



“Reproductive endocrine phenotypes relating to *CHD7* mutations in humans”

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AUTHORS AND THEIR CONNECTION TO THE CHARGE SYNDROME FOUNDATION:



Ravikumar Balasubramanian, PhD, MRCP (UK), is an Assistant Professor of Medicine at the Harvard Medical School and a faculty member in the Reproductive Endocrine Unit of the Department of Medicine, Massachusetts General Hospital, Boston, MA. His areas of interest include genes which are involved in growth and other endocrine issues. His studies have highlighted the biologic roles of genes regulating neural crest cells (*CHD7*) and axonal guidance (*TUBB3*) in the etiology of isolated growth hormone deficiency.



William F. Crowley Jr., MD, is the Daniel K. Podolsky Professor of Medicine at the Harvard Medical School and Director of the P50 National Centers for Translational Research in Reproduction and Infertility at the Reproductive Endocrine Unit of the Department of Medicine, Massachusetts General Hospital, Boston, MA. His research over the past 40 years has focused on improving the understanding of the normal physiology of the neuroendocrine control of human reproduction, using this information to develop treatments for reproductive disorders, and teaching others to use and further this research. The Crowley group has long-term experience in Kallmann syndrome. They studied *CHD7* variants in patients with hypergonadotropic hypogonadism with and without anosmia (absent or decreased sense of smell).

SUMMARY OF THE PAPER:

Abstract: Gonadal defects are reported in 60-80% of individuals with CHARGE syndrome (CS). They primarily present clinically as pubertal delay/failure and infertility. These defects result from congenital deficiency of the hypothalamic hormone Gonadotropin-releasing hormone (GnRH), and manifest biochemically as hypogonadotropic hypogonadism (low sex steroid hormone levels with inappropriately normal or low gonadotropin levels, HH). In a minority of individuals with CS, additional endocrine defects including growth hormone deficiency, multiple pituitary hormone deficits and primary hypothyroidism may also be seen. *CHD7* mutations disrupt the targeting of olfactory axons (nerves associated with sense of smell) and the migration of GnRH-synthesizing neurons during embryonic development, resulting in congenital idiopathic hypogonadotropic hypogonadism (IHH) and anosmia or hyposmia. IHH and anosmia are two features that define human Kallmann syndrome. Since these features of Kallmann syndrome are constituent phenotypes within CS, recent studies have investigated the role of *CHD7* mutations in individuals with IHH. A small percentage of cases of Kallmann syndrome

and normosmic form of IHH (without additional CS features) have been found to have missense mutations in *CHD7*. These observations suggest that *CHD7* protein function is critical for the embryonic development of GnRH neurons and neuroendocrine regulation of GnRH secretion.

Additional summary: Endocrine features in CS can include hypogonadism (micropenis, undescended testes) pubertal failure, infertility, low sex steroid hormone level, growth hormone (GH) deficiency, pituitary hormone deficiency, and hypothyroidism. The endocrine system is complex, with a number of interconnecting and feedback systems, including the hypothalamic-pituitary-gonadal (HPG) axis in utero and neonatal periods. As with many other aspects of CS, the HH and anosmia result from defective migration of neuronal cells rather than a primary pituitary defect. **Section 2.1 of the paper discusses the endocrine features of CS and treatments which should be considered, from early testosterone for penile growth to bone density screening and fertility treatment in adults, with a reference for further information.** The incidence of growth hormone deficiency in CS is estimated to be about 9% and a rare subset of individuals with CS may have structural pituitary abnormalities.

From clinical aspects of CS, the authors move on to their research. One way to look at the endocrine aspects of CS is to look at individuals with Kallmann syndrome (KS) – who have HH and anosmia without most of the other features of CS. [Many individuals with CS have KS as *part* of their CS.] A small number of individuals with isolated KS have missense mutations in *CHD7*. Zebrafish and mouse studies looking at equivalent mutations confirm that some missense *Chd7* mutations can cause HH without CS. As with semicircular canal development (see the [Choo](#), et al. paper in this series), GnRH neurogenesis appears to be very sensitive to the mildest dysregulation of *CHD7* function – in humans and animals both. They go on to discuss many of the other genes which are known to interact with the *CHD7* protein.

The authors recommend that any patient with HH also be evaluated for possible features of CS. The presence of hearing loss, cleft lip/palate or other features are an indication for *CHD7* testing. They recommend that all individuals with CS be screened for endocrine abnormalities. And, of course, more research is needed to more fully understand the endocrine aspects of CS.

WHAT DOES THIS MEAN TO FAMILY/PERSON WITH CHARGE?

Relatively little has been published on the endocrine features of CS, which makes this a very important paper. It includes information about what systems may be affected and what screening may be appropriate. It does not provide specific treatment recommendations, but these should be tailored to each individual in any case. This is potentially a very useful paper to many families.

SHOULD I READ IT? SHOULD ONE OF MY DOCTORS READ IT?

Yes, and yes. Section 2.1 includes descriptions of potential endocrine features of CS and contains a reference to more detailed information. The paper does a good job of describing some of the intricacies of the endocrine system. To date, it is the best source of this information on CS. Take a copy of it to your endocrinologist. And, as Dr. Kim Blake has been saying for years or even decades, “Everyone should have an endocrinologist by age 3.”

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