

Table: Genetic causes of isolated hypogonadotropic hypogonadism.

Gene	Locus	Gene product	OMIM
<i>KAL1</i>	Xp22.2	Anosmin (KAL1)	308700
<i>FGFR1</i>	8p11.2-p11.1	Fibroblast growth factor receptor 1 (KAL2)	136350
<i>PROK2</i>	3p21.1	Prokineticin 2 (KAL4)	607002
<i>PROKR2</i>	20p13	Prokineticin receptor 2 (KAL3)	607123
<i>NELF</i>	9q34.3	Nasal embryonic luteinizing hormone-releasing factor	608137
<i>GPR54</i>	19p13.3	G-protein coupled receptor 54	604161
<i>GNRHR</i>	4q21.1	Gonadotropin-releasing hormone receptor	138850

hyposmia was initially found to have a heterozygous mutation in *FGFR1* (Ser342Leu—chromosome 8p11.2-p11.1); the proband's father and sister had the same *FGFR1* mutation; the father had delayed onset and the sister normal timing of puberty. In vitro studies demonstrated that the Ser342Leu mutant of *FGFR1* acted in a dominant-negative manner. A heterozygous 8 bp deletion in the negative elongation factor (*NELF*) resulting in a truncated product was later identified in the proband, his mother and his brother; the latter 2 subjects underwent normal puberty. The authors suggested that loss of a single copy of *FGFR1* resulted in a less severe phenotype than did loss of a single copy (allele) of both *FGFR1* and *NELF*. In pedigree #2, two sisters with IHH (no evident spontaneous ovarian function) were found to have inactivating mutations in both *GNRHR* alleles (Gln106Arg, Arg262Gln—chromosome 4q21.2) ie, the sisters had compound heterozygosity. Their father had a history of delayed puberty and carried the Arg262Ser mutation, while

both *GNRHR* and *FGFR1* manifested only delayed puberty is uncertain. The investigators concluded that disorders thought to be monogenic in origin and that manifest variable degrees of clinical involvement may actually be oligogenic due to the involvement of 2 (possibly even more) different genes whose mutations sum to produce the clinical phenotype.

Pitteloud N, Quinton R, Pearce S, et al. Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. *J Clin Invest.* 2007;117:457-63.

Editor's Comment: A gene mutation has been found in only 30% of patients with IHH. Other genes that regulate migration of GnRH neurons and synthesis and release of or response to GnRH await identification. Clearly the concept of digenic inheritance of disease is one that may well be applicable to many disorders of the endocrine and other systems.

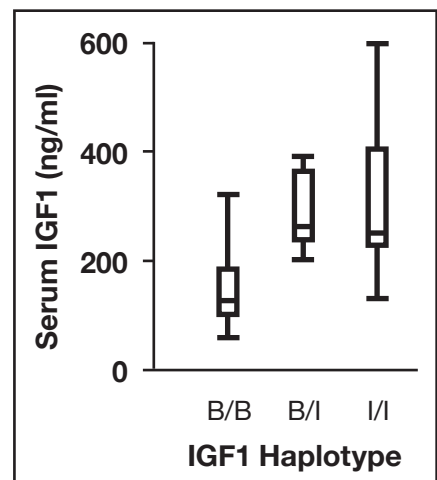
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IGF-I Allele in Small Size Dogs

Intrigued by the great diversity in size among the dog family (Canidae), these investigators first identified by genome-wide scan a skeletal size-related quantitative trait locus (QTL) on chromosome 15 within a single breed—the Portuguese water dog (PWD), a breed with great inter-individual variation in size. They next examined the relationship of single-nucleotide polymorphisms (SNPs) within this QTL to skeletal size in large and small Portuguese water dogs. They found one such SNP in this QTL to be associated with size that was near the gene encoding insulin-like growth factor-I (*IGF1*). Designating the haplotypes I and B, the investigators found that Portuguese water dogs homozygous for haplotype I were larger in size and had higher serum IGF-I concentrations than did dogs that were homozygous for haplotype B; they calculated that 15% of the variability of skeletal size within this breed could be accounted for by this *IGF1* haplotype (Figure 1). Performing the same SNP analyses in more size-homogeneous small ($n=23$, <9 kg) and giant ($n=20$, >30 kg) canid breeds, the authors found skeletal size to be related to an *IGF1* haplotype characterized

by 20 SNPs that was shared by all small breed dogs (and one in particular designated SNP 5 A) (Figure 2). Sequencing of *IGF1* revealed a SNP in exon 3 and several

Figure 1. Serum levels of IGF1 protein (ng/ml) as a function of haplotype. Serum levels of IGF1 protein were assayed in 31 PWDs carrying haplotypes B and I. Box plots show the median (center line in box), first and third quartile (box ends), and maximum and minimum values (whiskers) obtained for each category: homozygous B/B ($n=15$), heterozygous B/I ($n=7$), and homozygous I/I ($n=9$).



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SNPs in flanking genomic sequences (promoter region) and introns that were unique to small breeds but no specific variant related to size was definitely identified.

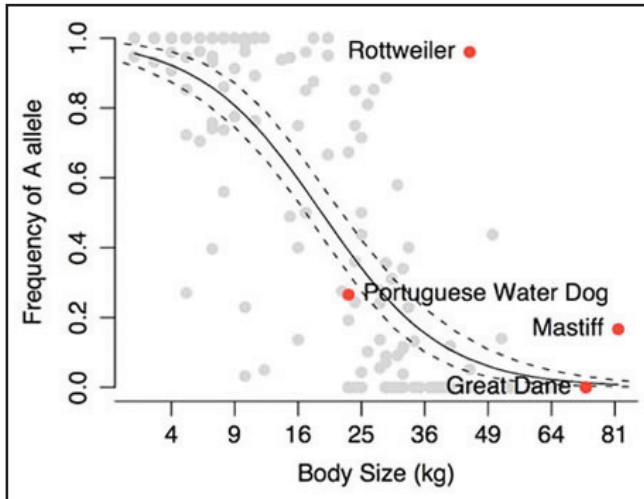


Figure 2. Association of body size and frequency of the SNP 5 A allele. Binomial regression of allele frequency on square root of mean breed mass. Dashed lines indicate the 95% confidence interval on the predicted equation line as estimated from nonparametric bootstrap resampling. Between 5 and 109 (median = 22) dogs were genotyped for each of 143 breeds. The PWD is highlighted in red along with three giant breeds that have larger breed average masses than is predicted by their SNP 5 allele frequency. Reprinted with permission from Sutter NB, et al. *Science*. 2007;316:112-5. Copyright © AAAS 2007. All rights reserved.

The authors concluded that “a narrow ... genomic region holds the variant ... (in *IGF1*) ... responsible for ... size in a disparate set of small ... (and giant) ... dog breeds ...”

Sutter NB, Bustamante CD, Chase K, et al. A single *IGF1* allele is a major determinant of small size in dogs. *Science*. 2007;316:112-15.

Editor's Comment: Although previous studies have identified a relationship between serum levels of *IGF-I* in various dog breeds and have been related to growth in humans, the fact that it is tissue and not serum *IGF-I* values that determine growth must be remembered.¹ The findings in this report should in no way be construed or utilized to support the use of recombinant human (*rh*) *IGF-I* in the treatment of children with idiopathic short stature, a contentious practice.² The use of *rhIGF-I* is of limited value in patients with severe *IGF-I* deficiency due to growth hormone (*GH*) resistance due to inactivating mutations of the genes encoding the *GH* receptor or *STAT5* or due to development of neutralizing antibodies to *rhGH*; it is not indicated nor particularly efficacious in other short stature children while exposing them to significant risks.

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References

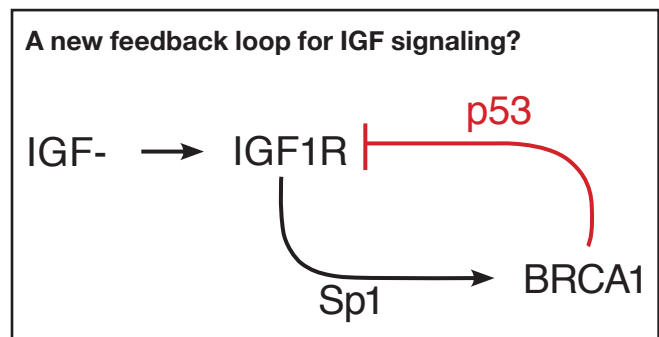
1. Yakar S, Liu JL, Stannard B, et al. *Proc Natl Acad Sci USA*. 1999;96:7324-9.
2. Rosenbloom AL. *J Pediatr*. 2007;150:7-11.

IGF-I and BRCA1: A New Feedback Loop?

The growth hormone (*GH*)/insulin-like growth factor (*IGF*) system plays an important role in normal breast physiology and carcinogenesis. *GH* receptor (*GH-R*),¹ *IGF-I* and type 1 *IGF* receptor (*IGF1R*) knock-out mice show impaired mammary ductal development from reduced proliferation in the terminal end buds.² Conversely, transgenic mice over-expressing human (*h*)*IGF-I* or *hIGF-II* have reduced apoptosis and hence, delayed breast involution that normally occurs with the cessation of suckling and lactation.² Further, dysregulated *GH/IGF* signaling has been implicated in breast cancer, a subject extensively reviewed elsewhere.^{3,4}

Maor et al therefore sought to investigate the regulatory relationship between gene expression of *IGF1R* and the breast and ovarian cancer susceptibility gene (*BRCA1*), a major tumor suppressor in breast carcinogenesis. As indicated by Western immunoblotting and RT-PCR, *BRCA1* expression was induced by treating MCF-7 breast cancer cells in vitro with *IGF-I* or *IGF-II*. Using *BRCA1* promoter-luciferase reporter constructs, *IGF-I* treatment of MCF-7 and *BRCA1*-null HCC1937 breast cancer cells significantly enhanced promoter activity of the full-length *BRCA1* promoter but not a minimal *BRCA1* promoter deletion construct that lacks binding sites of the transcription factor *Sp1*. *Drosophila*-derived, *Sp1*-null Schneider cells were then co-transfected with the *BRCA1*

reporter construct and an *Sp1* expression vector, which led to an almost 12-fold increase in *BRCA1* promoter activity. Conversely, Mithramycin A, an *Sp1*-inhibitor, inhibited the *IGF-I*-stimulated *BRCA1* expression and promoter activity in MCF-7 cells. Likewise, siRNA against *Sp1* markedly reduced *BRCA1* protein levels in MCF-7 cells. Binding of *Sp1* to the *BRCA1* promoter, as indicated by chromatin immunoprecipitation (*ChIP*) assay, was enhanced by *IGF-I* treatment of the MCF-7 cells. Finally, transfection of an anti-*BRCA1* siRNA, versus a scrambled siRNA, increased the proportion of MCF-7 cells arrested at *SubG0* and reduced those at the *G2/M* phase in response to *IGF-I* treatment.



As shown by this paper (black), *IGF1R* signaling induces *BRCA1* gene expression via *Sp1*. As previously shown (red), *BRCA1* represses *IGF1R* via *p53*.