

Mutations in *PROP1* Cause Familial Combined Pituitary Hormone Deficiency

The investigators identified 4 families with combined pituitary hormone deficiency due to homozygous or compound heterozygous inactivating mutations of *PROP1*, the "prophet of *Pit-1*," a transcription factor necessary for expression of *POU1F1* (the human homologue of mouse *Pit1*). *POU1F1* is essential for differentiation of the somatotrope, lactotrope, and thyrotrope. Its deficiency results in hypoplasia of the pituitary gland and subnormal secretion of growth hormone (GH), prolactin (PRL), and thyrotropin. *PROP1* has 3 exons encoding a 226 amino acid paired-like homeodomain protein with DNA binding properties. Each of the 3 mutant *PROP1* genes resulted in decreased DNA binding of the product and, hence, to decreased transactivation of a reporter gene. Patients with mutations of *PROP1* lacked not only GH, PRL, and thyrotropin

secretion but also luteinizing hormone and follicle-stimulating hormone as well, and were sexually immature. Magnetic resonance imaging revealed hypoplastic pituitaries. The authors concluded that *PROP1* is important for differentiation of gonadotropes and, through expression of *POU1F1*, of somatotropes, lactotropes, and thyrotropes.

Wu W, et al. *Nature Genet* 1998;18:147-149.

Editor's comment: *These elegant studies identify yet another gene necessary for differentiation of the anterior pituitary that now includes Lhx3 (LIM homeodomain Zn-binding transcription factor), POU1F1, GH-releasing factor, and its receptor.*

Allen W. Root, MD

Frequency of Inherited Bleeding Disorders in Women With Menorrhagia

Menorrhagia is a common gynecologic problem and accounts for 12% of referrals to gynecologists. It involves abnormal uterine bleeding occurring at regular intervals that is excessive in amount and duration. Adolescent girls may have excessive uterine bleeding as they establish their menstrual periods; however, if it is persistent, then a gynecologic evaluation is warranted. There are many etiologies. However, if the pelvic examination is normal, then genetic bleeding disorders should be considered.

Kadir et al screened 150 women with menorrhagia in order to find out what proportion of women with menorrhagia have a genetically related bleeding disorder. Uterine blood loss was assessed by means of a pictorial blood assessment chart. The following were determined for each woman: full blood count, blood grouping, activated partial thromboplastin time, factor VIII activity, von Willebrand factor antigen activity, and factor XI levels.

The authors found that 26/150 (17%) women with menorrhagia who had a normal pelvic examination had a genetically related bleeding disorder: 15/26 had mild von Willebrand's disease; 3/26 had moderate to severe von Willebrand's disease; 4/26 had mild factor XI deficiency; 1/26 had mild von Willebrand's disease and factor XI deficiency; 1/26 had combined von Willebrand's disease, factor XI deficiency, and factor X deficiency; 1/26 was a carrier of hemophilia A; and 1/26 had platelet dysfunction. Overall, 13% had von Willebrand's disease and 4% had factor XI deficiency. Menorrhagia since menarche was noted in 11/123 women (8.9%) without a bleeding disorder, 13/20 women (65%) with von Willebrand's disease, and 4/6 (66.7%) with factor XI

deficiency. Women with von Willebrand's disease and factor XI deficiency had prolonged activated partial thromboplastin time. They found that individuals with von Willebrand's disease had a history of easy bruising, bleeding after tooth extraction, postpartum hemorrhage, and postoperative bleeding.

The authors suggest that clinicians treating individuals with menorrhagia should take a careful medical history and test for inherited bleeding disorders, especially von Willebrand's disease. More than 50% of the affected women would have been missed if screening had been done only on the basis of symptoms.

Kadir RA, et al. *Lancet* 1998;351:485-489.

Editor's comment: *Kadir et al found that 1 in 6 women presenting with menorrhagia and a normal pelvic exam has a hereditary bleeding disorder. They point out that they may have a selected population. Nevertheless, the diagnosis of a hereditary bleeding disorder has important implications for prenatal diagnosis, genetic counseling, and future invasive procedures for the affected woman. Because von Willebrand's disease is so common (1.4% of the population), it seems likely that cases of menorrhagia that may be due to von Willebrand's disease are being missed. Although the incidence of bleeding disorders in adolescent females will be less than in adult women, some cases of bleeding disorders—particularly von Willebrand's disease—are being missed. Endocrinologists and gynecologists should be aware of this possibility and avoid it by taking a thorough history and screening for the disorder.*

Judith G. Hall, MD