

The cryptic biological determinism of “sexual orientation”. Study on homosexual determinism

All attempts to demonstrate biological determinism of homosexuality lack sufficient rigour

The first thing to note is that **sexual identity**, defined by the sex of male or female, and sexual orientation, defined by the gender, *are different things*, although they sometimes tend to be confused. Gender has no scientific basis and is rooted in a cultural movement that responds to liberal social norms and individual behaviours.

Although there are no accurate statistics in this respect, the prevalence of non-heterosexual males and females in human populations has been estimated to be between 2% and 7% in western countries; gay movements, however, have put forward a hypothetical 10%. The difficulty lies in the application of a reliable criterion to characterise the trait. The scale generally used is that proposed by American entomologist Alfred Kinsey (1894–1956), who tried to study human sexuality from a purely animal perspective.



In a series of reports written between 1948 and 1953, Kinsey – considered by many as responsible for the sexual revolution in the US – reached the conclusion that human sexuality is

polymorphic. The result of applying the disputed Kinsey scale, based on a personal declaration, was that, in men, the extremes were exaggerated between completely gay or completely heterosexual, compared with bisexuals, while in women, the distribution appeared descending from heterosexuals to homosexuals, with a higher proportion of bisexuals than among men [1].

Independently of the sex, this finding presents the difficulty of interpreting sexual orientation based on a genetic determination consisting of single or major genes, which would allow classification into clear Mendelian phenotypic classes (which is the case of monogenic systems that clearly delimit phenotypes). In fact, after more than 50 years of research and 15 years since the culmination of the Human Genome Project, the “gay gene” or a single gene related with homosexuality is still missing, despite the many studies conducted. Furthermore, sexual orientation is not a consistent or stable trait, which contradicts its possible genetic determinism.

If single genes are ruled out, if there is a genetic basis for homosexuality, it should be assumed that it is determined by multiple minor genes or polygenes, related to complex qualitative trait loci (QTL), which act by combining their effects for the manifestation of the trait, usually depending on environmental influences.

Before we discuss the results of analyses conducted in this respect, it should be noted that in the manifestation of traits dependent on polygenic systems, there may be a significant environmental influence. In such case, phenotypic variance, PV, depends not

only on the genetic component, GV, but also on an environmental component, EV, and on the genotype-environment interaction, GEV, as follows:

$$PV = GV + EV + GEV$$

In the cases of polygenic systems, to determine the importance of the genetic component of the trait versus the influence of the environment, a parameter called heritability needs to be estimated, which reveals the part influenced by the genes with respect to the total variability:

$$H = GV/PV = GV/(GV + EV).$$

Could "Sexual orientation" be inherited?



In turn, in calculating heritability, we need to know the variance due to the environment. This is not always easy, but in the case of human behavioural traits, scientists have tried to resolve the issue by studying the consistency of the trait in identical (monozygotic) twins brought up in the same or different environment, as we shall see later.

Before doing so, it should be clarified that the influence of the environment on the expression of human behavioural traits, such as any type of sexual orientation, refers to the influences received during childhood and adolescence when the personality is built. In this sense, the different types of sexual orientation have been related with psychobiographical factors, such as poor education by parents, loneliness, sadness, lack of self-esteem and personal self-acceptance, lack of confidence, fear, sexual abuse or mistreatment in childhood and adolescence, rejection by classmates, narcissism, social phobia, lack of identification with one's own sex, absence of father or mother in childhood, etc. [2]. In this respect, the influences received from birth to sexual maturity are particularly critical.

In any case, analysis of the possible genetic basis of sexual orientation should refrain from any classification, moral judgement, social pressure, political interests, etc. Apart from cataloguing a person as homo- or heterosexual based on a personal declaration, studies have been conducted on comparative neuroanatomical and anatomical biological traits, concordance in genetically identical twins and molecular markers in the genomic DNA. The main findings are summarised very briefly below.

Neuroanatomical and anatomical studies



In 1992, Simon LeVay, a neurologist at the Salk Institute in San Diego (California), published a study which he believed showed that the INAH3 region — a cell group of the interstitial nuclei of the anterior hypothalamus — of a small sample of presumably heterosexual men was more than double the same region in homosexual men. LeVay concluded that the structural differences in the brains were present from birth or even earlier, thereby contributing to establish the sexual orientation of the male. Nevertheless, he admitted that any conclusion in this aspect was speculative,

as the response of each brain to androgens entails complex molecular processes that involve the interaction of receptors and a series of unknown proteins encoded by genes that were unidentified at that time. One objection to this study is the very small number of individuals in which the analyses were performed. From an experimental point of view, one sample from one individual, or even two dozen individuals, for a study of a quantitative trait as sensitive as sexual orientation is unacceptable and lacks rigour. Objections were also made due to the fact that the study had been carried out on the brains of people who had died of AIDS, which could have affected the trait analysed.

Two years later, William Byne, a researcher at New York State Psychiatric Institute,



Colombia University, showed that, although INAH3 is a sexually dimorphic trait, the differences between males and females are in the neuronal number and not in the neuronal size or density. In his study, he showed that in homosexual men, as in the brains of women, fewer neurons were observed, without this implying that these differences may be related to sexual orientation [4].

Studies on the ratio between the length of the index and ring fingers (generally known as the “2D:4D ratio”), which some authors had believed were correlated with sexual orientation, have also been inconclusive. In a study published in *Nature* in a sample of more than 700 Californian adults, the right-hand 2D:4D ratio of homosexual women was significantly lower than in heterosexual women, as occurs in men [5]. However, other studies on this same trait have given mixed or even conflicting results [2].

Twin studies



It is generally accepted that a trait has a genetic basis when it occurs more often among genetically-related family members than with other individuals in the population. Therefore, one way to approach the study of the genetic basis of the different forms of sexual orientation is by comparative analysis in monozygotic or identical twins with respect to fraternal twins or non-twin siblings.

These types of studies attempt to assess the degree of concordance of the trait, homosexual or heterosexual, among pairs of monozygotic and fraternal twins, taking into account at the same time the environmental factor, i.e. if they were raised in the same or different environment, which allows the heritability to be estimated. The different studies conducted by various authors in the 1950s gave mixed and even conflicting results, probably due to the arbitrary nature of the scale used in the classification of the trait. More recent studies have found a concordance of homosexuality between monozygotic twins of 20%-37% for men and 24%-30% for women, depending on the more or less restrictive classification of the scale used, which suggests the possible existence of a moderate genetic component, but also important environmental influences of a social and biological nature [7].

In general, the studies conducted in different populations conclude that the concordances are too low to support the hypothesis of a genetic basis for homosexuality.

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Studies with molecular markers

Another way of approaching the quest for genetic factors associated with the different patterns of sexual orientation is by using the information provided by DNA sequences of the genome of groups of homosexual compared to heterosexual individuals. The problem is confined to the search for so-called “molecular markers”. These are distinctive details on the DNA sequences of a specific region of the genome. The advantage of this type of analysis, if the correlation between certain markers and the phenotypic trait in question is proven, is its great objectivity and diagnostic value.

In 1993, researcher Dean Hamer and his colleagues at the National Cancer Institute in Bethesda (Maryland) performed linkage analysis between 22 microsatellite markers located on the X chromosome and homosexual orientation in 40 families in which there were two gay brothers and no indication of non-maternal transmission [8]. Their results showed that there were five markers on the Xq28 region (a region close to the end of the long arm of the X chromosome) which segregated jointly with the homosexual orientation in 33 of the 40 sibling pairs analysed. The result was confirmed a couple of years later by the same authors [9].

However, in 1999, Canadian clinical neurologists, who had conducted a study with a larger number of family groups than Hamer, concluded that there is no relationship between homosexual behaviour and the so-called Xq28 molecular markers [10]. The greatest criticism of Hamer’s work was the absence of a control group, i.e. it lacked some required references to support the quantitative results obtained by comparison.

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Given the opportunity offered by the knowledge of complete sequences of the human genome, other types of molecular markers different from microsatellites, but equally useful, were soon applied to search for linkage with the trait being investigated, in this case homo- or heterosexuality. Among the various types of molecular markers that can be used in this type of analysis, the most widely used are so-called SNPs – single nucleotide polymorphisms – which have given excellent results in the diagnosis of genetically determined diseases. Initial analyses with SNPs, applied to the search for linkage between SNPs and homosexuality were carried out and published in 2012, in a sample of nearly 8,000 men and 5,500 women. As with the microsatellites, no correlation was found either with the Xq28 region or with sexual orientation [11].

Paradoxically, in a larger study published two years later, Sanders and colleagues found a significant association between sexual orientation and some SNPs located on the Xq28 region and on another region of chromosome 8, confirming Hamer's 1993 findings [12].

More recently, at the Annual Conference on Human Genetics held in Boston (USA) in October 2018, a group of researchers from the Broad Institute in Cambridge, Massachusetts, and Harvard Medical School presented the findings in an even larger population sample, having found what appear to be four genetic variants associated with what researchers call non-heterosexual behaviour. This study analysed the molecular markers in the genome of people who answered "yes" or "no" to the question of whether they had ever had sexual relationships with someone of the same sex. For the comparative analysis, they used samples from two sources: the United Kingdom Biobank study and the private company 23andMe. The study included 450,939 people who said that their relationships had been exclusively heterosexual and 26,890 people who said that they had had at least one homosexual experience, who were classified as individuals with "non-heterosexual" behaviour. Nevertheless, the authors noted the heterogeneity of the sexual experiences in the second group, which ranges from people who had always had same-sex relationships to others who had only had same-sex relationships once or twice.

The investigators looked for common molecular markers in the DNA of people from the "non-heterosexual" group and identified four variants on chromosomes 7, 11, 12 and 15. Of these markers, two were specific to men who reported same-sex experiences: one was located on a region of the DNA of chromosome 15, which has been previously found to be associated with baldness in men, while the other marker was located in a region related with the olfactory receptors on chromosome 11. Researcher Andrea Ganna, who presented the paper at the Boston conference, suggested that this factor is related with sexual attraction.

However, at the presentation, he insisted that the molecular variants detected had still not been related with actual genes and that it is still not clear if they are located in coding regions (exons) or non-coding regions of the genome (remember that only 2% of the human genome is coding), so the four DNA genetic variants identified may not be reliably related with sexual orientation. As the author said of these molecular variants, "there's really no predictive power".

The four genetic variants identified were correlated with a greater propensity to experience mental health disorders, such as depression and schizophrenia in both sexes, and bipolar disorder in women. In the presentation, it was suggested that these types of psychological disorders could be a consequence of the discrimination to which people with non-homosexual orientation are sometimes subjected. This argument is difficult to relate with a simple genetic determination, and in any case could be related with a polygenic system.

In fact, at the conference presentation, Ganna said: "I'm pleased to announce there is no 'gay gene'. Rather, 'non-heterosexuality' is in part influenced by many tiny genetic effects". That is, we could be looking at the detection of several QTLs, regulated by polygenes, which in turn depend on their quantitative manifestation of an environmental influence, as happens with others related with mental illnesses such as schizophrenia, depression, etc., which are also of this type.

The fact that the authors of the paper suggest that some of the chromosomal regions found related with non-heterosexuality coincide with those associated with depression or other mental disorders, greatly influenced by environmental factors, could suggest that in any event it concerns QTLs. What seems more questionable is to associate these neurological disorders with the “discrimination” experienced by people from LGBTQ groups.

Physiological studies. Hormonal effects.



Another of the most widespread hypotheses for those who attribute biological or genetic factors as determinants of the sexual orientation that reveals itself in childhood or adolescence is the theory that proposes hormone imbalances during embryonic and foetal development. The hormone level during pregnancy is very complex, with critical moments in which an excess or deficiency of certain hormones can give rise to disorders in sexual development, with consequences on the gonadal and sexual phenotype of the child at birth. In fact, the effects of congenital abnormalities due to hormone imbalance of at least five

hormones that affect gonadal development (testosterone, dihydrotestosterone, oestradiol [derived from testosterone by the action of the enzyme aromatase], progesterone and cortisol) have been described.

Each hormone has a critical period of action, especially from week 7, when the testicles or ovaries have already begun to differentiate and the external genitalia begins to develop. The genes responsible for the synthesis of these hormones or their receptors in the target cells are those that, in the case of mutation or alteration of their expression, could lead to some cases of gonadal dysgenesis. However, hormone imbalances may also occur caused by stress or other physiological factors during pregnancy. Thus, maternal stress during pregnancy has been related with an imbalance in the cortisol level with an effect on gonadal development, the nervous system and subsequent sex-typed behaviour in early childhood [14].

It has also been shown that more than 90% of cases of congenital adrenal hyperplasia (CAH), one of the most widely studied hormonal abnormalities in women, are the consequence of a mutation in the CYP21A2 gene, which encodes an enzyme that helps synthesise cortisol, which may lead to genital virilisation. These cases are classified as structural or functional abnormalities relative to genital development. However, recent studies show that maternal stress during pregnancy does not significantly explain the differences in the population of homosexual or heterosexual sons or daughters [16].

The findings of different studies on the effects of hormones on sexual orientation tendencies related with fraternal birth order are also contradictory [17].

Although there is some evidence that women with lesbian tendencies on average show possible prenatal exposure to higher androgen levels than groups of non-lesbian women,

more than 50 years of studies have failed to demonstrate that biological factors, genes or hormones, decisively influence the development of female sexual orientation [18], nor have they demonstrated differences in male hormone levels in the prenatal stage between homo- and heterosexual men [19].

Genetic gonadal dysgenesis should not be confused with sexual orientation...

There may be cases in which mutations or epigenetic alterations in the genes or regions of the genome involved in gonadal development determine their elimination, silencing or overexpression, giving rise to structural dysgenesis in gonadal development or hormone imbalances, with consequences in the development of the male or female genitalia. The effects of mutations in any of the many genes involved in gonadal development are the main cause of most cases of gonadal dysgenesis, such as sex reversal, ambiguous genitalia, pseudohermaphroditism, etc. These cases, which have a genetic cause, should not be confused with sexual orientation, wherein the reasons are primarily of a psychobiographical nature. In any case, these paediatric abnormalities merit all the care that affected people deserve and, where possible, pharmacological or surgical correction is an obligation of the doctors who treat them.

In a recent editorial in *Nature*, it was found that doctors often tend to use surgical methods in the rare cases that present ambiguous genitals when the baby is born in order to make them coincide with the biological sex, which can be counterproductive [20]. Mistakes are often made. We should recall American psychologist and sexologist John Money (1921–2006), considered as the man who introduced sex reassignment surgery, who used as a guinea pig a boy who, in response to the concerns of his parents following a botched circumcision procedure, was subjected to a sex change to a girl. The sex change in this boy, called Bruce, turned into a girl who they called Brenda, marked the ruination of both him as a person and his entire family, including his twin brother. Bruce never wanted to be a girl and when he reached adulthood, wished to return to his natural condition of male, but it was already too late. Both he and his twin brother ended up committing suicide. More recently, in 2004, the *New England Journal of Medicine* published the case of follow-up of 14 genetic males with gonadal dysfunction who had undergone surgery at birth to change their genitalia to female. Of these, eight ended up identifying as males and the surgery caused them great anguish [21].

The American Psychiatric Association and the World Health Organisation suggest that the desire to change sex is a disorder or alteration of personality, not of genetics or human physiology. It is very important to take into account that transgender surgeries, to change sex, are irreversible. Therefore, in a case where children of three years of age or older reject their own sex, it is important to reach a definitive and reliable medical, paediatric and psychological diagnosis, as a basis to establish an appropriate treatment plan.

In conformity with Mayer and McHugh, “Hormonal conditions that contribute to disorders of sex development may contribute to the development of non-heterosexual orientations in some individuals, but this does not demonstrate that such factors explain the development of sexual attractions, desires, and behaviors in the majority of cases” [22].

Conclusions

Fifty years of research with neuroanatomical studies, genetic studies on twins and analysis of molecular markers in the DNA have not revealed any genes or regions of the human genome related with sexual orientation.

1. **All attempts to demonstrate biological determinism of homosexuality lack sufficient rigour and have failed to provide any kind of conclusive evidence.**
2. **The reality is that human beings are born with a chromosomal, genetic and gonadal sex that are normally concordant. An individual's sex is the result of the development of the internal and external reproductive system and also the male or female brain type, influenced by genetic and hormonal signals.**
3. **Rarely, some mutations or physiological factors may alter the organogenesis of the genitalia and result in structural or functional dysgenesis, giving rise to an atypical sexual identity.**
4. **Sexual orientation, or gender identity, is something that is acquired irrespective of the genetic constitution and that might not coincide with the biological sex.**
5. **In cases where children of three years of age or older reject their own sex, it is important to reach a definitive and reliable medical, paediatric and psychological diagnosis, as a basis to establish an appropriate treatment plan.**

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