In search of genes for stroke

Stroke is the third most common cause of death and the leading cause of long-term disability worldwide, but it has proven resistant to genetic investigation. Strong evidence suggests that genetic variation has a role in its pathogenesis, and although there has been no shortage of candidate gene studies, few (if any) genes have been irrefutably associated with stroke—a story that has been repeated for a host of other common diseases.1

Relations between gene variants and the traits or diseases they influence generally fall into two models. For diseases that have a predictable familial pattern of inheritance, the gene variants or alleles responsible tend to be rare, and possession of the mutated gene is both necessary and sufficient to cause disease. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a notable example of a monogenic disease in which stroke is a cardinal manifestation. The vast majority of symptomatic strokes, however, do not cluster in families in any appreciable pattern. In late-onset complex traits, such as stroke, it is widely believed that multiple variants involving multiple genes each have a relatively modest effect on disease risk. Unlike the mutations in NOTCH3 that cause CADASIL, these alleles are thought to be common among the general population and, by virtue of their prevalence, contribute substantially to disease burden despite their small effect size.

Whole-genome association studies, such as that described by Matarin and colleagues in this issue, allow investigators, for the first time, to search for these common alleles of small-to-moderate effect with an unbiased approach, by testing known single-nucleotide polymorphisms (SNPs) across the genome for association with disease. Because these studies involve simultaneously testing hundreds of thousands of SNPs, the possibility of discovering a chance (ie, false positive) association becomes a certainty unless the p value threshold is set sufficiently low (p<5×10⁻⁷ in Matarin and colleagues’ study, for example). Associations that are declared significant at such a low threshold, however, can still represent false-positive results. Ultimately, only replication of the finding in independent datasets can provide unequivocal evidence for a bona fide genotype-phenotype correlation.

Although conservative thresholds of significance are essential for such studies, they raise the possibility that SNPs that are truly associated with disease will be inappropriately rejected if their corresponding p values do not pass the predefined threshold. Only by increasing the number of study participants can investigators reduce both the possibility of a false-positive finding and the likelihood of rejecting SNPs that are truly associated with disease.

Indeed, lessons from recently released whole-genome studies underscore the importance of large sample sizes to improve statistical power to discover an association. Sladek and colleagues undertook a genome-wide association study of 694 type 2 diabetes patients and 669 controls, and fast-tracked the 59 most “promising” SNPs for replication in another 5511 samples.5 They reported four novel susceptibility loci containing common variants (27–40% allele frequency) but with small effects on disease risk (odds ratios in the range of 1.14 to 1.27).

In this issue of The Lancet Neurology, Matarin and colleagues describe a genome-wide association study in which approximately 400 000 SNPs were genotyped in 249 patients with ischaemic stroke. Allele frequencies for each SNP were compared with those in 268 controls recruited as part of a prior study. This publication—the first genome-wide association study for stroke—is an important step forward for stroke genetics. The group responsible for ascertaining and phenotyping the cases have been pioneers in the development of...
tools for multicentre genetic studies. Investigators in
the International Stroke Genetics Study (ISGS)\(^6\) and the
Siblings With Ischemic Stroke Study (SWISS)\(^7\) recognised
that only through collaboration could large numbers of
carefully phenotyped subjects be assembled; thus, these
researchers developed and validated tools to ensure
uniform characterisation of patients across multiple sites,
and the studies have become models for development of
subsequent multicentre genetic stroke studies.

Matarin and colleagues have set an important standard
for those who follow, by committing to full release of
the raw genotype and phenotype data (for almost all
participants) and results of the association analysis into
the public domain. This approach is being widely adopted
throughout the genetics community, and assures
maximum utility by enabling investigators worldwide to
examine and analyse the data with fresh ideas.

A crucial limitation of the present study is its sample
size. When completed, the researchers’ study will include
a total of 1500 stroke cases and 1500 controls. Power
will exceed 80% only to detect SNPs with odds ratios
greater than 1·5 and frequencies in the population that
exceed 20% (at \(p<5\times10^{-7}\)). In fact, a study the size of
the ISGS might not be large enough to identify alleles of
sufficient frequency to be associated with stroke. The
International Stroke Genetics Study (ISGS) protocol.

The discovery of genes that contribute to stroke risk
will revolutionise the prevention of the leading cause
of combined death and disability in the developed
world and will help to identify novel pathways for
pharmacological intervention. Matarin and colleagues
have taken a first crucial step towards that goal.

Pathological gambling in Parkinson’s disease

The rapid proliferation of opportunities to gamble money
on the internet, in casinos, and even on some budget
airlines has raised concern that pathological gambling
could reach epidemic proportions, especially among
young people in the near future. Pathological gambling
was first reported with anti-Parkinsonian medication 7
years ago,\(^1\) but raised few initial concerns. Subsequently,
a number of tragic cases have been reported in the
international press where fortunes have been recklessly
dissipated and lives ruined. High-profile legal cases have
followed, with pharmaceutical companies being sued
for large settlements.\(^2\) This attention has, in turn, fuelled