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Targeted Review

Genetics of cognition in epilepsy

Robyn M. Busch [a,b,c,*], Imad Najm [a,c], Bruce P. Hermann [d], Charis Eng [e]

[a] Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[b] Department of Psychiatry & Psychology, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[c] Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[d] Charles Matthew Neuropsychology Section, Department of Neurology, University of Wisconsin, Madison, WI, USA
[e] Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA

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ABSTRACT

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.

Key questions

1. What evidence is there to suggest that genetics plays a role in general cognitive ability?
2. What evidence is there to suggest that genetics plays a role in specific cognitive functions?
3. Do genetic factors play a role in cognitive dysfunction associated with epilepsy?
4. What are the existing challenges in identifying the genetic factors that underlie cognition?
5. How can research in epilepsy uniquely inform future investigations into the role of genetics in cognition?

Definitions

1000 Genomes Project — a collaboration among research groups in the US, UK, 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 have 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 compared with 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 the DNA

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* Corresponding author at: Cleveland Clinic Epilepsy Center, Neurological Institute, 9500 Euclid Avenue, P57, Cleveland, OH 44195, USA. Tel.: +1 216 444 9042; fax: +1 216 444 4525.
E-mail address: buschr@ccf.org (R.M. Busch).

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sequence itself (e.g., DNA methylation, posttranslational histone modifications, and noncoding RNAs) [7]. For information on how the definition of epigenetics has evolved over time, see [8].

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 (GWAS) — 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].

linkage disequilibrium — measure of the statistical association of allele frequencies at two or more loci [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:, www://genome.gov; Note: Most definitions were taken verbatim from the cited sources.

1. 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.

2. 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 that 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% in 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 and 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 nonsyndromic 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 nonsyndromic 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 2806 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 3511 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].

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

While not as highly heritable as overall intelligence, possibly due, in part, to differences in test reliability, 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

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