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Editor's Note

What starts puberty is still intriguing scientists as well as clinicians. This unique developmental event in human life renders not only a reproductive capacity but profoundly influences the psychosocial identity of the individual.

Dr. Topaloglu and colleagues have attempted to answer this question by studying a group of familial cases in whom natural puberty had not occurred, namely, patients with idiopathic hypogonadotropic hypogonadism. The authors interrogate the exact genetic underpinnings of this particular phenotype by whole exome sequencing coupled with autozygosity mapping. Through their previous ground-breaking work, these researchers have identified the roles of such genes as TAC3, TACR3, and KISS1 which constitute the Neurokinin and Kisspeptin signaling leading to our current understanding of the GnRH pulse generator. In their present work, they (in collaboration with Dr. Leygue's group in Canada) report in our Journal an exciting new puberty gene. SRA1 (Steroid receptor RNA activator 1) encodes for a nuclear hormone receptor coregulator.

Nuclear hormone receptors (NRs) mediate the transcriptional responses to a wide range of physiological stimuli and thus function as important regulators of development, metabolism, and reproduction. NR coregulators, by functioning as coactivators or corepressors of NR activity, play pivotal roles in mediating hormone action. SRA1 was originally described as a functional ncRNA involved in the regulation of gene expression by steroid receptors. More recently, SRA isoforms were identified that were also able to encode for a protein now referred to as the Steroid Receptor RNA Activator Protein (SRAP). SRA and SRAP now define a very intriguing bi-faceted genetic system, where both RNA and protein products of the same gene play specific and sometimes overlapping roles in cell biology. *SRA1* gene products functioning as a protein and/or a noncoding functional RNA act as co-regulators of nuclear receptors including sex steroid receptors as well as SF-1 and LRH-1, the master regulators of steroidogenesis.

It is evident from the eloquent studies reported here that inactivating mutations of the *SRA1* gene cause complete normosmic IHH, hence pubertal failure in humans. Further, there are circumstantial evidence to suggest that SRA1 may prove to be of paramount importance in puberty. SRA1 stands as an intriguing gene with its functioning protein as well as noncoding RNA products, which may account for the complexity, versatility, and elusiveness of the pubertal process, especially when one considers the fact that actions of nuclear receptor coregulators can spatially and temporally vary to become activators or repressors of the target nuclear receptors depending on the cellular and promotor context.

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