NEWS

Sex may mediate heritability in amyotrophic lateral sclerosis

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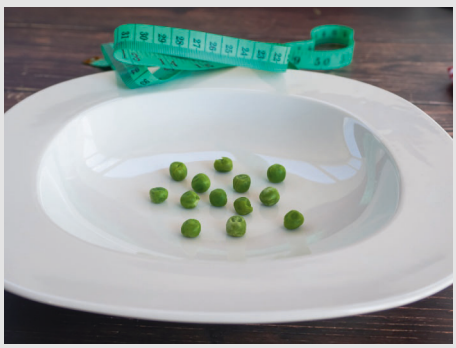
Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that leads to loss of muscle control. The fatal condition has long been suspected of having a genetic basis, as it tends to run in families and, in European populations, four gene variants explain more than half of familial cases. These observations, however, do not show the degree to which genetic factors contribute to the clinical phenotype or to the variation in lifetime risk of developing the disease. In a recent study published in *JAMA Neurology* (https://jamanetwork.com/journals/jamaneurology/article-abstract/2737804), Ryan et al. estimate the lifetime risk of developing ALS and the heritability of the condition in the Irish population. The researchers conducted a population-based parent–offspring heritability study where they assessed ALS cases recorded in the Irish ALS register, a collection of family history, demographic, and clinical data on all individuals who received an ALS diagnosis in Ireland from 1995 through 2017. They also examined the status of a hexanucleotide repeat expansion in *C9orf72*, which accounts for more than 30% of all known familial cases of ALS, in registered patients diagnosed between 2008 and 2017. The register included 32 patients whose parents also had ALS. The investigation revealed that age of onset was younger for individuals with a parental history of the condition (58 years) than the rest of the cohort (65 years). Where age-of-onset data were available for affected parents and their offspring, the researchers found that children were much younger when symptoms began (52 years) compared with their parents (70 years). The scientists also found that first-degree relatives of patients with ALS have a higher lifetime risk of developing the disease than the general population (1.4% vs. 0.3%). Additionally, the researchers determined that genetic factors account for about half (52%) of the lifetime risk of developing the disease. When the team assessed *C9orf72* status within families, they found 10 of 14 patients (71%) whose mothers had ALS carried the repeat expansion. In contrast, only four of nine patients (44%) whose fathers had ALS also carried it. Overall, heritability was higher from father to son and mother to daughter (59%) than for opposite-gender relatives (36%). Mother–daughter pairs showed the highest heritability estimates (66%), indicating a potential gender-mediated effect. Altogether, the findings show that genetics accounts for about 50% of the variance in ALS, suggesting that nongenetic elements contribute approximately equally to the condition. Ryan and colleagues conclude that high heritability estimates warrant further research to identify additional causative genes. —*V. L. Dengler, News Editor*

Researchers identify gene variants associated with anorexia



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Anorexia nervosa is a serious and sometimes fatal eating disorder. People with anorexia cope with emotional disturbances by severely restricting the amount of food they eat, exercising excessively, and/or forcing themselves to vomit after consuming food. As a result, people with the illness often have a very low body mass index (BMI). Even after therapeutic intervention, people struggling with the disease frequently fall back to dangerously low weights; death from starvation can occur. The condition affects 0.9% to 4% of women and 0.3% of men. Although studies in twins found heritability estimates of 50% to 60%, the condition is viewed primarily as a mental health disorder. Few studies examine the illness from a genetic perspective. However, in a recent genome-wide association study (GWAS) in *Nature Genetics* (https://doi.org/10.1038/s41588-019-0439-2), Watson et al. identify eight risk loci, some of which correlate with metabolic and anthropometric traits. The findings suggest metabolic as well as psychiatric components contribute to the disease. The researchers drew on data from the Anorexia Nervosa Genetics Initiative (ANGI) and the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) to conduct a GWAS including nearly 17,000 anorexia cases and more than 55,500 controls of European ancestry from 17 countries. The analysis identified eight risk loci above genome-wide significance ($P < 5 \times 10^{-8}$). Many more loci approached the significance threshold. Watson and colleagues followed up the GWAS analysis by testing single-nucleotide polymorphism (SNP)-based genetic correlations with other traits such as anxiety, years of education, physical activity, and body fat percentage. They found genetic links to other mental health disorders such as obsessive–compulsive disorder, major depressive disorder, and anxiety disorders. Yet the investigation also revealed associations with metabolic and anthropometric measures that are stronger in anorexia than in other psychiatric disorders. The researchers detected significant negative genetic correlations between anorexia and fat mass, fat-free mass, BMI, obesity, type 2 diabetes, fasting insulin, insulin resistance, and leptin and significant positive correlations with high-density lipoprotein (HDL) cholesterol. Covarying for genetic associations of BMI attenuated genetic correlations between anorexia and fasting insulin, leptin, insulin resistance, type 2 diabetes, and HDL cholesterol. The findings suggest anorexia may share genetic variation with these metabolic phenotypes independent of BMI. A bidirectional causality analysis revealed BMI-lowering alleles may increase anorexia nervosa risk. Altogether, Watson and colleagues conclude metabolic dysregulation may influence the ability of anorexia sufferers to maintain a healthy weight. The researchers suggest that focusing on metabolic and psychiatric contributions to the disease may improve outcomes. —*V. L. Dengler, News Editor*