Genome-wide association studies: a powerful tool for neurogenomics

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As their power and utility increase, genome-wide association (GWA) studies are poised to become an important element of the neurosurgeon's toolkit for diagnosing and treating disease. In this paper, the authors review recent findings and discuss issues associated with gathering and analyzing GWA data for the study of neurological diseases and disorders, including those of neurosurgical importance. Their goal is to provide neurosurgeons and other clinicians with a better understanding of the practical and theoretical issues associated with this line of research. A modern GWA study involves testing hundreds of thousands of genetic markers across an entire genome, often in thousands of individuals, for any significant association with a particular disease. The number of markers assayed in a study presents several practical and theoretical issues that must be considered when planning the study. Genome-wide association studies show great promise in our understanding of the genes underlying common neurological diseases and disorders, as well as in leading to a new generation of genetic tests for clinicians. (DOI: 10.3171/2010.10.FOCUS09186)

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A goal of molecular genetics is to discover the genetic architecture of human phenotypes, especially diseases. The research community has recently made great strides toward associating loci (genes) with phenotypes (diseases), but much work remains.⁸⁰ These advances have resulted from significant increases in the scale and power of genetic-linkage tests, which have grown from candidate-gene analyses to GWA studies.

Genome-wide association studies are intended to address some of the shortcomings of traditional candidate-gene linkage tests. Classic linkage studies are typically difficult to conduct, at least in part because they require a priori knowledge about the biology of the disease under study (to select candidate genes) as well as a familiarity with the genetic variants (that is, mutations) in the candidate genes that could alter function or expression.¹¹³ Additionally, there is an inherent bias in the candidate-gene approach stemming from the typically small number of genes that are selected for testing. The low-throughput nature of candidate-gene studies obviously makes them ill suited for testing roughly 30,000 genes and the millions of observed genetic variants in the human genome.

There has been a significant increase in the number of GWA studies being conducted, with ~400 published to

date.^{52,53} In general, these studies have 1) reinforced the importance of the genetic variation that underlies phenotypic variation, 2) illustrated that genetic variation almost always results from multiple Mendelian mutations rather than a single mutation, and 3) demonstrated that genetic variation typically explains only a small fraction of the observed phenotypic variation.^{4,80,114} Within the field of neuroscience, recent GWA studies have provided insights into the genetic basis of many common neurological diseases and disorders (Table 1). Such studies have been conducted for conditions including Parkinson disease,^{39,67,93,113} malignant gliomas,^{23,95,109,143} multiple sclerosis,^{7,29,90} Alzheimer disease,^{15,18,41,72,73} autism,^{3,8,22,45,75,107,133} schizophrenia,^{25,119,138} lumbar disc disease,¹³¹ idiopathic scoliosis,^{43,140} and restless-leg syndrome.^{36,139}

Without doubt, the field of genomics is going to play a central role in the clinical care of the future neurological patient. Physicians will therefore need to have at least a basic understanding of the research tools and concepts routinely used in this field. The purpose of this review is to familiarize the clinician with the fundamentals of GWA studies and to highlight their potential clinical application.

Genome-Wide Association Models

Recent progress toward understanding human genetic variation has advanced genetic-linkage and genet-

Abbreviations used in this paper: GWA = genome-wide association; HWE = Hardy-Weinberg equilibrium; SNP = single-nucleotide polymorphism.

TABLE 1: Genome-wide association studies of common diseases and disorders of the brain, spine, and nervous system*

Condition Studied	Reference
<i>neurooncology</i>	
glioma	109
high-grade glioma	143
neuroblastoma	77
high-risk neuroblastoma	24
cerebrovascular disease	
intracranial aneurysm	20
hemorrhagic stroke	9
ischemic stroke	47, 79, 144
<i>neurological disease</i>	
age-related macular degeneration	62
Alzheimer disease	2, 15, 18, 26, 41, 72, 73, 96, 103, 135, 136
amyotrophic lateral sclerosis	21, 27, 34, 35, 38, 63, 105, 129, 130
Creutzfeldt-Jakob susceptibility	81
multiple sclerosis	6, 7, 12, 28, 29, 57, 59, 90
Parkinson disease	42, 76, 93
progressive supranuclear palsy	82
restless legs syndrome	36, 104, 139
<i>brain function & physiology</i>	
cognition	97, 108
memory	94
pain	60
brain vol	12
sleep	46
attention deficit hyperactivity disorder	5, 64, 65, 68, 83, 87, 117
autism	75, 133
bipolar disorder	13, 40, 51, 106, 115, 116, 137, 145
major depressive disorder	85, 120
panic disorder	91
neuroticism	111, 128
schizophrenia	25, 58, 61, 66, 88, 89, 110, 112, 118, 119, 121, 132, 138
personality dimensions	123
<i>addiction</i>	
alcohol dependence	125
methamphetamine dependence	126
nicotine dependence	17, 19, 37, 124, 127

* Compiled from information contained in the National Human Genome Research Institute GWA study catalog.^{52,53}

ic-association studies from candidate-gene analyses to GWA studies.⁹⁸ The power of the GWA approach lies in the breadth and number of genetic variants tested during the course of a study. The GWA study also has the advantage of being an unbiased search for the genetic variants associated with a particular disease and therefore offers the possibility of discovering new associations of genes and pathways with diseases.⁴

Genome-Wide Association Theory

A phenotype is an observable trait produced by an underlying genotype. The genetic differences among individuals in the human population are commonly called “mutations” and most frequently are single-nucleotide changes within the DNA sequences of genes.^{11,80} Many mutations are expected to be harmful and thus to be removed from the population by natural selection. Fewer mutations are expected to be beneficial or fitness neutral, and such mutations can persist in a population over time while proceeding to fixation (every individual carries it) or loss (lost by the actions of selection and drift); with either fate, any genetic variation is lost and therefore not observable. Prior to being fixed or lost, a mutation is carried by only part of the population and is referred to as a “polymorphism.” Single-nucleotide polymorphisms are commonly used as genetic markers in GWA studies and are the focus of this review—although alternative genetic features can be used for GWA studies. These alternatives may be particularly useful for GWA studies of psychiatric disorders, in which genetic features such as gene copy-number variations^{14,45,107,119} and gross chromosomal rearrangements⁸ appear to be important to the genetic etiology of this class of diseases.

The aim of a typical GWA study is to associate one or more SNPs with a particular disease phenotype (Fig. 1). The tested SNPs are not expected to be the causal genetic factors; rather, they are used to mark (“tag”) particular regions of chromosomes that likely contain many genetic variants in high linkage disequilibrium with the tested SNP. Linkage disequilibrium occurs when 2 or more alleles at distinct genetic loci occur together significantly more or less frequently than expected by chance based on the constituent allele frequencies. Single-nucleotide polymorphisms are therefore an efficient way to screen many mutations at once, and thus identify chromosomal locations within which the true causal variants are likely to reside. In fact, the true causal variant may not itself be a nucleotide mutation—it may be an insertion or deletion mutation.

Genome-wide association studies differ in their assumptions about the type of genetic variation underlying the disease of interest. Most such studies operate under the “common disease/common variant” hypothesis, which proposes that phenotypic variation is the result of many common SNPs, each of which contributes only a modest effect.¹⁰⁰ An alternative hypothesis, the “multiple rare variant” hypothesis, proposes that phenotypic variation results from the potentially more modest effects of many rare SNPs.⁹⁸ These two hypotheses are not necessarily mutually exclusive—the variation underlying a disease may fall into both categories; rather they are in-

Fig. 1. Schematic representation of a GWA study. **Left:** A mutation (black circles) entering and spreading through a population over time. **Right:** A contingency table in which the mutation is significantly more abundant among the cases than the controls.

tended to guide the design, analysis, and interpretation of GWA studies.

Genetic variation can interact differently to produce the particular disease under study. It can interact additively, in which case alleles confer a mean effect that does not depend on the state of other alleles, or nonadditively, which means that the effect of an allele results from dominance effects and epistatic interactions with other loci. Additive genetic variation is most commonly considered in GWA studies, in which SNPs are typically considered as independent entities.⁴ Recently, there has been significant progress toward developing statistical models that assess nonadditive genetic effects, and these models promise to greatly enhance the scope and power of GWA studies.^{30,32}

Genome-Wide Association Study Design

The design of a GWA study primarily depends on the specific project goals, but practical factors such as budget and time must be considered as well. The most common design for a GWA study is the case-control format, in which there is a cohort of cases (affected individuals) and a cohort of controls (unaffected individuals). The individuals in the case cohort are assumed to have a greater prevalence of disease-causing alleles than those in the control cohort,⁸⁰ a hypothesis that can be assessed by one or more statistical methods discussed below.

Power is the most critical aspect to consider when designing a GWA study. Study power determines the likelihood that a trial will detect significant genetic differences between case and control populations, if any such differences truly exist. Sample size profoundly affects

the study power, and, in general, the largest sample that is feasible to genotype should be used. Study power can also be increased by carefully controlling for any population substructure and by cautiously selecting the control population.^{4,11,80}

The individuals in the case and control populations are assumed to be "unrelated," which means that their ancestral relationships are distant and therefore unknown.¹¹ However, the case and control individuals should not be so unrelated that there are distinct subgroups that share a common ancestry (for example, Western European or African heritage). When such subgroups exist, there is said to be population substructure or population stratification, which can be especially problematic when correlated with the case-control delineation. Population stratification can produce false-positive signals because some genetic variants can occur at different frequencies in the two groups as a result of ancestry, even though they are unrelated to the disease under study. Many statistical methods exist to control for population stratification^{11,80} and have been implemented in common software packages such as PLINK.⁹⁹ Furthermore, recent evidence has suggested that many concerns about population stratification may be overinflated; however, every effort should be made to eliminate its effects.^{11,80,137}

Selection of the control population is crucial to the success of a GWA study. Common-control populations, which are genotyped populations that can be used across studies, have been successfully utilized in GWA studies.¹³⁷ The main concerns about common controls are the presence of population stratification and the potential loss of power given the presence of latent (undiagnosed) disease

in the control population. A study-specific control population is almost always ideal, but can greatly increase the time and cost of a GWA study (controls must be genotyped) and is subject to selection bias when differences, in addition to the disease under study, exist between cases and controls.⁸⁰ Historical controls, which are previously genotyped individuals used in current studies, have the potential to reduce study power when there is significant genetic divergence between extant cases and historical controls. Historical controls may be the best option available, however, and recent evidence has suggested that some of the drawbacks may be overcome by increases in sample size.¹³⁷

An alternative study design is “family-based association” in which genetic tests are performed within families. Family-based association studies offer strong control of background genetic differences at the cost of overall study power. The additional costs associated with studying large numbers of families and recent improvements in statistical methods to control for population stratification make family-based studies attractive for only specialized circumstances.⁸⁰

Genome-Wide Association Study Methods

Genotype Calling

Genotyping is the phase in which an instrument determines (“calls”) the genotype, or state of both alleles, at every SNP locus tested. Genotype calling is typically performed in a high-throughput manner by using highly automated instruments, such as those commercially available from Affymetrix and Illumina. Commercial genotyping instruments use high-density microarrays of SNPs (“SNP chips,” informally) that have been identified through projects such as the International HapMap Consortium.⁵⁶

The latest generation of commercial SNP genotyping platforms can routinely test ~ 2 million genetic loci in a single assay. The loci include ~ 1 million SNPs and an approximately equal number of copy-number variants; a state-of-the-art instrument with robotic automation can generate ~ 40–50 million genotypes per day. However, investigators in most published studies have used earlier genotyping platforms that tested ~ 300,000–500,000 SNPs. One advantage of commercial genotyping platforms is that the selection of high-quality SNPs to test is no longer a challenge left to individual researchers. The latest genotyping platforms include SNPs that are spaced, on average, 1–2 kilobases apart and cover ~ 95% of the human genome, including sex chromosomes and mitochondrial genomes. Current genotyping instruments poorly sample regions of the human genome with infrequent restriction enzyme sites, which precludes isolating SNPs in these regions. An additional benefit of commercial platforms is that they lead to further standardization of the SNPs tested across studies.

Quality Control of Genotype Data

Genome-wide association studies produce enormous amounts of data, and therefore data quality is of para-

mount importance. Rigorous quality control measures must be implemented at each stage of the study—from DNA extraction and amplification through to analyzing and interpreting the data. A common source of errors is genotype calling, which must strike a balance between stringency and call rate. If base calling is excessively stringent, then most markers will have a low call rate, which can inflate the false-positive rate.¹¹ On the other hand, overly relaxed genotype calling will produce significant numbers of miscalled genotypes. Finally, a threshold call rate must be selected, and SNPs whose call rates fall below this threshold should be excluded from consideration. Individuals with low overall call rates should be removed because such rates suggest that their DNA samples may be problematic.

Each marker should be tested in the control population to ensure it is in HWE, which describes the expected genotype frequencies (based on allele frequencies) in a randomly mating population in the absence of selection, mutation, and migration.⁵⁰ Extreme deviations from HWE might be symptomatic of genotype calling errors, and such markers can generally be removed with impunity.⁸⁰ On the other hand, moderate deviations from HWE may be expected in the cases, and therefore the inclusion threshold should not remove these markers because they may provide additional information when searching for disease-associated SNPs.^{11,142} The HWE inclusion threshold must be carefully selected to balance overall inclusiveness with the purging of potentially problematic markers. A flexible and powerful approach is the use of the observed distribution of HWE values for each marker to determine an appropriate threshold for inclusion.¹³⁷

There are a few remaining aspects to consider when implementing quality-control measures. Individuals whose genotype does not agree with their stated ethnicity or sex should not be included. Methods should be implemented to ensure all individuals in the study share a common ancestral background (for example, all of Western European descent) to minimize population substructure. Individuals with evidence of genetic syndromes (for example, fragile-X syndrome or trisomy 21) should also be excluded. In family-based studies, markers with unusually high rates of Mendelian errors—potentially a sign of frequent miscalling of genotypes—should be discarded.^{11,80}

Testing for Association

After obtaining a high-quality set of genotypes, a GWA study typically moves into the analysis phase during which SNPs are tested for their association with the phenotype of interest. This phase essentially consists of applying one or more statistical tests of association to each marker tested. There are several statistical models available, although the viable options may be constrained by the study design (for example, phenotypic variable). The statistics underlying these methods can be quite difficult to understand, and therefore only the general features of the most common tests are discussed herein. The interested reader is encouraged to investigate one of many recent reviews for more detailed treatments of GWA study statistics.^{11,134}

A significant problem with many tests of association

is the extensive multiple-testing burden;^{11,80,134} this problem becomes more significant as the number of SNPs tested increases. Multiple-testing burden refers to the increased false-positive rate that results from performing multiple independent tests on the same data set. Several methods exist to correct the p values for multiple testing and reduce the likelihood of false-positive signals.^{10,54,134} The most conservative approach is a Bonferroni correction in which individual p values are each multiplied by N (the number of SNPs tested) to maintain the false-positive rate at a desired level. More flexible and relaxed false-discovery rate (FDR) calculations can be used as well.¹⁶ Such corrections yield a greater number of potential SNPs positively associated with the disease under study, but also create a greater risk of including false-positive associations. Simulation models can also be used to empirically determine a threshold p value that appropriately balances overall inclusiveness with false-positive risk. Under any multiple-testing correction approach, the required p value for attaining significance for any particular SNP is exceedingly small because modern GWA studies effectively conduct hundreds of thousands of statistical tests.

The most basic test for a single SNP in a case-control design is that for independence between the 2 rows (cases and controls) and 3 columns (genotypes) of a contingency table.¹¹ A chi-square or Fisher exact test would be an appropriate statistical test. Alternatively, one could use a Cochran-Armitage test, which is based on the differences in allele counts rather than genotype counts, and may be more powerful for complex traits for which the contribution of individual SNPs is thought to be roughly additive.⁸⁰

More advanced statistical approaches based on regression modeling are routinely used when analyzing GWA data. Logistic regression models are suitable for case-control studies in which the phenotype is binary (for example, presence or absence of a disease), whereas a linear regression or an ANOVA model is suitable for testing continuous phenotypes (for example, degree of spine curvature in a scoliosis study). One advantage of using regression models is that epistatic interactions between SNPs can be readily incorporated into the model, as can other covariates such as age or sex. An important theoretical consideration is that regression-based methods assume that phenotypes are observed prospectively, whereas most GWA studies select individuals based on phenotype and then determine the genotype.¹¹

Family-based association studies model SNP flow through pedigrees. Software packages such as MERLIN and LAMP (freely available at <http://csg.sph.umich.edu>) are widely used suites of programs for the analysis of large pedigree data sets.¹ MERLIN is designed to test quantitative trait association, whereas LAMP^{69,70} is intended for discrete trait association. Both software programs use likelihood statistics to assess the relative probabilities of alternative patterns of gene flow through the pedigrees in the data set.

Interpretation of Results

Once a set of associated SNPs has been identified, a search for additional evidence to support the observed

association must begin. Ideally, the study would be replicated with a different population of cases and controls to ensure that the same SNPs would be identified in these new individuals. Such replication may not be feasible, however, for reasons such as cost or time.

Vendor-supplied annotation files can be used to determine the physical and genomic location of each SNP within the genome. The annotation for each SNP may also include additional information, such as whether the SNP is located within a gene (intronic/exonic) or an intergenic region. Using this information, one can search databases such as Entrez for additional DNA, RNA, or protein sequence information, or Medline can be queried for other studies corroborating an observed SNP association. For example, genes adjacent to an associated SNP can be checked to determine if any have prior evidence linking them to the disease under study, which could identify genomic locations that might be good targets for more extensive sequencing efforts.

Limitations of GWA Studies

Theoretical Limitations

There is appreciable work to be done on the practical and analytical front for improving the current generation of GWA methods. First and foremost, even the most powerful GWA study can only explain a small percentage of the observed phenotypic variation. This fact partially emphasizes the need for models and methods that explicitly consider the interactions of genes with their environment. Gene-by-environment interactions present a significant practical challenge to GWA studies; it is extremely difficult to determine the relevant times and environmental variables to measure.^{31,33} In the future, statistical methods that consider the interactions between multiple genetic variants must be advanced.^{32,55} The power to model and detect epistatic interactions among mutations in a genome offers great hope to more completely explain phenotypic variation and uncover a greater number of loci. Loci that are not strongly associated with a trait individually may be very strongly associated when considered in combination with other mutations.

Genome-wide association studies only test for a statistically significant association of a marker with a trait and cannot make a causal statement. The direct test for causality between associated SNPs and their flanking genes would involve the mutation of each candidate gene and the determination of the resulting phenotype. Obviously, this is impossible with humans, but other organisms, such as yeast, mice, and primates, may be good surrogate models for the human disease. One or more of these model organisms might be useful in refining the set of associated SNPs and further understanding the genes and pathways mutated in diseased individuals. It is a long road from a GWA study to determining which genes and pathways are defective in the diseased state; however, GWA analysis can be an important first step in identifying otherwise unknown genes and pathways involved in diseases.

Practical Limitations

At present, the most significant practical limitation for GWA studies is cost. Genotyping is expected to cost ~ \$500 per individual, not considering the necessary instrumentation. Current genotyping instruments require a significant initial investment of roughly \$300,000. Alternatively, research service providers can be contracted for some or all stages of data production (DNA extraction, genotyping, and so forth). Significant costs may also be associated with obtaining sufficient high-quality data, especially for rare diseases with a low incidence. Moreover, significant time and resources may be required to generate the genetic data (genotyping) for the control population.

The large amounts of data generated during the course of a GWA study must be processed on relatively powerful computers with a large storage capacity. Additionally, computer software may need to be developed in-house to store and analyze the data, or existing software programs may need to be acquired. Commercial software packages are available to analyze the data, and there are freely available options as well.

Clinical Applications of GWA Studies

Genetic Testing

In addition to identifying a set of alleles associated with a particular disease, the GWA approach can be used to identify risk alleles, that is, those that appear to confer an increased risk for developing a disease. Genetic risks have been based on family history or candidate gene testing. Genome-wide association approaches may one day be able to provide a comprehensive picture of an individual's risk for developing any of a wide range of disorders.

Although it has been proposed that risk calculations based on GWA data might ultimately replace those based on family history,¹⁰² genetic tests have gained only limited acceptance in the medical community.^{48,49} The clinical utility of genetic testing has been difficult to demonstrate for a variety of reasons, but significant effort is currently being expended to overcome these obstacles. Single-nucleotide polymorphisms implicated in the most powerful GWA studies typically explain only a small fraction of the observed variation for a disease, which partly stems from a combination of methodological and practical limitations. Genome-wide association tests carry significant direct costs. It has been difficult to demonstrate their cost-effectiveness because 1) risk loci have typically low penetrance, 2) the benefits of genetic testing are hard to quantify because treatment for the disease may improve over time or a patient's adherence to preventive measures may decline over time, and 3) there is a potential cost to the patient in terms of stigmatization by society or psychological stress resulting from his or her knowledge about potential future disease.¹⁰¹ Nonetheless, GWA screens have been conducted for a number of diseases of neurosurgical importance.¹¹⁴

Malignant glioma is the most common type of primary brain tumor, and the prognosis remains poor despite surgical and oncological advancements.^{43,74} As in

other types of cancer, there is great interest in identifying susceptibility loci for these aggressive tumors. Such loci would allow for the estimation of the risk of developing malignant glioma in a particular individual during his or her lifetime. Significantly at-risk individuals could be monitored more closely, with the hope that increased surveillance might lead to earlier detection and better treatment outcomes.

Recently, authors of a large GWA study were able to identify 5 genetic loci that appear to confer a significant risk for the development of malignant gliomas.¹⁰⁹ The SNPs identified potentially support the importance of the cyclin-dependent kinase inhibitor 2A–cyclin-dependent kinase 4 (CDKN2A-CDK4) signaling pathway, as well as the genes involved in genomic stability and telomere preservation. A few of the genes and chromosomal regions have been implicated in other types of cancer. Interestingly, 2 of these loci appear to be associated with a greater risk for the development of high-grade gliomas.¹⁴³ One of the chromosomal regions identified is the 9p21 region in which the *CDKN2B* gene resides. This gene participates in the control of cell division and is frequently deleted in high-grade gliomas. The other identified chromosomal region is 20q13 in which *RTEL1* is located. The *RTEL1* gene encodes a DNA helicase that is critical for the maintenance of telomere length.

Idiopathic scoliosis is the most common childhood spine disorder, affecting almost 3% of children globally.^{140,141} The disease appears to cluster within families, although the precise mode of inheritance has yet to be determined. A recent GWA study revealed significant linkage of a region of chromosome 8 with idiopathic scoliosis, specifically with the *CHD7* gene.⁴⁴

Lumbar disc disease is a significant source of disability, and one of the most common disorders seen in neurosurgical practices.⁹² A recent small-scale GWA study demonstrated an association between a region of chromosome 21 and lumbar disc disease.¹³¹ The results of this study are encouraging, although larger and more densely sampled GWA studies must be conducted to corroborate the data. Furthermore, lumbar disc disease may present special problems relating to phenotype scoring since many individuals carry asymptomatic disc herniations.

Diagnostics, Tumor Grading, and Prognosis

The GWA study framework also holds great promise for molecular diagnostics in medicine. Molecular diagnostics use genetic markers to ascertain the clinical status of a patient's tissue sample. For example, a patient's brain tumor tissue sample is traditionally sent for anatomical pathology analysis. In the future, a patient's specimen may be sent to a genetics laboratory for analysis. The potential advantages of genetics-based diagnostics are that such analyses are typically unambiguous, unbiased, and completely objective. There is still much work to be done for this field to move from potential applications to effective clinical solutions.

Recently, significant progress has been made toward developing molecular diagnostics for brain tumors, in particular malignant gliomas. For example, there is a great deal of interest in developing tumor-grading meth-

ods based on the genetic states of tumors rather than their anatomical appearance.^{86,122} These methods would use genetic markers as an adjunct to traditional grading of tumors by a pathology lab. There is also significant interest in developing tumor prognosis classifiers based on genetic markers, with some recent success.⁹⁵ Progress has been made in developing artificial-intelligence classifier models that predict survival time based on the genomic expression patterns of select genetic loci.^{71,78}

Personalized Medicine and Tumor Drugs

Lastly, we note that GWA studies may one day lead to clinical regimens that are individually tailored to each patient. For instance, genetic testing is routinely being done for oligodendrogliomas, with the 1p/19q screen for chemotherapeutic effectiveness. However, the GWA approach permits screening for more markers in a single sweep and offers much more precision in associating genotypes with clinically important phenotypes. In addition, understanding genes, as opposed to chromosome arms, will allow for a deeper understanding into the molecular genetic mechanisms behind drug function and metabolism, and lead to better therapies in the future.^{84,122}

Conclusions

Genome-wide association studies hold great promise for decrypting the complex genetic architecture of many diseases. Furthermore, GWA approaches have the potential to power a new generation of genetic tests, which one day may be used to estimate an individual's risk for a particular disease or to predict which chemotherapeutic agent or biological treatment will be most effective. As the costs decline and the analytical methods become more powerful, genetic testing may become a feasible option for patients seeking to understand the health risks conferred by the mutations residing in their DNA. Given their advancement to date, the current generation of neurosurgeons and neurologists can expect to use patient genetics as part of their clinical decision-making at the bedside.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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