CENTER FOR RNA BIOMEDICINE

RNA Innovation Seminar
Monday, September 18th at 3:00pm
ABC Seminar rooms, Biomedical Research Science Building (BSRB), 109 Zina Pitcher

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"RNA splicing in Pituitary Insufficiency and Growth Disorders"

Abstract:

The pituitary gland is essential for growth, the stress response, fertility, and other physiological functions. Pituitary insufficiency is a genetically heterogenous disorder that affects 1/4000 children. Mutations in thirty genes are reported to cause pituitary-based growth insufficiency, yet ~84% of the patients have no molecular diagnosis. Known causes of isolated growth hormone (GH) deficiency include mutations in the *GH1* gene or the receptors that stimulate GH secretion. Alternative splicing normally produces two isoforms of GH, a 22 kDa biologically active form and a 17.5 kDa form that inhibits secretion. The majority of dominant cases of isolated GH deficiency are caused by mutations that affect splicing, including exonic splice enhancers, resulting in increased production of the 17.5 kDa isoform. Mutations in the pituitary transcription factor POU1F1 cause multiple pituitary hormone deficiencies, including GH. Multiple isoforms of POU1F1 are generated by alternative splicing. The POU1F1α isoform acts as a transcriptional activator, and the larger, POU1F1β isoform acts as a repressor. Although the POU1F1α isoform predominates, it has a very poor splice acceptor sequence which likely requires yet unidentified splice enhancers. We screened 72 unrelated patients for mutations that could explain their growth insufficiency. We identified a dominant mutation in the *GH1* gene in a 3-generation pedigree with isolated GH deficiency. This mutation inhibits GH secretion. We identified variants in the POU1F1β isoform and are in the process of assessing the effect of these changes on splicing and repressor function. Molecular diagnosis for growth disorders is valuable for predicting disease progression and future risk.