REVIEWS

Genetics of Human Sexual Behavior: Where We Are, Where We Are Going

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DOI: 10.1002/smrj.46

ABSTRACT

Introduction. One of the never-ending debates in the developing field of sexual medicine is the extent to which genetics and experiences (i.e., "nature and nurture") contribute to sexuality. The debate continues despite the fact that these two sides have different abilities to create a scientific environment to support their cause. Contemporary genetics has produced plenty of recent evidence, however, not always confirmed or sufficiently robust. On the other hand, the more traditional social theorists, frequently without direct evidence confirming their positions, criticize, sometimes with good arguments, the methods and results of the other side.

Aim. The aim of this article is to critically evaluate existent evidence that used genetic approaches to understand human sexuality.

Methods. An expert in sexual medicine (E.A.J.), an expert in medical genetics (G.N.), and two experts in genetic epidemiology and quantitative genetics, with particular scientific experience in female sexual dysfunction (A.B.) and in premature ejaculation (P.J.), contributed to this review.

Main Outcome Measure. Expert opinion supported by critical review of the currently available literature.

Results. The existing literature on human sexuality provides evidence that many sexuality-related behaviors previously considered to be the result of cultural influences (such as mating strategies, attractiveness and sex appeal, propensity to fidelity or infidelity, and sexual orientation) or dysfunctions (such as premature ejaculation or female sexual dysfunction) seem to have a genetic component.

Conclusions. Current evidence from genetic epidemiologic studies underlines the existence of biological and congenital factors regulating male and female sexuality. However, these relatively recent findings ask for replication in methodologically more elaborated studies. Clearly, increased research efforts are needed to further improve understanding the genetics of human sexuality. **Jannini EA, Burri A, Jern P, and Novelli G. Genetics of human sexual behavior: Where we are, where we are going. Sex Med Rev 2015;3:65–77.**

Key Words. Genetics; Sexual Behavior; Female Sexual Dysfunction; Xq28; Premature Ejaculation

Introduction

Because many of the factors associated with male and female sexual function and dysfunction (e.g., personality, anxiety) are now believed to have a genetic basis, this field has more and more become a focus of attention for behavioral geneticists [1,2]. Specific methodologies within genetic research provide uniquely powerful means to dissect the "multidimensionality" in a quantifiable manner, to shed light on individual variations in sexual function and to understand the underlying interplay of genetic and environmental factors. Most of the genetic epidemiologic studies conducted so far on human sexuality have used the classical twin approach to estimate the relative genetic contribution [3,4]. Twin research is the

workhorse of genetic epidemiology and is critical to distinguishing between the role of nature versus nurture in contributing to complex traits as well as to quantify the relative importance of each component [5].

However, other genetic approaches have also been used in order to quantify the role of genes in human sexual behaviors. Many heritability studies have provided evidence of clear genetic influences on several aspects of sexual behavior, such as age at first sexual intercourse [6], fidelity to a partner, the desire to become parents [7,8], sexual desire and arousal [9], and the propensities for marriage [10] and/or multiple mating [11]. The majority of these studies have suggested a key role of the dopamine (DA) and serotonin (5HT) pathway genes in regulating human sexual behavior. Despite proof of moderate genetic influence, quantitative genetic studies, however, underline the importance of environmental factors involved in changes of the central activities of these neurotransmitters and in the subsequent impact on sexual behavior.

In this context, the two genes that appear to be closely related with sexuality are the DA receptor D4 and D2 (*DRD4* and *DRD2*, respectively). Although evidence is still preliminary, the *DRD4* gene polymorphisms have been associated with sexual desire and arousal [9]. Furthermore, polymorphisms of the long alleles of the gene *DRD4* 48 bp VNTR (variable number tandem repeat) appear to be associated to an increase in sexual novelty [12]. However, a meta-analysis comparing published studies of novelty seeking and this polymorphism did not confirm this association, which has been found with another polymorphism in the gene, the -521C/T [13]. Genes *DRD4* 48 bp VNTR 3R+ seem to be related to the age of first sexual intercourse [14]. In contrast, children with 4/7 genotypes showed worse response to new stimuli compared with 4/4 genotypes. This study corroborates only in part previous results on the link between the DRD4 gene and human temperament [15].

Another gene involved in human sexual behavior is the serotonin *5-HT$_{2A}$* gene, as mediator of the sexual side effects of antidepressants. Subjects carrying the GG genotype of the *5-HT$_{2A}$* gene (see later), for example, have been found to have a greater risk of suffering from a sexual dysfunction compared with subjects carrying the GA genotype [16].

The activity of the neurohypophysis and of its secretion has been robustly linked to the propensity for monogamy in several animals, as oxytocin (OX) acting on maternal behavior and vasopressin (AVP) more on paternal behavior. With all the limits of twin studies dealing with complex behaviors, Cherkas et al. explored the hereditary nature of infidelity and number of sexual partners showing a percentage of heritability of 41% and 38%, respectively [17]. They also found a strong genetic link between the two traits. Although the role of the *AVP* gene in infidelity is unclear, there is evidence of the influence of the gene in the pair bond. A study found a strong association between a polymorphic repeat sequence in the 5′ flanking region of the gene *AVPR1A* encoding one of the AVP receptor subtypes (V1aR), and proneness for monogamous behavior in men [18]. The *AVPR1A* repeat polymorphisms (RS3) are associated with partner bonding, perceived marital problems, marital status, and marital quality as perceived by their spouses, thus suggesting an association between a single gene and pair-bonding behavior and demonstrating that the well-characterized influence of AVP on pair-bonding in voles [18] may be of relevance also for our species. Large genetic studies evaluating about 1.7 million single-nucleotide polymorphisms (SNPs) recently provided evidence for genetic assortative mating (GAM, the nonrandom mating pattern in which individuals with similar genotypes and/or phenotypes mate with one another more frequently than would be expected under a random mating pattern [19]) in the U.S. population, but the strength of this association is substantially smaller than the strength of cultural, or, better, educational assortative mating (EAM [20,21]) in the same sample [22]. In other words, when the preference for those who are either similar (homogamy—"*birds of a feather flock together*") or dissimilar (heterogamy—"*opposites attract*") to themselves was studied, it was found that genetic similarity (GAM) explains at most 10% of the assortative mating by education levels (EAM) [22].

We will use two examples of human sexual physiology (the genetic regulation of sex appeal and attractiveness and the genetic influence on sexual orientation) and two examples of human sexual dysfunctions (female sexual dysfunction and premature ejaculation [PE]) in order to represent where we are and where we are going with the genetics of human sexual behavior.

Genetics of Sexual Attractiveness

The preference for facial attractiveness is part of biological, rather than cultural, heritage; this hypothesis is sustained by studies showing at least