There are still many questions to be addressed. Plants have a remarkable ability to distinguish between friends and foes, allowing *Rhizobia* to enter the root while keeping other pathogenic bacteria outside. Could this tRF regulation be critical to distinguish symbiotic and pathogenic bacteria? In other words, do plant pathogenic bacteria also use tRFs to hijack the host cellular machinery and trigger disease? It is also unknown how bacteria produce tRFs or whether they are produced under normal growing conditions or the specific tRFs necessary to trigger nodulation are only produced when needed. Recent studies have demonstrated that sRNAs are transferred from pathogen to host by using extracellular vesicles (*7*, *8*). Future work might address whether tRFs are also transported in vesicles from the bacterial cell to the host and whether the vesicles guide the tRFs to the appropriate AGO protein.

"...these genes are critical for the early stages of the establishment of the root nodulation process..."

Since the discovery in the late 19th century of biological symbiotic nitrogen fixation, efforts have focused on the transfer of the trait into cereals and other nonleguminous crops (*9*). This would reduce the use of nitrogen-based fertilizers, cutting down the economic and environmental cost of agriculture, without diminishing yield. However, this naturally occurring process is complex and finely regulated, and success in its transfer depends on a comprehensive understanding of the mechanics behind the legume-rhizobium symbiosis. The discovery of tRFs as key symbiotic regulators arguably brings us one step closer to the use of this beneficial natural phenomenon in a broader range of plant species. ■

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GENOMICS

How do genes affect same-sex behavior?

Genetic loci linked with same-sex sexual behavior cannot predict orientation of individuals

By **Melinda C. Mills**

Studies have indicated that same-sex orientation and behavior has a genetic basis and runs in families, yet specific genetic variants have not been isolated (*1*). Evidence that sexual orientation has a biological component could shape acceptance and legal protection: 4 to 10% of individuals report ever engaging in same-sex behavior in the United States, so this could affect a sizeable proportion of the population (*2*). On page 882 of this issue, Ganna *et al.* (*3*) report the largest study to date, comprising almost half a million individuals in the United Kingdom and United States, identifying genetic variants associated with same-sex sexual behavior. They provide evidence that genetic variation accounts for a small fraction of same-sex sexual behavior and uncover a relationship to the regulation of the sex hormones testosterone and estrogen as well as sex-specific differences. They also reveal complexity of human sexuality.

The genetic basis of same-sex orientation and sexual behavior has evaded discovery, largely because of the challenges of using small and nonrepresentative cohorts. Initial evidence focused mostly on gay men, providing indirect and often speculative evidence of a relationship with fraternal birth order, prenatal exposure to sex hormones, neurodevelopmental traits, or maternal immunization to sex-specific proteins (*4*). Work in the 1990s isolated a relationship with the Xq28 region on the X chromosome (*5*, *6*). Subsequent studies found similarity in the sexual orientation of identical twins, with genetics explaining 18% (for women) and 37% (for men), with the remainder accounted for by directly shared environments (such as family or school) and nonshared environments (such as legalization or norms regarding same-sex behavior) (*7*). Many of these studies could not be replicated, and although twin and family studies found a genetic basis, they could not isolate variants associated with same-sex orientation at specific genetic loci.

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The study of Ganna *et al.* involved a genome-wide association study (GWAS), in which the genome is analyzed for statistically significant associations between single-nucleotide polymorphisms (SNPs) and a particular trait. SNPs are single-nucleotide base differences in DNA that allow the measurement of variation in a population. The approach of using a large cohort, sex-specific analyses, and complex measures of sexuality (for example, proportion of same-sex partners to total sexual partners, attraction, and identity) allowed the detection of genetic—and even sex-specific—variants that had evaded prior research.

Ganna *et al.* analyzed the association of ever having sex with a same-sex partner with SNPs in genomes from the UK Biobank (408,995 individuals) and from 23andMe (68,527 individuals from the United States), with more males having engaged in same sex behavior than females across equally sex-divided cohorts. They discovered five loci that correlate with ever having same-sex behavior: two loci across both sexes, two in males, and one in females. Comparatively, the average number of loci found in all GWASs from 2005 to 2018 is 13.6, but as cohort sizes increased to over a million, many GWASs since 2016 now find hundreds or even thousands of loci (*8*). One of the most intriguing findings of Ganna *et al.* are differences in genetic contribution between males and females to same-sex sexual behavior and the weak across-sex genetic correlation of 0.63. A genetic correlation of 1 denotes perfect association with genetic variation between the sexes, a score of 0 denotes no correlation. For comparison, related traits such as reproductive behavior have a high genetic correlation between males and females of 0.86 for an individual's age when they have their first baby and 0.97 for the number of children ever born to an individual (*9*). They speculate that the reason for the differences in genetic contribution between the sexes may be biological (related to testosterone and estrogen) and nongenetic factors, such as gendered social norms about sexual behavior. It is also noteworthy that Ganna *et al.* do not find evidence that sexual orientation is associated with variants on the X chromosome (*5*, *6*).

When using a different technique called SNP-heritability—comparing the genetic similarity of all unrelated individuals in the sample with their phenotypic similarity of same-sex sexual behavior—Ganna *et al.* found that genetics could eventually account for an upper limit of 8 to 25% of same-sex sexual behavior of the population. However, when all of the SNPs they identified from the GWAS are considered together in a combined score, they explain less than 1%. Thus, although they did find particular genetic loci associated with same-sex behavior, when they combine the effects of these loci together into one comprehensive score, the effects are so small (under 1%) that this genetic score cannot in any way be used to predict same-sex sexual behavior of an individual. This difference between the population SNP-based estimates of 8 to 25% versus individual polygenic estimates (multiple SNPs combined) of the influence of genetic variation on same-sex sexual behavior of 1% is attributed to a lack of measuring rare variants; polygenicity, in which many variants have small effects; or nonadditive genetic effects, such as dominance or epistasis.

In 1948, the biologist Alfred Kinsey proposed the "heterosexual-homosexual rating scale," specific to men, which ranges from exclusively heterosexual to exclusively homosexual, measured with the same scale for all sexualities (*10*). Ganna *et al.* nuanced this approach and undertook an additional GWAS of the proportion of same-sex partners to total partners (using the UK Biobank data), and from 23andMe, the question "With whom have you had sex?" with answers ranging from "other sex mostly" across six categories to "same sex only." The genetic correlation identified in the GWAS of whether a person had ever engaged in sex with someone of the same sex and the more complex measure of proportion of same-sex partners was 0.73 for men but only 0.52 for women. This means that genetic variation has a higher influence on same-sex sexual behavior in men than in women and also demonstrates the complexity of women's sexuality. This may also reflect sex-specific social norms regarding the number of sexual partners women have, particularly given the age range of participants in this study. In addition to showing sex differences, what is striking is that these different measures of sexuality—proportion of same-sex partners and engagement in same-sex sexual behavior—are associated with different genetic loci and with other traits. The finding that the genetic effects differentiating heterosexual from same-sex sexual behavior are distinctive, particularly in relation to the number of sexual partners and other sexual measures (identification and attraction), challenges the use of Kinsey's scale across all groups. This reflects voices from the LGBTQ+ (lesbian, gay, bisexual, transgender, queer+) community arguing that a range of sexualities exist. Sexuality is dynamic, with the ability to express and realize sexual preferences, and is thus also shaped and regulated by cultural, political, social, legal, and religious structures.

Ganna *et al.* did not find evidence of any specific cells and tissues related to the loci they identified. Male-specific loci that were associated with ever experiencing same-sex behavior were linked to olfactory receptor genes, sensitivity to certain scents, and regulation of testosterone and estrogen by a variant located upstream of the transcription factor 12 (*TCF12*) gene, which is essential for gonad development in mice, and a variant located downstream of the sex-determining region Y (*SRY*) gene, which is responsible for male sex determination in humans.

A caveat common to most genetic discoveries (*8*) is that the study of Ganna *et al.* includes only European-ancestry populations from Western high-income countries (United Kingdom, United States, and Sweden for replication). The data also come from older individuals living under stricter social norms and legislative regulations (23andMe, mean age 51.3 years; UK Biobank, aged 40 to 69 years), overrepresented by higher socioeconomic status groups (*11*). Although a more complex continuum beyond two categories of ever having sex with someone of the same sex was possible by using the 23andMe cohort, these data had an unusually high number of individuals who ever had same-sex partners (19%), potentially biasing the data.

There is an inclination to reduce sexuality to genetic determinism or to resent this reduction. Attributing same-sex orientation to genetics could enhance civil rights or reduce stigma. Conversely, there are fears it provides a tool for intervention or "cure." Same-sex orientation has been classified as pathological and illegal and remains criminalized in more than 70 countries, some with the death penalty. Because Ganna *et al.* found that the genetic loci they isolated predict less than 1% of same-sex behavior of individuals, using these results for prediction, intervention, or a supposed "cure" is wholly and unreservedly impossible. Rather, by calculating the ceiling of what is potentially attributed to genetics with a SNP-heritability of 8 to 25% and isolating specific loci, this study serves as a guide to the potential magnitude of genetic effects we may eventually measure and a sign that complex behaviors continue to have small, likely polygenic, influences. Future work should investigate how genetic predispositions are altered by environmental factors, with this study highlighting the need for a multidisciplinary sociogenomic approach. ■

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