439Ser) in juvenile absence epilepsy, the EFHC1 variant

(c.1504C>T/p.Arg502Trp) and CACNA1H (c.589G>T/p.Ala197Ser) both with incomplete penetrance in juvenile myoclonic epilepsy and the GRIN2A variant (c.2011C>G/p.Gln671Glu) and the GABRB1 variant (c.1075G>A/p.Val359Ile) co-segregating with juvenile myoclonic epilepsy. Among these variants, GABRB1 was identified for the first time as a new potential causal gene for IGE.

Hereditary neurological diseases, including epilepsy, remain a debilitating disease and developing countries pay the highest price in terms of disability-adjusted life years. Despite the vast diversity of its populations, genetic studies in Africa, including the Democratic Republic of Congo and the city of Lubumbashi in particular, are limited and therefore there is an absence of genetic characteristics of epilepsy despite the high prevalence of the disease. This motivates us to conduct this type of work in Lubumbashi to understand the related specificities and provide a solution.

With the advent of next-generation sequencing technologies, the last decade has seen an explosion of responsible genes identified in patients with epilepsy and neurodevelopmental disorders; currently, more than 40 genes are considered true causes of genetic epilepsies, given that pathogenic variants of these genes are regularly identified in epileptic patients in a clinical and research context. The landscape of genetic testing is extremely diverse, ranging from targeted tests including monogenic tests to exome or genome sequencing. Targeted gene panel approaches for epilepsy are just as diverse, with some focusing on authentic primary epilepsy-causing genes and other broader gene panels often including genes related to syndromic disorders or candidate genes related to epilepsy due to their cellular and functional roles [31].

Despite the availability of an increasing number of antiepileptic drugs, up to 30% of people with epilepsy have treatment-resistant seizures; this has a significant impact on quality of life and exposes patients to a risk of various comorbidities and complications, including death [32]. Epilepsy can develop in the context of structural brain changes, such as injuries or malformations. However, in a significant proportion of patients, no structural alteration can be identified by neuroimaging [15]. Twin studies demonstrate a strong genetic contribution to various types of epilepsy and family studies suggest a strong genetic influence at the population level [33].

The Clinical Genome Resource (ClinGen) gene curation expert group offers such a mechanism by providing an evidence-based framework for evaluating the clinical validity of specific gene-disease associations using available genetic and experimental evidence. The evaluation of available genetic evidence at the case level and in this regard, the underlying genetic architecture of early-onset epilepsies, with a strong contribution of de novo variants. In the study by Rehm, et al., eight of the 16 genes in their pilot curation phase obtained a maximum genetic evidence score of 12 points in the existing ClinGen gene curation framework, suggesting that sufficient genetic evidence according to ClinGen criteria is easily obtained for both well-established genetic causes of epilepsy, including SCN8A and KCNQ2 and more recently involved genes such as KCNA2 and ALG13 [34].

It was reported in 2023 that nearly 80% of the 50 million people living with epilepsy live in low-income countries, including the Democratic Republic of Congo (DRC) and this situation represents a heavy health and socioeconomic burden because the gaps in etiological diagnosis and therapeutic coverage exceed 75%. In Africa, particularly in the part south of the Sahara, disease studies are limited to clinical descriptions, which alone do not allow for a diagnosis and determination of the genetic specificity of hereditary pathologies, especially epilepsy and for providing targeted therapies and counseling to patients and their families. Therefore, although several genes have already been associated with epilepsy, it is still important to find new genes and/or genetic variants to deepen the understanding of this disease in our context and guide the implementation of new therapeutic modalities in our communities. As a result, we believe that the African population still holds a vast genetic diversity that could lead to phenotypic variability compared to other populations, as questions arise about the reason for antiepileptic treatment resistance in a patient followed for epileptic seizures that are well classified in a syndrome defined by the International League Against Epilepsy. This often forces the clinician to change antiepileptic drugs several times and fall into the therapeutic trial-and-error ladder in our communities and therefore we understand the importance of recent advances such as new genotyping techniques and whole-exome or genome sequencing that have accelerated the speed of DNA sequencing and greatly facilitated the discovery of disease genes through positional cloning, which allows for rapid identification of the causes of hereditary diseases and the discovery of mutations in populations to guide the treatment in patients living with epilepsy.

Research Question

As this literature review shows in its heterogeneous aspect, the Democratic Republic of Congo and the city of Lubumbashi in particular do not escape this reality where we note the absence and/or ignorance of the genetic factors and/or characteristics of epilepsy, which unfortunately contrasts with the high prevalence of the disease and leaves the clinician perplexed about the management of epilepsy when treatment is initiated and the patient continues to have epileptic seizures. Considering the impact of the north-south geographical gradient, we ask ourselves whether there are other types of genetic mutations and/or genetic variants related to epilepsy found in Lubumbashi, DR Congo or are they the same as those described in the literature?

Hypothesis

Given that there is a diversity of epilepsy genes and clinical phenotypes and in view of the geographical gradient in the pathogenesis of epilepsy, we hypothesize that there would be other types of genetic mutations related to epilepsy in Lubumbashi, whose molecular description would improve the understanding of this disease and its management in our population and could reduce this burden.

Objectives and Interest of the Work

Objectives

General Objective: The general objective of our study is to:

- Establish the links of genetic causality of familial epilepsy in Lubumbashi

Specific Objectives: Specifically, in this study, we want to:

- Determine the types of genetic mutations and/or genetic variants in patients with familial epilepsy in Lubumbashi
- Determine the phenotypes of familial epilepsy and its correlation with the genotypes encountered in Lubumbashi

Choice and Interest of the Work

a. Due to the lack of genetic data related to epilepsy, this study will allow for a biobank of DNA data that can serve as a research resource for neurogenetic studies in Lubumbashi and Central Africa.
b. This study will help in the identification and characterization of new genes (reference genes) for epilepsy in Lubumbashi. These genes could probably be important in the normal function of the nervous system and also have important pathophysiological implications, as well as modifying the concept of epilepsy management not only in our community but also in other populations.

Methodology

Framework and Study Location

Our investigations are conducted at the Joseph Guislain Brothers of Charity Neuropsychiatric Center of Lubumbashi, the University Clinics of Lubumbashi and the Jason Sendwe Provincial General Reference Hospital of Lubumbashi.

Study Type

Synthetic table of studies carried out in this work (Table 1).

Specific Objectives	Study Type	Population Studied
1. Specific Objective Determine the phenotypes of familial epilepsy and its correlation with the genotypes encountered in Lubumbashi	A cross-sectional analytical study on patients living with epilepsy with a family history of epilepsy in Lubumbashi	72 patients were collected.
2. Specific Objective Determine the types of genetic mutations and/or genetic variants in patients with familial epilepsy in Lubumbashi.	A matched case-control study (trio study: 1 case for 2 controls) of patients living with epilepsy with a family history of epilepsy.	5 matched families or 15 samples

Table 1: Synthetic table of studies.

This study spanned a period from October 2020 to October 2024, which included epilepsy cases that presented for consultation during the study period. The case subject is the selected epileptic person. The exposure is the presence of a gene predisposing to epilepsy (reference gene). The control is a parent, brother, sister, first cousin or grandparent of the epileptic person. We reconstructed the family tree up to 3 generations:

- The first generation consists of the grandparents of the patient living with epilepsy
- The second generation consists of the parents of the patient living with epilepsy
- The third generation consists of the patient living with epilepsy, their brothers, sisters and first cousins. Thus, transmission is considered recessive when there is a skip of one generation without an epileptic patient and it is considered dominant when there is a case of epilepsy in each generation

Study Population

Patients aged 40 years or younger with epilepsy and their families received at the aforementioned investigation sites, with a notion of familial epilepsy discovered or reported during the consultation, were considered as potential candidates for this study.

Sample

We performed a stratified probabilistic sampling during this study for the selection of subjects who participated in it.

Inclusion Criteria:

- Patients aged 40 years or younger with epilepsy who signed the consent and/or assent to participate were considered in this study. This age was targeted because hereditary seizures tend to be expressed earlier
- However, we also included patients with late-onset seizures with a family history of epilepsy
- Be of the Black race and Congolese nationality (not from a mixed-race background)
- A cerebral CT scan was performed

Non-inclusion Criteria

Genetic pathologies in which epilepsy is not the essential symptom, such as Trisomy 21, were excluded from this study. Any epileptic or control subject with a hemoglobin level below 8 g% was also excluded (because this level could create a predisposition to generate a convulsive seizure and create a selection bias).

Data Collection Material

Data was collected and stored on data collection forms. At the end of each week, we systematically verified all the completed forms to ensure that they were properly filled out and to correct any errors the same day or the next day by re-consulting the files or registers. The family tree is established for the patient to see the recessive (if there is a generation skip) or dominant (disease present in each generation) nature.

Definition of Concepts

- Familial epilepsy: Family history of epilepsy
- Hereditary epilepsy: Epilepsy caused by genetic mutations, transmissible from parents to child
- Symptomatic epilepsy: Epilepsy secondary to a detectable brain lesion
- Sequencing: Procedure for determining the linear order of nucleotides of DNA in each cell of the organism
- Genome: The set of genetic information of an organism contained in each of the cells in the form of a chromosome
- Exome: The part of the genome that contains exons (the parts of genes that are expressed for protein synthesis)

Data Collection Method

The questions are open-ended. The patient themselves and/or the parents and/or companions of people living with epilepsy are subjected to the same questionnaire (see appendix). This was completed by a clinical examination, which will allow us to reduce selection bias.

Study Phases

- *Recruitment:* Subjects were recruited by the principal investigator and his associates in the neurology departments of the Jason Sendwe Provincial General Reference Hospital, the Dr. Joseph Guislain Brothers of Charity Neuropsychiatric Center of Lubumbashi and the University Clinics of Lubumbashi. Other family members living with epilepsy were recruited through initial family contacts and/or their doctors. Our goal is to be as explicit as possible in the written and verbal consent procedures to ensure that all participants agree to join the study without excessive coercion. The principal investigator reserves the right to refuse any sample that, in his opinion, was given as a result of excessive coercion
- *Pre-selection:* Medical records supporting the diagnosis were taken and evaluated by the principal investigator and his associates to determine if the subject met the diagnostic criteria. The suitability for inclusion in the protocol was considered after reviewing the medical records. Subjects identified as meeting the diagnostic criteria were invited to come to the different follow-up appointments

Number of Visits and Subject Time Commitment

This protocol was initially implemented during the neurological consultation that was carried out at the aforementioned structures. Families were contacted by phone by a counselor or by the investigator for the collection of additional information on family history and access to the study.

Chronological Order of Study Procedures

Complete medical histories were gathered for each individual. This included information concerning pregnancy, childbirth, developmental stages and neurological disorders. Multigenerational family histories were obtained by establishing the family tree up to 3 generations. Invasive procedures were limited to blood collection (3.5 ml) using a 5 cc syringe with a fixed or winged needle. These samples were stored at -20°C with a laboratory refrigerator in 10 cc EDTA blood collection tubes after collection using P-10, P-100 micropipettes. The other selected controls were subjected to the same investigations only after they had completed the informed consent process. No therapeutic medication will be administered.

Laboratory Exome Sequencing Protocol

- *Sequencing Location*

The samples are genetically analyzed at the Intergen Genetics and Rare Diseases Diagnosis Research and Application Center Co. Ltd. Address: Mustafa Kemal Mah. 2119. Sokak No: 5 Çankaya/ANKARA Central Registry Number: 047801464 2900016 Tel: +90 312 428 48 14 - Fax: +90 312 428 26 93 - www.intergen.com.tr - info@intergen.com.tr Document No: INT.KGE.FRM.21 24.08.2021 Rev.Date / No: --/00

- *General Consideration*

The analysis is performed to identify and characterize new epilepsy genes in Lubumbashi to explain the clinical (phenotypes) and genetic characteristics of the patients. These genes could probably be important in the normal function of the nervous system and also have important pathophysiological implications, as well as modifying the concept of epilepsy management not only in our community but also in other populations. Only observations with potential clinical significance for the phenotype are reported. Incidental findings are reported only if clinical action is necessary. Heterozygous variants of patients living with epilepsy are reported only at the request of the family. Only variants classified as pathogenic or likely pathogenic according to ACMG criteria are included in the report, whether they are incidental findings or heterozygous variants associated with epilepsy. Variants of Uncertain Significance (VUS) are reported only if they are relevant to the clinical indication. A Variant of Uncertain Significance (VUS) is on the verge of being classified as pathogenic if it is supported by evidence such as high scores on prediction tools, low frequency in the population, relevant bibliographic data and a strong clinical correlation with the preliminary diagnosis.

- *Exome Sequencing*

During the test, the DNA was first fragmented into small pieces, then enriched for exon and exon-intron junction regions, which are the most frequently altered regions of human DNA, allowing for the detection of monogenic diseases. DNA isolation was performed using standard French protocols. Genetic library preparation and exome enrichment were carried out using the TWIST human Comprehensive Exome kit. The enriched libraries were sequenced on the MGIT 7 instrument using PE150-FCL.12, 5 Gbp cartridges, which represents an average target coverage of 100 to 120x. The data were submitted to the GATK (Genome Analysis Toolkit) best practices workflow at the Intergen Genetics Center in Ankara, Turkey.

The raw reads were aligned to hg38 using bwa men 0.7.17. Then, the steps of duplicate marking and base recalibration were performed by GATK4. Variant calling was performed using two distinct algorithms, GATK UnifiedGenotyper and GATK HaplotypeCaller and both were complementary (Van Der Auwera et al. 2013). "GATK practices" refers to the "Best Practices" of GATK. These are bioinformatics protocols and pipelines carefully documented and optimized by the Broad Institute to maximize the accuracy and reproducibility of variant detection. These practices cover all steps, from the initial processing of raw sequencing data to obtaining a reliable list of genetic variants. Low-quality variants from two sets were eliminated based on read depth strand bias and quality parameters using the GAT SelectVariants option [35].

Key Stages Recommended by the Broad Institute

1. Raw Read Quality Control

- Before any analysis, it's crucial to ensure that the sequencing data are of good quality. Tools like FastQC are often used to evaluate reads (sequenced DNA fragments)
- Sequencing adapters (short sequences added to DNA fragments) and low-quality bases are often trimmed or eliminated (for example, with tools like Cutadapt or Trimmomatic)

2. Read Alignment to the Reference Genome

- Cleaned reads are then aligned (mapped) to a reference genome (e.g., GRCh38 for humans)
- The result of this step is an alignment file (usually in BAM or CRAM format)
- BAM (Binary Alignment/Map) and CRAM (Compressed Reference-oriented Alignment Map) Formats
- BAM is the compressed binary version of the human-readable SAM (Sequence Alignment/Map) format. It's optimized for storage and fast computer access and its accompanying index file (.bai) allows for quick access to specific genomic regions. Each record in a BAM file contains detailed information about a sequenced read and its alignment, including the read's sequence, base quality scores, alignment position and CIGAR string (which describes alignment operations like matches, insertions and deletions)
- CRAM is a more recent evolution of BAM designed for even more efficient compression. Its main innovation is that it stores reads by recording only the differences between the read's sequence and the reference genome, resulting in a significant reduction in file size (30% to 50% or more). CRAM can also be compressed with or without loss of information

3. Alignment Pre-processing

- This is a critical step of the GATK Best Practices to improve variant calling accuracy. It includes several sub-steps:
  - *Adding Read Groups:* Ensures each read is associated with a read group containing important information (sample, library, etc.)
  - *Marking Duplicates:* Identifies and marks reads from the same original DNA fragment (often due to PCR amplification). These duplicates are ignored during variant calling to avoid false positives
  - *Local Realignment around Indels:* (Less critical with recent GATK versions) Corrects alignment errors at the edges of small insertions or deletions
  - *Base Quality Score Recalibration (BQSR):* Corrects systematic errors in the quality scores assigned by the sequencer, thus improving the reliability of each base

4. Variant Calling

- This is where GATK is most powerful. The primary tool for detecting germline (inherited) SNPs and Indels is GATK HaplotypeCaller
- HaplotypeCaller reconstructs haplotypes (DNA sequences along a chromosome) and uses a probabilistic model to identify where variants are present and their genotype
- Intergen also uses GATK GermlineCNVCaller to infer copy number variations (CNVs), which are deletions or duplications of larger genomic regions

5. Variant Filtering

- Raw variants called by GATK can contain false positives. Filters are applied to eliminate low-quality variants. Intergen mentions removing low-quality variants based on parameters such as strand bias, read depth and call quality

6. Functional Annotation of Variants

- Once high-quality variants are identified, they are annotated to understand their potential impact. Tools like ENSEMBL's Variant Effect Predictor (VEP) are used to determine if a variant is synonymous, non-synonymous, truncating or if it affects a regulatory region

- Intergen also mentions comparing variants of interest with an in-house disease variant database

7. Visualization and Interpretation

- Variants of interest are often manually visualized using software like IGV (Integrative Genomics Viewer) to visually confirm the variant call

8. Variant Classification

- Variants are interpreted based on ACMG (American College of Medical Genetics and Genomics) criteria to assess their pathogenicity (whether they are the cause of a disease)

9. Final Annotation

- High-quality and significant variants are submitted for functional annotation using ENSEMBL's Variant Effect Predictor [36]

10. Prioritization of Variants

- Rare variants (MAF < 1%) with a high impact, unknown significance, and/or potential splicing effects were prioritized. Other variants with potential effects on the observed phenotype were also analyzed

11. Visual Verification

- Variants of interest were visually verified on IGV and compared to an internal disease variant database by the Intergen Genetic Diagnosis Center in Ankara, Turkey [37]

12. Classification

- The classification of variants was performed taking into account the recommendations of the ACMG and ClinGen. It is important to consider that variant classification is based on current scientific knowledge and is progressive

Study Parameters

Sociodemographic Characteristics:

- Sex: male (M), female (F)
- Age (date of birth: day/month/year)

Clinical Parameters:

- Age of seizure onset (in years)
- Family history of epilepsy: brother/sister, parents, grandparent, paternal/maternal side.
- Clinical form of the epileptic seizure:
  - Generalized seizure: GTC (Generalized Tonic-Clonic), atonic seizure, tonic seizure, myoclonic seizure, absence seizure
  - Focal seizure: partial (without altered consciousness), complex (with altered consciousness)

Paraclinical Parameters:

- EEG: search for paroxysmal grapho-elements (spike-wave, polyspike, polyspike-wave, notched slow waves with synchronous spikes)
- Cerebral CT scan: search for the absence of a lesion in the cerebral parenchyma
- Exome sequencing: search for the type of mutations and/or variants in the selected epileptic patients and controls

Statistical Studies

Data were collected and entered using Epi InfoTM version 7.2.1.0 and SPSS software. Univariate analysis was used to calculate the frequency in terms of percentage for qualitative variables. The calculation of the mean, median and standard deviation was used for the analysis of quantitative variables. Bivariate analysis was used to compare the means according to the distribution of sociodemographic, clinical and paraclinical characteristics. The chi-squared test will be performed. The Odd Ratio (OR) with a 95% Confidence Interval (CI) and a significance was set for $OR > 1$ and a $p < 0.01$ to find the link between the variables.

Definition of the Disease, Exposure and Sequencing Procedure

- Case subject (the disease): the epileptic person selected for the study
- First exposed control: the parent of the selected patient
- Second exposed control: the brother or cousin of the patient, whether or not they have epilepsy
- Recessive transmission: characterized by a skip of one generation before an epileptic patient appears, according to the pedigree
- Dominant transmission: characterized by the presence of a case of epilepsy in each generation, according to the pedigree study

- Exome sequencing procedure:
  - After collecting peripheral blood using P-10, P-100 micropipettes, these samples were stored at -20°C with a laboratory refrigerator in 10 cc EDTA blood collection tubes. In the laboratory, DNA was extracted for whole-exome sequencing

Ethical Considerations

The completion of this thesis, through the different stages carried out, respected the ethical principles guiding all scientific research. We took into account the four bioethical principles: autonomy, justice, non-maleficence and beneficence [38,39]. We obtained authorization from the Medical Ethics Committee of the University of Lubumbashi by letter referenced No: Approval: UNILU/CEM/2024/2018, issued on 01/23/2024. All study participants gave their informed consent to the survey team before the administration of the questionnaire and the collection of blood samples, either directly (adults) or indirectly (parents and/or companions of children). Participation in this study did not present any direct benefit for the patients living with epilepsy or their matched family members at the time of the study; however, the results stemming from this study could benefit other people in the same conditions. The principles of respect for research integrity guided the completion of this work through the different phases [40].

Study Limitations

Given that genetic analyses are expensive, it will not be possible to sequence all 72 patients to be matched with 2 other controls, for a total of 216 samples. Only 5 families are sequenced with their 2 matches total 15 samples, to present the first informative results; the others would only be sequenced if significant funding is obtained. Another limitation is the refusal by many families to allow blood to be drawn for analysis outside the country due to mystico-religious considerations.

Results

The results of the present study concern both the general characteristics of the sample and those of the family tree. The first part concerns the prevalence of familial epilepsy in Lubumbashi, the average age of patients and their sex.

A. General characteristics of the sample.

Prevalence

This Fig. 1 shows the percentage of familial epilepsy cases within the sample.

It appears from this figure that familial epilepsy is present at Lubumbashi in 11.23%.

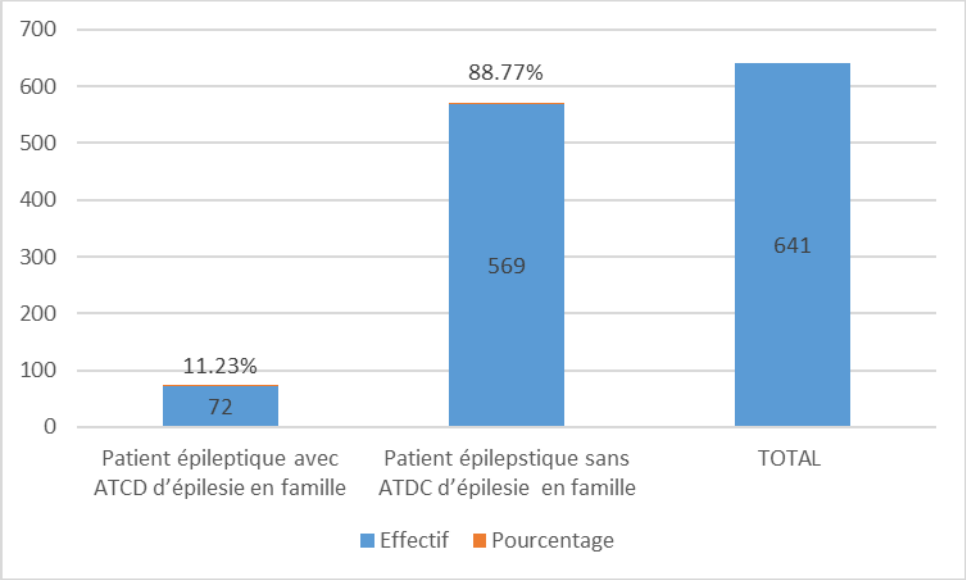


Figure 1: Prevalence of familial epilepsy.

Age and Sex Table 1. Distribution of patients by mean age.

The mean age and median of patients with a history of familial epilepsy are shown in the following Table 2.

Age Moyen Des Patients			
Obs	Mean		Std Dev
72	15,24 ans		11,03
Median			Mode
25%	14 ans	75 %	17 Ans
7 years		20 years	

Table 2: Mean age of patients.

It appears from this table that the patients had a mean age of 15.24 ± 11.03 years, with a median of 14 years, 7 years at the 1st quartile and 20 years at the 3rd quartile. The distribution of patients according to their sex is shown in the Fig. 2 below.
It emerges from this Fig. 2 that the sex ratio is 1.32, in favor of men.

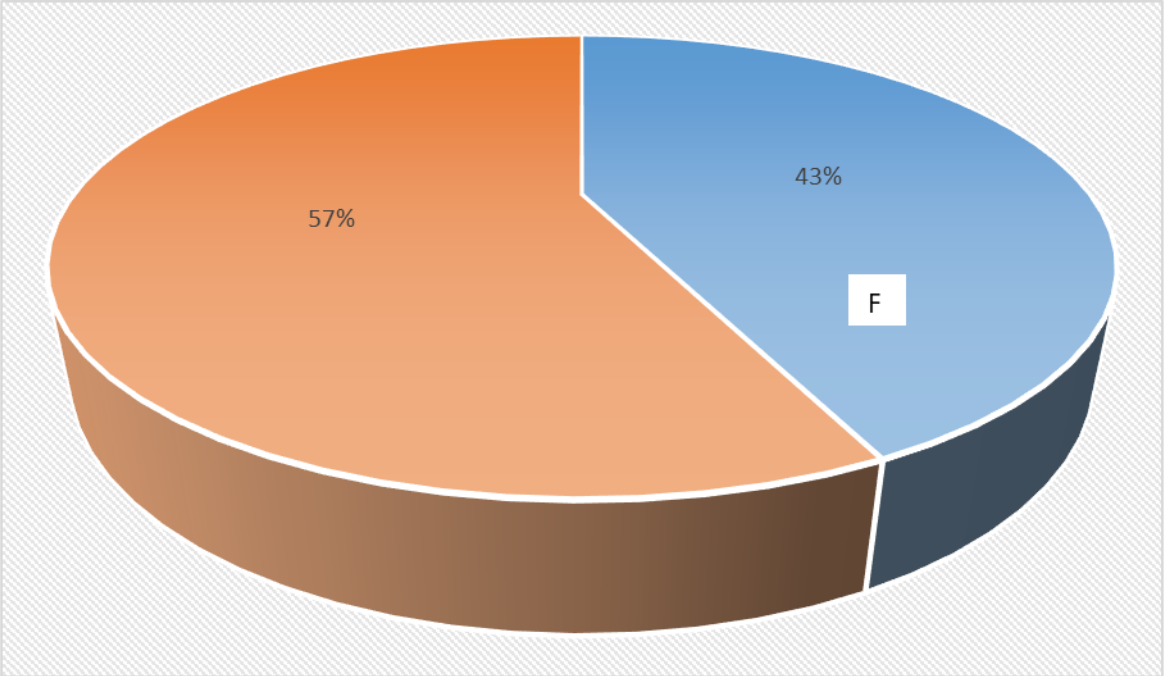


Figure 2: Distribution of patients by sex.

Distribution According to Other Parameters
Table 3-5 and Fig. 3-7 present other types of patient distribution.

Type of Seizure	n	%
Partial seizure secondarily generalized	3	4,17%
Complex partial seizure	3	4,17
Myoclonic	3	4,17
Atonic seizure	3	4,17
Tonic seizure	1	1,39
Absence seizure	6	8,33%
Generalized tonic-clonic seizure	51	70,83%
Simple partial seizure	2	2,78%
Total	72	100

Table 3: Distribution of patients according to seizure types.

We observe from this table that generalized tonic-clonic seizures were the most common with 70.83% of cases, followed by absence seizures with 8.33% of cases. The frequency of other seizures ranged between 1.39% and 4.17% of cases. The EEG results in patients with a family history of epilepsy are shown in Fig. 3 below.

a. Distribution of Patients According to EEG Results

Our results show that EEG was performed in the majority of patients (63.49% of cases) and was normal in 27.78% of cases and abnormal (presence of paroxysmal grapho-elements) in 35.71% of cases. The non-performance of this examination represented 38.57%.

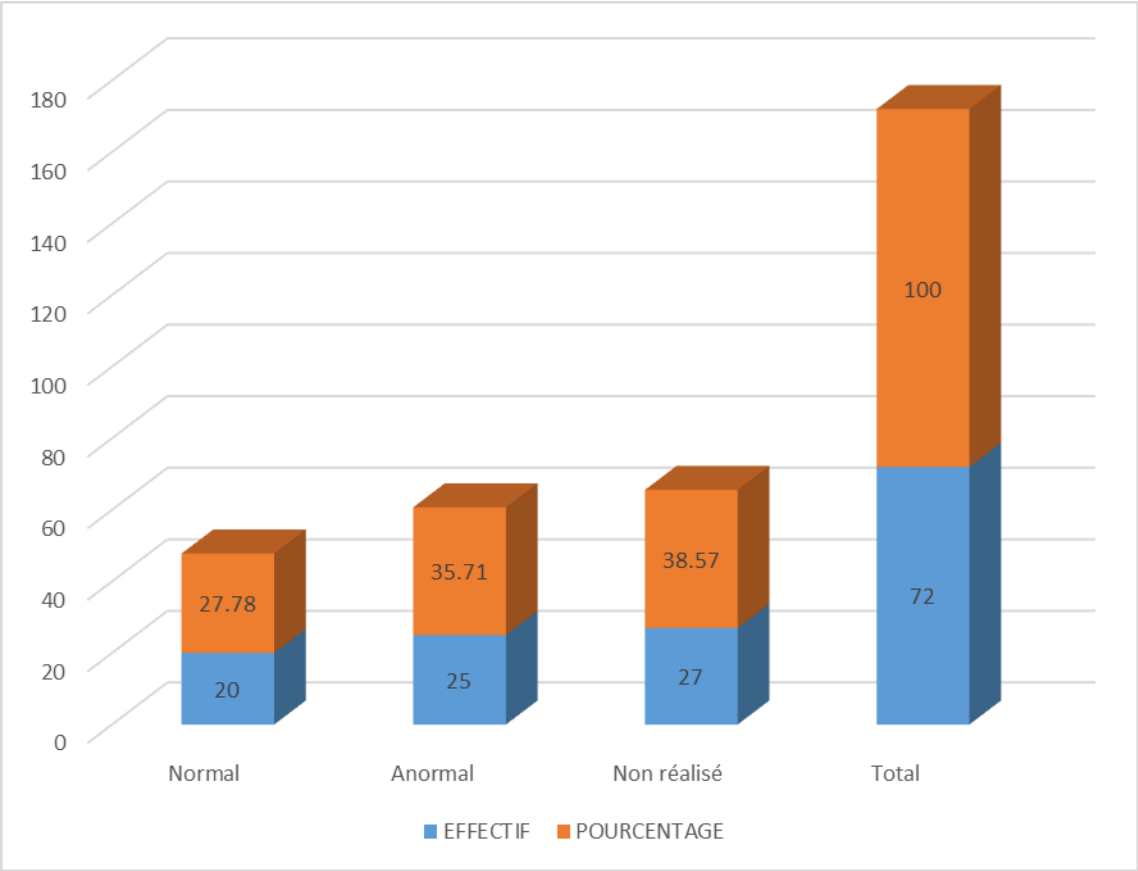


Figure 3: According to EEG results.

Furthermore, the results of the patients' therapeutic journey, shown in Fig. 4, indicate that in 48.61% of cases, patients had followed a drug treatment before arriving at the hospital and that traditional treatment (36.11%) and prayer (9.72%) accounted for a total proportion of 45.83%.

b. According to Mode of Transmission

In Figure 4, we considered the autosomal dominant and autosomal recessive modes.

We deduce from this figure that epilepsy is transmitted in the autosomal dominant mode in 41.67% of cases and in the autosomal recessive mode in 33.33% of cases.

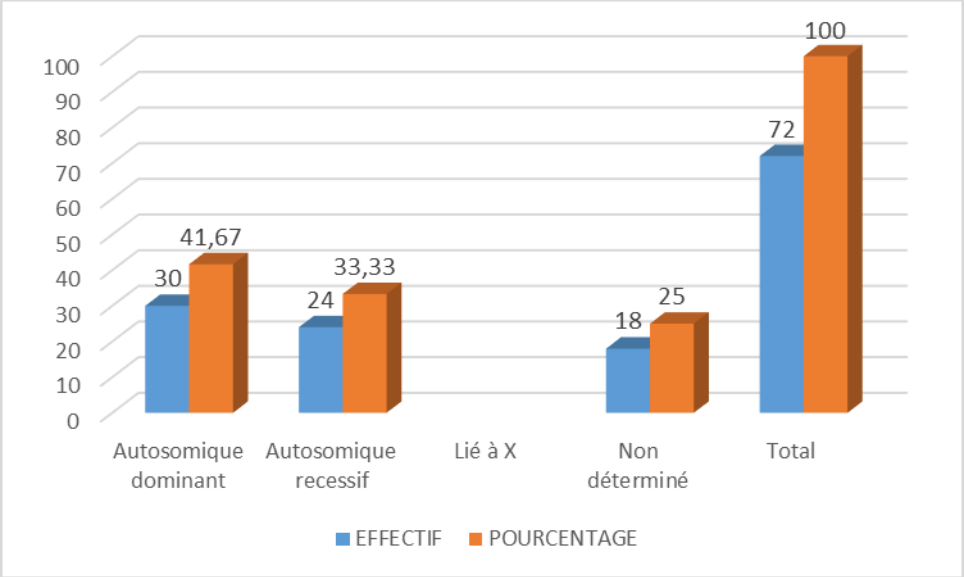


Figure 4: Distribution of patients according to the mode of transmission by pedigree.

c. According to Consanguinity Between Parents

The results regarding the notion of consanguinity between the parents of patients living with epilepsy are shown in Fig. 5-7, indicating that no patient resulted from a consanguineous marriage.

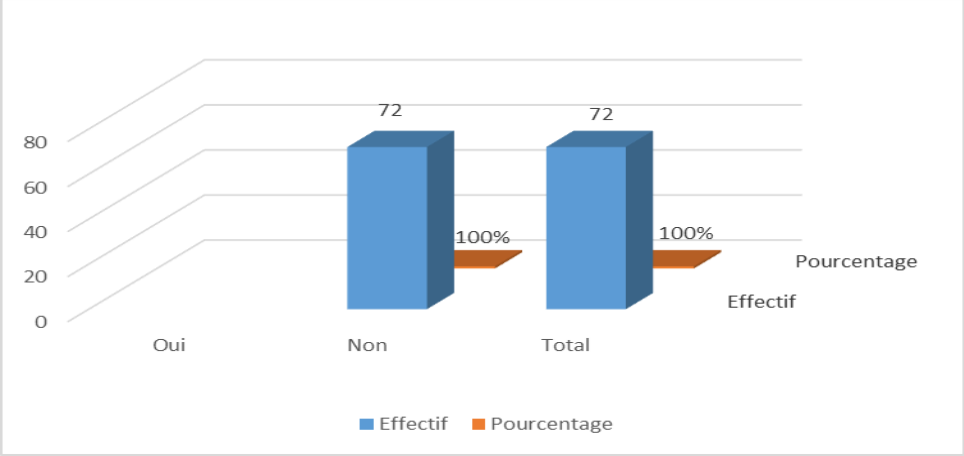


Figure 5: Distribution of patients according to the notion of consanguinity between the parents of patients living with epilepsy.

Distribution of patients according to two associated parameters.

	Types of Seizures																
	ABSENCE		CGTC		ATONIC		P.C		P.S.G		P.S		TONIC		MYOCLONIC		TOT
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
F	2	6,45	20	64,5	2	6,45	1	3,23	2	6,45	2	6,45	1	3,23	1	3,23	72
M	4	9,76	31	75,6	1	2,44	2	4,88	1	2,44					2	4,88	
	6		51		3		3		3		2		1		3		
CGTC: Generalized Tonic-Clonic Seizures, PC: Complex Partial Seizure, PS: Simple Partial Seizures, F: Female, M: Male.																	

Table 4: Distribution of patients according to sex and seizure type.

Reading this table shows us that generalized tonic-clonic seizures are present in considerable proportion in both sexes (64.5% of cases for females and 75.6% of cases for males) followed by absence seizures in males with 9.76% of cases, for a corrected chi-square of 6.1.

According to Mode of Transmission and Seizure Type

	Types of Seizures																
	ABSENCE		**CGTC**		**ATONIC**		**P.C**		**P.S.G**		**P.S**		**TONIC**		**MYOCLONIC**		**TOT**
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
TD	2	6,45	21	70	2	6,45	2	6,45	2	6,45					1	3,33	
TR	3	12,5	15	62,5	1	4,17			1	4,17	2	8,33	1	4,17	1	4,17	
IN	1	5,56	15	83,3			1	5,56							1	5,56	
TOT	6		51		3		3		3		2		1		1		
TD: Dominant Transmission; TR: Recessive Transmission; ID: Undetermined																	

Table 5: Distribution of patients according to mode of transmission and seizure type.

It appears from this table that CGTC are transmitted in 70% of cases according to the autosomal dominant mode and in 62.5% of cases according to the autosomal recessive mode, while absence seizures are transmitted in 12.5% of cases according to the autosomal recessive mode, with a corrected chi-square of 11.46.

Sequencing Results

Presentation of Sequenced Cases Based on Pedigree and Exome Sequencing Results (Fig.5,6)

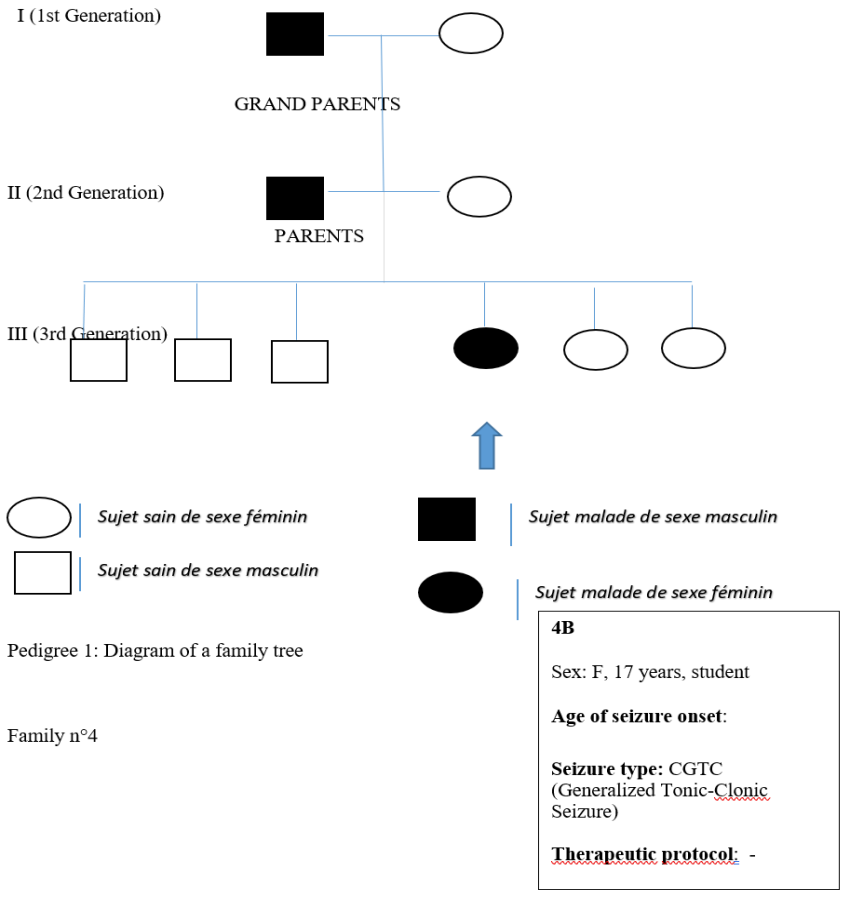


Figure 5: Presentation of Sequenced Cases Based on Pedigree.

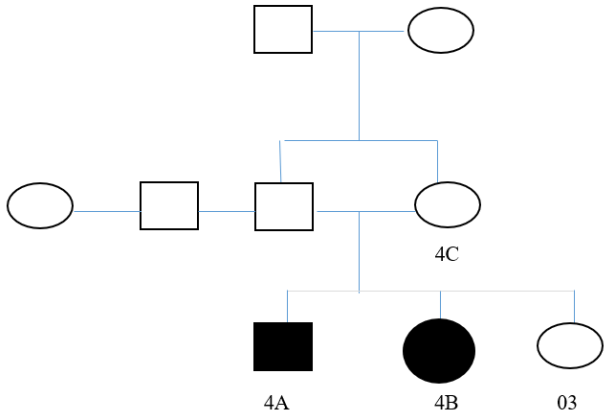


Figure 6: Presentation of exome sequencing.

Sequencing Result

Presentation: Sequencing Information Sheet for Family 1

Patient's Information			
First Name : Last Name :	ID No : 4A M	Date of Birth : 18/11/2010	Ethnicity :
Spouse's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Mother's Information			
First Name : Last Name :	ID No : 4C	Date of Birth : 04/02/1985	Ethnicity :
Father's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Affected Family Member's Information			
First Name : Last Name :	ID No : 4B F	Date of Birth : 04/05/2008	Relationship with Proband : Sœur à 4A
Contact Information			
Patient's or next of Kin's Email ID : Contact Number (WhatsApp) :			
Race : Asian	Sampling Date :		
Requesting Physician : □ Dr Patrice NTENGA □ Tél : +243 99 835 16 95	Email Address : jacobntenga@gmail.com		Hospital/Department : Département de Neuropsychiatrie Université de Lubumbashi, DRC
Sample type : □ EDTA tube □ Extracted DNA □ Other :	Indication for Testing : □ Diagnosis □ Prenatal Testing □ Cascade Screening		□ Carrier Screening □ Family Screening □ Targeted Variant testing
Testing done Previously at Interge□: ☐Yes No If Yes, Please mention patient ID :			
Important Notes: The APPROXIMATE reporting period of the genetic test was given to you. The Turnaround time may be EXTEND due to technical reasons. RARELY, we may need new samples. Additional tests and repetitive studies may be necessary to obtain a reliable result from the test. I approve sending of the reports to the list given below. ☐ To me ☐ Referring Hospital/ Center ☐ To My Physician Name and Sign of the patient or legal representative (Handwriting): Name and Sign of owners of other samples or legal representative (Handwriting):			

Family n°1

1A: Sex: F, 11 years old, student

1B

Sex: F, 7 years, student

Age of seizure onset: 3 years

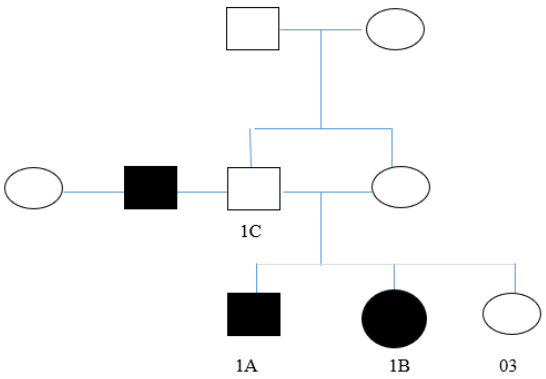
Seizure type: The natural disappearance of seizures.

: Protocole thérapeutique : -

Age of seizure onset: 2 years.

Seizure type: CGTC (Generalized Tonic-Clonic Seizure)

Therapeutic protocol: Monotherapy: DPK



Pedigree 3: Presentation of sequenced Family 1.

Sequencing Result

Presentation: Sequencing Information Sheet for Family 2

Patient's Information			
First Name : Last Name :	ID No : 1A F	Date of Birth : 20/04/2014	Ethnicity :
Spouse's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Mother's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Father's Information			
First Name : Last Name :	ID No : 1C	Date of Birth : 24/03/1985	Ethnicity :
Affected Family Member's Information			
First Name : Last Name :	ID No : 1B F	Date of Birth : 29/07/2018	Relationship with Proband : Sœur à 1A
Contact Information			
Patient's or next of Kin's Email ID : Contact Number (WhatsApp) :			
Race : Asian	Sampling Date :		
Requesting Physician : □ Dr Patrice NTENGA □ Tél : +243 99 835 16 95	Email Address : jacobntenga@gmail.com		Hospital/Department : Département de Neuropsychiatrie Université de Lubumbashi, DRC
Sample type : □ EDTA tube □ Extracted DNA □ Other :	Indication for Testing : □ Diagnosis □ Prenatal Testing □ Cascade Screening		□ Carrier Screening □ Family Screening □ Targeted Variant testing.
Testing done Previously at Interge☐: ☐s No If Yes, Please mention patient ID :			
Important Notes : The APPROXIMATE reporting period of the genetic test was given to you. The Turnaround time may be EXTEND due to technical reasons. RARELY, we may need new samples. Additional tests and repetitive studies may be necessary to obtain a reliable result from the test. I approve sending of the reports to the list given below. ☐ To me ☐ Referring Hospital/ Center ☐ To My Physician Name and Sign of the patient or legal representative (Hand Writing) : Name and Sign of owners of other samples or legal representative (Hand Writing) :			

Family n°3

3A: Sex: M, 17 years old, student

3B

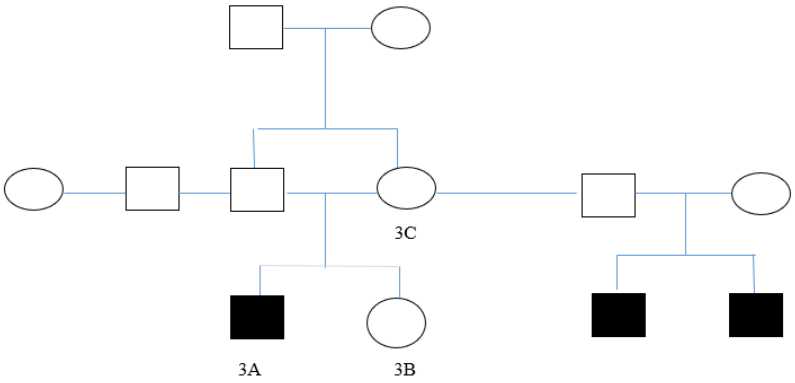
Sex: F, 21 years

Age of seizure onset: -

Seizure type: -

Therapeutic protocol: -

Age of seizure onset: 2 years
Seizure type: ABSENCE
Therapeutic protocol: Bitherapy: DPK + KEPPRA



Pedigree 4: Presentation of sequenced Family 3.

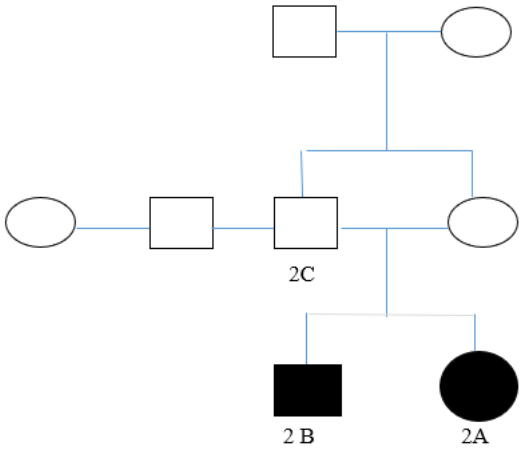
Sequencing Result

Presentation: Sequencing Information Sheet for Family 2

Patient's Information			
First Name : Last Name :	ID No : 3A M	Date of Birth : 08/05/2008	Ethnicity :
Spouse's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Mother's Information			
First Name : Last Name :	ID No : 3C	Date of Birth : 04/03/1970	Ethnicity :
Father's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Affected Family Member's Information			
First Name : Last Name :	ID No : 3B F	Date of Birth : 18/07/2004	Relationship with Proband : Sœur à 3A
Contact Information			
Patient's or next of Kin's Email ID : Contact Number (WhatsApp) :			
Race : Asian	Sampling Date :		
Requesting Physician : □ Dr Patrice NTENGA □ Tél : +243 99 835 16 95	Email Address : jacobntenga@gmail.com		Hospital/Department : Département de Neuropsychiatrie Université de Lubumbashi, DRC
Sample type : □ EDTA tube □ Extracted DNA □ Other :	Indication for Testing : □ Diagnosis □ Prenatal Testing □ Cascade Screening		□ Carrier Screening □ Family Screening □ Targeted Variant testing
Testing done Previously at Interge☐: ☐Is No If Yes, Please mention patient ID :			
Important Notes : The APPROXIMATE reporting period of the genetic test was given to you. The Turnaround time may be EXTEND due to technical reasons. RARELY, we may need new samples. Additional tests and repetitive studies may be necessary to obtain a reliable result from the test. I approve sending of the reports to the list given below. ☐ To me ☐ Referring Hospital/ Center ☐ To My Physician Name and Sign of the patient or legal representative (Hand Writing) : Name and Sign of owners of other samples or legal representative (Hand Writing) :			

Family 2	**2 B** Sex: M, 23 years **Age of seizure onset**: 14 years **Seizure type:** ABSENCE **Therapeutic protocol**: he is no longer on treatment

2A: Sex: F, 18 years old, student
Age of seizure onset: 9 years
Seizure type: ABSENCE
Therapeutic protocol: Bitherapy: DPK



Sequencing Result

Presentation: Sequencing Information Sheet for Family 4

Patient's Information			
First Name : Last Name :	ID No : 2A F	Date of Birth : 05/05/2007	Ethnicity :
Spouse's Informationh			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Mother's Information			
First Name : Last Name :	ID No :	Date of Birth :	Ethnicity :
Father's Information			
First Name : Last Name :	ID No : 2 C	Date of Birth : 07/01/1975	Ethnicity :
Affected Family Member's Information			
First Name : Last Name :	ID No : 2 B M	Date of Birth : 18/07/2004	Relationship with Proband : Frère à 2 A
Contact Information			
Patient's or next of Kin's Email ID : Contact Number (WhatsApp) :			
Race : Asian	Sampling Date :		
Requesting Physician : □ Dr Patrice NTENGA □ Tél : +243 99 835 16 95	Email Address : jacobntenga@gmail.com		Hospital/Department : Département de Neuropsychiatrie Université de Lubumbashi, DRC
Sample type : □ EDTA tube □ Extracted DNA □ Other :	Indication for Testing : □ Diagnosis □ Prenatal Testing □ Cascade Screening		□ Carrier Screening □ Family Screening □ Targeted Variant testing.
Testing done Previously at Interge☐ : ☐s No If Yes, Please mention patient ID :			
Important Notes : The APPROXIMATE reporting period of the genetic test was given to you. The Turnaround time may be EXTEND due to technical reasons. RARELY, we may need new samples. Additional tests and repetitive studies may be necessary to obtain a reliable result from the test. I approve sending of the reports to the list given below. ☐ To me ☐ Referring Hospital/ Center ☐ To My Physician Name and Sign of the patient or legal representative (Hand Writing) : Name and Sign of owners of other samples or legal representative (Hand Writing) :			

In Table 6,7, we present the results of the sequenced families in the first and those evaluating the clinical validity of specific gene-disease associations (concordance) ACMG in the second, respectively.

Family Code		Gène - variant	Genomic Coordinates	Read Frequency and Variant Fraction	Allele Frequency	Bibliographic Reference	Zygosity	Criteria
3	3A	CACNA1INM_021096.4c.2059A>G p. (Met687Val)	chr22-39658218A>G	116,97-45%	0,0001%	PMID (PubMed Identifier)	Heterozygous	ACMG
	3B	Idem					Heterozygous	
	3C	Idem					Heterozygous	
4	4A	ATP2B1;NM_001366521.1 c3356G>Ap.(Arg1119Gln)	chr12-89591291C>T	43,41-49%	0,0001%	PMID	Heterozygous	ACMG
	4B	Idem					Heterozygous	
	4C	Idem					Heterozygous	
1	1A	SCN3A;NM_006922.4 c.5164_5166delins AAG p.Al1722Lys)	chr2-165090987TGC>CTT	137,135-50%		PMID	Heterozygous	ACMG
	1B	Idem					Heterozygous	
	1C	No mutation					Normal	
		OTHER VARIANT OF MEDICAL SIGNIFICANCE: Gene G6PD; NM_001360016.2 c.202G>A p. (Val68Met)					Heterozygous Low penetrance	
2	A	NPRL2; NM_006545.5 c171-9A>G(IVS2-9A>G)	chr3-50349842T>C	86,99-54 %	0,0013%	PMID	Hétérozygote	ACMG
	B	Idem					Hétérozygote	
	C	Idem					Hétérozygote	

Table 6: Sequencing results by family.

	Genetic Mutation Type			
	Evidence to evaluate the clinical validity of specific gene-disease associations (concordance) ACMG			
	Auteurs			
Seizure Type	Ntenga P	phenotype-genotype concordance."		Other Authors:
ABSENCE	CACNA1INM_021096.4c.2059A>G p. (Met687Val) NPRL2 ;NM_006545.5 c171-9A>G(IVS2-9A>G)	YES	YES NO	Zhi-Jian, et al., 2023 SLC2A1 c.376C>T/p.Arg126Cys)

Idiopathic GTCS	ATP2B1;NM_001366521.1 c3356G>Ap.(Arg1119Gln)	YES	NO	Zhi-Jian et al, 2023 IQSEC2 c.4315C>T/p.Pro1439Ser) Elena Poggio (2022), Soumya et al. (2022), Rahimi (2022) Trouble Comp + Epilep
	SCN3A;NM 006922.4 c.5164_5166delins AAG p.Al1722Lys	YES	NO(CGI)	Liu XR, et al., 2021 Rehm, et al., 2015. SCN8A, KCNQ2, KCNA2 ALG13, CACNA1H HCN2, SLC12A5KCNMA1, SLC2A1

Table 7: Presentation of results based on phenotype (clinical) - genetic concordance.

Discussion and Description of the Genes Found

General characteristics of the sample.

1) Prevalence of Familial Epilepsies

Our study collected 72 families with a history of familial epilepsy out of a total of 641 patients diagnosed with epilepsy, representing a prevalence of 11.23%. This result is consistent with findings from other authors, such as M. Ndiaye et al. in Senegal, who reported a general frequency of familial epilepsy at 11%.

A similar finding was made by Kuate-Tegueu Callixte in Cameroon in 2014, who found that over half (57.1%) of patients living with epilepsy had a family history of the condition. Of these, 11.4% had two family members with epilepsy and 10% had three or more family members affected by the disease [41].

2) *Notion of Consanguinity*

Lamine Thiam in Senegal (2020), in his study on the clinical and paraclinical aspects of idiopathic childhood epilepsy, showed that out of 18 children followed for idiopathic epilepsy, parental consanguinity and family history of epilepsy were found in 1 and 6 children, respectively (5.5% and 33.3%) [42]. Our study's prevalence of 11.23% without any notion of parental consanguinity (Fig. 5) suggests an inherited nature that needs to be demonstrated. For many years, the role of ion channels in epilepsy has been suspected based on physiological arguments, as ion channels (Na+, K+) are responsible for generating action potentials and many anti-epileptic drugs act directly or indirectly on their function. Recent molecular genetics data have confirmed this role, with studies of familial epilepsy forms implicating genes that code for subunits of ion channels or receptor channels [43]. In their studies on epilepsy, a family history of the disease was found to be 2 to 3 times more common in patients with epilepsy than in controls [44-46]. Literature has shown that consanguineous marriages are common in some cultures in Asia, particularly in Indian or Muslim communities. In one study in India, consanguineous parents were more frequent among patients than controls (13.1% vs. 6.6%) (2.6; 95% CI: 1.5-4.4). The association with consanguinity is stronger in generalized epilepsies than in localized ones and in idiopathic or cryptogenic epilepsies than in symptomatic ones [45,47].

3) Average Age and Sex

As shown in Table 2 and Fig. 2, the average age at diagnosis for patients with epilepsy in our cohort is 15.24±11.03 years, with a maximum of 20 years for 75% of cases and a mode of 17 years. Zubcevic reported an average age at diagnosis of 5 years. Many other studies report a high frequency of seizures with a hereditary character in children [48-50]. In their studies, Dadah Samy Mohamed Lemine, et al., in Senegal and Mukuku O, et al., in the DR Congo reported an average age of patients with epilepsy around 8 years in Senegal, with a peak in the 5 to 10-year age group [51]. A male predominance was also observed in our study with a sex ratio of 1.32. This male predominance could be explained by a possible neurobiological difference between the neurons of male and female subjects, leading to different responses to brain injuries [51]. This male overrepresentation could also be explained in our communities by the underreporting of the disease in young women of marriageable age. Amina Chentouf, et al., in Algeria found a sex ratio of 1.35 in favor of the male sex in their study on the clinical characteristics and hereditary profiles of epilepsies, with no mention of X-linked transmission. [20].

4) *Type of Seizures*

We found that generalized tonic-clonic seizures were the most common, accounting for 70.83% of cases, followed by absence seizures with 8.33% of cases. The frequency of other seizures ranged from 1.39% to 4.17%. In his study on epilepsy and schooling

in Congolese epileptic children, Ntenga Parice, et al., [29]. found that generalized tonic-clonic seizures were the most frequent, with 41.7% and a p-value of 0.04, followed by absence seizures with 33.3% and a p-value of 0.67. The high representation of generalized tonic-clonic seizures could be justified by their dramatic and easily recognizable nature, as well as by the population's lack of awareness of other non-convulsive seizure manifestations. This same finding has been made in most studies conducted in Africa [51,20].

Genetic Section

1. Mode of Transmission of the Pathology According to the Pedigree

We observed from Figure 4 that the autosomal dominant mode of transmission accounts for 41.67% of cases, while the autosomal recessive mode of transmission accounts for 33.33% of cases. This result contradicts that of MEFOUNG Ephrata Samuel (2021) [52], for whom the autosomal recessive mode of transmission represented more than half of the cases. However, our results are consistent with a study conducted in Algeria (2015) by Chentouf A, et al., who found a high prevalence in favor of the autosomal dominant mode [20].

These differences could be justified by the different sample sizes, which are not large enough to characterize a distribution on a national scale and determine the predominance of one mode of transmission over another.

2. Description of the Genes

Gene ATP2B1 [53-55]

1. Definition and Nature of the ATP2B1 Gene: NM_001366521.1 c.3356G>A (p.Arg1119Gln)

The ATP2B1 gene codes for PMCA1 (Plasma Membrane Calcium ATPase 1), a calcium pump located in the plasma membrane of our cells. Its main physiological role is to maintain intracellular calcium homeostasis, precisely regulating the concentration of calcium inside cells.

- Understanding the Gene Nomenclature
  - Gene ATP2B1: The gene's name, standing for "ATPase plasma membrane Ca2+ transporting 1". It codes for the PMCA1 protein.
  - NM_001366521.1: The accession number of the reference transcript (mRNA) for this gene in the NCBI RefSeq database. The ".1" indicates the version of the transcript, which is crucial for unambiguously describing mutations.
- Interpretation of the Mutation: c.3356G>A (p.Arg1119Gln)
  - c.3356G> A: This refers to the coding DNA sequence (cDNA). The mutation is at the 3356th nucleotide, where a Guanine (G) has been replaced by an Adenine (A).
  - p. (Arg1119Gln): This refers to the protein sequence. The change in the DNA leads to the replacement of the amino acid Arginine (Arg) at position 1119 with Glutamine (Gln). This is a missense mutation.

2. Key Physiological Functions of the ATP2B1 Gene [53-55].

- *Calcium Export from the Cell:* PMCA1 actively pumps calcium ions (Ca^{2+}) out of the cell, which is crucial as high intracellular calcium can be toxic and interfere with many cellular functions
- *Blood Pressure Regulation:* ATP2B1 plays a role in regulating blood pressure by modulating the contraction of vascular smooth muscle cells.
- *General Cellular Calcium Homeostasis:* PMCA1 is ubiquitously expressed, highlighting its fundamental role in maintaining calcium levels in almost all eukaryotic cells.
- *Calcium Signaling:* By controlling calcium levels, ATP2B1 indirectly participates in many calcium-dependent cellular signaling pathways.
- *Brain Development and Neuronal Function:* Mutations in the ATP2B1 gene have been associated with neurodevelopmental delays, mild intellectual disability and language delays, suggesting its involvement in brain function.
- *Insulin Sensitivity Regulation:* Research indicates that ATP2B1 may influence insulin sensitivity by regulating the calcium/calmodulin signaling pathway.
- *Osteoclast Development and Survival:* It plays a dual role in the differentiation and survival of osteoclasts (cells involved in bone resorption) by regulating calcium oscillations.

3. Consequence of the Mutation in the ATP2B1 Gene

This is a missense mutation, resulting in a single amino acid change. The severity of the impact depends on the nature and position of the amino acid. The replacement of the basic, polar Arginine with a polar but uncharged Glutamine could potentially alter the structure or function of the protein. The location of Arginine at position 1119 is in an important region of the PMCA1

protein. Studies have shown that missense mutations in this gene, especially those affecting key functional domains, can significantly decrease the calcium pump's ability to export calcium from the cell. The neurological consequences of ATP2B1 mutations are attributed to the disruption of intracellular calcium regulation in neuronal cells. Calcium is a vital secondary messenger involved in many neuronal processes. The main neurological consequences are:

- *Global Developmental Delay (GDD) and Intellectual Disability (ID):* The most frequently reported consequence, with delays in acquiring key developmental milestones.
- *Language Delay:* Speech and language development are often affected.
- *Motor Delay:* Motor skills, such as walking, can be delayed.
- *Epileptic Seizures (convulsions):* A significant percentage of individuals with ATP2B1 mutations experience seizures of various forms.
- *Rarity of Specific Monogenic Mutations:* Mutations in single genes like ATP2B1 are generally rare in the general population with epilepsy. However, the clinical and research community recognizes ATP2B1 as a relevant gene for epilepsy in syndromic contexts.
- *Underlying Mechanisms of Seizures:* The neurological consequences are attributed to the disruption of calcium regulation, which is essential for neurotransmitter release, synaptic plasticity, neuronal development and excitability. Unregulated excess of intracellular calcium can lead to neuronal hyperexcitability, potentially contributing to seizures.
- *Hypotonia:* A decrease in muscle tone.
- *Brain MRI Abnormalities:* Structural brain alterations have been reported in some individuals.
- *Behavioral Disorders:* Abnormal behaviors have been described.
- *Ataxia (less frequently):* Problems with movement coordination.

Discussion of the ATP2B1 Gene [55,56].

Frequency and Phenotypes of Mutations in Epilepsy

Mutations in the ATP2B1 gene are a very rare cause of epilepsy. In contrast to genes like SCN1A or KCNQ2/3, which are mutated in a significant proportion of cases (for example, SCN1A is responsible for 35% of Dravet Syndrome cases), the contribution of ATP2B1 is minimal. This explains why it is often associated with rare neurodevelopmental syndromes. A 2022 study identified de novo variants of ATP2B1 in a cohort of 12 individuals with neurodevelopmental disorders, among whom 6 individuals (50%) presented with epileptic seizures of different forms [55].

Gene CACNA11

Physiology to Pathology of the Identified Gene

1. General Characteristics of the Gene: CACNA11; NM_021096.4 c.2059A>G p. (Met687Val)

- Gene: CACNA11 ("Calcium Voltage-Gated Channel Auxiliary Subunit Alpha 11").
- Variant Name: NM_021096.4 c.2059A>G p. (Met687Val).
- c.2059A>G: Adenine (A) at position 2059 is replaced by a Guanine (G) in the DNA.
- p. (Met687Val): The amino acid Methionine (Met) at position 687 is replaced by Valine (Val) in the protein.
- Zygosity: Heterozygous. The person has one mutated copy and one normal copy of the gene.
- Heredity: Autosomal dominant. A single mutated copy can be sufficient to cause the disease. This inheritance pattern often shows variable age of onset, incomplete penetrance and differential expression, meaning that some family members with the variant may be unaffected or have partial symptoms. Family screening is recommended to clarify the clinical significance of the variant.

Physiological Roles of the CACNA11 Gene

- Formation of Voltage-Gated Calcium Channels: CACNA11 provides instructions to create a subunit of voltage-gated calcium channels. These channels are proteins that form pores in cell membranes, allowing calcium ions to enter.
- Regulation of Calcium Influx: Calcium channels are crucial for regulating calcium entry into cells in response to changes in the cell's membrane potential, especially in the nervous system.
- Cell Communication and Neuronal Functions: Calcium influx is vital for nerve cell communication, neurotransmitter release, muscle contraction and gene expression regulation.
- In summary, the CACNA11 gene is fundamental for controlling calcium entry into cells, which has a direct impact on

electrical signaling and cellular functions, particularly in the brain and nervous system [57, 58].

Consequence of the Mutation in the CACNA11 Gene

A mutation in the CACNA11 gene can lead to a neurodevelopmental disorder with speech problems and with or without seizures. According to a recent study, 87% of patients with CACNA1A gene mutations were diagnosed with epilepsy and these mutations could lead to a wide range of seizure phenotypes.

Mechanisms Underlying Epilepsy in Case of Mutation

The CACNA1H gene codes for the alpha-1H subunit of the T-type calcium channel (also called Cav3.2). These channels play a crucial role in neuronal excitability, particularly in the thalamus, a brain region involved in generating cortical rhythms and seizures, especially absence seizures.

Mechanisms Underlying Epilepsy in Case of CACNA1H Mutation c.2059A>G p. (Met687Val)

The specific mutation is a missense mutation that leads to the substitution of Methionine with Valine at position 687 of the Cav3.2 protein. The mechanisms by which "gain of function" mutations like this one contribute to epilepsy are mainly related to an increase in neuronal excitability:

- *Increased T-type Calcium Current (Gain of Function):* The mutation can shift the activation curve to more negative potentials, causing the channel to open more easily or slow down inactivation, prolonging the channel's opening. This leads to neuronal hyperexcitability, promoting the generation and propagation of epileptic discharges.
- *Impact on Thalamocortical Oscillations:* Cav3.2 channels are particularly important for generating normal and pathological rhythmic oscillations (like the 3 Hz spike-and-wave discharges of absence seizures). Hyperactivity of these channels can disrupt these oscillations, transforming them into synchronous discharges that spread to the cortex, causing epileptic seizures.
- *Altered Neuronal Electrical Properties:* The mutation can directly affect the intrinsic properties of neurons, making them more prone to paroxysmal discharges.
- *Indirect Change in Gene Expression:* Some research suggests that increased Cav3.2 activity can influence calcium-regulated transcription factors, modifying the expression of genes involved in neuronal development or synaptic plasticity, which could contribute to a long-term epilepsy-prone environment [59,60].

Discussion of the CACNA1A gene [61,62].

Frequency and Phenotypes of Mutations in Epilepsy

The CACNA1A gene mutation is a rare cause of epilepsy. Its frequency in the general epileptic patient population is very low. Available data primarily comes from cohorts of patients with rare epilepsies or epileptic encephalopathies, where the percentage is higher.Furthermore, the rarity of these mutations contrasts with that of genes more commonly associated with epilepsy, such as SCN1A (linked to Dravet syndrome), where the mutation rate can reach 35% in familial cases.

Gene SCN3A; NM_006922.4 c.5164_5166delinsAAG p. (Ala1722Lys)

- Physiology to Pathology of the Identified Gene [63, 64, 65].

1. General Characteristics of the Gene:
   - Gene SCN3A: Provides instructions for a protein subunit that is part of a sodium channel. These channels are essential for the normal function of nerve and muscle cells.
   - NM_006922.4: The accession number of the reference mRNA sequence for the SCN3A gene.
   - c.5164_5166delinsAAG: This is the DNA variant nomenclature. It means the nucleotides at positions 5164, 5165 and 5166 were deleted and a new sequence of nucleotides (AAG) was inserted in their place.
   - p. (Ala1722Lys): This is the protein variant nomenclature. The amino acid Alanine (Ala) at position 1722 has been replaced by Lysine (Lys).
2. Clinical Significance: The variant is classified as a "Strong Variant of Uncertain Significance (SVUS)."
3. Family Implications: The patient and their sister are heterozygous for this variant, while their father is normal.
   - Physiological Roles of the SCN3A Gene (Sodium Voltage-Gated Channel Alpha Subunit 3). The SCN3A gene codes for the alpha subunit of the Nav1.3 sodium channel.

These channels are crucial for generating and propagating action potentials in neurons and muscle cells.

- Expression and Role in Fetal Brain: Nav1.3 is highly expressed in the fetal brain and plays an important role in the development and folding of the cerebral cortex (gyrification).
- Neuronal Electrical Activity: These channels allow positively charged sodium ions to enter brain cells, activating neurons and enabling the transport of electrical signals.
- Role in Neuronal Plasticity: Although its expression is low in the normal adult brain, Nav1.3 can be upregulated in response to nervous system injuries, suggesting a role in post-injury neuronal plasticity.
- Involvement in Neuropathic Pain: Nav1.3 also induces increased excitability of sensory neurons, a lower nociceptive threshold and neuropathic pain

o Consequence of the Mutation in the SCN3A Gene [66,64].

Mutations in the SCN3A gene are responsible for a range of neurological conditions called SCN3A-related neurodevelopmental disorders (SCN3A-NDD). These complications can vary in severity:

- Severe and Early-Onset Epilepsies:
o Developmental and Epileptic Encephalopathy (DEE): Characterized by intractable seizures with developmental delays.
o Familial Focal Epilepsy with Variable Foci: Milder forms may include focal epilepsy with or without brain malformations.
o Most pathogenic variants (about 91%) lead to a gain of function of the channel, causing increased sodium channel activity and neuronal hyperexcitability.
- Malformations of Cortical Development (MCD): More than 75% of individuals with SCN3A-related disorders have brain malformations, often bilateral diffuse or perisylvian polymicrogyria (multiple small convolutions creating excessive folding of the cerebral cortex).
- Developmental Delays and Intellectual Disability: All affected children show some degree of developmental delay, which can include speech/language delay and intellectual disability.
- Oral Motor and Speech Disorders: Difficulties with speech, swallowing and tongue movements.
- Autonomic Dysfunctions: Episodes of asymmetrical facial flushing, excessive sweating, apnea and bradycardia.

Gene G6PD; NM_001360016.2 c.202G>A p. (Val68Met) [67-70].

1. *General Information*

- G6PD gene: This is the gene for Glucose-6-Phosphate Dehydrogenase (G6PD). This enzyme plays a crucial role in red blood cell metabolism, protecting them from oxidative stress.
- NM_001360016.2: This is the accession number for the reference mRNA sequence of the G6PD gene.
- c.202G>A: This is the nomenclature of the variant at the DNA level (coding sequence). The c. indicates that the variation is described at the coding sequence level. The 202G>A means that the Guanine (G) nucleotide at position 202 in the DNA sequence has been replaced by Adenine (A).
- p. (Val68Met): This is the nomenclature of the variant at the protein level. The p. indicates that the variation is described at the protein level. Val68Met means that the amino acid Valine (Val) at position 68 of the protein has been replaced by the amino acid Methionine (Met) due to the DNA change.

2. *Clinical Significance*

This variant is classified as Pathogenic with low penetrance. This indicates strong evidence that this variant is a direct cause of a disease.

- Inheritance: X-linked. This means the gene is located on the X chromosome.
- In females (who have two X chromosomes), if only one copy carries the variant, they may be carriers and have milder symptoms or be asymptomatic due to X-inactivation.
- In males (who have only one X chromosome), if their single X chromosome carries the variant, they will generally develop a more severe form of the disease.

3. *Neurological Consequences of the G6PD Gene Mutation;* NM_001360016.2 c.202G>A p. (Val68Met) [71,72].

Although the most well-known consequences of G6PD deficiency are hematological (hemolytic anemia, neonatal jaundice), neurological complications can occur, particularly in severe cases or specific contexts.

- Kernicterus (Bilirubin Encephalopathy): This is arguably the most severe neurological complication, primarily seen in newborns with G6PD deficiency. Severe, untreated neonatal jaundice can lead to the accumulation of toxic levels of bilirubin

in the brain, causing irreversible brain damage. Symptoms can include lethargy, poor feeding, fever, high-pitched crying, changes in muscle tone and seizures. This can result in lifelong disabilities.

- Cerebral Oxidative Stress: G6PD is essential for the production of NADPH, a key component of cellular defense against reactive oxygen species (ROS). A G6PD deficiency can lead to increased oxidative stress not only in red blood cells but potentially in other tissues, including the brain. Although less directly studied for the specific c.202G>A p. (Val68Met) mutation, a general G6PD deficiency can impair the ability of brain and nerve cells to fight oxidative stress, potentially contributing to neurodegeneration and affecting neuronal survival.
- Altered G6PD activity in the brain could lead to high oxidative stress, affecting calcium mobilization, neuronal apoptosis, ion transport and excitotoxicity, thus impacting brain homeostasis.

4. *Implications:*

- Since there is a possibility of mild symptoms in female carriers due to X-inactivation, clinical evaluation of the individual is recommended.
- There is a 50% risk for the carrier to transmit this variant to their offspring.

The NPRL2 Gene, NM_006545.5 c171-9 A >G (IVS2-9 A>G) [73-75]

Definition: The NPRL2 gene (for "Nitrogen Permease Regulator-Like 2") is an important gene in the human body.

Physiology

- Function: The NPRL2 gene provides instructions to make a protein that is part of a protein complex called GATOR1.
- GATOR1 Complex: This complex plays a crucial role in regulating a cellular signaling pathway called the mTOR pathway (mammalian Target Of Rapamycin).
- mTOR Pathway Role: The mTOR pathway is fundamental for many cellular processes, including:
  - Cell growth and division
  - Metabolism
  - Protein production
  - Autophagy (the process of recycling cellular components)
  - In the brain, it regulates the development and adaptability (plasticity) of nerve cells.
- GATOR1 Regulation on mTOR: The GATOR1 complex acts as a negative regulator of the mTORC1 pathway (a sub-complex of mTOR), especially when amino acid levels in the cell are low. In other words, it helps to "brake" mTORC1 activity.
- Clinical Implication: Mutations in the NPRL2 gene can lead to a dysfunction of the GATOR1 complex, which causes hyperactivity of the mTOR pathway. This hyperactivity is strongly associated with certain diseases, including:
- Familial Focal Epilepsy with Variable Foci (FFEVF): This is the most known association. Hyperactivation of the mTOR pathway in the brain can cause changes in neuronal connections and increased excitability of these cells, which can trigger seizures.
- Potential role as a tumor suppressor: Studies suggest that NPRL2 may also have a tumor suppressor function and decreased NPRL2 expression has been associated with some cancers.

Meaning of the Variation NM_006545.5 c.171-9 A > G (IVS2-9 A>G): This variation signifies a change from an adenine (A) to a guanine (G) at the 9th nucleotide position upstream of the beginning of exon 2 (or intron 2) of the NPRL2 gene. This type of intronic variation is particularly important because it can affect RNA splicing.

- C.171-9 A > G: This is the standard HGVS (Human Genome Variation Society) nomenclature for describing a variation in the complementary DNA (cDNA), which corresponds to mRNA. The c. indicates cDNA. The 171-9 indicates the position, with -9 meaning the variation is located 9 nucleotides upstream of position 171 within the intron before the exon. A > G indicates the base change.
- IVS2-9 A>G: This is an older, but still commonly used, notation that confirms the location. IVS2 means "Intron 2 Splice site," and -9 confirms the position.
- Consequences of Splicing Variation: A variation in a splicing site can lead to exon skipping, intron retention or the activation of a cryptic splice site. These modifications can alter the protein's sequence, make it non-functional or lead to its premature degradation, which can have pathological consequences.

Underlying Mechanisms of Epilepsy in the Case of an NPRL2 Mutation [76-78]

The NPRL2 gene is a subunit of the GATOR1 protein complex, which is a crucial negative regulator of the mTORC1 signaling pathway.

1. GATOR1 Loss-of-Function and mTORC1 Hyperactivation:

- Pathogenic mutations in NPRL2 (and other GATOR1 complex genes like DEPDC5 and NPRL3) lead to a loss of function of the GATOR1 complex.
- The normal role of GATOR1 is to brake mTORC1 activity.
- When GATOR1 function is lost due to an NPRL2 mutation, this brake is released, leading to abnormal and constitutive hyperactivation of the mTORC1 pathway.
- The c.171-9 A > G splicing variant can disrupt normal mRNA splicing, leading to a truncated, unstable or non-functional NPRL2 protein.

2. Consequences of mTORC1 Hyperactivation in the Brain:

- Focal Cortical Dysplasia (FCD): Although many GATOR1-related epilepsies are non-lesional, FCD (a cortical malformation associated with severe, often drug-resistant epilepsy) has been reported. mTORC1 hyperactivity is known to disrupt neuronal migration, cell proliferation and synapse formation, which can lead to architectural brain abnormalities.
- Neuronal Hyperexcitability and Excitation/Inhibition Imbalance:
- Increased Intrinsic Neuronal Excitability: mTORC1 activation can influence the expression of ion channels, such as voltage-gated sodium channels (e.g., Scn1A), leading to increased strength of neuronal action potentials and hyperexcitability.
- Synaptic Alterations: Hyperactivity can cause aberrant connections between neurons or an imbalance between excitatory and inhibitory signals, promoting seizure propagation.
- GABAergic Network Dysfunction: Studies in animal models show that GATOR1 loss of function can reduce the density of inhibitory GABAergic neurons' dendrites, decreasing inhibition and increasing network excitability.
- Amino Acid Metabolism Abnormalities: mTORC1 is sensitive to amino acids. NPRL2 mutations can alter amino acid homeostasis in the brain. Some recent studies suggest an increase in glycine, a neurotransmitter, which may contribute to synaptic dysfunction and epilepsy.
- Increased Neuronal Size: mTORC1 hyperactivation is associated with increased cell growth, which can manifest as dysmorphic and hypertrophied neurons, typical of "mTORopathies."

Therapeutic Options

Since mTORC1 pathway hyperactivation is the key mechanism of epileptogenesis in GATORopathies, mTOR inhibitors are the most promising therapeutic target.

- Rapamycin (Sirolimus) and its analogs (Everolimus):
  - These are well-known mTOR inhibitors already approved for other "mTORopathies" like Tuberous Sclerosis Complex (TSC), where they have shown a significant reduction in seizure frequency.
  - Mechanism: They bind to the FKBP12 protein and this complex then binds to and inhibits mTORC1 activity.
  - Application in NPRL2-related epilepsy: Preclinical studies on animal models have shown that rapamycin can significantly reduce seizure frequency.
- Gene Therapies and Nucleic Acid-Based Approaches:
  - These are largely in the preclinical research stage but represent the future of precision medicine for genetic epilepsies.
  - Gene Replacement/Correction Therapy: The idea is to introduce a functional copy of the NPRL2 gene or correct the existing mutation to restore normal GATOR1 function.
  - Antisense Oligonucleotides (ASOs): For a splicing variant like c.171-9 A > G, ASO strategies could be used to correct the abnormal splicing. Success has been achieved with other neurological diseases (like spinal muscular atrophy with nusinersen).
- Ketogenic Diet: This high-fat, low-carbohydrate diet is known for its effectiveness in certain drug-resistant epilepsies. It may have a moderating effect on the mTOR pathway, though the exact mechanisms are not fully understood in this specific context.
- Epilepsy Surgery: For patients with identifiable and localized structural brain abnormalities (like FCD), epilepsy surgery can be an option, especially for those refractory to conventional treatments.

Conclusion

Our study of the clinical and genetic aspects of familial epilepsy revealed that:

- The prevalence of familial epilepsy in Lubumbashi is 11.23%
- Generalized tonic-clonic seizures and absence seizures are the most frequent in Lubumbashi, with 70.83% and 8.33% of cases, respectively
- The discovery of other genetic variants/mutations related to epilepsy in Lubumbashi after whole-exome sequencing highlights the difficulties in managing patients with epilepsy
- The genetic variants/mutations found in cases of idiopathic generalized tonic-clonic seizures in Lubumbashi are ATP2B1 and SCN3A, while those associated with absence epileptic seizures are CACNA1I and NPRL2
- These findings should be shared with chemists to open a path for the synthesis of targeted medications

Recommendations

- To patients with epilepsy and their families: Consult with experts for rational management of epilepsy
- To political and administrative authorities: Make epilepsy a public health priority to encourage investment in research and enable the synthesis of medications for targeted epilepsy management

Conflict of Interest

The investigators declare no material or financial conflict of interest related to this study.

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