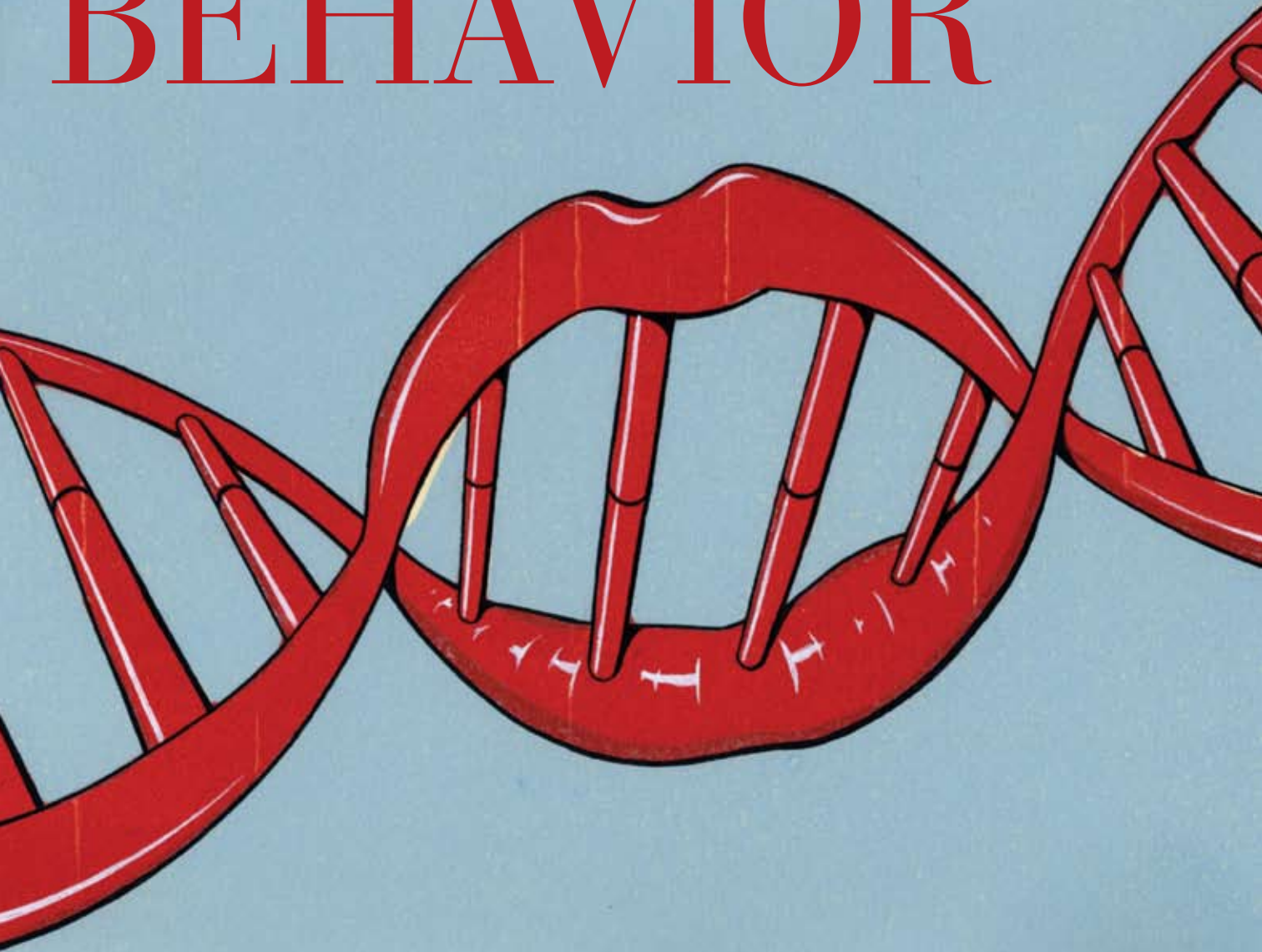


THE GENETICS OF FEMALE SEXUAL BEHAVIOR



Understanding how common variants in the human genome are associated with sexual behaviors will improve the diagnosis of disorders and shed light on behavioral tendencies. Novel genes are used to highlight new pathways for future drug development—greatly needed in the area of female sexual health.

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Rapid progress in genome science over the past few years has already had an impact on research in different fields.¹ Genetic research on human behaviors and female sexuality lags far behind research about common diseases; however, results from heritability studies have shown clear genetic influences on age at first intercourse, number of sexual partners, fidelity, sexual functioning, and sexual dysfunction. Unreplicated candidate gene studies have implicated genes involving dopamine, serotonin, and vasopressin, but these results are far from conclusive.

In this article, we critically discuss current genetic studies on female sexual behavior and highlight the importance of future genetic research.

How: Genotyping techniques and study designs

Genotyping and other newly established technologies enable us to routinely scan human DNA for up to a million genetic markers (eg, single nucleotide polymorphisms), covering most of the common variants in most of our genes.

There are several study designs that behavioral geneticists use to detect genetic influences on behaviors and disorders (SIDEBAR). These include studies of family correlations, adoption studies, and twin studies. Unlike other designs, the study of twins enables us to separate family environment from genetic effects and to accurately account for age and cohort effects.

In the comparison of monozygotic (MZ, identical) and dizygotic (DZ, nonidentical) twins, significantly closer similarities in MZ twins for the factor of interest indicate a clear genetic influence. This greater similarity implies heritability (SIDEBAR). Within any population, the influence of specific genes is assessed by association studies. Initially, association studies targeted specific known (candidate) genes; more recently, they have been using multiple gene markers in a blind fashion called a genome-wide scan.²

Female sexual dysfunction

Female sexual dysfunction (FSD) includes disorders of desire, arousal, orgasm, and pain.³ FSD is a highly prevalent health problem, with detrimental effects on women's quality of life.⁴ Knowledge about the etiology of FSD combines biological, psychological, and interpersonal factors. Only recently has emphasis shifted to genetic factors.



KEY POINT

Genetic variations in dopamine and serotonin genes may have a role in disorders of desire and arousal.

Frequency of orgasm in twin studies

The genetic and environmental influences on the self-reported frequency of orgasm in women during sexual intercourse and masturbation were investigated in 2 concurrent but independent twin studies (N=4037; N=3080).^{5,6} The prevalence of women who never or rarely achieved orgasm was similar in both studies: 32% to 35% reported difficulties with orgasm during intercourse; 18% to 21%, during masturbation. Furthermore, significant heritability estimates were reported: 31% to 34% for difficulty reaching orgasm during intercourse; 45% to 51%, during masturbation. Notably, both studies found a huge variance in the ability to achieve orgasm during intercourse compared with masturbation, suggesting different subgroups for future research. Although neither study used validated questionnaires, the results in both studies were strikingly similar and reassuring.

Desire and arousal: Dopamine and serotonin genes

Preliminary evidence shows a genetic influence on desire and arousal, particularly regarding the role of dopamine and serotonin genes. Working with a small

sample of Israeli students (N=148), Ben Zion et al looked at self-reported scores of sexual desire and arousal in relation to 5 specific regions on the DRD4 (dopamine receptor) gene.⁷ The authors found the DRD4 5-locus haplotype (19%) to be significantly associated with desire, arousal, and function scores, but they did not separate the results of the men from those of the women.

Another molecular genetic study examined a variant of the serotonin 5HT2A gene, previously suggested to mediate the sexual side effects of antidepressants (N=89).⁸ The authors found that participants carrying the GG genotype of the 5HT2A gene were significantly more likely to have sexual dysfunction than those carrying the GA genotype.

Mating and bonding

Population studies have documented the heritability of such behaviors as infidelity, number of sexual partners, and age at first sexual intercourse. Studies to link these behaviors to specific genes have been promising but must be replicated.

Fidelity and number of partners

A twin study by Cherkas et al explored the heritability of infidelity and lifetime number of sexual partners (N>1600).⁹ Heritability estimates were 41% for infidelity and 38% for number of sexual partners. A strong genetic correlation between infidelity and number of partners was reported (0.47), showing a genetic link between the 2 traits. Encouraged by genetic research on pair-bonding animals,¹⁰ Cherkas et al examined possible associations of infidelity with the arginine vasopressin 1A receptor gene (AVPR1A).⁹ They identified 3 possible but nonsignificant linkage areas associated with infidelity and number of sexual partners, but they were unsuccessful in associating either behavior with the AVPR1A gene.

A study of 4925 Finnish twins aged 23 to 27 years old offered support for a genetic influence on number of partners.¹¹ Exploring 3 sexual health variables (abstinence/initiation of sexual intercourse, number of sexual partners, and age at first sexual intercourse) by using self-reported information, the investigators found significant genetic and non-shared environmental influences for all 3 measures.

What Is Heritability (H²)?

Definition: The proportion of phenotypic variation in a population that is attributable to genetic variation.

How it is determined: It is most frequently estimated by comparing twins. Identical twins (monozygotic, MZ) are twice as genetically similar as nonidentical twins (dizygotic, DZ). Therefore, heritability is approximately twice the difference in correlation between MZ and DZ twins.

$$H^2 = 2(r[MZ] - r[DZ])$$

r = Coefficient of relatedness
For MZ, r = 1.0; for DZ, r = 0.5

How it is used: Heritabilities greater than 60% are considered to be high. Heritabilities ranging from 25% to 59% are moderate but still clearly significant. The greater the error of the measurement, the lower the heritability estimate.

Ms Burri reports that she has received a grant from Pfizer. Dr Spector reports that he has received grants from Pfizer and Merck Sharp & Dohme and is a consultant to Oo Pharmaceuticals and Servier.

Key Concepts in Genetic Research

Branches of genetics

- **Population genetics:** Examines the forces that may alter the genetic composition of a population in time (eg, mutation, intermixture between groups, and random changes incurred by the sampling process in reproduction from generation to generation)
- **Molecular genetics:** Addresses the expression of genes by studying their structure and function
- **Epigenetics:** Describes the mechanism by which chemical switches affect the activity of genes, turning them on and off or modifying their function, without changing the DNA structure

Key terms

- **Gene:** Units of heredity information that consist of DNA
- **Allele:** An alternative form (variant) of a gene
- **Genotype:** The total set of alleles/genes possessed by an organism
- **Phenotype:** The observable characteristics of an organism, determined by the genetic makeup and environmental influences
- **Haplotype:** A set of alleles that tend to be inherited together
- **Gene locus:** The specific place on a chromosome where a gene is located
- **Candidate gene:** Any gene thought likely to cause a disease

- **Genetic marker:** A gene or DNA sequence on a known chromosome location that is associated with a particular gene or trait
- **Single nucleotide polymorphism (SNP):** A DNA sequence variation that occurs when a single nucleotide in the genome differs between members of a species (eg, ACGTTTA vs ACGTTTC)
- **Familial aggregation:** Occurrence of a trait in more members of a family than can be readily accounted for by chance

Types of genetic studies

- **Genetic association study:** Similar to a case-control study; determines whether a genetic variant is associated with a disease or trait by determining whether single-locus alleles or genotype frequencies are different between 2 groups (eg, cases vs controls)
- **Linkage study:** A study in families aimed at establishing linkage between genes and a trait. Linkage is the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome
- **Genome-wide association study (GWAS):** A GWAS tries to identify genetic associations with observable traits by examining the genetic variation across the whole human genome (300 to 1 million markers)

KEY POINT

Twin studies have shown significant genetic influences on age at first sexual intercourse.

Large studies examining numbers of partners have associated specific genes with certain sexual behaviors. In one study (N>2500), there was an association between the dopamine transporter gene DAT1 and the self-reported number of sexual partners among young men but not among women.¹² In another (N=717), an association was shown between the A1 DRD2 allele and having had fewer sexual partners in the past year.¹³

Age at sexual initiation

Previous twin studies have also reported significant genetic influences on age at first sexual intercourse.^{14,15} In a recent study, Waldron et al found that genetic influences on teenage pregnancy were nonsignificant in a younger twin cohort, whereas the older cohort showed significant heritability of both teenage pregnancy and age at first sexual intercourse.¹⁶ These results suggest the role of changing cultural attitudes and environment.

Miller et al looked for potential candidate genes by analyzing associations between 3 dopamine receptor polymorphisms and the age at first sexual intercourse in men and women (N=414).¹⁷ A significant association with the DRD2 allele was found, being stronger among men than women. Offering some general support to those findings recently, albeit on different genes, Guo and Tong found an association between the relatively rare DRD4 3-repeat allele and first intercourse (N=2552).¹⁸ Prichard et al found 2 polymorphisms within the AVPR1A (vasopressin) gene to be associated with age at first sexual intercourse in men and women (N=2085).¹⁹

Sexual orientation

The limited behavioral genetic investigations to date on female sexual orientation provide some inconsistent evidence for a heritable component. However, the genetic findings imply that sexual orientation is more a matter of biology (genetic



KEY POINT

Genetic findings imply that sexual orientation is more a matter of biology than a factor of culture and family upbringing.

TABLE 1

Genes Implicated in Female Sexual Behavior

Gene	N	Significant Association
DAT1 Dopamine transporter gene	2500	Number of sexual partners ¹²
DRD2 Dopamine D2 receptor gene	414 717	Age at first sexual intercourse ¹⁷ Fewer sex partners in the past year ¹³
DRD4 Dopamine D4 receptor gene	148 2552	Desire, arousal, and function ⁷ Sexual transition ¹⁸
5HT2A Serotonin	89	General sexual dysfunction ⁸
AVPR1A Vasopressin	2085	Age at first intercourse ¹⁹

susceptibility) with an element of random lifestyle influences than a factor of culture and family upbringing.

Differing interpretations of twin studies

Studies conducted on exclusively female samples are rare. Bailey et al reported significant heritability estimates for homosexual orientation in a sample of female twins and adoptive sisters.²⁰ In contrast, a study on female nonsiblings was not able to distinguish between genetic and shared environmental sources, although familial aggregation was reported.²¹

A study on twins enrolled in the Australian Twin Registry provided strong evidence for the existence of additive genetic influences on the phenotype sexual orientation in males and females.²² Additive genetic influences result in many gradations between the 2 extreme genotypes, because the overall effect of genetic alleles on the phenotype is a combination of the alleles' individual effects. (Conversely, with nonadditive genetic effects, the genes interact with each other by altering their effects; for example, one dominant gene erases the effects of another.) Considering the additive genetic findings, it is more than likely that homosexuality is not an "either-or" phenomenon but rather a continuous trait influenced by numerous genes. Heritability estimates in the Australian twin study ranged from 50% to 60% in women (N=4901).²²

In contrast, Bailey and Zucker used the same Australian twin sample and assessed sexual orientation, childhood gender nonconformity, and continuous gender identity.²³ This group found that only childhood gender nonconformity was significantly heritable for both men and women.

The few positive results with regard to genetic influences on female sexual orientation are confirmed by recent studies on gender identity disorder (GID). GID has been associated with sexual orientation by a considerable amount of evidence.²³ Several twin studies reported significant heritabilities for GID ranging from 37% to 62% (N=1891; N=314).^{24,25} Those findings support a strong heritable component to GID and may strengthen the assumption that childhood gender nonconformity is the heritable component of adult sexual orientation.²⁶

Unsuccessful efforts to locate a specific gene

So far, the only linkage study trying to find potential gene loci and candidate genes in female homosexuality has been unsuccessful.²⁷ The absence of an effect is inconclusive and likely due to nonrepresentative samples, inadequate gene coverage, and very small sample sizes.

Future directions

Genetic research related to female sexual behavior trails behind genetic research in other areas. Many of the candidate gene studies mentioned are probably false positives because they rely on very small sample sizes and so far have not been replicated (TABLE 1). The heritability results, however, are consistent and point toward significant genetic contribution, because they show little or no shared family environmental effects and significant heritability estimates for most forms of female sexual behavior (TABLE 2).

Recently, geneticists have realized that genes are not the only factor in genetics; chemical switches affect the activity of genes without changing the DNA

TABLE 2

Heritability Rates of Female Sexual Behavior

Sexual Behavior	N	Heritability (H ²)
Masturbatory orgasm difficulties ^{5,6}	4037; 3080	45%; 51%
Intercourse orgasm difficulties ^{5,6}	4037; 3080	31%; 34%
Infidelity ⁹	1600	41%
Number of sexual partners ⁹	1600	38%
Sexual orientation ²²	4901	50%-60%

structure of the genes. Called epigenetic variations, these differences are known to result in markedly different phenotypes in genetically identical animals.²⁸ There is some evidence that epigenetic effects²⁹ also occur in humans³⁰ and can be inherited. Developing methods of defining epigenetic variations in humans is a future challenge of genetic research.

In the future, a better understanding of the interactions between genes and the environment could guide the development of treatments for sexual problems in women and help to destigmatize their complaints. ■

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Study volunteers needed



We are looking for volunteers who are suffering from any form of female sexual dysfunction (FSD), including:

- HYPOACTIVE SEXUAL DESIRE DISORDER
- AROUSAL DISORDER
- ORGASM DISORDER
- SEXUAL PAIN DISORDER

The study aims to identify certain genes and biomarkers that might be involved in the different subtypes of FSD.

The procedure is easy and strictly confidential.

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