Characterizing Mixed Pedigrees in Families with Normosmic Isolated Hypogonadotropic Hypogonadism (nIHH) and Kallmann Syndrome (KS)

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Isolated gonadotropin-releasing hormone (GnRH) deficiency is caused by a decreased amount or absence of GnRH. In the context of a normally functioning anterior pituitary gland this deficiency is termed idiopathic hypogonadotropic hypogonadism (IHH). IHH leads to absent or incomplete puberty and infertility and can also cause non-reproductive phenotypic anomalies. GnRH deficiency can either be normosmic or associated with anosmia. Kallmann syndrome (KS) is the association of hypogonadotropic hypogonadism and anosmia. In this study we examined mixed GnRH deficiency pedigrees, those with both normosmic isolated hypogonadotropic hypogonadism (nIHH) and Kallmann syndrome (KS), to determine the genes that are responsible for the phenotype in these families and to further characterize these pedigrees. These pedigrees were then compared to pedigrees in which there was a consistent smell phenotype segregating through the family. Utilizing the database of study participants at Massachusetts General Hospital's Reproductive Endocrine Unit, pedigrees exhibiting multiple family members with GnRH deficiency were examined. These pedigrees were characterized as either exhibiting a consistent smell phenotype (control pedigrees) or an inconsistent smell phenotype (mixed pedigrees). These pedigrees were then assessed for the disease segregation that was occurring in the family. Rare sequence variants segregating through the families were characterized by utilizing protein prediction models (PolyPhen 2, SIFT, Mutation Taster) and a literature review. Limited functional data was also available. Pedigrees were characterized as either exhibiting monogenic inheritance or not exhibiting monogenic inheritance. Pedigrees not exhibiting monogenic inheritance are thought to be exhibiting digenicity, oligogenicity, haploinsufficiency, variable expressivity, or be affected by other non-genetic modifiers. Results show that a higher percentage of the mixed pedigrees exhibit non-monogenic segregation. Results also indicate that a higher percentage of the phenotypically consistent pedigrees exhibit monogenicity ($p<0.05$). Additionally, the mixed pedigrees have a higher percentage of families exhibiting digenicity. FGFR1 comprised the highest percentage of RSVs in both groups. These results support the emerging data that nIHH and Kallmann syndrome exhibit oligogenicity as well as direct future research and demonstrate that pedigrees with an inconsistent smell phenotype are a potentially fruitful place to begin the search for new genes playing a role in GnRH deficiency.