Title: *PROP1*-Related Combined Pituitary Hormone Deficiency *GeneReview* – *HESX1* Variants

Author: de Graaff L

Date: August 2014

Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

## Specific variants in *HESX1*

- Dattani et al [1998] found a homozygous missense *HESX1* variant (p.Arg160Cys) in a brother and sister with septooptic dysplasia, agenesis of the corpus callosum, and CPHD (OMIM 182230).
- Individuals homozygous for the recessive variant p.Arg160Cys had septo-optic dysplasia (SOD/Morsier syndrome) with agenesis of the corpus callosum and CPHD [Brickman et al 2001].
- Individuals with a monoallelic variant had milder phenotypes suggesting that they result from haploinsufficiency of the HESX1 protein [Tajima et al 2003].
- In 2011, Vivenza et al describe a novel mutation (c.357+3G>A), identified at the heterozygous state in an IGHD patient. This mutation prevents the generation of one of the alternative isoforms normally produced by the wild-type allele, predicting a truncated HESX1 protein. The mutation is likely to cause IGHD in the heterozygous patient by interfering with the downregulation of HESX1 expression mediated by alternative splicing and nonsense-mediated decay.
- In 2011, Durmaz et al found a novel homozygous mutation (R160H) within the homeodomain of HESX1, which, is the first to be described in humans. Neuroimaging studies revealed anterior pituitary aplasia, a normal posterior pituitary gland, and a thin pituitary stalk but no midline abnormalities. Optic nerve studies showed no pathology. *HESX1* mutation causing an R160H substitution can result in panhypopituitarism without midline defects.
- Also in 2011, Reynaud et al studied 83 patients with pituitary stalk interruption syndrome and found one novel *HESX1* homozygous nonsense mutation generating a truncated protein, resulting in total loss of homeodomain and co-repressor binding. This *HESX1* p.Arg109X mutation leads to a severely truncated protein including the homeodomain that is involved in DNA binding and required to recruit components of N-CoR-associated co-repressors
- In 2013, a novel heterozygous sequence variant (c.142A>T, p.T48S) was found in *HESX1* in one PSIS patient by Yan Yang et al.

## References

Brickman JM, Clements M, Tyrell R, McNay D, Woods K, Warner J, Stewart A, Beddington RS, Dattani M. Molecular effects of novel mutations in Hesx1/HESX1 associated with human pituitary disorders. Development. 2001;128:5189-99.

Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Martensson IL, Toresson H, Fox M, Wales JK, Hindmarsh PC, Krauss S, Beddington RS, Robinson IC. Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. Nat Genet. 1998;19:125-33

Durmaz B, Cogulu O, Dizdarer C, Stobbe H, Pfaeffle R, Ozkinay F. A novel homozygous HESX1 mutation causes panhypopituitarism without midline defects and optic nerve anomalies. J Pediatr Endocrinol Metab. 2011;24:779-82.

Reynaud R, Albarel F, Saveanu A, Kaffel N, Castinetti F, Lecomte P, Brauner R, Simonin G, Gaudart J, Carmona E, Enjalbert A, Barlier A, Brue T. Pituitary stalk interruption syndrome in 83 patients: novel HESX1 mutation and severe hormonal prognosis in malformative forms. Eur J Endocrinol. 2011;164:457-65.

Tajima T, Hattorri T, Nakajima T, Okuhara K, Sato K, Abe S, Nakae J, Fujieda K. Sporadic heterozygous frameshift mutation of HESX1 causing pituitary and optic nerve hypoplasia and combined pituitary hormone deficiency in a Japanese patient. J Clin Endocrinol Metab. 2003;88:45-50.

Yang Y, Guo QH, Wang BA, Dou JT, Lv ZH, Ba JM, Lu JM, Pan CY, Mu YM. Pituitary stalk interruption syndrome in 58 Chinese patients: clinical features and genetic analysis. Clin Endocrinol (Oxf). 2013;79:86-92.