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Genetics of Cognition in Epilepsy

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Definitions

1000 Genomes Project - a collaboration among research groups in the US, UK, and China and Germany to produce an extensive catalog of human genetic variation that will support future medical research studies. It will extend the data from the International HapMap Project, which created a resource that has been used to find more than 100 regions of the genome that are associated with common human diseases such as coronary artery disease and diabetes. The goal of the 1000 Genomes Project is to provide a resource of almost all variants, including SNPs and structural variants, and their haplotype contexts. This resource allows genome-wide association studies to focus on almost all variants that exist in regions found to be associated with disease. The genomes of over 1000 unidentified individuals from around the world has been sequenced using next generation sequencing technologies. The results of the study will be publicly accessible to researchers worldwide [1, 2]

aneuploidy – an abnormal chromosome complement resulting from either the absence of a chromosome(s) or the presence of an additional chromosome(s)[3]

ENCODE - the National Human Genome Research Institute (NHGRI) launched a public research consortium named ENCODE, the **Encyclopedia Of DNA Elements**, in September 2003, to carry out a project to identify all functional elements in the human genome sequence [4, 5]

endophenotype – measurable components unseen by the unaided eye along the pathway between disease and distal phenotype– may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature. Endophenotypes represent simpler clues to genetic underpinnings than the disease syndrome itself[6]

epigenetics – versatile activity states of a gene, whereby a set of chromatin-modifying actions leads to a change in genetic activity, without affecting DNA sequence itself (e.g., DNA methylation, posttranslational histone modifications, non-coding RNAs)[7]. For information on how the definition of epigenetics has evolved over time, see [8].

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Definitions

epistasis - a circumstance where the expression of one gene is affected by the expression of one or more independently inherited genes*

genome wide association study - a genome-wide association study is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations are identified, researchers can use the information to develop better strategies to detect, treat and prevent the disease. Such studies are particularly useful in finding genetic variations that contribute to common, complex diseases, such as asthma, cancer, diabetes, heart disease and mental illnesses*

HapMap (short for “haplotype map”) - the nickname of the International HapMap Project, an international project that seeks to relate variations in human DNA sequences with genes associated with health. A haplotype is a set of DNA variations, or polymorphisms, that tend to be inherited together. A haplotype can refer to a combination of alleles or to a set of single nucleotide polymorphisms (SNPs) found on the same chromosome. The HapMap describes common patterns of genetic variation among people* [9, 10]

heritability (h^2) – the proportion of the total variance of a quantitative trait that is attributed to genetic factors[3]

phenotype - an individual’s observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors

single nucleotide polymorphisms (SNPs) - a type of polymorphism involving variation of a single base pair. Scientists are studying how single nucleotide polymorphisms, or SNPs (pronounced “snips”), in the human genome correlate with disease, drug response, and other phenotypes*

* Courtesy: National Human Genome Research Institute: Talking Glossary of Genetic Terms; Note: Most definitions provided here are taken verbatim from the cited sources

Introduction

With the completion of the Human Genome Project and the advent of more advanced sequencing platforms capable of high throughput genotyping at reduced cost, research on the genetics/genomics of cognition has expanded rapidly over the past several decades. This has been facilitated even further by global consortia including *HapMap*, *1000 Genomes Project*, *ENCODE*, and others, which have made information regarding genetic variation and genomic functional elements readily available to all researchers. Thus, the goal of this Targeted Review is not to provide an exhaustive review of the existing literature on the role of genetic factors in cognition. Rather, we will highlight some of the most consistent findings in this field, review the research in epilepsy to date, and provide a background within which to set forth unique opportunities epilepsy may provide to further elucidate the role of genetics in cognition.

What evidence is there to suggest that genetics plays a role in general cognitive ability?

The genetic basis of intelligence has been contemplated at least as far back as the 19th century[11]. The vast majority of studies on this topic, which predated molecular genetics, focused on examining the similarities in general cognitive ability between closely related individuals. Meta-analytic research using data obtained from family, adoption, and twin studies suggested the *heritability* (h^2) of intelligence is about 50%[12]. However, further investigations on this topic have revealed that the heritability of intelligence actually changes in a linear fashion with age from approximately 40% in childhood up to 80% by middle age[13, 14]. Regardless of specific study design and type of intelligence measure

used, results of heritability studies suggest that genetic factors significantly influence intellectual functioning.

Much of our knowledge regarding the role of genetic factors in cognition has been gained through the study of individuals with intellectual disability (ID), previously termed mental retardation. The diagnostic criteria for ID include deficits in intellectual functioning and adaptive behavior that occur during the developmental period[15]. There are many genetic syndromes with associated ID demonstrating that intellectual deficits can result from a number of different genetic anomalies including *aneuploidy* (e.g., Down syndrome), recurrent deletion or duplication of chromosomal regions (e.g., Angelman, Prader-Willi, and Williams syndromes), and mutations in single genes (e.g., neurofibromatosis, tuberous sclerosis). There are a host of X-linked conditions with associated ID (e.g., Rett and Fragile X syndromes) as well[16–19]. Genetic anomalies also underlie non-syndromic ID, in which intellectual impairment represents the only obvious manifestation of the disease[18, 20]. In fact, molecular genetic studies have resulted in the identification of hundreds of genes associated with non-syndromic ID, and it has been estimated that ID may result from mutations in 10% or more of autosomal genes[16]. This is not surprising given that the Online Mendelian Inheritance in Man (OMIM) website, which provides an online catalog of human genes and genetic disorders, currently produces 778 hits for “intellectual disability” and 2,806 hits for “mental retardation”[21]. While a genetic or metabolic cause can be identified in approximately 50 to 65% of individuals with ID in the moderate to severe ranges, only about 20% of milder forms of ID have an identified cause[22]. Taken together, these findings suggest that intact cognitive functioning is dependent on a complex relationship between various genes and their downstream products.

Unfortunately, despite the high heritability of intelligence, it has been difficult to identify genetic factors reliably associated with intact intellectual functioning in healthy individuals[23]. A recent *genome wide association study* (GWAS) of intelligence that examined over 500,000 *single nucleotide polymorphisms* (SNPs) in over 3,511 unrelated, healthy adults found that 40% of the variance in crystallized intelligence and 51% of the variance in fluid intelligence among the individuals in their sample could be accounted for by *linkage disequilibrium* between the SNP markers they used and unidentified causal variants[24]. Interestingly, the SNP data alone, when applied to an independent sample, accounted for only 1% of the variance in intelligence. This led the authors to conclude that intelligence, like many other complex traits, is highly polygenic and likely to be influenced by many genes, each with rather small effects[24].

Certainly, there is an advantage to assessing the role of genetics in cognition by using measures of global intellectual functioning. Intelligence measures often have better reliability than tasks assessing specific cognitive abilities. In conjunction with high heritability estimates of intelligence, this provides increased statistical power for research in behavioral genetics[25]. However, twin studies have demonstrated that there are notable genetic influences on specific cognitive abilities that are independent of the genetic influences on overall intelligence[26]. Further, cognitive dysfunction observed in individuals with neurologic disease is often limited to one or two primary cognitive domains in the context of intact intellectual functioning. Thus, to identify the mechanisms that underlie

specific cognitive deficits, such as those observed in focal epilepsies, much behavioral genetic research now focuses on examination of specific cognitive processes, such as memory and executive functioning[24].

What evidence is there to suggest that genetics play a role in specific cognitive functions?

While not as highly heritable as overall intelligence, possibly due in part to differences in test reliability, it is clear that genetic factors play a substantial role in specific cognitive functions as well. Most cognitive domains show heritability estimates between 35% and 70% with variability based on the specific cognitive domain investigated and type of cognitive tasks administered within that domain[27–29].

Over the past several decades, many studies have sought to identify genetic factors involved in cognitive functioning both in healthy individuals as well as in those with neurological or neuropsychiatric disorders. The most extensively studied genes to date are the apolipoprotein (*APOE*) genes. These two genes, which are located on the long arm of chromosome 19, were initially identified using a genetic association paradigm and found to be strongly associated with both familial and sporadic late-onset forms of Alzheimer's disease (AD)[30–32]. Apolipoprotein E (ApoE) is the major lipid carrier molecule in the CNS and is involved in neural maintenance as well as neuritic growth and repair after injury, including regeneration of axons and myelin[33]. Three allelic variants of ApoE exist, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, with substantial differences in behavior. Data from *in vitro* studies demonstrate that $\epsilon 3$ has a role in stabilizing microtubules, stimulating neuritic growth, and promoting accumulation of cytoplasm; whereas $\epsilon 4$ inhibits neuritic growth and the branching of neurites[34, 35]. ApoE $\epsilon 4$ binds the least avidly to cytoskeletal proteins[32], is the least protective against oxidative stress[36], and can be neurotoxic[37]. In addition, $\epsilon 4$ more avidly binds to amyloid β protein than $\epsilon 3$, promoting more rapid aggregation of amyloid, which accumulates in the brain as a component to neuritic plaques, contributing to the neuronal damage and dysfunction observed in AD[38, 39].

Given its clear role in Alzheimer's disease, in which memory is the first and most significant cognitive ability affected, the role of ApoE $\epsilon 4$ in memory has been investigated in numerous studies across many populations ranging from normal young adults to elderly demented patients. ApoE $\epsilon 4$ is rather consistently found to be detrimental to memory functioning. In fact, a relatively recent review on this topic identified only five studies that have failed to find this effect[40]. Thus, it is not surprising that neuroimaging reveals greater structural brain changes in $\epsilon 4$ carriers, including more severe degeneration and less plastic dendritic changes[41] as well as greater temporal and hippocampal volume loss[42]. While the vast majority of research on the role of *APOE* polymorphisms in cognition has focused on memory, the $\epsilon 4$ allele has also been associated with poorer performance on measures of attention[27, 28] and executive functioning[43].

BDNF, brain-derived neurotrophic factor, is another gene that has shown a rather consistent association with memory performance in healthy adults as well as in individuals with neurological or neuropsychiatric disorders. *BDNF* is a neurotrophin expressed throughout

the brain, particularly in the hippocampus and prefrontal cortex[44]. This neurotrophin regulates neuronal survival and plasticity, promotes neurogenesis, and participates in long-term potentiation and hippocampal function during learning and memory processing[45, 46]. A frequent single nucleotide polymorphism has been identified in this gene in which methionine (Met) is substituted for valine (Val) at codon 66 (Val66Met). This polymorphism is associated with altered cortical and hippocampal morphology as well as decreased volume in the hippocampus, parahippocampal gyrus, and amygdala[44, 47] relative to individuals who are homozygous for the Val allele. The Met allele has also been associated with poor memory performance on neuropsychological measures[48] and reduced activity within the hippocampus on functional MRI during memory tasks[49]. A relationship between the BDNF Val/Met polymorphism and performance on executive function tasks has also been reported[48, 50].

Another gene that has received a lot of attention in recent years is catechol-o-methyltransferase (*COMT*). *COMT*, a postsynaptic enzyme mapped to chromosome 22q11, is involved in metabolic degradation of released dopamine in the frontal lobes and, hence, exerts significant influence over dopamine levels in prefrontal regions of the brain[48]. A Val to Met amino acid substitution at codon 158 of the protein sequence (Val158Met) has been identified that effects enzymatic thermostability. The Met allele reduces *COMT* activity thereby increasing available dopamine[50]. Studies have shown that individuals homozygous for the Met allele demonstrate better performance on measures of executive function than Val carriers, particularly on problem-solving tasks[48]. Consistent with these findings, Met carriers demonstrate more efficient physiological response in the prefrontal cortex on functional MRI during performance on working memory tasks than Val carriers[51] and increased volumes in a number of brain regions, including the hippocampus and amygdala[52]. There is also some evidence that Met/Met homozygotes perform better on memory measures than individuals with other genotypes[53].

The three genes discussed here represent those that have been the most widely studied with rather consistent findings. A host of additional genes have been identified as potentially important to memory and other aspects of cognitive functioning in healthy individuals, and those genes that have been found to be associated with episodic memory performance in more than one sample are summarized in Table 1. A great deal of genetic research has also been conducted to identify genes related to neuropsychiatric disorders that involve cognitive dysfunction (e.g., schizophrenia, attention-deficit/hyperactivity disorder, autism). It is beyond the scope of this article to review each of these genes in turn; however, excellent review articles have been published on these topics[54–58].

Unfortunately, the vast majority of candidate genes that have been associated with specific cognitive functions to date have failed replication in subsequent studies. In fact, *APOE* is likely the only candidate gene whose association with cognition withstands genome-wide correction and meets the current standards for establishing scientific credibility[59].

Do genetic factors play a role in cognitive dysfunction associated with epilepsy?

Most of the existing evidence to suggest that genetic factors play a role in cognition in epilepsy arises from the study of genetic syndromes associated with recurrent seizures and cognitive impairment. One example is tuberous sclerosis complex (TSC). TSC results from inactivating mutations in one of two genes, *TSC1* or *TSC2*, which lead to hyperactivity of the mammalian Target of Rapamycin (mTOR) pathway[60]. Germline mutations with an autosomal-dominant inheritance pattern are observed in approximately one-third of patients with this disorder while de novo mutations account for the remaining two-thirds of TSC cases[61]. In this disorder, hamartomas can develop in multiple organ systems including the brain. Cerebral cortical tubers are present in more than 80% of individuals with TSC, and this disorder has several common neurological manifestations including epilepsy, mental retardation, autism, and ADHD[62]. Research has indicated that approximately 44–70% of individuals with TSC experience intellectual impairment[63–65], and mutation type and location are related to the degree of intellectual impairment observed[66]. Research regarding specific cognitive functions in this population suggests that even patients with normal range IQ scores often show reduced performance in other aspects of cognitive functioning (e.g., memory, attention, executive function)[67–69]. Similar findings have arisen in other genetic syndromes that involve both epilepsy and cognitive dysfunction, providing further support for a role of genetic factors in cognition in patients with epilepsy. A summary of epilepsy syndromes that involve intellectual disability or other cognitive dysfunction with associated genetic anomalies is provided in Table 2. Interestingly, there is very high comorbidity between epilepsy, intellectual disability, and autism spectrum disorders. In fact, it is estimated that approximately 30% of children with epilepsy have autism spectrum disorder and/or developmental disabilities, raising the possibility of shared underlying mechanisms[70, 71]. All of these conditions can result from disrupted synaptic plasticity during crucial points of brain development, and many of the genes that have been identified in such conditions to date are related to such mechanisms.

The role of genetic factors in cognition in individuals with non-syndromic epilepsies remains largely unknown. In fact, we are only aware of three published studies that have demonstrated a role of genetic factors, namely ApoE, in cognition in patients with epilepsy. Gambardella et al.[72] studied memory performance in patients with mild, well-controlled nonlesional TLE. They demonstrated that $\epsilon 4$ -carriers' performance was lower on a verbal list learning task than patients without an $\epsilon 4$ allele, particularly among patients with long disease duration (i.e., >25.5 years). Subsequently, Busch and colleagues[73] examined the role of ApoE $\epsilon 4$ in verbal and visual memory performance before and after anterior temporal lobectomy in adults with pharmacoresistant seizures. An interaction was observed between $\epsilon 4$ status and duration of epilepsy such that $\epsilon 4$ -carriers with a long duration of epilepsy demonstrated significantly lower memory scores than $\epsilon 4$ -carriers with a short duration of epilepsy. In contrast, memory performance among non- $\epsilon 4$ -carriers did not vary as a function of duration of epilepsy. This pattern of relationships was observed on all memory indices, including both verbal and visual memory measures, on both immediate and delayed memory trials. Interestingly, there were no significant effects of surgery in this study, suggesting that

the observed relationships between $\epsilon 4$ and duration of epilepsy on memory were not significantly impacted by temporal lobectomy. Most recently, Palanisamy and colleagues[74] investigated the role of ApoE $\epsilon 4$ in cognition, as assessed with the Mini Mental State Examination (MMSE), in two adult epilepsy samples. They found that $\epsilon 4$ -carriers had significantly lower MMSE scores than non- $\epsilon 4$ -carriers.

Two additional studies have been conducted to examine the role of genetic factors in cognition in epilepsy, both with negative results. Coimbra et al.[75] studied the relationship between human prion protein (*PRNP*) gene variants and cognitive performance on a neuropsychological battery that included measures of intellectual functioning, memory, and confrontation naming in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. After controlling for potential confounding factors, they found no relationship between *PRNP* variants and cognition. More recently, Manna and colleagues[76] examined the potential effects of a polymorphism in the serotonin receptor gene (*HTR2A*) on memory performance in patients with mild, nonlesional TLE. While the *HTR2A* T allele was associated with an earlier age at seizure onset, there was not relationship between this allele and memory performance.

To our knowledge there have not been any studies examining the role of other candidate genes in cognition in non-syndromic, focal epilepsies. Further, we are unaware of any GWAS on cognition in individuals with epilepsy.

What are the existing challenges in identifying the genetic factors that underlie cognition?

Despite the boom of research on the genetics of cognition over the past couple decades, our knowledge on this topic remains surprisingly limited. Results of GWAS, which showed great success in identifying monogenic, Mendelian disorders, have been rather disappointing when applied to complex illnesses and cognitive constructs. With the exception of some of the candidate genes we have discussed here, most notably *APOE*, the vast majority of genes that have been identified to date for their role in cognitive processes have had small effect sizes, inconsistent replication across studies, and/or unclear mechanisms. In fact, a review of the existing literature on episodic memory revealed that only about 7% of the variance in this cognitive ability is accounted for by the genes that have been identified to date[40]. Thus, the issue of “missing heritability”[29, 77] applies not only to complex diseases, but to complex traits like memory and other cognitive processes. There are some important factors to consider in the search for missing heritability in future cognitive genetic studies, which are briefly mentioned here.

It is clear that most cognitive abilities likely involve many genes with small effects. Further, given the complexity of most cognitive constructs, there are likely to be *epistatic* effects as well as gene x environment interactions[78]. However, most studies to date have focused on identifying individual genes related to specific cognitive abilities, without consideration for potential interaction effects. This may account for some of the missing heritability in memory and other cognitive functions. Indeed, those studies that have made use of more

complex statistical models to investigate the genetics of different cognitive processes (e.g., working memory, episodic memory) have identified epistatic effects between genes[79–81].

It is also becoming increasingly clear that the search for missing heritability in cognition must extend beyond exomic (i.e., protein-coding) regions of the genome. Those regions of the genome that were once termed “junk DNA” are now recognized to play an important role not only in manifestation and course of different diseases, but in symptom presentation and severity. Thus, examination of the regulatory features of the genome will be important for future cognitive research as will investigation of *epigenetic* factors (e.g., histone modifications, DNA methylation, microRNA), which have recently been shown to impact cognitive functions, such as intelligence, learning, and memory[22, 82–86].

Given the complexity of cognitive processes (e.g., memory, executive functioning), it is also imperative to develop more concise *phenotypes* for cognitive constructs. Most behavioral genetic studies in patient populations have used composite scores from neuropsychological measures to assess the construct of interest, which is not likely to be sufficient for genetic research. Even though the subprocesses that underlie a cognitive function may be phenotypically similar and load on a single factor in factor analytic research, this does not necessarily imply sharing of the same genetic influences. For example, a recent twin study that examined the genetic architecture of the Tower of London, an executive functioning task, suggested that two related genetic factors underlie different aspects (i.e., speed and efficiency) of this cognitive measure[80]. Similarly, research has demonstrated that genetic influences may vary among different cognitive measures within the same cognitive domain (e.g., story recall versus figure recall memory measures)[87]. Finally, one must not assume that just because a cognitive domain has demonstrated heritability that all cognitive measures developed to assess that domain are also heritable[88]. Indeed, there are a number of mainstream cognitive measures frequently used in clinical neuropsychological practice, such as the Wisconsin Card Sorting Test, that have been shown to have very little heritability based on data acquired from twin studies [89, 90]. As these examples clearly demonstrate, the neuropsychological measures used to assess a particular cognitive ability along with the subprocesses that underlie that ability are oftentimes incredibly complex as they pertain to genetics or molecular biology. As a result, cognitive phenotyping must be done thoughtfully with careful consideration of the constructs that underlie performance within the domain of interest as well as the likely heritability of the particular construct. Certainly, information derived from existing cognitive neuroscience paradigms will be quite useful in this regard.

Research will also benefit from the identification of relevant *endophenotypes* between genetic factors and cognitive constructs. Neuroimaging studies have been proposed to provide potentially important endophenotypes in this regard given that brain structure, as assessed by volumetric measures, is highly heritable with rates ranging from .40 to .95, depending on the brain region assessed[91, 92]. There is also evidence to suggest that findings observed on functional neuroimaging are highly heritable with variation related to brain region, imaging paradigm, and quantification methods[93]. Therefore, in recent years, researchers investigating the role of genetics in cognition have begun to incorporate advanced neuroimaging techniques into their research paradigms. While it is becoming

apparent that the genetic architecture of structural brain phenotypes are just as complex as cognition and other complex traits[94], some researchers have reported that the inclusion of neuroimaging variables, both structural and functional, in cognitive genetic research increases statistical power to identify the role of genetic/genomic factors on brain function, thus allowing for the detection of meaningful effects with smaller sample sizes[46, 95]. Nevertheless, the overall utility of such measures to serve as reliable endophenotypes between genetic factors and cognition remains to be seen.

The search for endophenotypes has a long history in psychiatric genetics. The goal is to identify factors that are heritable and that can be measured objectively, but that are much closer to the biological processes underlying a particular disorder or trait than to the overarching phenotype. Many identified endophenotypes for complex disorders/traits, such as neuroimaging studies mentioned above, have proven to have genetic architectures that are just as complex as the overarching phenotype[96]. Nevertheless, researchers continue to search for potentially important endophenotypes for cognition, which may be more reliably measured than the broader phenotype and may serve as important biomarkers for cognitive dysfunction[96].

How can research in epilepsy uniquely inform future investigations into the role of genetics in cognition?

There is a high prevalence of cognitive dysfunction in patients with epilepsy. Approximately 30% of patients with epilepsy have intellectual disability, and up to 50% of patients with focal epilepsies experience specific cognitive deficits, often associated with the region of seizure onset and related neural pathways. Many cognitive domains can be impacted by seizures including language, attention, processing speed, executive function, and memory. While a host of demographic and disease-related variables that contribute to cognitive dysfunction in patients with epilepsy have been identified over the years, a substantial proportion of the variance in cognition in patients with focal epilepsy remains unaccounted. Genetic factors clearly play a role in cognitive function and dysfunction; yet, outside of syndromic epilepsies that involve ID, this is virtually unexplored in individuals with epilepsy.

Many patients with epilepsy report cognitive issues as one of the most troubling aspects of their seizure disorder[97], which clearly impacts quality of life. Therefore, identification of the genetic factors involved in cognition in epilepsy is essential not only to expand our understanding of the biological underpinnings of cognitive dysfunction in these individuals, but to inform treatment options. Recent research has focused on developing agents that can modify epigenetic processes in an attempt to reverse cognitive impairment or enhance normal cognition. Much of this research has been conducted using mouse models of Alzheimer disease and neurodevelopmental disorders with reported success[98, 99]; however, drug trials in humans are currently underway to determine the utility of such agents in neurodegenerative disorders. Hence, identification of the genetic/genomic contributors to cognitive dysfunction in patients with epilepsy may have huge implications for treatment in the future.

Examination of the role of genetic/genomic factors in cognition in epilepsy may also provide some unique opportunities, not readily available in other neurological disorders or psychiatric conditions, to expand knowledge of the role of genetics/genomics in cognition more broadly speaking:

Prevalence

Epilepsy is one of the most common neurological disorders, affecting over 50 million people worldwide. Genome wide association studies and other genetic research paradigms require substantial sample sizes in order to provide sufficient power to detect genes with small effects or genetic interactions (e.g., gene x gene or gene x environment interaction effects).

Comorbidities

Epilepsy frequently co-occurs with neurodevelopmental disorders that involve prominent cognitive dysfunction and known genetic susceptibility. As noted previously, a substantial portion of individuals with epilepsy also have ID, autism spectrum disorders, or ADHD. The frequent co-occurrence of these conditions raises the possibility of shared underlying mechanisms and may provide a unique opportunity for investigation[100].

Neurophysiology

Electroencephalography is an important part of epilepsy evaluation and diagnosis that can provide pertinent information regarding seizure onset and propagation for use in cognitive genetic studies. Further, invasive EEG monitoring is completed in a subset of surgical candidates, allowing for stimulation of specific brain regions as well as measurement of neuronal activation. Magnetoencephalography is also becoming more widely used.

Neuropsychological Testing

As noted, cognitive dysfunction is common in individuals with epilepsy; therefore, many individuals with epilepsy undergo cognitive assessment as part of school-based evaluations, disability determination, or clinical work-up. Further, patients with pharmacoresistant seizures often complete a comprehensive neuropsychological evaluation as part of preoperative investigations. Thus, cognitive data are readily available on a large subset of patients with epilepsy.

Neuroimaging

Advanced neuroimaging, such as MRI, is often obtained in the course of routine care for patients with repetitive seizures. Patients with pharmacoresistant, focal epilepsies often complete functional neuroimaging studies (e.g., PET, SPECT, fMRI) as part of investigations to determine surgical candidacy. Such techniques provide a way to examine the potential influence of genomic factors on brain function in a non-invasive manner[95] and, as noted above, may serve as endophenotypes between genomic factors and cognition.

Brain Tissue

One effective treatment option for pharmacoresistant, focal seizures is resective surgery. Very few neurological disorders allow one to examine the organ of interest while the patient

is still living. Surgical specimens from patients who have undergone epilepsy surgery provide a unique opportunity to conduct molecular genetic studies to directly examine transcription and gene expression in epileptogenic and nonepileptogenic regions of the brain.

Clearly, the relationship between genetic/genomic factors and cognition is quite complex, and there are likely to be a host of important intermediate endophenotypes. The detailed clinical testing conducted in patients with medically refractory epilepsy in preparation for epilepsy surgery may provide the endophenotypic information necessary not only to develop an understanding of the role of genetics/genomics in cognition in epilepsy but to broaden our knowledge of the role of genetics/genomics in cognition more broadly (Figure).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Questions (answered)

1. What evidence is there to suggest that genetics plays a role in general cognitive ability?

Twin and family studies suggest the heritability of intelligence ranges from 40–80%. Both syndromic and non-syndromic forms of intellectual disability can result from a wide range of genetic anomalies. The genetic factors associated with intact intellectual functioning have been more difficult to identify, and research suggests that intelligence is polygenetic and likely influenced by many genes.

2. What evidence is there to suggest that genetics plays a role in specific cognitive functions?

Twin and family studies suggest the heritability of specific cognitive abilities ranges from 35–70%, depending on the domain and how it is assessed. Apolipoprotein E (*APOE*), brain derived neurotrophic factor (*BDNF*), and catechol-o-methyltransferase (*COMT*) are the most widely studied genes with respect to cognition. While these genes have been related to memory and executive functioning as well as alterations in structure and function of associated brain regions in a number of studies, *APOE* is the only gene whose association with cognitive phenotypes survives genome-wide correction.

3. Do genetic factors play a role in cognitive dysfunction associated with epilepsy?

Genetic anomalies have been identified in a number of epilepsy syndromes with associated cognitive impairments, such as tuberous sclerosis complex. Unfortunately, the role of genetic factors in cognition in individuals with non-syndromic, focal epilepsies remains largely unknown. Research in this arena has been limited to a handful of candidate gene studies. The ApoE ε4 allele has been associated with memory impairment in patients with temporal lobe epilepsy in several studies. Recent studies examining the potential role of the human prion protein (*PRNP*) and the serotonin receptor gene (*HTR2A*) in cognition in patients with focal epilepsies resulted in negative findings.

4. What are the existing challenges in identifying the genetic factors that underlie cognition?

Most cognitive constructs are quite complex and likely to involve many genes with small effects that are difficult to detect using traditional methods. The search for the “missing heritability” of cognition must extend beyond individual genes to include examination of gene-gene and gene-environment interactions, regulatory features of the genome, and epigenetic factors. Given the complexity of cognitive processes, it is also imperative to develop more concise phenotypes and endophenotypes for cognitive constructs.

5. How can research in epilepsy uniquely inform future investigations into the role of genetics in cognition?

The detailed clinical testing (e.g., neurophysiological, neuropsychological, neuroimaging) conducted in patients with medically refractory epilepsy in preparation for epilepsy surgery may provide the endophenotypic information necessary not only to develop an understanding of the role of genetics in cognition in epilepsy but to broaden our knowledge of the role of genetics in cognition more broadly. Further, surgical specimens from patients who proceed to epilepsy surgery provide a unique opportunity to conduct molecular genetic studies to directly examine transcription and gene expression in epileptogenic and nonepileptogenic regions of the brain and their relationship to cognitive performance.

Highlights

- Cognitive functions are highly heritable and likely polygenic.
- *APOE*, *BDNF*, and *COMT* are involved in memory and executive functioning.
- Genetic anomalies underlie many epilepsy syndromes with cognitive impairments.
- The role of genetic factors in non-syndromic focal epilepsies is largely unknown.
- Clinical data and surgical specimens from epilepsy surgery patients may further knowledge of genomic factors underlying cognition.

Figure 1. Detailed clinical testing conducted in patients who undergo surgery for medically refractory epilepsy may expand knowledge of the role of genomics in cognition

A) Most cognitive genetic studies to date have directly examined the relationship between genes (via candidate gene or genome wide association studies), derived from DNA from peripheral blood samples, and cognition. B) More recently, researchers have been able to better identify genes associated with cognition by including structural and functional MRI studies as endophenotypes between genes and cognition. C) Data obtained from patients with epilepsy who undergo surgery for treatment of seizures may provide a unique opportunity to investigate the role of epigenetics, proteomics, and transcriptomics from resected brain tissue. D) as well as a host of other potentially important endophenotypes (e.g. scalp and intracranial EEG, cortical stimulation MEG, PET, SPECT) that may further elucidate the role of genomics in cognition.

Table 1

Other candidate genes associated with episodic memory in more than one sample

Gene Abbreviation	Gene Name	Chromosome	Population
<i>CAMTA1</i>	calmodulin-binding transcription activator 1	1	Healthy young adults[91]
<i>CLSTN2</i>	calsyntenin 2	3	Healthy young adults[93, 95] Healthy adolescents[101]
<i>CTNBL1</i>	catenin, beta like 1	20	Healthy young adults[97]
<i>GRM3</i>	glutamate receptor, metabotropic 3	7	Schizophrenia, unaffected siblings, and healthy adults[102] Healthy adults[103, 104] Schizophrenia[104]
<i>GRIN2B</i>	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	12	Healthy adults[103] Schizophrenia[104]
<i>HTR2A</i>	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	13	Healthy young adults[105–108] Healthy older adults[107] Healthy older adult twins[109]
<i>KIBRA</i>	kidney and brain expressed protein	5	Multiple populations including healthy young and older adults, individuals with subjective memory complaints, individuals from aging and memory studies (see Milnik et al.[110] for review)
<i>PDYN</i>	prodynorphin	20	Healthy older adults[111]
<i>PRKCA</i>	protein kinase C, alpha	17	Healthy Adults[103, 104] Schizophrenia[104]
<i>SYNJ2</i>	synaptojanin 2	6	Healthy older adults[112]

Table 2

Epilepsy syndromes that often involve intellectual disability or cognitive dysfunction that have been associated with genetic anomalies*

Epilepsy Syndrome	Cognitive Findings	Associated Genes	Chromosome
Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)[113, 114]	Generally normal intelligence, although rare families with intellectual dysfunction have been reported; Reduced executive functioning and memory performance in some patients	<i>CHRNA2</i> <i>CHRNA4</i> <i>CHRNA2</i> <i>KCNT1</i>	8 20 1 9
Benign Epilepsy of Childhood with Centrottemporal Spikes (BECTS) / Rolandic Epilepsy[115, 116]	Generally normal intelligence; Impairments in speech, language, attention, and executive function in some patients; Cognitive impairments often persist after seizure remission.	<i>GRIN2A</i>	16
Early Infantile Epileptic Encephalopathy with Suppression Bursts / Ohtahara Syndrome [117–119]	Profound intellectual disability in most patients	<i>KCNQ2</i> <i>SCN2A</i> <i>ARX</i> <i>CLDK5</i> <i>SLC25A22</i> <i>STXBP1</i>	20 2 X X 11 9
Epilepsy and Mental Retardation Limited to Females (EFMR)[120, 121]	Variable developmental trajectory ranging from normal to always delayed; A large subset show developmental regression after seizure onset, which often results in intellectual disability; Cognitive impairments typically persist after seizure remission.	<i>PCDH19</i>	X
Epilepsy-Aphasia Syndromes (EAS) [§] [122, 123]	Acquired aphasia; In some syndromes more global cognitive and behavioral regression is observed	<i>GRIN2A</i> <i>SRPX2</i>	16 X
Malignant Migrating Partial Seizures of Infancy (MMPSE) [124, 125]	Developmental regression after seizure onset with profound intellectual disability; Often accompanied by cortical visual impairment	<i>KCNT1</i> <i>SCN1A</i> [†] <i>TBC1D24</i> <i>SLC25A22</i>	9 2 16 11
Myoclonic Astatic Epilepsy (MAE) / Doose Syndrome[115]	Normal early development; Variable cognitive outcome related to epilepsy course; Subset show global cognitive declines	<i>SCN1A</i> [†]	2
Severe Myoclonic Epilepsy of Infancy (SMEI) / Dravet Syndrome[115, 126–128]	Normal early development with progressive cognitive decline after seizure onset, often resulting in ID and behavioral impairment	<i>SCN1A</i> [†] <i>SCN2A</i> <i>GABRG2</i> <i>SCN1B</i>	2 2 5 19
Tuberous Sclerosis Complex[63–66]	Intellectual dysfunction present in 44–70% of individuals; Patients with normal intelligence often show specific deficits in attention, memory, or executive functioning	<i>TSC1</i> <i>TSC2</i>	9 16

* Epilepsy syndromes with an identified genetic cause, but without associated cognitive morbidity (or in which cognition has not been adequately researched) are not included in this table.

[§] Epilepsy aphasia syndromes with identified *GRIN2A* mutations include Landau-Kleffner Syndrome, epileptic encephalopathy with continuous spike and wave during slow-wave sleep (ECSWS), and atypical rolandic epilepsy with speech impairment.

[†] *SCN1A* mutations have been identified in a host of epilepsy syndromes[129, 130], some of which are not included in this table.