Pedigree Analysis as a Tool for Determination of Gender Ratio Bias in GnRH Deficiency

Marie Discenza, Cassandra Buck, Meghan Connolly, MaryAnn Campion
Boston University School of Medicine, Boston, Massachusetts

Isolated gonadotropin-releasing hormone deficiency (IGD) is characterized by impaired gonadotropin secretion leading to low levels of circulating luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the presence of hypogonadism. IGD is a syndrome with several subtypes, including Kallmann syndrome (KS) and normosmic isolated hypogonadotropic hypogonadism (nIHH), which display clinical and genetic heterogeneity. The low prevalence of the disease and small family size due to the reproductive challenges of individuals with IGD make the study of molecular etiologies difficult. Challenges in identification and characterization of causative genes have also been attributed to oligogenicity, incomplete penetrance and variable expressivity. The aim of this project was to methodically calculate an updated gender ratio among a study cohort of participants with IGD. This information will be helpful in genetic counseling settings and can increase understanding of the variability of clinical presentations. Using the database of study participants at Massachusetts General Hospital's Reproductive Endocrine Unit, pedigrees with recorded gonadotropic releasing hormone (GnRH) deficiency were examined, and inheritance patterns were inspected and verified. When removing gender-skewing factors, in pedigrees of individuals with KS, nIHH, constitutional delay of puberty (CDP) and hypothalamic amenorrhea (HA), a male-to-female gender ratio was determined to be 1.3:1. This figure is smaller than the previously reported ratio of 4:1, suggesting that there are proportionally more affected females than previously believed. This calculation may bring more attention to the phenotypic spectrum of IGD and should be kept in mind to ensure that KS and nIHH are included in differential diagnosis considerations for males and females who present with clinical features. Analysis of additional individuals may lead to explanations for the gender bias that exists between males and females, providing more accurate genetic counseling to patients and families.