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FEMALE SEXUAL DYSFUNCTION AND DISORDERS (A PASTUSZAK AND N THIRUMAVALAVAN, SECTION EDITORS)

A Review of Genome Wide Association Studies for Erectile Dysfunction

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Abstract

Purpose of Review To review large cohort genome wide association studies for erectile dysfunction.

Recent Findings Two recent genome wide association studies using the Genetic Epidemiology Research in Adult Health and Aging cohort, UK Biobank, and the Partners HealthCare Biobank have identified an association between unique single nucleotide polymorphisms involved in the regulatory activity of single-minded homolog 1 (*SIM1*) and risk of erectile dysfunction. *SIM1* is involved in the leptin-melanocortin pathway and may contribute to centrally mediated erectile dysfunction.

Summary Identification of novel loci associated with erectile function from genome wide association studies will help expand the understanding of the breadth of pathways that contribute to erectile dysfunction. This will help accelerate studies of novel therapies for the treatment of erectile dysfunction.

Keywords Erectile dysfunction · Sexual dysfunction, physiological · Genome-wide association study · Genetic therapy · SIM1 protein, human

Introduction

Erectile dysfunction (ED) is the inability to get or maintain a penile erection and is one of the most common medical conditions in men. ED impacts nearly a third of men over 50 years old [1, 2]. Aging, obesity, diabetes, cardiovascular disease, and smoking are identifiable risk factors for ED [3].

There is a growing interest to identify genetic factors contributing to the development of ED. An early twin study was one of the first to support the heritability of ED [4]. Fischer et al. conducted a health survey among 890 monozygotic and 619 dizygotic twin pairs from the Vietnam Era Twin Registry. ED was assessed using two questions inquiring about the difficulty of having or maintaining an erection. The heritability estimate for ED was 29% for having and 36% for maintaining an erection when adjusted for various ED risk factors. This was one of the first studies to support a genetic component to ED.

A number of candidate gene studies have linked gene polymorphisms in specific genes with ED risk. Candidate gene polymorphisms have been identified in endothelial nitric oxide synthase (eNOS), Angiotensin Converting Enzyme (ACE), the androgen receptor, transforming growth factor-β1 (TGF-β1), and methylenetetrahydrofolate reductase (MTHFR) [5]. However, these studies are often difficult to reproduce given the variability between study populations, which is the major limitation of these studies. Additionally, there is a concern for false positive associations, especially in candidate gene studies performed in large homogenous cohorts. A meta-analysis of eNOS gene polymorphisms and risk of ED found a positive association between these polymorphisms and ED risk [6••]. In a review of 13 studies examining the association between the G894T and T786C eNOS polymorphisms and ED risk, a significant association between these polymorphisms and ED risk was observed in Caucasians and Asians. Additionally, the intron 4 VNTR polymorphism was associated with ED risk among Caucasians. Another meta-analysis of insertion/deletion polymorphisms in the ACE gene did not find a significant

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association between polymorphism and ED risk among 6 case-control studies [7].

A number of the shortcomings of candidate gene studies are addressed by genome-wide association studies (GWAS). GWAS assess genetic variants among many individuals to identify unique genotype-phenotype associations [8]. These types of studies better accommodate the biology of the disease process and lead to clinical advances through identification of new disease biomarkers, drug targets, and personalized therapeutics [9]. To date, there have been two large GWAS for ED which have identified strong gene candidates linked to the disease.

Here we review the use of GWAS for the study of ED and discuss advantages and limitations. We also highlight recently published GWAS for ED.

Advantages and Disadvantages of Genome-Wide Association Studies (GWAS)

GWAS use millions of genetic variants from individual genomes from large cohorts to identify genotype-phenotype associations. Initially, this experimental design was met with criticism. Since the early GWAS were published in the 2000s, nearly 70,000 associations have been reported between genetic variants and specific medical conditions [10]. There has been a greater acceptance of GWAS studies in recent years. Sharing of genetic data and the availability of GWAS summary statistics in the public domain has dramatically increased utilization of this experimental design [11, 12]. Currently, there are hundreds of large whole-genome datasets accessible by researchers, including the UK Biobank.

The association of genetic variants with phenotypic traits does not translate to identification of causal variants or genes, a key consideration for this experimental design. GWAS rely on linkage disequilibrium, which refers to the non-random association of alleles at two or more loci [13]. Natural selection, the size of the population, and the mutation rate at certain loci each contribute to linkage disequilibrium [13]. The association of genetic variants with a disease condition due to linkage disequilibrium leads to the initial identification of a locus of interest. However, additional investigation is needed in order to establish causality between a genetic variant and the disease.

There are several factors that determine the potential utility of GWAS for a specific disease process, including the number of loci and alleles at each loci impacting the disease phenotype, the degree of heterogeneity of the disease phenotype, and the sample size [9]. One of the major limitations of GWAS is accounting for multiple comparisons [9], which poses a statistical challenge that may decrease power and lead to false positive findings. This is commonly addressed using Bonferroni correction and larger sample size. Although, the associations determined using GWAS may be modest even with larger sample sizes, the biological insight gained is not proportional to the strength of the association because GWAS do not utilize clinical aspects of the condition to identify linked genes or variants [14]. Additionally, detailed phenotyping is imperative to prevent confounding from genetic variants associated with comorbid conditions. For example, genetic variants of peripheral vascular disease and diabetes, may be more common in men with ED, but not necessarily associated with ED alone.

However, novel drug targets have resulted from GWAS findings. Nearly 100 genetic variants have been identified in Type 2 Diabetes using GWAS [9], and GWAS have provided essential data on insulin and pancreatic islet cell regulation. The highlight of this application of GWAS has been identification of genetic variants and gene sequencing of the *SLC30A8* gene, a zinc transporter in pancreatic islet cells, loss of function mutations in which are protective against type 2 diabetes [15]. This has led to development of ZnT-8 antagonists for the treatment of diabetes [15].

ED confers a substantial burden on the U.S. healthcare system, costing over $15 billion dollars annually [16]. As such, there is a clear financial incentive to develop more effective, better tolerated, and less invasive ED treatments. Additionally, novel therapies may improve the burden of ED on overall and health-related quality of life. However, few novel targets for development of ED drugs have been identified in the last decade. GWAS may help identify novel drug targets for ED similar to what these studies have done in other disease processes such as diabetes. Drug targets that are supported by genetic association have a higher rate of getting to phase III trials and may offer opportunities for drug development [17].

Review of GWAS for Erectile Dysfunction

Although nearly 70,000 associations have been reported between genetic variants and various medical conditions, relatively few GWAS studies have been performed for ED [10]. However, three GWAS conducted in large cohorts are highlighted below (Table 1).

Hotaling et al. was one of the first to publish a GWAS for ED using a large cohort [18]. This study was a sub-group analysis from the UroEDIC (Epidemiology of Diabetes and Interventions and Complications) study that assessed urologic and sexual health within EDIC, an observational follow-up of the Diabetes Control and Complications Trial (DCCT). Five hundred and ninety-four white men with Type I diabetes provided data on erectile function. Genotyping was performed using Illumina Human1M Beadchip Microarray (Illumina Inc., San Diego, CA, USA). The authors found several SNPs on unadjusted models in or near the Activated

Table 1 Large genome wide association studies in erectile dysfunction

Reference	Associated gene	SNP	Cohort	*p* value*
Hotaling [18]	*ALCAM* (chromosome 3)	rs9810233	DCCT/EDIC	7×10^{-7}
		rs1920201	DCCT/EDIC	9×10^{-7}
Jorgenson [19••]	*SIM1* (chromosome 6)	rs17185536-T	GERA	3.4×10^{-25}
		rs17185536-T	UK biobank	6.8×10^{-14}
Bovijn [23••]	*MCHR2-SIM1* (chromosome 6)	rs57989773-C	UK biobank	3.0×10^{-11}
		rs57989773-C	EGCUT	NS
		rs57989773-C	PHB	9.84×10^{-5}

Standard GWAS significance criteria considered at $p < 5 \times 10^{-8}$

Abbreviations: *SNP*, single nucleotide polymorphism; *ALCAM*, activated leukocyte adhesion molecule; *DCCT*, diabetes control and complications study; *EDIC*, epidemiology of diabetes interventions and complications study; *SIM1*: single-minded homolog-1; *GERA*: genetic epidemiology research in adult health and aging; *MCHR2*, melanin concentrating hormone receptor 2; *EGCUT*, estonian genome center of the University of Tartu; *PHB*, partners health care biobank; *NS*, non-significant.

Leukocyte Cell Adhesion Molecular (*ALCAM*) on chromosome 3 associated with ED risk. The G allele of rs1920201 was associated with increased risk of ED ($p = 8.6e-07$) as well as rs9810233, ($p = 6.98e-07$). On multivariate analysis, the G risk alleles for SNPs rs1920201 (OR = 2.26, 95% CI 1.63–3.14) and rs9810233 (OR = 2.32, 95% CI 1.67–3.22) were associated with ED risk. Multivariate models were adjusted for age, duration of diabetes, baseline HbA1c and mean HbA1c from DCCT/EDIC, and randomization to intensive glycemic therapy (secondary prevention cohort only). This was the first study to demonstrate 2 SNPs near *ALCAM* as possible genetic predictors of ED in white men with type I diabetes. A candidate gene analysis (derived *a priori*) was also conducted but there were no significant results in this cohort.

More recently, Jorgenson et al. performed a GWAS in a large, diverse group of 37,000 men within the Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort [19••]. Findings from this cohort were than validated in an independent cohort of nearly 225,000 men within the UK Biobank. The authors identified a single locus on chromosome 6 with multiple noncoding SNPs associated with ED ($p < 5 \times 10^{-8}$). On replication analysis, five selected SNPs at this locus were significantly associated with ED in the UK Biobank cohort ($p < 10^{-13}$), with the rs17185536 SNP located in an evolutionarily conserved region. Rs17185536 was associated with increased risk of ED across different races and ethnic groups, and is located within a topological associating domain containing several genes including single-minded homolog 1 (*SIM1*). *SIM1* encodes a transcription factor in the leptin-melanocortin pathway [20]. Several prior studies have suggested a role of this pathway in erectile function with melanocortin receptor agonists demonstrating penile erection in early clinical studies [21]. Animal studies using Melanocortin receptor 4 null mice have demonstrated impaired sexual performance [22]. The risk alleles were cloned into human embryonic kidney 293T cells using an enhancer assay vector. The investigators found that rs17185536-T (risk) allele caused differential enhancer activity of *SIM1*, suggesting a relationship between rs17185536 and *SIM1*. However, the impact of this variant on actual erectile function remains unknown. Nevertheless, this is one of the most extensive analyses of genetic factors related to ED using GWAS to date, and highlights a possible novel pathway leading to ED.

Bovijin et al. performed a similar GWAS using the UK Biobank and the Estonian Genome Center of the University of Tartu (EGCUT) and the Partners HealthCare Biobank (PHB) [23••]. ED was diagnosed based on international classification of disease (ICD)-10 codes, use of oral PDE5 inhibitors, or history of surgical intervention for ED based on procedural codes. Genome wide analysis revealed a single significant locus for ED at chromosome 6q16.3, with the lead variant rs57989773. A pooled meta-analysis estimated an odds ratio of 1.20, $p = 5.71 \times 10^{-14}$ for this variant and association with ED.

The authors then performed several functional analyses at this locus, supporting a role for *SIM1* in the pathogenesis of ED. They visualized chromosome conformation capture interactions using 3D Genome Browser in human embryonic stem cells [23••]. This showed a high contact probability between *SIM1* and the rs57989773 variant. Contact probability is the relative number of times that the two regions were sequenced together. Functional correlations were also established between the *SIM1* promoter and the Melanin Concentrating Hormone Receptor 2 (*MCHR2*)-*SIM1* intergenic region using a similar technique in endothelial progenitor cells. These observations suggest a possible causal relationship between the rs57989773 variant and *SIM1* in the setting of ED.

SIM1 is expressed within the hypothalamus and its potential role in ED is likely to be central. Therefore, the VISTA enhancer browser was then used to look at other elements within the *MCHR2-SIM1* region [23••]. In mouse embryos, the regulatory human element (hs576) that is located just

downstream of the rs57989773 variant was found to drive enhancer activity within the midbrain. These findings suggest that the *MCHR2-SIM1* region contains a neuronal enhancer.

Future Directions for Genetic Based Therapy for Erectile Dysfunction

Identification of novel genes and alternative pathways involved in the pathogenesis of ED is appealing for the development of targeted therapeutic or gene therapy. Targeted therapies are small molecules or antibodies that are designed to alter gene expression [24]. Small molecules are able to penetrate the cell membrane and interact within the cell compared to antibodies which target specific antigens on the cell surface and cause intracellular effects through transmembrane receptors [24]. However, the effects of these targeted therapies are likely short-lived. Targeted therapies have been explored as novel therapeutic options for alternative pathways in ED pathogenesis. Alternative targets which have been previously explored for ED treatment are summarized in Table 2. Centrally acting targeted therapies such as dopamine agonists and melanocortin agonists as ED therapies have been explored in preclinical and early clinical studies, with further development limited due to unwanted secondary side effects [25]. Similarly, peripherally acting agents including guanylyl cyclase activators/stimulators and RhoA/Rho kinase inhibitors have not progressed beyond Phase II clinical trials in the absence of results demonstrating efficacy [25].

There is also considerable interest in gene therapy applications for ED. This approach is appealing for ED treatment due to the relative ease of administration (direct injection into the corpora) and low turnover rate of corporal smooth muscle cells, which may produce a durable effect even with a single treatment, when compared to other targeted therapies [26]. Gene therapy involves the injection of exogenous genetic material directly into the penis [26]. To reduce immunogenicity associated with direct gene transfer, a modified approached has been explored. Stem cells are isolated from a variety of sources including adipose tissue, bone marrow, urine, placenta, umbilical vein endothelium tissue, and amniotic fluid and cultured in vitro [26]. The therapeutic gene is transferred to the stem cell using either a viral or non-viral vector. These modified stem cells are then injected directly into the target.

Table 2 Alternative targets for erectile dysfunction studied in prior clinical trials

Central pathway targets
Dopaminergic agonists
Melanocortin receptor agonists
β-lactamase inhibitors
Peripheral pathway targets
Phosphodiesterase inhibitors
Soluble guanylyl activators/stimulators
Rho-A/Rho-kinase inhibitors

The use of isolated stem cells for ED therapy has been explored in several preclinical and clinical studies. However, only a single human study has utilized genetically modified stem cells with molecular targets of interest for ED therapy [27, 28]. Several preclinical ED animal models with cavernous nerve injury or streptozotocin induced diabetes after corporal injection of stem cells [29]. The most commonly studied stem cells for ED are adipose-derived stem cells. Clinical studies using isolated stem cell therapy for ED are limited [28].

Genetically modified stem cells with molecular targets of interest have been studied in animal studies. Pigment epithelium-derived factor transfected adipose stem cells, K^+ (ATP) channel transduced human corporal smooth muscle and human embryonic kidney cells, and prepro-calcitonin gene-related peptide using an adenoviral vector have been injected into rat models of ED with restoration of erectile function [30–32]. A single human study of gene transfer in men with ED has been completed [27]. Eleven patients with ED were given a corporal injection of a DNA plasmid containing human slow-poke (hSlo), which encodes a subunit of the smooth muscle Maxi-K channel [27]. There were no serious side effects observed. Patients who received the highest dose realized an improvement in erectile function based on IIEF scores.

Despite the numerous candidate gene studies for ED, there have been few reproducible results from ED gene therapy studies that have been substantial enough to support a larger study. Identification of novel genes associated with ED risk in large cohorts using GWAS has the potential to change this and fuel gene therapy studies.

In recent years, there has been a significant interest in CRISPR-Cas based genome editing systems for targeted gene therapy [33, 34•]. Gene targeting using CRISPR-Cas9 systems is based on pairing of unique nucleic acid sequences. This eliminates the need for novel DNA-binding proteins for gene targeting which is time intensive and carries a higher chance of off target effects. The CRISPR-Cas system is a mechanism of adaptive immunity used to cleave invading nucleic acids by prokaryotes.

Most CRISPR-Cas systems rely on a guide RNA that is used for gene targeting [33, 34•]. The targeting sequence is followed by a space sequences which flanks Cas. Cas is a nuclease which cleaves the target nucleic acid and allows for subsequent gene deletion, gene insertion, translocations, and single-base editing. Currently, gene editing strategies for other clinical conditions rely on ex vivo cell manipulation, with administration of these cells to the target organ system. There are notable limitations to CRISPR gene editing technologies, as well as concern regarding undesirable secondary effects, including off-target effects of specific targeting

sequences as well as immunogenicity of Cas proteins [33, 34•]. Furthermore, there are limits to the size of genes that may be included within the vector. For example, adenovirus, a commonly used viral vector, has limited capacity (approximately 35 kB) to accept new genetic information for gene editing.

Currently, the American Urological Association (AUA) guidelines and the Sexual Medicine Society of North America (SMSNA) position statement on therapies for ED consider stem cell and gene therapies investigational [35]. As stem cell and gene editing therapies for ED enter preclinical testing, safety and efficacy is yet to be determined.

Ultimately, a better understanding of the genetic underpinnings of ED will facilitate new therapies and prevention. GWAS are poised to identify genes which may be involved in disease development and those that may serve as biomarkers for diagnosis and preventive screening. Additionally, identification of alternative central pathways in the pathogenesis of ED, may help improve the understanding of sexual dysfunction in both men and women.

Conclusions

There is growing interest in identifying the genetic origins of ED and development of novel therapeutic targets. GWAS have been able to address many of the challenges of candidate gene studies and the utilization of this study design has increased with sharing of genetic data and the availability of GWAS summary statistics in the public domain. Recently, two GWAS studies have identified loci adjacent to *SIM1* which may confer increased ED risk through hypothalamic dysregulation. With the identification of novel gene targets, gene therapy is an attractive future therapy for ED, however it is in the very early stages. Furthermore, investigation of centrally mediated genetic contributors of ED has the potential to provide a better understanding of the pathways involved in sexual function.

Compliance with Ethical Standards

Conflict of Interest Dr. Patel has nothing to disclosure regarding the material discussed in this article.

Dr. Pastuszak reports his associations with Endo Pharmaceuticals – advisor, speaker, consultant, research and fellowship support; Antares Pharmaceuticals – advisor; and Woven Health – founder and leadership position.

Dr. Hotaling reports associations with Endo Pharmaceuticals – research and fellowship grant; Boston Scientific – fellowship grant; Nanonc, StreamDx, Andro360 – leadership position/founder.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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