REVIEWS

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

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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

partial agreement between different cultures regarding facial attractiveness [23,24], and by studies showing that the tendency to prefer attractive faces emerges early in development [25]. Men with an XY genetic pattern, irrespective of hetero- or homosexual orientation, prefer faces (female or male, respectively) with enhanced dimorphism [26]. This evidence was demonstrated in a morphing experimental setting [27], where heterosexual and homosexual male subjects chose images of female and male faces with higher masculine or feminine characteristics.

In the wake of these findings, other authors have recently tried to comprehend the nature of some mating behaviors. Gersick and Kurzban studied some covert sexual signals, such as the coy glance or the invitation to "*grab a coffee sometime*" [28]. In the animal kingdom, these covert sexual signals are usually absent. In fact, because Darwinian selection should facilitate males with high genetic quality to have the highest reproductive probability, genetic quality should correlate with clear mating signals. According to this, the human male should send the female the most intense and clear sexual signals, in order to increase both the probability of being chosen as sexual partner and to ensure a number of offspring. However, why humans commonly use covert sexual signals remains an open question. It has been hypothesized that because mating may have a social risk related to social characteristics, human males have developed an alternative way to show their genes' quality (for example, social intelligence, and social flexibility), which is a modulation of signal intensity. Only when the social cue (i.e., the potential sexual partner) is considered relevant, does the male adopt a clear mating strategy [29]. The adoption of a covert sexual behavior may also be "functional" to establish extramarital relationships. As for mating strategies, the sexual dimorphism between genders is reflected in the propensity to be unfaithful, but also in the different emotional value, both sexes accord the infidelity.

The minimum investment of a man in reproduction is considerably smaller than that of women's (i.e., 1 ejaculation vs. 9 months' pregnancy plus breastfeeding and costly maternal caregiving). Hence, the biological evidence that men have considerably less to lose by employing short-term mating strategies suggests that men are genetically more likely to be unfaithful than females [30–33]. Interestingly, a recent study has correlated male infidelity with the chronotype, also known as "morningness/eveningness." The chronotype (the tendency of humans to go to sleep early or late in the evening, and, as a consequence, to wake up early or late in the morning), seems a genetically based behavior influencing the propensity to infidelity [34,35]. In particular, individuals with a wake–sleep pattern (favoring being more active in the evenings or at night) are more likely male and have a higher tendency to have extramarital relationships. This evidence may be explained with several hypotheses, not always clarifying the role of genetic or epigenetic factors: men at all ages have a tendency to sleep fewer hours than women [36–38]. In fact, the chronobiological regulator melatonin reaches its zenith earlier at night in females than in males [39]. Natural selection might encourage the development of male eveningness in order to promote new social and mating opportunities [40,41]. On the other hand, males and females, genetically and/or culturally, differ also in the way they perceive and experience infidelity [42]. In particular, it has been shown that reactions toward infidelity differ between males and females on the basis of the type of infidelity, sexual or emotional. In line with evolutionary and parental investment theories where males have a "biological necessity" to guarantee themselves reproductive success, they are more affected by female sexual infidelity, rather than by emotional infidelity. These data seem to be cross-cultural. In addition, another issue may explain that why males suffer are more affected by sexual infidelity. This has been related to the uncertainty of paternity due to the genetic modification, characteristic of our species, leading to the almost unique phenomenon of the concealed ovulation [43,44]. In fact, males never have the certainty of investing in the care of offspring that really share their genetic pool. The hypothetical care of another male's offspring might jeopardize their own genetic pool.

Genetics of Sexual Orientation

Evidence has been produced showing the importance of genetic factors in the development of sexual orientation [45]. A major role of genetics and congenital factors in human homosexuality is suggested by the evidence that bisexual or homosexual behavior is largely practiced in nature, in close to 1,500 species, ranging from primates to gut worms, being well documented for 500 of these [46].

The impact of genetic and epigenetic factors seems different in male and female homosexuality.

Female homosexuality has been more likely related to hormonal, epigenetic mechanisms. Women with congenital adrenal hyperplasia (CAH), overexposed to high levels of testosterone during the prenatal imprinting, have much higher rates of homosexual orientation when compared with non-CAH women [47]. It should also be noted that male and female homosexuality may be qualitatively different traits (e.g., alleles predisposing to male homosexuality may be more similar to those predisposing to female heterosexuality, than female homosexuality).

Research on families and twin methodologies has produced consistent evidence that genes influence male sexuality, with sexual orientation showing higher concordance rates in identical twins than in same-sex fraternal twin pairs. However, molecular research has not yet produced compelling evidence for specific genes [48]. Although it has been well established that having older brothers increases the odds of homosexuality in men, the route by which this occurs has not been fully resolved. Even the robust and elegant evidence solving the Darwinian paradox (how an anti-reproductive gene may survive) needs to be confirmed in larger samples [49]. The fertility advantages of carrying the "gene" of male homosexuality (if any), using arguments similar to that known for the thalassemia trait (that may confer a degree of protection against malaria, prevalent in the regions where the trait is common), may confer a selective survival advantage on carriers, thus perpetuating the mutation. Finally, despite several interesting evidences (Table 1), never successfully confirmed or denied, the genetics of male homosexuality seems more debated at political, or journalistic levels, than, unfortunately, in the scientific field. The inability to find and verify gene involvement suggests that methodological or biological factors significantly influence this research. It is possible that a large part of the heritability of homosexuality is still missing, probably because of insufficient exploration of rare genetic variants and/or epigenetic factors.

Are Female Sexual Dysfunctions Genetically Determined?

The polyetiology of female sexual dysfunction (FSD) remains unclear, likely due to physical characteristics (for example the fluctuating hormonal regulation), to the cultural factors, and to the profound complexity of the underlying psychophysiological processes. Although the past decade has seen a significant increase in research efforts to enhance our understanding of the origins and diversity in female sexual function, most of the studies suffer from lack of replication and other practical problems (particularly epidemiological studies) [59]. However, we are seeing the beginnings of a two-pronged approach to studying FSD—the first to map out the epidemiology of the construct (using psychometric methods) and the second to conceptualize female sexual function as multidimensional, including physiological responses (e.g., lubrication, orgasm), which are shaped by other psychological proximate factors (including contextual and interpersonal ones).

Heritability and Genetic Covariation

The very first genetic epidemiologic studies conducted on female sexual function focused on

Table 1 Genetics and male homosexuality

Target	Finding	References
Twin studies	**100% concordance** between homosexual MZ twins, and only a 12% concordance for DZ twins.	Kallmann [50]
	52% of monozygotic twins, 22% of DZ twins, and 11% of adoptive brothers were homosexual.	Bailey and Pillard [51]
Xq28	An estimated level of **Xq28 allele** sharing between gay brothers is 64% instead of the expected 50%.	Hamer [52]
	The Xq28 linkage **is not completely confirmed**. Evidence for linkage at three other sites—on chromosomes 7, 8, and 10.	Mustanski et al. [53]
	Linkage between the Xq28 markers and sexual orientation was detected for the homosexual male families, but **not for the lesbian families**.	Hu et al. [54]
	Confirmation of previous linked region (maximum 2-point LOD = 2.99, maximum multipoint LOD = 2.76)	Sanders et al. [55]
8cen	**Linkage found** (maximum 2-point LOD = 4.08, maximum multipoint LOD = 2.59)	Sanders et al. [55]
Fertility	Genetic factors influencing homosexuality contribute to **female fecundity** of the maternal line.	Camperio-Ciani et al.; Camperio Ciani et al.; Iemmola and Camperio Ciani; Ciani et al. [49,56–58]

From Jannini et al. [45], mod. DZ = dizygotic; LOD = logarithm of odds score; MZ = monozygotic.

female orgasmic frequency. Two independent twin studies investigated the genetic and environmental influences on the frequency of orgasm in women during sexual intercourse and during masturbation [3,4]. Responses between monozygotic (MZ) co-twins correlated by 31% and 54% for the items on orgasm frequency during sexual intercourse and masturbation, respectively, whereas the corresponding dizygotic (DZ) twin correlations were 16% and 34%, leading to assessed heritability estimates of 31% and 34% for frequency of orgasm during sexual intercourse, and 45% and 51% of for orgasm during masturbation. The remainder of variation was explained by unique environmental influences (e.g., lifestyle) and little or no variance due to family environment.

In two more extensive genetic epidemiologic studies conducted in Finland and the United Kingdom, researchers focused on all dimensions of FSD (desire, arousal, lubrication, orgasm, satisfaction and sexual pain) [60,61]. Both working groups attempted to explain the joint contribution of environmental and genetic factors across these six dimensions. The results of their multivariate analyses showed some heterogeneity in the six subdomains, but revealed that most of the observed phenotypic variances in all subdomains were due to unique environmental influences (76% 84%). The genetic effects were modest, ranging 0–39% for additive and 0–24% for nonadditive genetic effect. Additionally, a substantial overlap in additive and nonadditive genetic and nonshared environmental influences between the different subdomains was found, offering an explanation to the high rate of comorbidity observed in FSD.

Hunting the Genes

Although moderate, evidence from these twin studies provide the legitimate ground for the identification of genes contributing to FSD that could help pin down neural circuits involved in these complex processes as well as delineate underlying physiological and molecular components. Such research, however, remains scarce. A limited number of candidate gene studies have reported associations with the 5-HT_{2A} gene and low desire/arousal, as well as the DRD4 5-locus with desire/arousal and overall sexual function—although they all relied on very small samples and remained unreplicated [9]. A very recent study focused on 17 SNPs located in estrogen receptor (ER) genes and their involvement in women's sexual desire and genital arousal (i.e., lubrication). Scanning over 2,448 Finnish twins, the authors reported nominally significant main effects on sexual desire for three ER-linked SNPs, but none for subjective or genital arousal [62].

So far, the most extensive molecular genetic study on FSD—scanning the whole genome (over 2.5 million SNPs) for potential susceptibility loci—only found spurious evidence for an involvement of the 5-HT_{1E} receptor gene and the parvalbumin gene (*PVALB)* in women's sexual function [63]. Again, interpretation of the results asks for acknowledgment of certain study limitations such as the relatively high mean age of the sample (57 years), which restricts generalization of the results to other age groups. Furthermore, the results also need replication in much larger samples.

Genetic Involvement "Yes"—Genetic Determinism "No"

Hence, genetic epidemiologic research suggests that genes do indeed contribute to FSD, but suggests also that environmental factors and gene (G)-environment (E) interactions (G × E; a phenotypic effect of interactions between environment and genes; see Figure 1) play an even more important role in the development of FSD. Hence, the concept of "genetic determinism" in relation to FSD is erroneous and needs to be corrected. As research has shown, genes do not determine FSD phenotypes—by further completely excluding environmental influences—but they do influence basic interindividual differences in sexual functioning and susceptibility to FSD. Here, the concept of "polygenic frameworks" needs to be mentioned, in which the FSD phenotypes are not seen as dichotomies ("normal" versus "dysfunctional"), but rather as dimensions influenced by a number of additive and interactive genetic and environmental effects [5]. So, the question therefore is not whether, but how, the actions of given genes and environmental factors influence particular aspects of female sexual functioning.

This misconception of what "proof of a genetic influence" means, in combination with the fear of medicalization and pathologization, has made it difficult for behavioral genetic research to be established within the field of sexual medicine. But especially, the debates surrounding medicalization and pathologization of FSD can be informed by taking a multidimensional approach to the construct, such as looking for patterns indicative of latent dimensions in the epidemiological data. As such, behavior genetic research can help provide

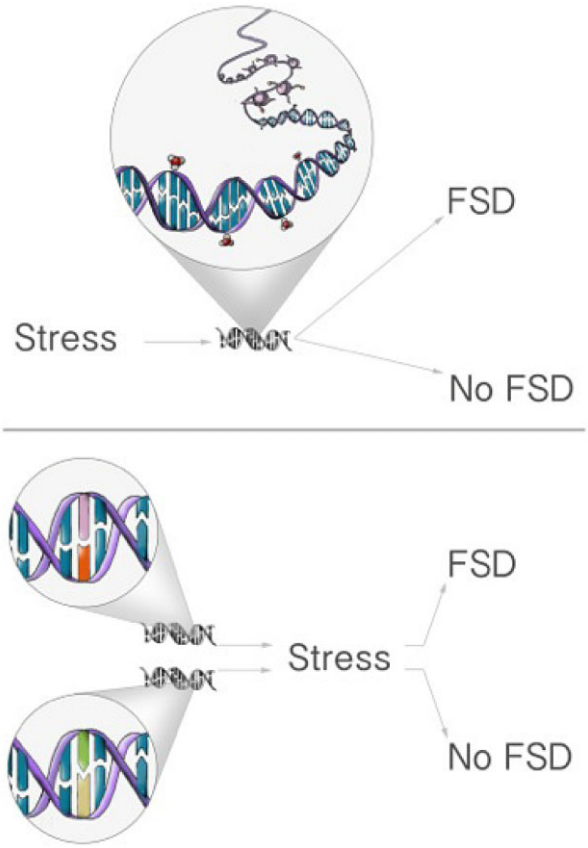

Figure 1 The genes-by-environment interaction model. The model describes how genetic (G) and environmental (E) factors jointly influence the risk of developing a sexual problem. (Upper) Stress (E) can lead to changes in DNA epigenetic profiles (such as methylation or chromatin structures) and as a consequence lead to a specific sexual problem. (Lower) The effects of stress (E) differ according to an individual's genetic predisposition (G) to developing a sexual problem.

answers to other related questions, such as: What is the extent to which a sexual symptom or "problem" should be regarded a dysfunction? What constitutes a functional or nonpathological level of sexual function? What is the extent to which proximate causes of variations in sexual function (such as genetics and other biological factors or factors associated with learning, cultural, relationship, psychological and motivational, and social factors) are influenced by more fundamental questions about the ultimate purpose of sexual function (such as reproduction and fitness differentials)? This has knock-on consequences for how we decide on the importance of other psychological factors such as emotional bonding, relationship status, and satisfaction and pleasure. In many ways, a quantitative approach that focuses on individual variation in sexual functioning and the multidimensionality of etiologic pathways may enlighten the debates regarding the medicalization of female sexuality rather than entrench it further without resolution.

Where to Next?

Apart from the evidence supporting genetic influences on sexual problems, the importance of environmental stressors in FSD development has been supported, highlighting the crucial existence of G × E (see Figure 1). Such G × E interactions are thought to be mediated by epigenetic modifications of the genome, and epigenetic changes of the genome often arise in response to changes in the environment. Epigenetics, by explaining how personal history, social experiences, and other environmental factors (e.g., stress) impact on an individual's vulnerability to FSD [64], provides us with a new biologic framework for the cognitive-behavioral causes underlying FSD.

Female sexual function is a dynamic nonlinear process, and understanding this complex phenotype is a challenging task. Taken together, the findings suggest not only a genetic influence in FSD, but also highlight that unique experiences of each individual seem to be equally—if not more—important for the development of sexual problems. Context-specific variables like sexual problems in partners, relationship dissatisfaction, and different medical and psychological conditions have a major influence on a woman's sexual sensibility and motivation to participate in sexual activities. However, there is also a genetic susceptibility for FSD, which supports future search for candidate genes contributing to FSD. Finally, the heterogeneity observed suggests that the subdomains of FSD are distinct, offering support to the current classification system of FSD and pointing to the importance of research that aims at better disease definitions and nosological systems.

Genetics of PE

A heritable component in the etiology of PE has been hypothesized for more than seven decades. In an early review of 1,130 cases, Schapiro [65] noted that male family members of PE patients seemed to be at increased risk of suffering from PE themselves. Further evidence for familial resemblance in PE symptoms was demonstrated by Waldinger and his associates in 1998 [66]. Although familial resemblance can be seen as suggestive of a genetic

etiological component, similarity between biological relatives is not, in itself, a conclusive evidence for a genetic etiology, because family members also tend to share their environments to a greater extent than nonrelated individuals. Quantitative genetic studies, which most often utilize MZ and DZ twin pairs, can however separate between genetic and shared environmental variances, because MZ and DZ differ in terms of genetics, but not in terms of shared environment (for a comprehensive review of twin study methodology, see Plomin et al. [5]).

Quantitative Genetics in PE Research

Few studies have been conducted to elucidate the etiology of PE by quantitative genetic means. The first of these are a series of twin studies conducted on a population-based sample of Finnish male twins and siblings of twins [67–69], demonstrating that 28% of the variance in a composite variable measuring different aspects of ejaculatory function (including ejaculation latency time [ELT], perceived ejaculatory control, and satisfaction with ejaculatory function) was explained by genetic variance [68]. Most of the variance (72%) was accounted for by nonshared environmental experiences; shared environmental experiences did not contribute to PE symptoms. A later twin study conducted in Hungary was suggestive of significant genetic effects for PE based on concordance rates in MZ and DZ twins, although model fitting analyses were inconclusive likely due to the low number of informative twin pairs [70]. Although the samples in the twin studies conducted in Finland were relatively large (e.g., N = 3,946 in [68]), the frequency of severe PE symptoms, such as ELTs shorter than 1 minute, is relatively low in population-based samples (around 1.5% [68]). Twin studies rely on informative twin pairs for statistical analyses (i.e., both twins of a twin pair must provide data), and therefore, research on relatively rare diseases (such as lifelong PE diagnosed by stringent <1 minute ELT criteria) will require enormous population-based sample sizes in order to assemble a sufficient number of informative twin pairs where the rare condition is present. Thus, it is possible that the actual genetic contribution to severe PE subtypes is underestimated in population-based data (Figure 2).

PE is a complex, multifactorial disease [72–77], and this poses problems for genetic PE research because some symptoms may be under stronger genetic influence than others. As shown in Figure 1, this indeed appears to be the case for two

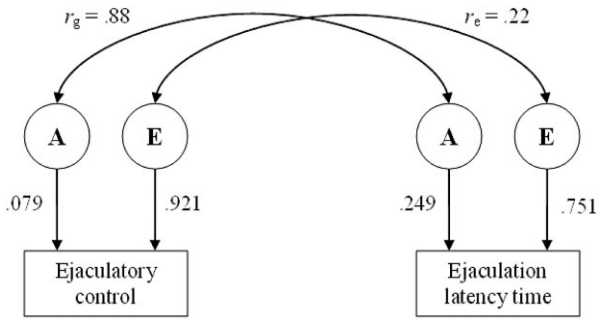

Figure 2 A bivariate model portraying additive genetic (A) and nonshared environmental effects on self-perceived ejaculatory control and ejaculation latency time. The single-headed arrows from the A and E parameters depict standardized proportions of phenotypic variance (i.e., so that 24.9% of the variance of the variable measuring ejaculation latency time is attributable to genetic effects.) Genetic and nonshared environmental correlations are shown next to the double-headed arrows. These correlations depict the extent to which the same genetic and nonshared environmental factors affect both phenotypes (e.g., the correlation between the two additive genetic parameters A is high at .88, meaning that it is largely the same genes—to an extent of 88%—that affect both ejaculatory control and ejaculation latency time). (From Jern [71], reproduced with permission).

key symptoms of PE, namely ELT and perceived control of the ejaculatory reflex [78]: the ELT phenotype has substantially stronger heritability at 24.9% compared with the ejaculatory control phenotype, the heritability of which was measured at only 7.9% (again, with nonshared environmental experiences accounting for the lion's share of the variance of both phenotypes). Interestingly, the genetic correlation between the two phenotypes was high (r_g = .88), suggesting that the same genes are largely accounting for the genetic variance in both. Furthermore, the nonshared environmental correlation was modest at .22, suggesting that the unique environmental experiences that contribute to a short ejaculatory latency are mostly different from the unique environmental experiences that contribute to perceived poor ejaculatory control. This illustrates a key problem in genetic research of PE: multiple symptoms must be present and taken into account for diagnostic purposes, but as different symptoms have different etiologies. Genetic associations for a holistic diagnosis may be challenging to obtain.

Molecular Genetics in PE Research

While quantitative genetic strategies can elucidate the extent to which a phenotype is under genetic

influence, they cannot provide information regarding the specific genes that influence a said phenotype. Genetic association studies involve testing associations between specific genetic loci and a phenotype. Since 2009, a handful of association studies have been conducted to investigate the genetic etiology of PE. All of these have utilized the candidate gene approach, an analytical strategy in which polymorphic regions in or near genes that have been hypothesized *a priori* to be associated with PE are tested for significance against a phenotypical measure (e.g., ELT). Most genetic association studies of PE [79–81] have used the case–control design, in which genotype frequencies in diagnosed PE patients are compared with genotype frequencies in unaffected controls. Other approaches, such as empirical investigations of statistical association of PE symptoms with genotypes in population-based samples, have also been utilized [82,83]. Typically, candidate gene studies are based on hypotheses from animal studies or pharmacological studies in humans. For example, the ejaculation-delaying properties of serotonergic drugs are well established from both animal and human research [84]; hence, 5-HT-related genes have been considered suitable candidates (and hence the term *candidate gene study*) for molecular genetics in PE research.

Serotonergic Genes in PE Etiology

Indeed, most candidate gene studies of PE have focused on serotonergic genes, with the degenerate repeat polymorphism *5-HTTLPR*, located in the promoter region of the 5HT transporter gene, being the most extensively studied [79,80,85–87]. The results have been highly variable: some studies reporting a protective effect of the short (S) allele but only within a group of PE patients (i.e., no significant difference in terms of allele or genotype frequencies was detected between cases and controls) [79]. Subsequent studies have reported an association in the opposite direction, that is, between the S allele and increased PE symptoms [80,81], whereas others still have reported no association between this locus and PE symptoms at all [78,87]. A recent meta-analysis [86] concluded that the S allele of the *5-HTTLPR* locus may be associated with PE, but the conclusions of this meta-analysis (and some of the papers it was based on) has been met with criticism [88], because genotype distributions in some studies have deviated from Hardy–Weinberg equilibrium (HWE) or have possibly employed error-prone polymerase chain reaction procedures during genotyping. Deviation from HWE may be indicative of procedural errors in the laboratory; however, HWE deviation is also expected in nature under some circumstances, such as nonrandom mating—that is, if PE increases or decreases a man's ability to attract a female sexual partner, genotype frequencies in genes associated with PE may deviate from HWE as a result [89]. This is certainly plausible in the case of PE, as many men with PE tend to avoid forming new sexual relationships [90]. Thus, further studies utilizing larger samples are required to elucidate the role, if any, of the *5-HTTLPR* locus in PE etiology.

In addition to *5-HTTLPR*, a number of SNPs have been subject to association studies in PE research, and much like the studies focusing on *5-HTTLPR*, the studies have yielded nonreplicable results where replication attempts have been undertaken. Luo et al. [91] reported associations between two 5-HT_{2C}-linked SNPs (rs3813929 and rs518147) and ELT in a case–control study in Han Chinese subjects. Jern et al. [82], in a study of six SNPs linked to the 5-HT_{1A}, $_{1B}$ and $_{2C}$-receptor genes, were not able to replicate the association between the rs3813929 locus and ELT as reported by Luo et al. [91], but instead reported significant associations between two 5-HT_{1B}-gene-linked loci (rs130058 and rs13212041) and ELT (only the association between rs130058 and ELT remained significant after controlling for multiple testing.) Janssen et al. [92] reported a significant association between the 5-HT_{2C}-linked SNP rs6318 between ELT within a group of PE patients (no control group was used); but no association between this SNP and ELT was found by Jern et al. [82] in a previous report. Likewise, Janssen et al. [93] reported an association between the 5-HT_{1A}-linked SNP rs6318 and ELT within a group of PE patients; Jern et al. [82] found no association with this SNP and ELT either.

Association Studies Focusing on Nonserotonergic Genes

Few genetic PE studies have ventured outside the realm of serotonergic genes, and of these, only two have investigated the same locus, namely the variable number tandem repeat polymorphism *DAT1*, which is linked to the DA transporter gene. Perhaps unsurprisingly, these two studies produced results pointing in diametrically opposite directions: Santtila et al. [83] found, in a population-based sample, an association between carriers of two copies of the 10-repeat (10R) allele and lower scores on a composite variable

measuring different PE symptoms. A year later, Safarinejad [94] reported that the 9R allele was more common in a group of PE patients compared with controls, thus contradicting the findings of Santtila et al. [83] (the 9R and 10R alleles are, overwhelmingly, the most common alleles at this locus, and so this polymorphism is commonly treated as a biallelic 9R/10R locus for purposes of statistical analyses). Associations between dopaminergic genetic polymorphisms and PE were also recently reported in a conference abstract by Jern et al. [95]. In a case–control study, two catechol-o-methyltransferase (COMT; an enzyme with a central role in the catabolization of DA) gene-linked SNPs, rs4680 and rs4818, were robustly associated with PE after controlling for multiple testing; however, none of the seven SNPs linked with DA receptors D1-D3 were significant predictors of PE in the same study. Interestingly, the rs4680 SNP is—much like the serotonergic *5-HTTLPR*—one of the most studied functional polymorphisms, and its valine-encoding allele, which in the aforementioned study was more prevalent among PE patients, has been shown to increase enzymatic activity, which in turn results in lower synaptic DA levels [96].

Possible associations between PE symptoms and a relatively large number of SNPs linked to the OX receptor and AVP receptors $_{1A}$ and $_{1B}$ genes were investigated by Jern et al. [97], reporting a heterozygote effect for one OX receptor gene-linked SNP (rs75775), but leaving open for interpretation which of the two possible alleles at this locus could have an influence on ejaculatory function. In a recent study, Jern et al. [98] investigated androgen-related genetic polymorphisms in PE etiology, including the well-studied androgen receptor gene-linked cytosine-adenine-guanine (CAG) repeat, reporting an association between the 5-α-reductase type 2 gene-linked SNP rs2208532 and ELT, but this association was no longer robust after controlling for multiple testing. However, a sex hormone binding globulin gene-linked SNP (rs1799941) was found after correction for multiple tests to moderate the association between salivary testosterone (T) levels and ELT, so that A:A genotype carriers expressed lower T levels as a function of increasing ELT compared to carriers of other genotypes at this locus.

Future Directions

Genes likely play a significant role in PE etiology, but the quest for identifying the actual genetic loci that contribute to PE etiology has not been successful. Candidate gene studies of PE (much like candidate gene studies in other fields of research) have yielded disappointing results. Most reported associations have not been subject to replication attempts, and where replication attempts have been made, they have tended to produce ambiguous results. This may in part be explained by discrepancies in study design (i.e., case–control designs involving patients vs. population-based studies) or methodological issues, such as discrepancies in how PE has been operationalized (e.g., composite measures involving different PE symptoms vs. ELT measures.). However, a very likely explanation to consider is that the candidate gene studies conducted thus far have been underpowered to detect genetic variation at this scale: indeed, most candidate gene studies in other fields of research have produced unreplicable, that is, probably spurious, results [99,100]. The advance of genome-wide association studies has shown that it is indeed possible to identify genetic loci in a fashion that will reliably replicate between studies, but the sample sizes required for successful replication are usually measured in the tens of thousands for most complex psychiatric disorders, and even then, a large proportion of the genetic variance usually remains unexplained [101]. To combat these problems (i.e., to avoid publication of unreliable results), many journals nowadays employ strict criteria for publication of genetic association studies, including focus on within-study replication in independent samples and sufficient statistical power (see Hewitt [102] for an example of such an editorial policy on candidate gene studies, this one at *Behavior Genetics*). Most of the genetic association studies focusing on PE have employed tiny samples, often with fewer than a hundred patients and controls, and sometimes even without control groups. The largest PE studies have enrolled just around 1,500 men [82,97]; however, these being population-based samples, the number of extreme cases (analogous to severe/lifelong PE) in these is, still, low. For genetic research on PE to be successful and reliable, future efforts should focus on facilitating international collaboration with the intention of pooling together samples from various research groups to achieve greater statistical power (although this may result in problems of its own, such as population stratification.) Studies should preferably employ fully empirical, genome-wide methods of analysis. Such an undertaking would be cost demanding and labor intense, thus meta-analytical approaches should be considered the

most reliable until this can be achieved. Collaboration on this scale would also benefit from careful advance planning to ensure that, for example, measures are comparable between samples. New technologies, such as next-generation sequencing, which allows, for the first time, the cost- and time-effective sequencing of a complete human genome, holding the promise to discover missing variants and novel genomic biomarkers.

Conclusion

Despite all the limitations highlighted here, genetics and subsequent molecular studies provide "proof of principle" that genetic association studies—if accurately conducted—can reveal candidate genes that contribute to male and female sexual functions and dysfunctions, thus offering the prospect of developing better strategies to detect, treat, and potentially prevent the problems. To achieve this, successful multidisciplinary collaboration of specialists is crucial. We consider dramatically urgent that the sexual health field combines resources and initiate large-scale collaborative studies to collect DNA from defined cases in large numbers similar to other studies of complex diseases and phenotypes.

Pharmacogenomics and pharmacogenetics, investigating the variations of DNA and RNA characteristics as related to (sexual) drug response and studying the influence of variations in DNA sequence on (prosexual and antisexual) drug efficacy and toxicity, will benefit of increased genetic knowledge in the field of sexual medicine [103]. Furthermore, a better understanding of the interactions between genes and lifestyle factors will help all sexual health caregivers with new therapeutic targets and insights, and most importantly, psychotherapeutic approaches to sexual dysfunctions could benefit from the concept that individual differences may have a genetic component.

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