Abstract citation ID: bvac150.970

Neuroendocrinology and Pituitary

LBMON114

Enrichment Of Rare Sequence Variants In Genes That Communicate Metabolic Signals To The GnRH System In Hypothalamic Amenorrhea

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Introduction: Functional hypothalamic amenorrhea (HA) is commonly associated with increased exercise or

decreased caloric intake and often with stress. We have previously demonstrated an increased burden of rare sequence variants (RSVs) in genes involved in GnRH ontogeny and upstream regulation in women with HA, but the role of metabolic and stress signaling to the GnRH neuronal system is poorly defined in this population. **Methods:** The study included 100 women with a confirmed diagnosis of HA. The control cohort consisted of 468 women (aged 45-65 years) drawn from the NIH ClinSeq® Project. Exome sequencing was performed on peripheral blood genomic DNA. A subset of 72 genes was analyzed that have been shown to: 1) link metabolic or stress with reproductive phenotypes or 2) integrate metabolic and stress pathways with control of GnRH secretion. Joint genotyping of case and control samples was performed using the GATK GenotypeGVCFs function, locus-filtering using the VariantRecalibrator function, and genotype refinement using CalculateGenotypePosteriors with computation of median depths. Median depth positions <10, positions failing GATK VQSR or GATK genotype quality scores <20 were excluded. RSVs were identified by < 1% frequency in any subpopulation in gnomeAD for all-subjects (AS) and < 1% frequency in non-Finnish Europeans for Caucasians (CS). Data were analyzed for AS and for CS using a one-sided Fisher exact test for metabolism genes and stress genes. An additional regression analysis was conducted on the number of RSVs in a given gene as a predictor of HA vs. control. Comparisons with a p-value of < 0.1 are reported. **Results:** HA patients exhibited an increased burden of RSVs in metabolism genes vs. controls (AS p=0. 043; CS p=0.105). The total number of RSVs per gene highlighted differences between HA and controls for the following genes: ADAMTSL1, GRINA, GRIN1, HCRTR1, TENM3, and NOS1 (AS p<0. 001, p=0. 032, p=0. 057, p=0. 082, p=0. 091, p=0. 095; CS p=0. 024, p=0. 044, p=0. 044, p NS, p=0. 086, p NS). Interestingly, RSVs in NOS1 and TENM3 appeared to be protective for HA (odds ratio <1 for both). In contrast, candidate stress genes were not significant in either the AS or CS (p=0.788, p=0.910). **Conclusions:** These data suggest that RSVs in genes involved in phenotypes or signaling pathways that link metabolism to GnRH secretion may predispose to development of HA in the setting of decreased energy balance, but not for stress-related genes. GRINA and GRIN1 are important components of glutamate signaling that facilitate both appetite and GnRH secretion either directly or through kisspeptin. HCRTR1 plays a similar role in linking appetite and GnRH secretion while NOS1, which facilitates kisspeptin signaling, may be protective. This work highlights the need for further studies to understand the potential roles of ADAMTSL1 and TENM3 as risk factors for HA.

Presentation: Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.