Unraveling the Genetics of Sexual Orientation: A Historical and Contemporary Perspective

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ABSTRACT Research into the genetic basis of homosexuality and broader sexual diversity has progressed from early 20th-century sexology to modern genomics. Von Krafft-Ebing and Hirschfeld first suggested heritable influences, and Kallmann's twin studies in the 1950s introduced a systematic framework to separate genetic from environmental contributions to sexual orientation. Twin and related designs subsequently reported heritability estimates of 31–74% in males and 27–76% in females. Despite periodic critiques, the equal-environment assumption has remained broadly methodologically robust. Genome-wide association studies (GWAS) marked a major advance. Although early studies were limited by sample size, recent large-scale GWAS have identified significant single-nucleotide polymorphism associations with same-sex sexual behavior, reinforcing a complex, polygenic architecture. Polygenic scores (PGS) or polygenic risk scores (PRS) now offer quantitative estimates of individual genetic predisposition and may help build integrative models of human sexual behavior when combined with environmental and developmental data. Future work should harmonize phenotype definitions across identity, attraction, and behavior; aggregate measures to reduce noise; and adopt systems-level, multi-omics approaches that move beyond reductionism. Interdisciplinary collaboration across genetics, neuroscience, psychology, and social sciences is essential, in addition to greater attention to understudied domains (female homosexuality, sexual fluidity, bisexuality, pansexuality/polysexuality, asexuality, and transgender/trans-sexuality). Community-based participatory research can improve inclusivity and real-world relevance. Overall, the field has moved beyond a single gay gene toward models integrating genetic, epigenetic, and environmental influences, with sexogenomics together with GWAS, PGS/PRS and system biology providing a unifying framework that also engages ethical and societal dimensions.

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The German psychiatrist Richard von Krafft-Ebing, author of the seminal work *Psychopathia Sexualis* (1886), and the German physician and sexologist Magnus Hirschfeld, who advanced the *Zwischenstufenlehre* [Doctrine of Sexual Intermediaries; 1922], were among the first to propose a potential genetic component to homosexuality, although their hypotheses were advanced through anecdotal observations and with divergent implications. Krafft-Ebing viewed homosexuality as an aberrant sexual behavior, consistent with prevailing moral and medical frameworks of the time.

In contrast, Magnus Hirschfeld, a pioneer in advocating sexual diversity [1], regarded homosexuality as a natural variation within the spectrum of human sexuality. According to Hirschfeld, the biological basis of homosexuality was underscored by familial clustering, particularly among siblings. Based on his observations and earlier reports, same-sex behaviors appeared to aggregate in family units, with studies reporting that up to 35% of homosexual males had similarly oriented brothers. This familial pattern was consistent with findings by Lang (1945) and Jensch (1941) [2], who noted a significant deviation in the expected sex ratio among siblings of homosexual males.

In addition to Hirschfeld [1], other key pioneers have shaped the scientific study of human sexuality. Havelock Ellis advanced a tolerant view of homosexuality as a natural variation rather than a pathology. Alfred Kinsey's large-scale surveys in mid-20th century America reframed sexual orientation as a continuum, exemplified by the Kinsey Scale, which profoundly influenced public and scientific discourse.

This research paved the way for the first systematic, scientifically rigorous investigations into the genetics of homosexuality conducted by Franz Kallmann in the early

1950s. Kallmann [2,3] was a pioneer in exploring the genetic underpinnings of psychiatric disorders and psychological traits. He employed twin studies to disentangle the influences of heredity and environment in psychiatric etiopathogenesis. He observed that "various forms of sex behavior … have been vulnerable to rather preposterous misapplications of that ancient dichotomy perpetuated in the presumably antithetic setting of the nature-nurture controversy" [2]. By introducing twin studies, he laid the groundwork for subsequent behavioral genetic research.

In recent decades, the seemingly intractable nature-versus-nurture debate [4] has been reframed. The American psychologist Eric Turkheimer articulated this shift through his "three laws of behavior genetics" [5]. Turkheimer's principles underscored the complex interplay of genetic and environmental factors: heritability plays a significant role in all human behavioral traits, genetic factors generally exert more influence on behavioral traits than the familial environment, and a portion of behavioral traits remains unexplained by either genetic or environmental factors. These principles apply to sexual behaviors, including homosexuality, where heritability and environment interact in complex ways.

SEXUAL ORIENTATION IS NOT DETERMINED BY A SINGLE "GAY GENE" BUT REFLECTS A COMPLEX, POLYGENIC TRAIT INFLUENCED BY GENETIC, EPIGENETIC, AND ENVIRONMENTAL FACTORS.

However, the optimism of Kallmann's prediction that "adequately selected and statistically refined combinations of twin-sibship studies … with cytological, biometric and endocrinological investigations in the given family units are virtually certain to play an essential part in the further advancement of our knowledge regarding the biological components of sexual maturation and the differentiation of sexual behavior patterns" [2] has not been realized.

Despite decades of research, the elusive search for a so-called *gay gene* has failed to yield conclusive findings. Instead, studies have produced a collection of inconsistent, controversial, and often irreproducible genetic loci [6,7].

In this review we provide a comprehensive overview of the key discoveries in the genetics of sexual orientation and their broader methodological implications. Special attention was given to charting a path for future research in this challenging but critical domain. By synthesizing historical and contemporary findings, we highlight the complexities of genetic research in understanding human sexuality while emphasizing the need for innovative approaches and interdisciplinary collaboration in future studies.

STUDIES ON TWINS REARED TOGETHER AND APART: INSIGHTS INTO HERITABILITY

The classical twin study, a foundational approach in genetic epidemiology, compares the resemblance of monozygotic (identical, derived from a single zygote) and dizygotic (fraternal, resulting from multiple ovulations) twins to estimate the heritability of traits and the proportion of variance attributable to genetic factors. This design, which has been instrumental in understanding the genetic basis of human traits, is one of the most robust and widely applied methods in the field [8]. While often attributed to Francis Galton, whose 1875 work predated a full understanding of monozygotic and dizygotic distinctions, it was Ronald Fisher who formalized the quantitative genetic theory necessary for heritability estimation [8].

Fisher's work demonstrated that dizygotic twins, like siblings, share on average 50% of their genes. This fact has been experimentally validated through genome-wide genotyping studies [8], such as Visscher et al. [9], which reported that gene-sharing among siblings has a standard deviation of approximately 4%. Notably, 2.5% of sibling pairs share between 45–48% of their genes, while another 2.5% share less than 42%, reflecting subtle variances in genetic relatedness.

A cornerstone of twin studies is the equal environment assumption, which posits that the environments experienced by monozygotic and dizygotic twins are comparable in their influence on traits of interest. Decades of scrutiny support the validity of this assumption, despite evidence that monozygotic twins may experience more similar treatment due to their genetic resemblance. Importantly, these differences in treatment have not been shown to systematically bias phenotypic traits of interest.

CHALLENGES AND ADVANCES: THE MISSING HERITABILITY PROBLEM

The advent of genome-wide association studies (GWAS) has provided new insights but also raised questions about the so-called *missing heritability problem*. GWAS suggests that single-nucleotide polymorphisms (SNPs) account for only about half of the heritability estimated from twin studies [10]. This discrepancy can be partially resolved by accounting for the incomplete coverage of rare variants in commercial SNP arrays and the linkage between SNP markers and causal variants. When these factors are adjusted, SNP-based heritability estimates

converge with those from twin studies [10]. Furthermore, analyses of densely genotyped sibling pairs yield heritability estimates consistent with traditional twin studies, underscoring that heritability is not missing but rather awaits discovery through more advanced molecular tools and larger datasets [8].

EXPLORING COMPLEX TRAITS: SEXUAL ORIENTATION AS A CASE STUDY

Twin studies have also been pivotal in examining complex traits such as sexual orientation. Kallmann [2,3], Pillard, and Bailey pioneered studies indicating that homosexuality exhibits heritability patterns, estimated at 31–74% for males and 27–76% for females [6]. For example, Whitam et al. [11] reported a concordance rate of 65.8% for homosexuality among monozygotic twins (34 male and 4 female pairs) compared to 30.4% among dizygotic twins. These findings suggest a substantial genetic component, although environmental influences also play a significant role. To disentangle shared (common) and non-shared (unique) environmental factors, researchers have adapted the classical twin study design to include twins raised apart. A notable example is the study by Eckert and colleagues [12], which examined six pairs of monozygotic twins reared apart. Among these, at least one individual in five pairs identified as homosexual, while one individual in the remaining pair identified as bisexual. Interestingly, female twin pairs exhibited discordance for homosexual behavior, hinting at sex- and gender-specific developmental pathways.

WHILE LARGE-SCALE GENETIC STUDIES HAVE IDENTIFIED RELEVANT SIGNALS, EVEN THOUGH ONLY PARTIALLY REPLICATED, IMPORTANT GAPS REMAIN, INCLUDING LIMITED RESEARCH ON FEMALE HOMOSEXUALITY, SEXUAL FLUIDITY, BISEXUALITY, PANSEXUALITY ASEXUALITY, AND TRANSGENDER IDENTITIES.

TOWARD A NUANCED UNDERSTANDING OF SEXUAL ORIENTATION

These studies highlight that homosexuality is likely a heritable complex trait shaped by a dynamic interplay of genetic and environmental factors. Fisher's variance decomposition techniques provide a framework for partitioning these influences. Evidence points to sex- and gender-specific differences in the heritability and developmental pathways of sexual orientation, with female homosexuality potentially following distinct and understudied trajectories [6,13]. Homosexuality and broader sexual diversity appear to result from a confluence of genetic predispositions, environmental exposures, and acquired traits. This nuanced perspective emphasizes the need for further research, particularly into the developmental pathways of female sexual orientation, which remain less well understood and dramatically understudied.

GENETIC LINKAGE STUDIES

In 1993, Hamer and colleagues [14] provided substantial evidence supporting a genetic factor in male sexual orientation. They arrived at this conclusion by examining family recurrence patterns and conducting molecular analysis of the X chromosome within families characterized by multiple homosexual brothers. Specifically, they were the first to propose that genetic loci associated with sexual orientation exist within a region spanning approximately 4 million base pairs located on the distal end of the X chromosome. The authors capitalized on the availability of chromosomal genetic maps densely populated with highly polymorphic markers, allowing them to employ standard techniques in modern human genetics, such as pedigree analysis and family DNA linkage studies, to investigate complex phenotypes and traits, including human sexuality.

The reception of this discovery has been mixed: some scholars and the media have reacted to this finding with optimism and excitement, along with doubt and critique [6,7]. While such a contribution may have increased awareness and acceptance of homosexuality, a replication study [15] has failed to corroborate Xq28 as the gay gene [14].

CANDIDATE GENE ASSOCIATION STUDIES

Studies utilizing the candidate gene approach investigate genetic variations within a predefined set of genes that are hypothesized to be associated with a particular trait or phenotype. Typically designed as case-control studies, this methodology offers a targeted and hypothesis-driven framework that can be advantageous in several ways. For example, it is relatively cost-effective and straightforward to implement compared to genome-wide approaches, making it accessible for smaller-scale research projects or studies with limited funding.

Despite these strengths, the candidate gene approach is increasingly criticized for its inherent limitations. One major drawback is its susceptibility to various forms of bias, including selection bias and publication bias, which can distort findings. In addition, the approach often experiences limited statistical power, particularly when

dealing with complex, polygenic traits influenced by numerous genes and environmental interactions. This limitation arises because the predefined genes are selected based on prior knowledge or assumptions, which may not always capture the true genetic architecture of the trait being studied. Moreover, the candidate gene approach has faced significant challenges in replicability and reliability. In many cases, the associations identified in these studies fail to hold up under more rigorous scrutiny or in larger, more diverse cohorts. A striking example of its limitations is its inability to uncover the molecular underpinnings of human sexuality, a complex and multifaceted trait. As noted by Bragazzi et al. [6], the candidate gene approach has been largely unsuccessful in providing meaningful insights into the genetic basis of human sexuality, highlighting the need for more comprehensive and robust methodologies.

GENOME-WIDE LINKAGE AND ASSOCIATION STUDIES

Genome-wide linkage and association studies represent significant technological and methodological advancements, even if the discovery of the putative genetic locus is sample size-dependent and, at least initially, most GWAS were statistically underpowered to detect significant associations. As such, once again, it is not surprising that, for example, the study by Sanders and co-authors [16] of 2308 individuals could not find any SNP reaching the statistical significance threshold, whereas Ganna and colleagues [17], using a sample of 477,522 individuals, could identify five significant SNPs related to same-sex sexual behavior, highlighting brain development, olfactory processing, and neuronal excitability as pathways potentially involved in the development of sexual orientation.

MOVING TO THE POLYGENIC RISK SCORES

A polygenic score (PGS) or polygenic risk score (PRS) represents an estimation of an individual's genetic predisposition to a specific trait or disease. This score is calculated based on the person's genetic profile and relevant data from GWAS. While current PGSs/PRSs typically account for only a small portion of trait variability, their strong association with the primary contributor to phenotypic variation, namely genetic predisposition, has led to their widespread use in biomedical research. PGSs/PRSs have diverse applications, including assessing the shared underlying causes between different traits, evaluating how useful genetic data is in predicting complex diseases, and as part of experimental investigations. For example, experiments may compare outcomes, such as gene expression or cellular responses to treatment, among individuals with low and high PGS/PRS values. With the continuous growth in GWAS sample sizes and the increasing power of PGSs/PRSs, they are poised to become pivotal tools in research and personalized medicine. However, despite their significance and expanding popularity, PGS/PRS-based approaches are still underutilized and studies harnessing such approaches are scarce, especially in the field of human sexuality.

A notable exception is given by a recent study [18], which explored the genetic and mental health correlations of gender diversity by analyzing PGSs/PRSs in two independent samples. The researchers aimed to determine whether gender-diverse individuals exhibited higher rates of mental health challenges due to genetic factors or environmental influences. The findings indicated that gender diversity was associated with increased mental health challenges, with externalizing behaviors being linked to the PGS/PRS for attention-deficit hyperactivity disorder and internalizing behaviors showing associations with PGSs/PRSs for depression and neuroticism. However, contrary to prior assumptions, gender diversity itself was not significantly correlated with neuropsychiatric PGSs/PRSs. Instead, the study found a strong positive association between nonbinary gender diversity and the PGS/PRS for cognitive performance, suggesting that cognitive capacity may play a role in the expression of gender diversity. In addition, binary gender diversity was positively associated with the PGS/PRS for non-heterosexual sexual behavior, reinforcing prior research on the genetic overlap between gender identity and sexual orientation. To validate these findings, the study examined a larger dataset using categorical gender identity classifications. This analysis confirmed that transgender and nonbinary individuals exhibited higher cognitive performance PGSs/PRSs than their cisgender counterparts.

While gender diversity was phenotypically linked to poorer mental health outcomes, its strongest genetic correlations were not psychiatric in nature but rather cognitive. The study also explored potential gene–environment interactions, finding that the relationship between gender diversity and mental health challenges was more pronounced in individuals with higher PGSs/PRSs for schizophrenia and depression, suggesting that genetic predisposition may interact with environmental stressors, such as discrimination or minority stress, to influence mental health outcomes in gender-diverse individuals.

In conclusion, the study challenges the assumption that gender diversity is inherently linked to psychiatric disorders at the genetic level, highlighting the complexity of the relationship between genetics, cognition, and gender identity. These findings are anticipated to contribute to a more nuanced understanding of the biological and environmental factors that shape human sexuality, including gender diversity, and mental health, emphasizing the importance of considering both genetic predispositions and social determinants in future research.

SUGGESTIONS FOR FUTURE RESEARCH

Genetic/genomic studies on homosexuality, and more broadly sexual diversity, have utilized a variety of measures and definitions of the complex trait under study, spanning from self-identification, attraction, fantasy, and behavior to corroboration from secondary sources, stereotypes, sexual feelings, and sexual behavior [6]. This finding may, at least partially, explain the discrepancies among the conclusions reported across different published studies.

The complexity of sexuality-related traits, encompassing various levels of identity belongings, personal feelings, psychological conditions, experiences, and behaviors, necessitates the aggregation of measures to mitigate against the noise that can arise from individual experiments, that need to be carefully reconciled, harmonized, integrated, and combined into a comprehensive, coherent theoretical framework that can really advance the studies in the field of human sexuality. The establishment of consensus on the most suitable variables to utilize is warranted as well.

FUTURE RESEARCH SHOULD ADOPT SYSTEMS BIOLOGY APPROACHES, HARMONIZE TRAIT DEFINITIONS, AND INTEGRATE LGBTQ+ COMMUNITY VOICES TO ENSURE INCLUSIVITY AND REAL-WORLD RELEVANCE.

The intricacies of biological (biochemical, biophysical, and physiological) [19] as well as psychological [20] conditions mandate a systems-based approach to overcome the drawbacks of reductionist and deterministic approaches and to pinpoint research areas and methodologies that can fully embrace the complexity of the topic under scrutiny in terms of inter- and intra-individual variability and determine which aspects are most relevant to both sexologists and the lesbian/gay/bisexual/transgender-transsexual/queer plus (LGBTQ+) community.

Given that this community is socially vulnerable, marginalized, and stigmatized, being disproportionately impacted by disparities in physical and mental health, community-based participatory research represents a major framework that centers on fostering equitable collaboration between scientific researchers, community members, and other stakeholders. Its goal is to enhance community health, diminish health disparities, and promote health equity. This adaptable approach actively involves the community and acknowledges and harnesses the diverse strengths and contributions of all research partners. It is also action-oriented, aiming not only to comprehend problems but also to generate jointly created solutions. Community-based participatory research-related principles encompass various elements: shared learning between academic and community partners, enhancing capacity and empowerment, advancing mutually advantageous knowledge and discoveries, promoting two-way communication in leadership and decision-making processes, and encouraging a lasting commitment to the cause of counteracting health disparities in the LGBTQ+ community [21,22].

There is a requirement for the amalgamation of various specializations and methodologies (medical, sexological, psychological, neurobiological, physiological, and genetic) to gain deeper insights into sexuality-related traits, and it is essential to draw lessons from each of these disciplines.

Furthermore, there is an urgent demand for more extensive research on various facets of human sexuality, that have remained relatively understudied, such as female homosexuality, sexual fluidity, sexuality in terms of sex- and gender-specific differences, and all the forms of sexual diversity (from bisexuality to pansexuality/polysexuality and asexuality, as well as trans-genderism/trans-sexuality) that are usually erased and hidden from a highly judgmental, heteronormative sexual landscape, to better capture and understand all the nuances in human sexuality.

TOWARD SEXOGENOMICS

During the century-long quest for the gay gene [23], researchers have coped with the frustration of apparently conflicting results, learning that homosexuality and more broadly sexual diversity are complex polygenic traits influenced by the interplay of multiple genes, each of which contributes a small part to the overall trait/phenotype, and non-genetic factors, making inheritance patterns multifaceted and not easily explained by the contribution of a single gene or factor. While there exists no single gay gene that can definitively predict or explain homosexuality and more generally speaking

Table 1. Overview of genetic approaches to studying sexual orientation

Approach	Key features	Main findings	Limitations
Twin Studies	Compare concordance between monozygotic and dizygotic twins	Heritability of 31–74% in males and 27–76% in females Higher concordance in monozygotic versus dizygotic twins	Equal environment assumption, limited sample sizes
Family aggregation	Examine recurrence within families and among siblings	Clustering of homosexuality in families Up to 35% of homosexual males have similarly oriented brothers	Largely anecdotal, confounded by shared environment
Linkage studies	Identify chromosomal regions linked to the trait	Initial evidence for Xq28 region, later replication failures	Small samples, inconsistent replications
Candidate gene studies	Hypothesis-driven testing of specific genes	No robust, reproducible associations	Low statistical power, selection bias
GWAS	Hypothesis-free genome-wide search for SNP associations	Five significant SNPs linked to same-sex sexual behavior, polygenic architecture	Requires very large samples, missing heritability
Polygenic scores (PGS/PRS)	Aggregate SNP effects into predictive scores	PGS/PRS linked to sexual behavior, gender diversity, and cognitive traits	Currently explain only small variance, underutilized in sexuality research

GWAS = genome-wide association studies, PGS = polygenic scores, PRS = polygenic risk scores, SNP = single-nucleotide polymorphisms

sexual diversity, it appears that a plethora of genetic variations may contribute to an individual's sexual orientation. However, complex pathways involving interactions among numerous genes involved in the development and functioning of the brain [24], particularly areas related to sexual attraction and identity, the expression of which can be modified by epigenetic factors and result in differential gene functions, without altering the underlying gene sequences.

The multifactorial inheritance of sexuality-related complex traits, including homosexuality, follows and exhibits multifactorial patterns, to which both genetic and environmental factors (and their non-linear interplay) contribute. Classical and modified (reared apart) twin studies have investigated the heritability of sexual orientation, mostly male homosexuality, within families, and, by partitioning the variance, have found a significant genetic component involved in shaping the trait. While looking at siblings, twins, and their biological relatives, has enabled the initial assessment of the likelihood of shared sexual diversity among family members, providing evidence for a genetic influence, the precise molecular mechanisms and pathways involved have remained largely unidentified and uncovered.

Studies that have scanned the entire genomes, instead of looking at specific genes, and recruited larger sample sizes, have gradually made emerge the hidden and complex polyphony of human sexuality and sexual diversity [25] [Table 1].

This signal amidst the noise suggests that a new, hypothesis-free, data-driven multidisciplinary field is emerging, that we call *sexogenomics*, the genomics of sexuality. This field of study is complex not only because of the complex nature of the polygenic trait under scrutiny and its putative factors underlying it, but also due to ethical and societal considerations that need to be carefully considered.

CONCLUSIONS

The multifaceted nature of sexual orientation underscores the need for further research to unravel the intricate interplay of genetics, biology, and environment in shaping human diversity in sexual orientation, with PGS/PRS-based approaches and systems biology/integrative omics frameworks appearing particularly promising [26].

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References

1. Bauer JE. Magnus Hirschfeld's Doctrine of Sexual Intermediaries and the Transgender Politics of (no-) identity. University of Amsterdam; 2004.
2. Kallmann FJ. Twin and sibship study of overt male homosexuality. *Am J Hum Genet* 1952; 4 (2): 136-46.

3. Kallmann FJ. Comparative twin study on the genetic aspects of male homosexuality. *J Nerv Ment Dis* 1952; 115 (4): 283-97.
4. Turkheimer E. Understanding the Nature–Nurture Debate. Cambridge University Press: 2024.
5. Turkheimer E. Three laws of behavior genetics and what they mean. *Curr Dir Psychol Sci* 2000; 9 (5): 160-4.
6. Bragazzi NL, Converti M, Crapanzano A, et al. Probing the genomic landscape of human sexuality: a critical systematic review of the literature. *Front Genet* 2023; 14: 1184758.
7. O'Riordan K. The life of the gay gene: from hypothetical genetic marker to social reality. *J Sex Res* 2012; 49 (4): 362-8.
8. Martin NG. Commentary: Discussion of 'The history of twins, as a criterion of the relative powers of nature and nurture' by Francis Galton (1875). *Int J Epidemiol* 2012; 41 (4): 917-9.
9. Visscher PM, Macgregor S, Benyamin B, et al. Genome partitioning of genetic variation for height from 11,214 sibling pairs. *Am J Hum Genet* 2007; 81 (5): 1104-10.
10. Young AI. Solving the missing heritability problem. *PLoS Genet* 2019; 15 (6): e1008222.
11. Whitam FL, Diamond M, Martin J. Homosexual orientation in twins: a report on 61 pairs and three triplet sets. *Arch Sex Behav* 1993; 22 (3): 187-206.
12. Eckert ED, Bouchard TJ, Bohlen J, Heston LL. Homosexuality in monozygotic twins reared apart. *Br J Psychiatry* 1986; 148: 421-5.
13. Diamond LM. The new genetic evidence on same-gender sexuality: implications for sexual fluidity and multiple forms of sexual diversity. *J Sex Res* 2021; 58 (7): 818-37.
14. Hamer DH, Hu S, Magnuson VL, Hu N, Pattatucci AM. A linkage between DNA markers on the X chromosome and male sexual orientation. *Science* 1993; 261 (5119): 321-7.
15. Rice G, Anderson C, Risch N, Ebers G. Male homosexuality: absence of linkage to microsatellite markers at Xq28. *Science* 1999; 284 (5414): 665-7.
16. Sanders AR, Beecham GW, Guo S, et al; MGS Collaboration; Gejman PV, Bailey JM, Martin ER. Genome-wide association study of male sexual orientation. *Sci Rep* 2017; 7 (1): 16950.
17. Ganna A, Verweij KJH, Nivard MG, et al; 23andMe Research Team; Lichtenstein P, Lundström S, Långström N, Auton A, Harris KM, Beecham GW, Martin ER, Sanders AR, Perry JRB, Neale BM, Zietsch BP. Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior. *Science* 2019; 365 (6456): eaat7693.
18. Thomas TR, Tener AJ, Pearlman AM, et al. Polygenic scores clarify the relationship between mental health and gender diversity. *Biol Psychiatry Glob Open Sci* 2024; 4 (2): 100291.
19. Bogaert AF, Skorska MN. A short review of biological research on the development of sexual orientation. *Horm Behav* 2020; 119: 104659.
20. Zietsch BP. Explanations for elevated psychiatric vulnerability in nonheterosexuals: environmental stressors, genetics, and the HPA and HPG. Psychiatric Disorders-Worldwide Advances 2011: 277-300.
21. Ricks JM, Arthur EK, Stryker SD, Yockey RA, Anderson AM, Allensworth-Davies D. A Systematic literature review of community-based participatory health research with sexual and gender minority communities. *Health Equity* 2022; 6 (1): 640-57.
22. Ventresca C, Martschenko DO, Wedow R, et al. The methodological and ethical concerns of genetic studies of same-sex sexual behavior. *Am J Hum Genet* 2024; 111 (10): 2107-16.
23. Jordan B. Clap de fin pour le «gène de l'homosexualité» - Chroniques génomiques [End of the road for the « homosexuality gene »]. *Med Sci (Paris)* 2020; 36 (2): 181-4. [French].
24. Kinnunen LH, Moltz H, Metz J, Cooper M. Differential brain activation in exclusively homosexual and heterosexual men produced by the selective serotonin reuptake inhibitor, fluoxetine. *Brain Res* 2004; 1024 (1-2): 251-4.
25. Glocer Fiorini L. Polyphonies of sexuality: debates about theories/debates about paradigms. *Int J Psychoanal* 2019; 100 (6): 1256-69.
26. Legato MJ. Gender-specific medicine in the genomic era. *Clin Sci (Lond)* 2016; 130 (1): 1-7. Erratum in *Clin Sci (Lond)* 2016; 130 (2): 125.

There's nothing that makes you so aware of the improvisation of human existence as a song unfinished. Or an old address book.

Carson McCullers (1917–1967), American novelist, short story writer, playwright, essayist, and poet

Capsule

Antithrombotic therapy after successful catheter ablation for atrial fibrillation

Whether successful catheter ablation for atrial fibrillation eliminates the need for long-term oral anticoagulant therapy is unknown. A total of 641 patients were assigned by **Verma** et al. to the rivaroxaban group and 643 to the aspirin group. A primary-outcome event occurred in 5 patients (0.31 events per 100 patient-years) in the rivaroxaban group and in 9 patients (0.66 events per 100 patient-years) in the aspirin group (RR 0.56; 95%CI 0.19–1.65; absolute risk difference at 3 years, −0.6 percentage points; 95%CI, -1.8 to 0.5; *P* = 0.28). New cerebral infarcts measuring less than 15 mm occurred in 22 of 568 patients (3.9%) in the rivaroxaban group and in 26 of 590 patients (4.4%) in the aspirin group (RR 0.89; 95%CI 0.51–1.55). Fatal or major bleeding (the composite primary safety outcome) had occurred in 10 patients (1.6%) with rivaroxaban and in 4 patients (0.6%) with aspirin (HR 2.51, 95%CI 0.79–7.95) at 3 years. The authors concluded that among patients who had had successful catheter ablation for atrial fibrillation at least 1 year earlier and had risk factors for stroke, treatment with rivaroxaban did not result in a significantly lower incidence of a composite of stroke, systemic embolism, or new covert embolic stroke than treatment with aspirin.

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