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Genetic basis of eugonadal and hypogonadal female reproductive disorders

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This review discusses the current state of our understanding regarding the genetic basis of the most important reproductive disorders in women. For clarity, these disorders have been divided into eugonadal and hypogonadal types. Hypogonadal disorders have been further subdivided according to serum gonadotropin levels. Our review focuses on historical and recent data regarding the genetics of the hypothalamic–pituitary–gonadal axis dysfunction, as well as the development and etiology of eugonadal disorders including leiomyomata, endometriosis, spontaneous ovarian hyperstimulation syndrome, polycystic ovarian syndrome, mullerian aplasia, and steroid hormone resistance syndromes. We discuss the known genes most commonly involved in hypergonadotropic hypogonadism (Turner syndrome and premature

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ovarian failure) and hypogonadotrophic hypogonadism (Kallmann syndrome and normosmic types). In addition, we summarize the current clinical testing approaches and their utility in practical application.

Introduction

Sexual and reproductive development and function in humans are critically dependent on GnRH-synthesizing neurons, which originate outside the brain and migrate during embryological development to the hypothalamus [1]. GnRH produced in the hypothalamic arcuate nucleus is released into hypophyseal-portal capillaries, reaching the anterior pituitary where it binds to its cell surface receptor on pituitary gonadotrope cells, inducing synthesis and secretion of the gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH). In turn, gonadotropins stimulate steroidogenesis in the gonads through interaction with their G-protein coupled receptors. Because of inhibitory feedback on the hypothalamus and anterior pituitary, sex steroid hormones control the synthesis of gonadotropins [2]. Recently, a number of other factors have been identified as important in the regulation of reproductive function, including gonadotropin inhibitory hormone, which directly inhibits pituitary gonadotrophin synthesis and release, kisspeptin, inhibins, antimullerian hormone, and many other growth factors [2].

Disorders of the human reproductive system can be classified based on the functional activity of the gonads as either hypogonadal (low estrogen state) or eugonadal (normal estrogen state). In the recent past, our scientific understanding regarding the genetic etiology of female reproductive dysfunctions has significantly increased [3]. In general, eugonadal conditions are much more common than hypogonadal disorders, but the molecular basis is much better known for hypogonadal conditions. Hypogonadal conditions also represent more severe clinical phenotypes compared to eugonadal dysfunction. The critical role of specific gene mutations has been relatively well established for many hypogonadal disorders, but only for two eugonadal disorders [i.e., ovarian hyperstimulation syndrome (OHSS) and mullerian aplasia]. For the other eugonadal disorders, such as leiomyoma, endometriosis, and polycystic ovary syndrome (PCOS), no specific causative genes have been identified. Association studies have shown certain loci that are linked with these disorders, but these data do not signify causation. Causation requires the demonstration of gene mutations that impair normal function, segregate with the disease phenotype, and have *in vitro* evidence demonstrating biological plausibility. This review summarizes the current scientific data available on the genetics of selected eugonadal disorders and hypogonadal conditions and provides practical recommendations for clinicians.

Eugonadal disorders

Leiomyomata

Uterine leiomyomas are monoclonal, diploid, somatic cell tumors that arise from uterine smooth-muscle tissue. Leiomyomata (fibroids) are one of the most common diseases in gynecological practice, occurring in at least half of women. Although many are asymptomatic, some women manifest heavy uterine bleeding and pelvic pain resulting in hysterectomy. The inheritance pattern of fibroids is largely unknown [4] except for some rare Mendelian types, which develop in unusual locations and are associated with other anomalies. Hereditary leiomyomatosis and renal tumors are caused by autosomal dominant mutations in the fumarate hydratase (*FH*) [5]. Diffuse leiomyomatosis and Alport syndrome, an X-linked dominant contiguous gene deletion syndrome affecting *COL4A*5 and *COL4A6*, consist of glomerulonephritis, hearing loss, and eye disease [6].

Classical cytogenetic analysis of uterine leiomyoma demonstrates low-frequency chromosomal aberrations, including 7q deletions, trisomy 12, and translocations at chromosome 12q14, which