

The Genetics and Epidemiology of Female Sexual Dysfunction: A Review

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ABSTRACT

Introduction. Female sexual dysfunction (FSD) is an often underestimated and common problem with serious effects on women's quality of life. Despite a high overall prevalence in the female population—exceeding that of male sexual dysfunction—until recently, little research has focused on this area. In contrast to the successful advances of genetic research in a wide variety of human diseases, genetic exploration in FSD lags far behind.

Aim. The aim of this review is to acquaint the reader with the current behavioral and molecular genetic research in the field of FSD.

Methods. Because of the heterogeneity of the included studies, we are providing a nonsystematic review.

Results. Recent epidemiological and candidate gene studies have suggested a strong genetic influence on female sexual functioning. While these findings provide a clear rationale for more genetic research in the field, they need to be replicated on a much larger scale to be definitive.

Conclusions. Successful identification of biomarkers and novel genes underlying FSD should improve the diagnosis, identification, and treatment of different subgroups. Future pharmacotherapeutic approaches to FSD will benefit from novel targets and the concept that individual variations have a genetic component may help destigmatize our views of sexual problems. **Burri AV, Cherkas LM, and Spector TD. The genetics and epidemiology of female sexual dysfunction (FSD): A review. J Sex Med 2009;6:646–657.**

Key Words. FSD; Female Sexual Dysfunction; Genetics; Epidemiology

Female Sexual Dysfunction (FSD)

Today, FSD is regarded as a multifactorial and progressive problem affecting between 19% and 50% of the female population, involving multiple anatomical, physiological, psychological, and social factors [1]. Since Masters and Johnson's first attempts, research has made some progress in delineating the multiple correlates of female sexual functioning and the pathoetiology underlying FSD, although far from complete [2]. Despite recent breakthroughs of the genetic etiology of many common human traits and diseases, only recently have genetic studies tried to explore the human genome and identify common variants related to FSD [3–5]. The aim of this review is to acquaint the reader with the current behavioral and molecular genetic research in the field of FSD as to our knowledge, no review has addressed this

before. While the heterogeneity of studies precluded a formal systematic review, we hope this provides a useful update to sex researchers. Potential limitations of the review might be gaps in literature searching because of nonsystematical reviewing. Nevertheless, the ultimate goal of this review was to bring the reader up-to-date with current literature on the genetics underlying FSD and to form a legitimation for future research in the area.

Classification and Definition

Several classification systems have been proposed for FSD in the past. The most widely used classification systems have been the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Diseases (ICD-10) [6,7]. Because of some inconsistencies in

Table 1 Consensus classification system for FSD [9]

Sexual desire disorder	
Hypoactive sexual desire disorder (HSDD)	Recurrent or persistent deficiency or absence of sexual fantasies and thoughts and a lack of receptivity to sexual activity that causes personal distress.
Sexual aversion disorder	Recurrent or persistent phobic aversion to and avoidance of sexual contact with a sexual partner precipitating personal distress.
Sexual arousal disorder	
	Recurrent or persistent inability to attain or maintain adequate sexual excitement, expressed as a lack of subjective excitement or a lack of genital or other somatic responses, which leads to personal distress.
Genital sexual arousal disorder	Absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur.
Subjective sexual arousal disorder	Complaints of impaired genital sexual arousal. Self-report may include minimal vulvar swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from nongenital sexual stimuli.
Orgasmic disorder	
	Recurrent or persistent difficulty, delay in or absence of attaining orgasm after sufficient sexual stimulation and following normal sexual arousal, which causes personal distress.
Sexual pain disorder	
Dyspareunia	Recurrent or persistent genital pain associated with sexual intercourse. It can be subdivided into deep and superficial pain.
Vaginismus	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, causing personal distress.
Other sexual pain disorders	Recurrent or persistent genital pain induced by noncoital sexual stimulation. This includes anatomic and inflammatory conditions.

both systems, and the need to define and classify FSD in a more uniform way, a consensus-based definition and classification system for FSD that includes guidelines for clinical evaluation and treatment was designed [8].

Based on the four major categories described in DSM-IV and ICD-10, the definitions of the individual disorders have been changed to reflect current clinical and research practice, and a new category of sexual pain disorder has been added. These definitions devised by the Consensus conference form the foundation for today's clinical assessment and diagnostics (Table 1). Further revisions based on pilot tests in clinical research on personal distress were presented at the 2nd International Consultation on Sexual Medicine: Men and Women's Sexual Dysfunction and are currently being tested for clinical validity [9,10].

The classification of FSD is heavily based on the conceptualization of the human sexual response cycle. Recently, Basson has constructed a new nonlinear model of female sexual response, in contrast to the linear, four-stage model of sexual response proposed by Masters and Johnson in 1966 [11,12]. Basson's model acknowledges that female sexual functioning proceeds in a more complex and diffuse manner than male sexual functioning and that the aim of sexual activity for women is not necessarily orgasm but rather personal satisfaction. On this circuitous way to reach physical or emotional satisfaction, there are many

points of vulnerability that may prevent a woman from feeling sexually fulfilled.

Prevalence and Incidence

Knowledge about the epidemiology of FSD is limited. The absence of dependable population-based data, inconsistent study designs, combined with a lack of standard uniformly applied definitions of FSD—especially regarding the degree of dysfunction and distress—and use of validated vs. nonvalidated outcome measures, have made it difficult to measure FSD or to compare the outcome of different studies [13–15].

In a well-written review, comparing epidemiological estimates of FSD, Spector and Carey found that orgasmic disorder ranged from 18% to 76% in clinics [16]. A more recent excellent review by Hayes et al. investigated FSD using data from previous prevalence studies. Among all the women with any sexual difficulty they found prevalence rates for sexual desire disorder ranging from 16% to 75% (mean 64%), 16% to 48% (mean 35%) for orgasm disorder, 12% to 64% (mean 31%) for arousal disorder, and from 7% to 58% for sexual pain (mean 26%). Only a proportion of women with sexual difficulty showed distress (21% to 67%) [17].

Not surprisingly, most epidemiological studies related to FSD use samples from primary care or specialty clinics, leading to higher estimates com-

pared to those from community samples. A recent study evaluating the prevalence of FSD in an outpatient gynecologic and urogynecologic clinic using the current International Consensus Classification found half of the attendees had some form of FSD ($N = 159$) [18]. Segraves and Segraves reported that out of 906 women who participated in a multisite pharmaceutical trial, 65% (475) had a primary diagnosis of hyposexual desire disorder (HSDD), at least two in five (41%) had one other sexual disorder and 18% had disorders in all three categories (desire, arousal, and orgasm) [19]. These figures are supported by Rosen who found comorbidity rates among the different subtypes of FSD of 67% in 329 women presenting at a gynecological clinic [20].

In recent years, several important population-based studies have greatly added to our knowledge. Probably the best (although not applying validated outcome measures) is the National Health and Social Life Survey (NHSLs) [21]. Using categories similar to the DSM-IV definitions, the NHSLs found an overall prevalence of FSD of 43% in U.S. women ($N = 1,921$) aged 18–59. Low desire was reported by one in five (22%), arousal problems by one in six (14%), a quarter (26%) suffered from an inability to achieve orgasm, and 7% from sexual pain. In a large, questionnaire-based study in the Asia-Pacific region, Nicolosi studied the prevalence of sexual dysfunction in middle-aged and elderly people ($N = 6,700$, n -women = 3,350) [22]. More than 30% of women complained of having at least one sexual dysfunction and the most frequently reported sexual dysfunctions among women were lack of sexual interest (27%), lubrication difficulties (24%), and an inability to reach orgasm (23%). Another very recent cross-sectional study on U.S. women ($N = 2,207$) revealed prevalence rates ranging from 26% (premenopausal) to 52% (menopausal) for low sexual desire, and a prevalence rate of 12% (surgically induced menopause) for hypoactive sexual desire disorder [23]. Ponzolzer et al. conducted a population-based study on 703 Austrian middle-aged women where 22% of them reported having desire disorders, 35% arousal disorders, and 39% orgasmic problems. Pain disorders were reported by 12.8% of the women [24].

Etiology

Physiological Factors

FSD is believed to be a multifactorial phenomenon, rarely caused by a single factor, although one

may predominate [2]. Knowledge about the pathoetiology of FSD involves anatomical, physiological, biological, medical, and psychological factors which in turn are affected by environmental variables (Table 2) [25,26]. In the past, research has identified many physiological factors of which hormones are viewed as one of the major driving forces of sexual behavior [27,28]. Altered hormonal levels especially have been shown to significantly interfere with female sexual functioning. Besides long-term use of the contraceptive pill, childbirth, breastfeeding, and pregnancy, menopausal transition and especially surgically induced menopause (e.g., because of hysterectomy or ovariectomy) have been reported to reduce sexual desire and arousal, to impair sensitivity of the breasts and clitoris, and to provoke vaginal dryness in many of the affected women [29–34]. These symptoms are likely to be related to the decrease in estrogen [35].

It has become increasingly evident that FSD can also occur secondary to a variety of chronic medical and gynecological conditions affecting vascular, neurological, and endocrine systems, and is therefore likely to have an organic basis [36]. This in turn can provide some important clues to the etiology of FSD. Gynecological conditions resulting in pelvic surgery and affecting uterine contraction represent an often underestimated cause of sexual dysfunction as do other gynecological conditions like vulvovaginal surgery, hysterectomy, and breast cancer [37–40].

Related to this variety of medical and physiological conditions, prescribed medication—e.g., antihypertensive, antipsychotic, and antidepressive (especially selective serotonin reuptake inhibitors, SSRI) medicines—over-the-counter medications, and illicit drugs are known to decrease sexual desire, to impair arousal and lubrication, and to delay or inhibit orgasm in women [41–43].

Psychosocial Factors

The psychosocial risk factors affecting women's sexual functioning are broad and comprise emotional difficulties, such as untreated anxiety, depression, stress, and a history of sexual abuse [44,45]. More recently, emphasis has been placed on interpersonal relationships and personality [26,44]. Relationship imbalances, marital conflicts, extramarital affairs of the partner, lack of trust, and intimacy have also been reported to affect women's sexuality, as do poor communication, the husband/partner's sexual performance, a woman's inability to express her desires, and a lack of

Table 2 A list of examples of factors that have been suggested to contribute to each subtype of FSD according to available study data as reviewed elsewhere [76–82]

Disorder	Medical factors	Psychosocial factors	Medications
Female hyposexual desire disorder	Menopause Endocrine disorders Lactation Hysterectomy Radiation General health Depression Pregnancy Breast cancer	Age Culture Relationship problems Sexual violence and abuse Gender identity Sexual identity Negative body image Anxiety	SSRIs Neuroleptics Chemotherapy Sedative-hypnotics Narcotics Antihypertensives Antipsychotics
Female sexual arousal disorder	Menopause Endocrine disorders Diabetes Multiple sclerosis Hypertension Obesity Hysterectomy Depression Pregnancy Breast cancer	Increasing age Alcohol and drug abuse Smoking Relationship problems Anxiety Sexual violence and abuse Anxiety	SSRIs Alcohol Heroin Antipsychotics
Female orgasmic disorder	Diabetes Endocrine disorders Multiple sclerosis	Younger age Relationship problems Negative body image	SSRIs
Sexual pain disorder	Menopause Vulvar vestibulitis Vulvar atrophy Fibroids Ovarian cyst	Negative sexual attitudes Sexual violence and abuse Relationship problems	None yet identified

knowledge about anatomical and physiological processes involved in sexual arousal and stimulation [46]. Most studies have only been small case series and potentially unreliable. However, in a recent large case control study of 2,632 subjects, Harris et al. reported specific personality traits—namely introversion, emotional instability, and not being open to new experiences—to be significant risk factors for orgasmic infrequency [47]. These personality traits have been proven to be highly heritable in the past and may well represent an important starting point for future studies on the etiology and positive treatment of FSD [48].

Genetics

Most human traits and behaviors are influenced to some extent by both genetic and environmental factors but it is a major challenge to separate out their influences (Figure 1). A classical epidemiological design increasingly used in human behavioral genetics to delineate genetic from environmental factors is the twin model, which also accounts for age and cohort effects [49]. Twin studies compare monozygotic (MZ) twins who share 100% of their genes to dizygotic (DZ) twins who have 50% of their genes in common. Signifi-

cantly closer similarity in the trait of interest observed in MZ twins compared with DZ twins is taken to be indicative of genetic influences on that trait and is known as “heritability,” a population-based statistic, measuring the proportion of phenotypic variation in a population that is attri-

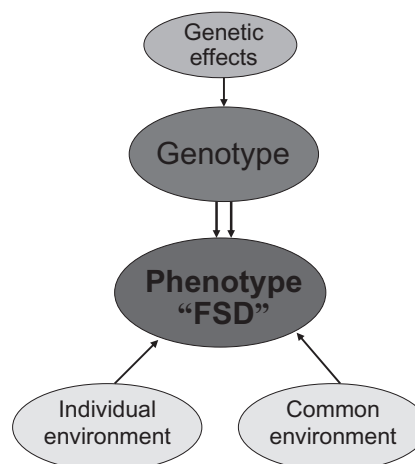


Figure 1 Illustration on how most human behaviors and traits are influenced by genetic and environmental factors. Environmental as well as genetic factors both influence the phenotype (means any observable characteristic of an individual).

Table 3 Frequency of orgasm problems in unselected women from 2 twin studies [4,5]

	Dunn et al., 2005 (N = 3,089)		Dawood et al., 2005 (N = 4,097)	
	Intercourse	Masturbation	Intercourse	Masturbation
Never	16%	14%	Never	14%
Less than a quarter of the time	16%	7%	Rarely	7%
A quarter of the time	8%	5%	Fairly often	14%
About half the time	13%	7%	Often	11%
Half to three quarters of the time	11%	8%	Usually	13%
More than three quarters of the time	23%	25%	Almost always	18%
Always	14%	34%	Always	5%

butable to genetic variation. Twin studies have shown that most human traits are in part influenced by genes, with some psychological and physiological disorders and characteristics indicating a strong heritability (e.g., schizophrenia up to 80%, polycystic ovary syndrome up to 80%, bipolar affective disorder up to 85%, height up to 90%, and body mass index up to 80%), others an intermediate level (e.g., personality traits up to 50% and breast cancer 25% to 45%) [48,50–54].

Following recent identification of the human genome, the latest analytical tool is the genome-wide association study (GWAS) which has proved fruitful to date in identifying potential genetic loci related to a variety of over 50 traits and disorders such as type 2 diabetes, obesity, and Crohn's disease [3]. To carry out a GWAS, researchers use thousands of either population case-control or family samples. GWAS involves a scan of the entire human genome in a blind fashion to detect small gene variations called single nucleotide polymorphisms (SNPs), which are associated with a particular trait or disease. To be able to scan the human genome, a comprehensive map of over 300,000 carefully selected SNPs is necessary. A related approach commonly used until recently is the candidate gene association study (CGAS). CGAS uses a selection of genes with a known or inferred biological function whose role makes it plausible that they may predispose to disease or the observed phenotype. Because CGAS looks at a limited number of selected SNPs, it is cheaper than a GWAS but suffers from needing to be lucky and knowing the biology in advance.

Epidemiologic Studies

Most of the genetic epidemiologic studies conducted on FSD so far have focused on female orgasmic dysfunction. Almost simultaneously, two independent twin studies investigated the genetic and environmental influences on the frequency of

orgasm in women during sexual intercourse and during masturbation. Twins participating in the large study conducted by Dawood et al. were drawn from the Australian Twin Registry (N = 3,080) and a total of 4,037 adult women enrolled in the TwinsUK registry participated in the study by Dunn et al. [4,5] Data in both studies were assessed through very similar, anonymous questionnaires on sexual behavior asking about frequency of achieving orgasm during intercourse and masturbation.

Tables 2 and 3 show that both studies found similar prevalence estimates with one in five women (18% and 21%, respectively) never/rarely having orgasm during masturbation, in contrast to one in three women (32% and 34%) never/rarely having orgasm during intercourse. Conversely, 5% and 14% of women in the two studies always experienced orgasm during intercourse with considerably more women being able to reach orgasm during masturbation. The MZ and DZ twin groups in both studies did not differ significantly with respect to average age, number of sexual partners or reported incidence of having been heterosexual and sexually active "at some point." No difference in the proportion of MZ and DZ twins in either of these categories could be detected. Univariate analysis in the Dunn study revealed significant twin correlations for both MZ and DZ twin pairs for all three items of interest. Responses between MZ cotwins correlated 31% and 54% for the items on orgasm frequency during sexual intercourse and during masturbation, respectively, while the corresponding DZ twin correlations were 16%, and 34%, leading to assessed heritabilities of 31% and 34% for frequency of orgasm during sexual intercourse, and 45% and 51% for frequency of orgasm during masturbation. The remainder of variation is explained by unique environmental influences (e.g., lifestyle).

Notably, both studies found a greater proportion of women unable to achieve orgasm during

intercourse compared with masturbation, suggesting a context specificity that could be mediated through different etiologies. In other words, during masturbation, the individual is in complete control of the physical and fantasy scenario while intercourse involves another individual with his specific sexual rhythm and patterns, which the woman has to respond to. Some of the variation related to the ability to achieve orgasm found in both studies may be due to anatomical differences, as suggested by the recent but small ultrasound study by Gravina et al., who found that women who do not experience vaginal orgasm have a significantly thinner vaginal wall [55]. Therefore, distinction of the different subgroups might be crucial for future research. Although neither of the two twin studies used validated or very extensive questionnaires, the results were strikingly similar which gives support to the significant genetic influence found in both studies.

In a very recent study, Witting et al. looked at the pattern of genetic and environmental influences on all different subtypes of FSD [56]. A large sample of Finnish female twins and female siblings ($N = 6,446$ and $N = 1,994$, respectively) filled in the Female Sexual Function Index (FSFI), which indicates individual differences on six subdomains (desire, arousal, lubrication, orgasm, satisfaction, and pain). Multivariate models revealed that most of the observed phenotypic variance in all six subdomains was due to nonshared (unique) environmental influences (76–84%). The genetic effects were modest, ranging from 0% to 15% for additive and from 0% to 24% for nonadditive genetic effects. These findings suggest that the subtypes of FSD are separate entities, thereby supporting the current classification system [8]. The unique experiences of each individual are the main factors determining FSD but there is also a genetic susceptibility for FSD which supports future exploration of possible candidate genes underlying FSD.

Why Genetics?

Adding to the clear heritability of FSD reported in the epidemiologic studies is the fact that most of the aforementioned risk and etiological factors related to FSD have been shown to have a clear underlying genetic basis. Besides biological variables, including hormones, morphological, and anatomical variations, and different medical conditions, several psychosocial candidates that affect FSD have been reported to be significantly heritable [57–59]. The candidates include personality traits, such as introversion with a clear heritability

ranging from 41% to 61% and psychiatric problems such as depression and bipolar disorder. [52,60,61]. Considering the clear heritabilities found for most etiological factors associated with FSD, a genetic susceptibility for FSD is likely. Studying the genetics of each etiological factor can therefore provide us with more insights into the genetic components underlying the complex phenotype FSD.

Implicated Genes

Animal Studies

Several animal model studies have successfully demonstrated a role for genetic influences on sexual motivation (desire) and performance capability (arousal/orgasm) [62,63]. Animal genetic studies have certain methodological advantages as sexual behavior can be examined easily by looking at lordosis behavior, an evolutionarily mating display, involving relative simple responses that are triggered by simple stimuli. Second, the application of the frequently used knockout technique (deletion of certain genes) allows direct determination of the specific behaviors that are encoded by these genes.

A series of studies on the role of estrogen suggests that estrogen receptor (ER) alpha gene expression plays a key role in facilitating reproductive behavior such as lordosis and interrelated behaviors in female mice. Pfaff et al. examined mice in which the gene encoding the alpha form of the estrogen receptor (ERalpha) had been knocked out. Comparison of ERalpha-, ERbeta-, and double knockout mice revealed that different patterns of sexual behaviors depend on different patterns of ER activity [63]. Rissman et al. used ER knockout (ERKO) to test female receptivity and found that ER is required for the display of sexual receptivity, but is not essential for female attractiveness [64]. These findings are supported by a study on aromatase knockout (ArKO) mice, which cannot aromatize androgen to estrogen because of a targeted mutation in the CYP19 gene. The ArKO mice showed significantly reduced levels of lordosis behavior [65].

A study on drosophila indicated that genetic manipulation of a single gene called “fruitless” in female fruit flies provoked sexual behavior patterns similar to those of male fruit flies [62]. In related fashion, the researchers found, male fruit flies that had the “fruitless” gene inactivated failed to show normal male sexual behavior. These findings suggest a profound impact of genetics on complex

sexual behavior, reinforced by the surprising fact that a single gene can have such far-reaching effects on complex behaviors and be so focused in what it controls. Humans have not been shown to have the “fruitless” gene, but they do actually have other genes in common with fruit flies. Whether or not these gene effects in animals readily translate to humans is still, however, speculative.

Studies in Humans

Significant variations in the expression of desire and arousal have long been considered to be the result of learned behavior patterns or psychosocial problems. However, recent advances in molecular genetic studies of humans further suggest that individual variations in some aspects of human sexuality are likely to be influenced by our genes. A recent study suggested that humans differ in their sexual drive because of genetic influences [66]. Based on the recent evidence that dopamine D4 agonists induce penile erection in rats through a central mechanism, Zion and his coworkers hypothesized that individual allelic differences in the D4 receptor gene (DRD4) might contribute to differences in human sexual desire, arousal, and function [67]. The idea that dopamine, through its different neuronal systems and receptor subtypes, might play a role in the control of several aspects of sexual behavior, however, is not new. Segraves et al. for example found an increase in sexual desire among 76 women with HSSD treated with the dopamine-reuptake inhibitor (bupropion) after they failed to respond to placebo [68].

In the Zion study, 148 healthy Israeli students filled in an online questionnaire on human sexual behavior [66]. Their self-reported scores of sexual desire and arousal were compared with five specific regions on the DRD4 gene. The group found the single most common DRD4 5-locus haplotype (19%) to be significantly associated with desire, arousal, and function scores. However, men and women differed significantly on desire and function scores, males scoring higher on desire and showing less “dysfunction” than women. To draw valid conclusions in terms of female sexual desire dysfunction separation of males and females is needed with much larger sample size and a replication of the results. Furthermore, future research should also take into account contextual factors such as partner’s role in sexual functioning. Nonetheless, the current study suggests a significant association between a common genetic polymorphism and aspects of human sexual behavior, and—if the study is confirmed—specific DRD4 agonists may not

only be useful for problems of erectile dysfunction but also for problems related to desire, arousal, and function in women as well as men.

A very small unreplicated candidate gene study (N = 89) looking at mediators of sexual side effects implicated by antidepressants found a variant of the serotonin 5HT2A gene (the 5HT2A -1438 G/A genotype) to be a significant predictor for lower desire/arousal scores in females [69]. This genotype however was not significantly correlated with the orgasm subscale. Pharmacogenetic studies related to FSD may indeed provide us with new candidate genes, as may the examination of sexual side effects arising from the pharmacological treatment of other physiological and psychological conditions.

Research on genetic influences on female sexual pain disorders is very scarce, but recent evidence on human pain sensitivity implies that genetic factors are important in determining response to human experimental pain [70]. There is also an important etiological contribution of genetic factors toward clinical pain states such as back and neck pain [71]. Regarding female sexual pain disorder, the few existing studies on the pathoetiology of dyspareunia concentrate on vulvar vestibulitis syndrome (VVS), a common subtype of dyspareunia, affecting mostly premenopausal women [72]. Recent studies point to a possible involvement of the gene coding for the interleukin-1 receptor antagonist, a down-regulator of proinflammatory immune responses, in VVS. A study conducted by Gerber et al. found a polymorphism at position +3,953 in the IL-1b gene to be significantly more frequent in women with VVS (N = 59; 40%) than in controls (N = 48; 25%) assuming that susceptibility to VVS might be influenced by carriage of this polymorphism [73]. These results are supported by earlier findings of Jeremias et al. who found an interleukin 1 receptor antagonist allele to be significantly more common in women suffering from VVS (N = 449) [74].

Future Directions

In conclusion, genetic research in FSD lags far behind genetic research in other areas. Only recently have the findings of heritability of most human behavior and disorders drawn the interest of genetic epidemiologists [75–77]. The heritability results for orgasmic dysfunction are consistent and point toward significant genetic contribution, and show little or no shared family environmental effects. Ideally, future epidemiologic studies should be conducted on much larger

Table 4 Possible candidate genes based on current research findings in human studies

Possible candidate genes	Findings from human research
Serotonin 5-HT _{1a}	Flibanserin, a novel 5-HT _{1A} agonist / 5-HT _{2A} antagonist has lately been investigated as potential treatment for generalized acquired HSDD and has shown to significantly increase desire and sexual functioning (Goldfisher, et al., unpublished data).
Oxytocin (OXT)	Circulating levels of OT increase during sexual arousal and orgasm in both men and women [83]. In multiorgasmic women increased OT levels are positively correlated with subjective reports of orgasm intensity [85].
Vasopressin (AVP)	Associations between two polymorphisms within the AVPR1A gene and age of first sexual intercourse in men and women [85]
Dopamine (DA)	Bupropion increases sexual desire among 76 women with HSDD [86]. D4 receptor gene (DRD4) contribute to individual differences in human sexual desire, arousal and sexual function [63].
Estrogen	Estrogen replacement therapy correlates positively with sexual desire and arousal in peri- and postmenopausal women [87].
Testosterone/	Testosterone replacement therapy improves desire and arousal accompanied by an increase in sexual fantasies [88,89].
Arginase	Testosterone patch improves sexual desire, arousal and satisfying sexual activity in women [86]. Indirectly regulates vaginal blood flow [90,91].

clinical samples, using clinically accepted validated questionnaires on FSD, which could further highlight possible genetic subgroups. However, these are difficult to perform and may not be realistic. The sparse existing candidate gene studies are promising although they are unreliable as they rely on very small sample sizes and have not been replicated so far. Another research limitation that needs to be mentioned for research and systematic assessment of the literature is the complexity and diversity of human sexual behavior, which does not represent a linear entity. There is considerable interdependence of FSD as a consequence of the dynamic process of sexual functioning and often comorbidity with other subtypes of FSD. To illustrate, a patient complaining about decreased desire might have a primary orgasmic disorder from insufficient stimulation, with decreased desire developing secondarily as a result of unsatisfying sexual encounters. In addition, significant sexual dysfunction might be linked to a broader emotional or medical problem, such as depression or endometriosis. Despite these limitations and challenges, significant genetic influences on female sexual functioning have been found, providing a strong case for more genetic research in the field of FSD to identify and understand common variants in the human genome. This identification of key genes and possible novel hormonal pathways that may be involved in every stage of the female sexual response will not only improve the diagnosis of subtypes of FSD, but also highlight new pathways for future drug development—much needed in female sexual health. The information arising from both CGAS and GWAS can be used

to develop better strategies to detect, treat, and potentially prevent disorders (Table 4). To achieve this, successful multidisciplinary collaboration of specialists is crucial. Recent successes—costing millions of dollars—from large-scale genome-wide scans of thousands of cases have found novel common genes for over 50 common traits and diseases such as heart disease, eye color, depression, and cancer [77]. Over 20 novel gene loci have, for example, been found for diabetes with this method [78]. If a fraction of that money could be used for female sexual health, major breakthroughs could occur. However, to do this, the sexual health field has to get its act together collaboratively and start collecting DNA from defined cases in large numbers, as other specialties are doing. The potential benefits are great. A better understanding of the interactions between genes and lifestyle factors will help us with new therapeutic targets and insights, and most importantly, psychotherapeutic approaches to FSD could benefit from the concept that individual differences may have a genetic component.

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Category 3

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