Genetic and Epigenetic Factors in Adolescent Epilepsy

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Adolescent epilepsy is a complex neurological disorder classified by recurrent seizures that typically manifests between ages 12 and 18. The onset and progression of epilepsy during adolescence takes place during a critical developmental period, which can have significant implications for long-term health. Adolescent epilepsy can manifest as monogenic or polygenic. The role of genetic and epigenetic factors in adolescent epilepsy is underexplored. The most notable epigenetic modification of adolescent epilepsy includes DNA methylation and histone modification, which significantly alter gene expression and pathophysiology. This reflects the critical gap in the current understanding of epilepsy in adolescents. This literature review looks at how genetic and epigenetic factors play a role in epilepsy that begins in adolescence. Genetics refers to inherited traits or changes in DNA, while epigenetics is how the environment affects genes without changing their DNA sequence. This review found that certain gene mutations can cause epilepsy, and environmental factors like stress can trigger epigenetic changes that lead to seizures. The study highlights the need for new, personalized treatments that target these genetic and epigenetic factors. Future therapies could include gene editing or medications that reverse harmful epigenetic changes. These advances offer hope for better ways to treat and manage epilepsy in adolescents.

Introduction

Epilepsy is a neurological disorder that causes repeated seizures due to abnormal electrical signals produced by brain cells[1]. This condition affects approximately 50 million people worldwide, making it one of the most common and disabling neurological disorders[2]. Epilepsy typically affects children and adolescents, with incidence peaking in early childhood and about 25% of newly global diagnosed cases represent adolescence[3]. Both genetic and epigenetic mechanisms play crucial roles in the onset, progression, and variability of seizure disorders in younger population[4].

Considering these influences, a developing brain exhibits heightened excitability, making adolescents particularly vulnerable to epilepsy[5]. This hyperexcitability is attributed to differences in neurotransmitter signaling pathways during developmental stages. This includes the delayed maturation of inhibitory GABAergic circuits relative to excitatory glutamatergic systems. Consequently, seizures at this age may induce structural and functional alterations in the brain that persist throughout adulthood[5].

The International League Against Epilepsy (ILAE) has classified epilepsy as a heterogeneous condition into several subtypes based on seizure type and underlying cause. Epilepsy can manifest shortly after auras, often referred to as simple partial seizures[6]. These seizures can impair brain function, with considerable damage seen in individuals with temporal lobe epilepsy[7]. Temporal lobe epilepsy seizures originate in the temporal lobes of the brain, these areas play a key role in processing emotions and managing short-term memory[8]. Auras are a warning symptom and typically last only a few seconds[9]. Although they are usually distinct from the main phase of the seizure, they can sometimes last longer than usual if they occur independently.

The epileptic duration of auras can be confirmed via testing if an aura evolves into a dialeptic seizure, which predominantly involves reduced responsiveness or awareness, subsequent to at least partial amnesia of the event[9]. It can also be confirmed if it results in a motor seizure, which involves the skeletal musculature resulting in the body to stiffen, jerk, spasm, or shake, or if there is a corresponding electroencephalogram (EEG) seizure pattern[10]. Auras reflect eight subgroups: (a) Somatosensory auras, (b) Visual auras, (c) Auditory auras, (d) Olfactory auras, (e) Gustatory auras, (f) Autonomic auras, (g) Abdominal auras, and (h) Psychic auras. Epilepsy is categorized into four primary types: (a) Left Mesial Temporal Lobe epilepsy, (b) Absence epilepsy, (c) Lennox-Gastaut Syndrome, and (d) Right Frontal epilepsy (see Table 1). Left Mesial Temporal Lobe epilepsy results from left mesial temporal sclerosis, and patients typically experience automotor seizures.

Epilepsy develops at any age, but in adolescence, developmental changes and genetic susceptibility shape the disease progression. Genetic factors are integral for understanding epilepsy. Mutations include changes to in ion channels, neurotransmitter receptors, and genes responsible for synaptic plasticity[11]. In some cases, specific gene mutations may predispose individuals to epileptic syndromes, such as juvenile myoclonic epilepsy, while others contribute to seizure

Table 1. The different types of auras

Aura Type	Description	Epilepsy Type	Occurrence
Visual Aura	Flashes of light, visual distortions, or hallucinations	Occipital Lobe Epilepsy	Common
Auditory Aura	Hearing sounds like ringing, buzzing, or voices	Temporal Lobe Epilepsy	Occasional
Gustatory Aura	Strange tastes (e.g., metallic or bitter)	Temporal Lobe Epilepsy	Less Common
Olfactory Aura	Smelling odors like burning rubber or rotten eggs	Temporal Lobe Epilepsy	Common
Somatosensory Aura	Tingling or numbness in certain body areas	Parietal Lobe Epilepsy	Occasional
Autonomic Aura	Changes in heart rate, sweating, or gastrointestinal discomfort	Temporal and Frontal Lobe Epilepsy	Common
Emotional Aura	Sudden feelings of fear, joy, or déjà vu	Temporal Lobe Epilepsy	Common
Motor Aura	Involuntary muscle jerks or movements	Frontal Lobe Epilepsy	Occasional

severity or drug resistance [12]. Recent advancements in genetic research have identified inherited and de novo(spontaneous) mutations that disrupt neural homeostasis, further highlighting the disease heritability.

Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA also play a crucial role in the pathogenesis of epilepsy. These changes, which do not alter the DNA sequence but influence gene expression, may result from environmental factors like stress, infections, or brain injuries during critical developmental windows [13]. Phosphorylation regulates the location of KCC2, a neuron specific type 2K+–Cl- cotransporter, which is known to cause infantile epilepsy in humans [1]. Such epigenetic dysregulation can affect genes involved in neuronal excitability, synapse formation, and plasticity, contributing to the onset and maintenance of epilepsy [1]. Non-coding RNA, regulates expression at the level of the gene and chromosome to control cell differentiation [14]. Furthermore, research suggests that epigenetic therapies targeting these modifications could open new avenues for treating drug-resistant epilepsy in adolescents.

Currently, diagnosing epilepsy involves multiple steps, including a detailed clinical history, neurological exams, and EEG recordings to capture abnormal brain activity. Brain imaging techniques such as MRI and CT scans help identify structural abnormalities. Genetic testing is becoming increasingly important in cases where epilepsy is suspected to have a genetic basis, particularly in adolescents [15]. Therefore, early identification of at-risk individuals through genetic screening could facilitate personalized interventions, improving clinical outcomes and reducing the long-term impacts of the disorder. With further research, the interplay between genetic predispositions and epigenetic influences may yield innovative strategies for prevention and treatment, addressing the unique challenges of adolescent epilepsy. Research on adolescents, genetics, and epilepsy is underexplored, emphasizing this gap as a motivation for the study. This review aims to provide a concise and pertinent summary of the state of the field to invigorate future developments in the study of adolescent epilepsy. The following research question will undergird and guide this literature review: What role do genetic and epigenetic factors play in the onset and progression of epilepsy during adolescence?

Genetic Mechanisms in Adolescent Epilepsy

Epilepsy is typified by recurrent seizures resulting from aberrant brain electrical activity. Its beginning and progression throughout life are influenced by genetic variables, which also impact childhood development. Considering genetic contributions as the onset of epilepsy, monogenic and polygenic represent two distinct types of adolescent epilepsy [16]. Monogenic epilepsy occurs by a change in a singular gene [17]. It includes both familial forms, where mutations are inherited, and severe forms resulting from de novo mutations, meaning the mutations occur spontaneously and are not inherited. A well-known example of monogenic epilepsy is caused by a mutation in the KCNQ2 gene, which encodes a potassium ion channel that plays a critical role in controlling neuronal excitability [18]. The ion channel on the surface of brain cells serves as a gate that controls the movement of potassium ions. They allow potassium ions to exit when the brain becomes hyperactive. This effectively calms the hyperactive brain cells. When the KCNQ2 gene is mutated, the function of the ion channel is impaired. This prevents proper regulation of brain cell activity and resulting in epileptic seizures. Two types of epilepsy linked to mutations in KCNQ2 result in various conditions, notably Benign Familial Neonatal Convulsions (BFNC) and Dravet Syndrome [7]. BFNC causes seizures in newborns but often goes away as the child grows [19]. In contrast, Dravet Syndrome is a more severe condition that starts in infancy and can lead to developmental delays and learning challenges [20]. While BFNC is often inherited from a parent, Dravet Syndrome is usually caused by a de novo mutation. It is important to note that KCNQ2-related epilepsies are considered monogenic, and the involvement of KCNQ2 in polygenic forms of epilepsy remains speculative. In most cases, genetic testing can identify the mutation responsible for monogenic epilepsy [21]. However, not all monogenic epilepsy is inherited. It could arise from de novo mutations. Treatment for monogenic epilepsy depends on the type, with milder cases like BFNC sometimes requiring little or no medication, while

severe forms like Dravet Syndrome may need a combination of drugs and special care[22]. In contrast, polygenic epilepsies result from mutations in multiple genes[16]. This type of epilepsy is less understood than monogenic epilepsy. This is because the relationship between mutations and the disease is more complicated. Thus, polygenic epilepsy is harder to diagnose and treat because it is not caused by just one gene. Several genetic mutations interact in polygenic epilepsy collectively contributing to the development of epilepsy. One example of polygenic epilepsy is Doose Syndrome. First identified as a distinct epilepsy syndrome in 1970 and later classified as symptomatic generalized epilepsy in 1989[23]. Doose Syndrome is easily observable as this condition includes muscle jerks (called myoclonic seizures) and sudden loss of muscle control (known as atonic seizures). Due to the complexity of polygenic epilepsy, traditional genetic testing may not be adequate for isolating the genetic causes of this form of epilepsy. The multitude of mutations and their interactions make it particularly challenging to identify specific genes responsible for the disorder. However, advances in genetic research like whole-exome sequencing are gradually improving our understanding of these interactions and their role in epilepsy.

Polygenic epilepsy also involves several types of seizures, such as tonic-clonic seizures (involving stiffening and jerking movements) and absence seizures (the individual experiences temporary dissociation). Some complex forms, like Lennox-Gastaut Syndrome, is associated with Tuberous Sclerosis and is characterized by generalized tonic, dialeptic, and astatic seizures[24]. These patients usually need a variety of treatments, including several medications and sometimes special diets like the ketogenic diet. Right frontal polygenic epilepsy is caused by right mesial frontal cortical dysplasia, with patients exhibiting left-arm clonic seizures and generalized tonic-clonic seizures. More importantly, each type of epilepsy has distinct features and requires tailored treatment plans.

Epigenetic Mechanisms in Adolescent Epilepsy

While epilepsy is commonly associated with genetic mutations, recent research also highlights how environmental and cellular factors change gene expression without changing the DNA sequence, called epigenetic mechanisms. Consequently, this plays a role in adolescent epilepsy. Epigenetic factors in epilepsy involve chemical changes like DNA methylation, which can suppress gene expression, and histone modifications that alter DNA accessibility. DNA methylation typically suppresses gene expression, while histone changes (e.g., acetylation or methylation) activate or repress genes[25]. Both mechanisms influence the onset and progression of epilepsy in adolescents by regulating gene expression and responding to environmental factors[26]. Since adolescence is a period of rapid brain development and heightened sensitivity to environmental changes, understanding these mechanisms is crucial for designing personalized treatment strategies[27]. DNA methylation is a primary epigenetic mechanism. It involves adding a methyl group to cytosine residues in DNA, which can change how genes are expressed[28]. While DNA methylation can alter gene expression, it often results in gene silencing, not always suppressing activity. In some contexts, methylation help activate certain genes[29]. Changes in DNA methylation patterns can affect the expression of the genes involved in neuronal function and excitability. Abnormal methylation can lead to the progression and onset of epilepsy by disrupting the balance between excitatory and inhibitory signaling in the brain, contributing to seizures[30]. DNA methylation has been found to increase within gene body regions, and interference with DNA methylation in epilepsy can alter gene expression and lead to epileptogenesis[31]. Histone modification is another important process that modifies DNA accessibility for transcription[32,16]. These chromatin structural alterations promote or inhibit gene expression. While more histone methylation reduces gene expression, higher histone acetylation increases it[33]. Because histone regulatory changes can impact the expression of genes connected to neuronal excitability, they have been associated with epilepsy. Studies on animals have shown that histone modification has provided a link between the changes that are mediated by histone modification and occur after epileptic seizures[34].

Epigenetic alterations impact DNA transcription, which in turn controls the expression of genes[35]. Genes involved in neuronal excitability, synapse function, and neurotransmitter release can have their expression disrupted by aberrant alterations in DNA methylation or histone modifications in epilepsy[36]. This imbalance impacts the development and course of epilepsy. Epigenetic variables, which affect DNA methylation and histone changes, can also be influenced by environmental factors such as stress, exposure to toxins, and food[37]. These alterations may impact gene expression, which may raise the chance of developing epilepsy and accelerate its course.

It is important to note that epigenetic changes, like histone modifications and methylation, can be reversible and influenced by environmental factors such as stress, toxins, or diet[37]. Epilepsy caused by epigenetic factors is dynamic because it stems from biochemical changes that do not affect the DNA sequence. This means the disorder develops over time in response to environmental influences[28]. On the other hand, epilepsy caused by genetic factors is considered static, as the genetic mutations responsible for the condition are typically present from birth, as seen in monogenic epilepsy[29]. The concept of static and dynamic epilepsy reflects how these processes affect the brain's function over time. However, this classification is not yet widely established in scientific literature, and the terms mainly describe the activity states of neurons in response to these mechanisms. In contrast, epigenetic

epilepsy results from chemical changes to DNA and histone modifications that influence gene expression without altering the DNA sequence[28]. Types of epigenetic epilepsy include issues with DNA methylation, histone modifications, gene expression regulation, or environmental factors. All of these have the power to influence the onset and progression of epilepsy by misregulating gene expression as well as responding to environmental factors. These mechanisms include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs[18]. Understanding the genetic and epigenetic foundations is crucial for creating personalized treatment plans, such as gene therapy, gene modification, and identifying biomarkers for early diagnosis and tailored interventions. The potential of these personalized treatment plans offers a hopeful view for the future of epilepsy management. Epigenetic variables that affect epilepsy include histone modifications, chemical alterations to DNA, and responses to environmental stimuli without changing the DNA sequence[28,29]. On the other hand, epilepsy caused by genetic modifications can be either polygenic or monogenic and is prompted by mutations in one or more genes[16]. Overall, epigenetic changes, such as DNA methylation and histone modification, play a major role in the onset and progression of epilepsy in adolescents by regulating gene expression and responses to environmental stimuli. Understanding these epigenetic mechanisms can provide valuable insights for developing customized epilepsy treatment plans.

Therapeutic Implications of Personalized Medicine in Adolescent epilepsy

In adolescent epilepsy, inherited genetic variants and epigenetic factors contribute significantly to disease susceptibility and progression. Genetic mutations in specific genes, such as SCN1A, SCN2A, and GABRG2, have been identified as increasing epilepsy susceptibility in adolescents[38]. Epigenetic changes, particularly in DNA methylation patterns, also play a crucial role as they impact gene expression related to neuronal signaling and inflammation. For instance, changes in the methylation of the MGMT gene are often observed in adolescents with epilepsy, highlighting the significant role methylation plays in the onset and progression of the disorder. Similarly, histone modifications such as DNA methylation and acetylation affect the chromatin structure, thereby influencing gene expression. Large-scale genome-wide association studies (GWAS) have already provided significant insights into the genetic underpinnings of epilepsy, identifying loci associated with generalized epilepsies, such as SCN1A and GABRA2, which are involved in ion channel function and neurotransmitter signaling[39]. Respectively, next-generation sequencing (NGS) has further advanced our understanding by enabling the identification of rare, de novo variants in genes such as DEPDC5 and CHRNA4, implicated in focal and generalized epilepsy syndromes[40]. Combining GWAS and NGS has also facilitated the discovery of polygenic risk scores (PRS), which predict seizure susceptibility and pharmacoresistance, offering a potential tool for personalized treatment strategies[41]. Moreover, integrative analyses leveraging next-generation sequencing (NGS) data have highlighted novel candidate genes such as PRRT2 and its role in synaptic vesicle cycling, which are critical for understanding epilepsy's cellular mechanisms[42]. GWAS meta-analyses have also expanded the catalog of epilepsy-associated genetic variants by incorporating data from diverse populations, addressing gaps in the representation of non-European ancestries[43]. These approaches are proving instrumental in identifying epigenetic modifications associated with epilepsy, as NGS-based methylation sequencing uncovers differential patterns in regulatory regions of the genome linked to seizure progression[44]. Together, these examples underscore the transformative potential of GWAS and NGS in elucidating the complex genetic architecture of epilepsy, paving the way for more effective and individualized therapeutic interventions.

Research into novel therapies, including CRISPR-Cas9, offers promise but requires thorough analysis of documented studies, especially in animal models and in vitro experiments, to evaluate its effectiveness and safety for epilepsy treatment. CRISPR-Cas9 is a powerful gene-editing technology that enables precise modifications to DNA, which could potentially correct genetic mutations associated with epilepsy. For instance, studies using animal models have shown CRISPR-Cas9's ability to reduce hyperactive neuronal activity[45]. Similarly, in vitro experiments demonstrate its potential for targeting and editing specific mutations linked to seizure disorders[46]. However, challenges like off-target effects, limited efficiency of traditional Cas9 proteins, and ethical concerns remain significant barriers[47]. New developments, such as base editors and prime editors, have been introduced to enhance precision and reduce unintended effects[48]. Thorough analysis of these studies helps ensure CRISPR-Cas9 can progress safely toward clinical applications for epilepsy. Histone deacetylase inhibitors (HDACi) have shown their potential as therapeutic tools by reversing abnormal gene expression patterns[16]. These inhibitors are particularly relevant to Temporal Lobe Epilepsy (TLE), a common but difficult-to-treat disorder. More research on differing therapeutic outcomes and potential side effects is needed to justify personalized strategies. Temporal Lobe epilepsy (TLE) is characterized by significant changes in gene expression that affect neurotransmitter signaling, ion channels, or synaptic structure[25]. Although HDACi has shown promise, it is important to identify therapies beyond pharmacological options to meet the varied needs of patients.

MiRNA is involved in the regulation of neuroplasticity, the organization of the cytoskeleton, and neuronal death,

which if malfunctioning can lead to temporal lobe epilepsy[49]. MicroRNAs (miRNAs) have also been identified as critical regulatory mechanisms in TLE[50]. Research indicates there are altered miRNA levels in the hippocampus of patients with TLE[51]. For instance, silencing of miRNA 134 with antisense oligonucleotides exhibits strong anti-seizure effects, while miRNA 128 is lethal[52]. These changes observed in the blood post-seizure suggest their potential as biomarkers. Researchers have identified nine new miRNAs that influence seizures, target transcription factors, neurotransmitter components, and neuroinflammation modulators in the past two years. Despite these advancements, challenges remain in replicating findings, isolating specific cell types and targets, and safely delivering miRNA-based treatments to the brain.

Non-pharmacological treatments, such as lifestyle changes and behavioral therapies, may also play supportive roles in managing epilepsy symptoms, although they are typically not replacements for pharmacological interventions[53]. More emphasis on these therapies is needed to give a fuller view of comprehensive, patient-centered care.

Therefore, a deeper understanding of genetic mutations, such as SCN1A, SCN2A, and GABRG2[54]. Along with epigenetic changes, such as MGMT methylation, it supports the development of personalized approaches to adolescent epilepsy treatment. As research advances, pharmacological and non-pharmacological therapies must be tailored to individual patient profiles to optimize outcomes and address the full spectrum of therapy-related risks and benefits.

Methods

A literature review was done by looking up relevant articles on PubMed and Google Scholar. These scholarly resources were chosen because they contain many reliable studies, like reviews, clinical trials, and peer-reviewed papers. The search used keywords such as "genetics,""epigenetics,"and "epilepsy."The selection process was thorough. First, only articles written in English were included. Next, the articles were picked if they directly related to the main focus of this study. The most important studies, like clinical trials, meta-analyses, and extensive literature, were prioritized because they provide stronger evidence. To find the best articles, their abstracts were read first. If an abstract showed that the article was highly related to this study, the entire article was reviewed. Multiple databases and many keywords were used to make sure the research covered a wide range of ideas and did not miss anything important.

The quality of the articles was also carefully checked. The studies were reviewed to ensure they had reliable data, clear methods, and strong connections to the topic of how genetics and epigenetics affect epilepsy, especially in teenagers. To make the information easier to understand, key details from the articles, like their main findings and how they studied epilepsy, were organized (as seen in Table 2). This helped summarize the important points without repeating all the references.

Results

This literature review found a major gap in epilepsy research is the precise identification of the disorder's genetic underpinnings. While genes like SCN1A and KCNQ2 have been implicated in specific epilepsy syndromes, much of the broader genetic landscape remains unexplored. Future studies should employ large-scale GWAS and NGS techniques to uncover novel genetic variants associated with epilepsy. Understanding these genetic factors will be crucial for developing targeted therapies.

The review highlights that both genetic and epigenetic factors play a significant role in the onset and progression of adolescent epilepsy. Genetic influences include monogenic mutations, such as those in the KCNQ2 gene, which cause conditions like Benign Familial Neonatal Convulsions (BFNC) and Dravet Syndrome, and polygenic mutations that contribute to more complex forms of epilepsy, like Doose Syndrome. These genetic factors alter ion channels, neurotransmitter systems, and synaptic plasticity, influencing seizure activity and treatment responsiveness. Epigenetic mechanisms, including DNA methylation and histone modifications, regulate gene expression without altering the DNA sequence. These modifications affect neuronal excitability and synapse formation and are influenced by environmental factors such as stress and diet. For example, DNA methylation can silence or activate genes, while histone changes can either promote or inhibit gene transcription. Both processes contribute to the development and maintenance of epilepsy by disrupting the balance between excitatory and inhibitory signaling in the brain.

The findings emphasize the importance of personalized medicine in treating epilepsy. Emerging therapies, such as CRISPR-Cas9 and histone deacetylase inhibitors (HDACi), show promise for targeting genetic and epigenetic factors. Non-pharmacological approaches, including behavioral therapies and lifestyle changes, also hold potential as supportive treatments. MicroRNAs, identified as critical regulators in epilepsy, offer exciting opportunities for biomarker discovery and new treatment strategies. Overall, this review underscores the need for a deeper understanding of the interplay between genetic predispositions and epigenetic influences to improve diagnosis and develop tailored interventions for adolescents with epilepsy.

Discussion

This study aimed to explore the genetic and epigenetic factors contributing to the onset and progression of epilepsy, focusing on adolescence. While significant insights have been gained, several limitations should be acknowledged as the field is

Table 2. Literature Review Table of Sources

Authors	Year	Title	Key Findings	Advancements in Epilepsy Comprehension
Dingledine, R., Varvel, N.H., & Dudek, F.E.	2014	When and how do seizures kill neurons, and is cell death relevant to epileptogenesis?	Tells us how seizures can cause neuron death, exploring significance in the development of epilepsy.	It sheds light on how protecting neurons might reduce epilepsy development.
Stafstrom, C.E., & Carmant, L.	2015	Seizures and epilepsy: An overview for neuroscientists	It breaks down different seizure types, epilepsy syndromes, and the biological mechanisms behind them.	Offers a well-rounded foundation for scientists entering epilepsy research.
Aaberg, K.M., et al.	2017	Incidence and prevalence of childhood epilepsy: A nationwide cohort study	The study identifies trends in childhood epilepsy, noting key demographics, and clinical factors.	It lays groundwork for early detection and tailored healthcare policies.
Sarkisova, K., & van Luijtelaar, G.	2022	The impact of early-life environment on absence epilepsy and neuropsychiatric comorbidities	It links environmental factors during early development to the onset of absence epilepsy and related mental health challenges, taking note of the critical role of childhood experiences.	Highlights environmental contributions to epilepsy and comorbidities.
Holmes, G.L., & Ben-Ari, Y.	2001	The neurobiology and consequences of epilepsy in the developing brain	This study explores how seizures affect a young brain's growth and development. It points out that epilepsy in children can disrupt their cognitive and brain development, potentially leading to long-term challenges.	It provides valuable insights into how to protect a child's developing brain from the harmful effects of seizures.
Hughes, J., et al.	1993	Premonitory symptoms in epilepsy	By investigating the warning signs that happen before seizures, this study shows how these symptoms can help predict seizures. This knowledge could give patients and caregivers time to prepare.	Offers practical tools for better seizure management and preparedness.
Wang, Y., et al.	2022	Animal models of epilepsy: A phenotype-oriented review	This research reviews how animal models are used to study epilepsy and test treatments. It emphasizes how these models make it easier to connect lab findings to real-world treatments.	Improves how we translate scientific discoveries into patient care.
Mayo Clinic	2023	Temporal Lobe Seizure	This resource provides a clear explanation of temporal lobe epilepsy, including its symptoms, possible causes, and treatments. It focuses on practical, easy-to-understand information for patients and families.	Makes epilepsy knowledge accessible and actionable for everyone.
Lüders, H., et al.	1998	Semiological seizure classification	This study organizes seizures based on their outward symptoms, making it easier for doctors to diagnose and treat epilepsy.	Helps improve the accuracy of epilepsy diagnoses and personalized treatment plans.
Cedars Sini		Motor Seizures	This article explains the unique features of motor seizures, helping doctors better understand and manage this type of epilepsy.	Provides detailed guidance on treating motor seizures effectively.

Oyrer, J., et al.	2017	Ion channels in genetic epilepsy: From genes and mechanisms to disease-targeted therapies	This research explores how tiny pathways called ion channels in brain cells can cause epilepsy. It also looks at how targeting these channels could lead to new treatments.	Connects cutting-edge science to the development of better therapies.
Borowicz-Reutt, K., et al.	2023	Genetic background of epilepsy and antiepileptic treatments	This study highlights how genetics influence epilepsy and how personalized medicine could create more effective treatments tailored to individual patients.	Brings us closer to custom-made treatments that suit each patient's unique genetic makeup.
Bale, T.L.	2015	Epigenetic and transgenerational reprogramming of brain development	This research shows how changes in gene expression caused by environment or experience can influence brain development, not just for one individual but for future generations.	Sheds light on how epilepsy risk might be passed down through families and influenced by lifestyle.
Moore, Y.E., et al.	2017	Seizing Control of KCC2: A New Therapeutic Target for Epilepsy	This study identifies KCC2, a protein that helps balance brain cell activity, as a promising target for new epilepsy treatments.	Suggests new ways to develop treatments that address the root causes of epilepsy.
Morrell, M.J.	2002	Stigma and epilepsy	This study discusses how epilepsy is often misunderstood, leading to stigma that affects patients' quality of life. Education and awareness campaigns are critical to reduce this stigma.	Highlights the importance of social understanding and support systems for epilepsy patients.
Löscher, W., & Schmidt, D.	2011	Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma	This article critiques the lack of significant progress in antiepileptic drug development and calls for innovative approaches to address treatment-resistant epilepsy.	Emphasizes the need for new research directions to improve patient outcomes.
Berg, A.T., et al.	2010	Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology	This report introduces updated terms and classifications for seizures, aimed at improving diagnosis and communication among medical professionals.	Simplifies and standardizes epilepsy language, making care more consistent worldwide.
Perucca, E., et al.	2007	Trends in antiepileptic drug discovery	This study reviews the progress and challenges in developing new drugs for epilepsy, highlighting both successes and areas that still need improvement.	Offers insights into the evolution of epilepsy treatments and future possibilities.
Sillanpää, M., et al.	2011	Long-term mortality of childhood-onset epilepsy	This research tracks the long-term outcomes of people diagnosed with epilepsy in childhood, finding increased risks but also identifying factors that improve survival rates.	Provides valuable data for improving the care and prognosis of children with epilepsy.
Löscher, W.	2017	Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs	Explores how animal models help researchers test potential new drugs and treatments that could prevent epilepsy or slow its progression.	Strengthens the connection between experimental research and real-world treatments.

French, J.A., et al.	2006	Treatment of refractory epilepsy: Clinical evidence and guidelines	This study compiles evidence on how to manage epilepsy that doesn't respond to standard treatments, offering practical guidelines for doctors.	Improves care for patients with treatment-resistant epilepsy.
Beghi, E., et al.	2005	The epidemiology of epilepsy in Europe: A systematic review	Provides detailed statistics on epilepsy rates across Europe, identifying patterns that could guide public health policies.	Supplies critical data for addressing epilepsy on a population level.
Engel, J. Jr.	2013	Seizures and Epilepsy	This textbook-style overview explains the basics of seizures and epilepsy, making it an essential resource for students and professionals.	Serves as a foundational guide for understanding epilepsy.
Fisher, R.S., et al.	2014	A practical clinical definition of epilepsy	This paper proposes a simple definition of epilepsy to help both doctors and patients identify and understand the condition.	Makes epilepsy diagnoses more straightforward and accessible.
Hitiris, N., et al.	2007	Predictors of pharmacoresistant epilepsy	Identifies factors that might make epilepsy less likely to respond to drugs, helping doctors predict treatment outcomes.	Guides more personalized and effective treatment plans.
Goldenberg, M.M.	2010	Overview of drugs used for epilepsy and seizures: Etiology, diagnosis, and treatment	It reviews the range of medications available for epilepsy, explaining how they work and when they're used.	Offers a comprehensive look at medication options for treating epilepsy.
Devinsky, O., et al.	2018	Cannabidiol: Pharmacology and therapeutic targets	Focuses on how cannabidiol (CBD) can be used to treat epilepsy, particularly in cases where other drugs fail.	Introduces promising alternative treatments for epilepsy.
Mathern, G.W., et al.	2014	Epilepsy Surgery	Explores how surgical procedures can help patients with epilepsy, especially those who don't respond to medication.	Demonstrates how surgery can provide life-changing results for certain patients.
Löscher, W., et al.	2020	Strategies for improving patient outcomes in epilepsy	Looks at various ways to enhance the quality of life for epilepsy patients, from better treatments to improved healthcare systems.	Emphasizes a holistic approach to managing epilepsy.
Tooley, U. A., Bassett, D. S., & Mackey, A. P.	2021	Environmental influences on the pace of brain development	This study highlights how environmental factors, such as socioeconomic status and early-life experiences, impact brain development.	Provides insights into how early environmental influences may contribute to the risk or progression of epilepsy.
Santos, B. P., et al.	2017	Genetic susceptibility in juvenile myoclonic epilepsy: Systematic review of Genetic Association Studies	A review of genetic studies reveals specific genes associated with juvenile myoclonic epilepsy, offering a better understanding of its heritability.	Advances knowledge about genetic risk factors and supports personalized approaches to treatment.
Citraro, R., et al.	2018	Role of histone deacetylases (HDACs) in epilepsy and epileptogenesis	Explores how HDACs, which modify gene activity, play a role in the development of epilepsy and its symptoms.	Suggests targeting HDACs as a potential treatment strategy.

Dhar, G. A., et al.	2021	DNA methylation and regulation of gene expression: Guardian of our health	Examines how DNA methylation, a process that controls gene activity, influences overall health and disease, including epilepsy.	Highlights the role of gene regulation in managing epilepsy.
Qureshi, I. A., & Mehler, M. F.	2010	Epigenetic mechanisms underlying human epileptic disorders and the process of epileptogenesis	Focuses on how epigenetic changes, like DNA methylation, contribute to epilepsy development.	Connects epigenetic science to new therapeutic possibilities.
Henshall, D. C., & Kobow, K.	2015	Epigenetics and Epilepsy	Explains how changes in gene activity without altering DNA itself contribute to epilepsy and its progression.	Emphasizes epigenetics as a key area for treatment innovations.
Lee, H.-T., et al.	2010	The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis	Though focused on atherosclerosis, this study provides insights into DNA and histone modifications relevant to epilepsy research.	Bridges knowledge across diseases to better understand epilepsy mechanisms.
Pulido Fontes, L., et al.	2015	Epigenetics and epilepsy	Reviews how epigenetic changes influence the risk and treatment of epilepsy.	Reinforces the role of gene regulation in future therapies.
Aboud, N. M. A.	2023	Genetics, epigenetic mechanism	Offers a detailed look at how genetic and epigenetic mechanisms interplay in disease development, including epilepsy.	Strengthens the foundation for genetic and epigenetic research.
Hwang, J.-Y., et al.	2012	Epigenetic Mechanisms in Stroke and Epilepsy	Highlights shared epigenetic mechanisms in stroke and epilepsy, opening doors for collaborative research and treatments.	Suggests cross-condition therapies targeting epigenetic changes.
Marsit, C. J.	2015	Influence of environmental exposure on human epigenetic regulation	Investigates how environmental factors alter gene regulation, impacting health and disease.	Links environmental risks to epilepsy through epigenetic pathways.
Roopra, A., et al.	2012	Epigenetics and epilepsy	Discusses how changes in the way genes are expressed can cause or worsen epilepsy.	Provides a roadmap for future research and targeted therapies.
Henshall, D., et al.	2016	MicroRNAs in epilepsy: Pathophysiology and clinical utility	Reviews how small molecules called microRNAs influence epilepsy and its treatment.	Points to microRNAs as potential diagnostic and therapeutic tools.
Krygier, M., et al.	2024	Next-generation sequencing testing in children with epilepsy	Shows how advanced genetic tests uncover new treatment possibilities for children with epilepsy.	Enhances precision in pediatric epilepsy diagnosis and care.
Genome-wide Mega-analysis	2018	Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies	Identifies genetic regions linked to epilepsy, offering clues to its biological causes.	Advances the understanding of epilepsy genetics and opens new avenues for treatment.
Buono, R. J.	2013	Genome-wide association studies (GWAS) and common forms of human epilepsy	Highlights GWAS as a vital tool for identifying genetic variants linked to common epilepsy types, emphasizing its potential for understanding genetic underpinnings.	Provides a framework for exploring the genetic architecture of epilepsy and identifying targets for therapeutic interventions.
Mei, D., Parrini, E., Marini, C., & Guerrini, R.	2017	The Impact of Next-Generation Sequencing on the Diagnosis and Treatment of Epilepsy in Pediatric Patients	Explores how next-generation sequencing (NGS) has transformed epilepsy diagnosis, enabling precise identification of genetic mutations in pediatric cases.	Demonstrates the clinical utility of NGS for personalized medicine in epilepsy management.

Habela, C. W., Schatz, K., & Kelley, S. A	2024	Genetic Testing in Epilepsy: Improving Outcomes and Informing Gaps in Research	Analyzes how genetic testing enhances diagnostic accuracy and informs treatment, while identifying knowledge gaps in epilepsy genetics.	Offers insights into bridging research gaps through advanced genetic testing technologies.
Dunn, P., et al.	2018	Next Generation Sequencing Methods for Diagnosis of Epilepsy Syndromes	Highlights NGS methods as critical for diagnosing rare and complex epilepsy syndromes, improving patient outcomes.	Positions NGS as a cornerstone for precision diagnosis and therapy in epilepsy.
Guan, Q., et al.	2024	CRISPR/Cas9-Mediated Neuronal Deletion of 5-Lipoxygenase Alleviates Deficits in Mouse Models of Epilepsy	Demonstrates that CRISPR/Cas9 technology effectively reduces epileptic deficits in mouse models by targeting specific genes.	Confirms the therapeutic potential of gene editing for treating epilepsy.
Barazesh, M., et al.	2021	CRISPR/Cas9 Technology as a Modern Genetic Manipulation Tool for Recapitulating Neurodegenerative Disorders in Large Animal Models	Discusses using CRISPR/Cas9 in large animal models to replicate neurological disorders, including epilepsy, for translational research.	Strengthens the role of CRISPR in modeling epilepsy for preclinical studies.
Wagnon, J. L.	2020	Promoting CRISPRa for Targeted Treatment of Epilepsy	Proposes CRISPRa (gene activation) as an innovative approach for treating genetic epilepsies by upregulating beneficial genes.	Suggests gene activation as a complementary strategy to traditional therapeutic approaches.
Carpenter, J. C., & Lignani, G.	2021	Gene Editing and Modulation: The Holy Grail for the Genetic Epilepsies?	Reviews advancements in gene editing, including CRISPR/Cas9, for epilepsy, addressing both therapeutic potential and challenges.	Frames gene editing as a transformative approach for managing genetic epilepsies.
Modell, A. E., et al.	2022	CRISPR-Based Therapeutics: Current Challenges and Future Applications	Examines the challenges and opportunities of CRISPR-based treatments, including applications in neurological disorders like epilepsy.	Highlights the need to refine CRISPR technologies for broader clinical application in epilepsy.
Lanza, M., et al.	2023	The Role of miR-128 in Neurodegenerative Diseases	Explores miR-128's role in neurological conditions, suggesting its relevance as a therapeutic target for epilepsy.	Identifies miR-128 as a potential biomarker and target for novel epilepsy treatments.
Ha, T.-Y.	2011	The Role of MicroRNAs in Regulatory T Cells and in the Immune Response	Investigates how microRNAs regulate immune responses, with implications for epilepsy via inflammatory pathways.	Connects immune regulation and microRNA activity to epilepsy pathogenesis.
Korotkov, A., et al.	2017	Systematic Review and Meta-Analysis of Differentially Expressed miRNAs in Experimental and Human Temporal Lobe Epilepsy	Identifies specific microRNAs linked to temporal lobe epilepsy, providing targets for therapeutic intervention.	Supports using microRNAs for diagnostic and therapeutic applications in epilepsy.
Morris, G., Reschke, C. R., & Henshall, D. C.	2019	Targeting microRNA-134 for Seizure Control and Disease Modification in Epilepsy	Demonstrates that silencing microRNA-134 reduces seizures and alters disease progression in epilepsy models.	Establishes microRNA-134 as a critical therapeutic target for epilepsy.
Alqahtani, F., et al.	2020	Non-Pharmacological Interventions for Intractable Epilepsy	Reviews non-pharmacological therapies such as neurostimulation and dietary modifications for epilepsy resistant to standard treatments.	Highlights the importance of alternative strategies for managing intractable epilepsy.

unstudied, and the findings should be interpreted cautiously. One of the main disadvantages of this study is the potential bias caused by its exclusive use of English-language literature. The focus on English-language studies might have excluded important research from non-English-speaking regions, limiting the global perspective. As a result, relevant studies, particularly those from regions with distinct genetic populations, that were written in other languages were overlooked. As a result, the results could not fairly represent the global variation in genetic and epigenetic factors linked to epilepsy. Future studies should include a greater diversity of studies to strengthen the generalizability of the conclusions.

As the field of epilepsy research advances, much is still unknown. Neither this paper nor other research papers have definitively found the actual cause of epilepsy, whether genetic or epigenetic. Despite the progress highlighted in this review, gaps in our understanding of epilepsy remain significant. Current knowledge does not fully explain how genetic and epigenetic factors interact with developmental changes during adolescence. While some reviewed studies offer valuable insights, they also have limitations, such as small sample sizes or lack of diversity in study populations. Addressing these gaps will require larger, more inclusive studies and improved methods for linking genetic findings to clinical outcomes.

One of the primary challenges in epilepsy research is the precise identification of genetic underpinnings. Although this work highlights genes like SCN1A, SCN2A, and GABRG2, the entire genetic landscape of epilepsy is still not well understood. Large-scale GWAS and NGS are required because of the complexity of genetic relationships and the potential impact of epigenetic modifications to gain a deeper understanding of epilepsy's genetic architecture. It is critical to realize that proposed therapeutic strategies like CRISPR-Cas9 gene editing and DNA splicing are still theoretical at this stage. These tactics are promising, but before they can be considered as practical therapy options, they must still get beyond many significant logistical, ethical, and technical challenges.

From a research perspective, this review highlights the importance of using advanced tools, like large-scale genetic studies, to uncover more about genetic and epigenetic causes. Scientists could also explore new treatments, like editing genes or targeting epigenetic pathways, though these methods are still far from being ready for use. More inclusive studies with diverse participants would help ensure the findings apply to people worldwide. As a result, this review opens doors to more effective treatments, deeper scientific understanding, and improved policies. However, it underscores the need for continued work in these areas to fully realize these opportunities.

The variety of epilepsy, particularly in its genetic and epigenetic manifestations, indicates that a one-size-fits-all strategy for therapy is insufficient. Another key area for research is the development of more personalized treatment plans. With its ability to tailor treatment regimens according to a patient's genetic composition, epigenetic profile, and clinical traits, personalized medicine has much potential. While ketogenic diets have been proven effective, their effectiveness level varies. This is why personally tailored treatment plans are better suited for recovery and as a cure for epilepsy. Through this, more research could lead to nonpharmacological treatments other than drugs, which are not suited for everyone. The success of ketogenic diets, for instance, has been shown to vary, which emphasizes the necessity for dietary therapies that are specifically customized based on each patient's individual genetic and metabolic profile. Subsequent investigations should integrate genetic and epigenetic information with clinical results to build customized therapy plans encompassing pharmacogenomics, dietary alterations, and lifestyle improvements. This integration should be facilitated by interdisciplinary collaboration among medical researchers, geneticists, neurologists, and pharmaceutical professionals, as each field brings unique insights and expertise. Even though pharmaceutical therapies are still the gold standard, not all patients will benefit from them, particularly if they have drug-resistant epilepsy or have experienced medication side effects. A potential field of research is investigating non-pharmacological treatments that target particular genetic or epigenetic pathways. For example, a better knowledge of the roles of DNA methylation and histone modification in epilepsy may result in novel treatments targeted at reversing these epigenetic modifications. As for epigenetic causes, more research could be done to find the specific mechanisms of how histone modification and DNA methylation work. This could be used to reverse the effects by repeating the process in reverse to theoretically undo the disorder. It may be possible to improve and customize methods like DNA methylation inhibitors and histone deacetylase inhibitors (HDACi) to restore normal gene expression patterns and neural function.

Another crucial objective is to conduct additional research on the role of histone modification and DNA methylation in the onset and progression of epilepsy. With advancements in gene-editing technologies like CRISPR-Cas9, there is potential to target and correct the genetic mutations that cause epilepsy directly. After specific epilepsy genes have been found, genetic sequences can be changed or replaced using gene splicing procedures. This strategy might lead to the development of therapeutic rather than symptomatic medications, providing a long-term remedy for people with genetically driven epilepsy. The main goals of research should be to assess the viability, safety, and ethical implications of these interventions, as well as any possible side effects and long-term effects of brain gene editing. Future studies should concentrate on developing tests to investigate how various genetic variations interact and influence epilepsy. One way to do this could be to create cell cultures or animal models that exhibit different combinations of genetic alterations present in epileptic individuals. Furthermore,

studies should investigate the therapeutic potential of gene-editing technologies in preclinical animals. To start, fix known mutations that cause epilepsy using CRISPR-Cas9, and evaluate the safety and efficacy of this approach. It is important to note that gene-editing technologies come with potential risks and ethical considerations, which should be thoroughly evaluated and addressed in future research. Moreover, investigating how environmental factors interact with genetic and epigenetic predispositions to influence the onset of epilepsy could provide insights into preventive measures and the development of interventions that mitigate the impact of environmental triggers. For instance, research could explore how environmental factors such as stress or diet influence these epigenetic changes, potentially leading to preventive strategies. If we could figure out how the amount of stress can cause an onset of epilepsy, new measures could be taken in place to hopefully prevent it in the future.

This study's literature analysis emphasizes the critical roles that histone modification and DNA methylation play in controlling the expression of genes linked to neuronal function and epilepsy. Future research should focus on identifying histone deacetylase inhibitors (HDACi) as possible medicinal medicines. This work is urgent and significant, as it could lead to breakthroughs in understanding and treating this complex condition. Nevertheless, there is still a long way to go before these discoveries are applied in a clinical setting, and further research is required to determine the safety and long-term implications of focusing on epigenetic pathways in the treatment of epilepsy.

The findings of this review highlight potential pathways for developing targeted treatments for adolescent epilepsy. Clinically, these insights could improve the personalization of care, offering treatments tailored to a patient's genetic and epigenetic profile. These findings could help doctors give better care to adolescents with epilepsy. By understanding the genetic and epigenetic factors involved, doctors might one day offer treatments that are more personalized, matching a patient's unique genetic makeup. For example, knowing which genes are linked to epilepsy might allow for earlier and more accurate diagnoses, leading to quicker treatment and possibly fewer seizures. This could mean better lives for adolescents with epilepsy and their families.

Additionally, these findings should inform healthcare policies by emphasizing the importance of funding for genetic testing and epigenetic research. The findings suggest that healthcare policies should prioritize funding for genetic and epigenetic research. For example, supporting programs that help families access genetic testing could lead to earlier diagnoses and interventions. Policies could also encourage investment in advanced treatments, such as drugs targeting epigenetic factors. Lastly, funding education and awareness campaigns could improve understanding of epilepsy and reduce stigma, helping adolescents with epilepsy feel supported and included in their communities.

Another restriction is the recentness and dependability of the sources employed in this investigation. It was challenging to critically evaluate the caliber and applicability of the evaluated papers' strong experience in epilepsy research. The accuracy and application of the conclusions may be impacted by outdated references, especially considering how quickly genetic and epigenetic research is progressing.

Conclusion

It is critical to understand that epilepsy is a complicated illness impacted by a variety of environmental, behavioral, genetic, and epigenetic variables. Although the focus of this study was on the genetic and epigenetic components, additional research is necessary to fully understand the equally important roles played by environmental variables and comorbidities. The results of this study may not be entirely applicable to other age groups or forms of epilepsy because it focused only on adolescence, a pivotal time for the emergence of epilepsy.

Finally, although this work provides valuable information on the prospect of tailored treatment regimens based on genetic and epigenetic profiles, it is important to recognize that these tactics remain speculative. A great deal of validation through clinical trials and careful ethical considerations will be required to produce such customized medicines. The importance of knowing the genetic and epigenetic components of epilepsy and the need for continued research to deepen our understanding of this complex disorder is emphasized in this literature review's conclusion. While the findings offer valuable insights into the genetic and epigenetic components of epilepsy, the research is still in its early stages. There is still much to learn, and more research is necessary to comprehend the complexities of epilepsy and develop customized efficient treatments for adolescent patients. For example, scientists are unable to pinpoint an exact cause for epilepsy but have a general idea of potential causes that work together to cause the onset of epilepsy.

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