

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.

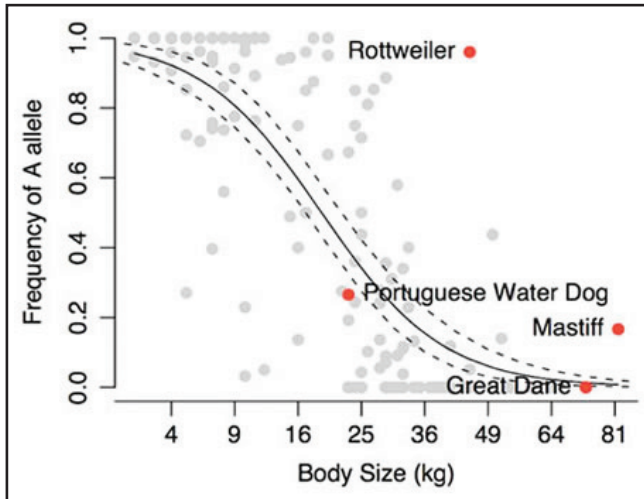


Figure 2. Association of body size and frequency of the SNP 5 A allele. Binomial regression of allele frequency on square root of mean breed mass. Dashed lines indicate the 95% confidence interval on the predicted equation line as estimated from nonparametric bootstrap resampling. Between 5 and 109 (median = 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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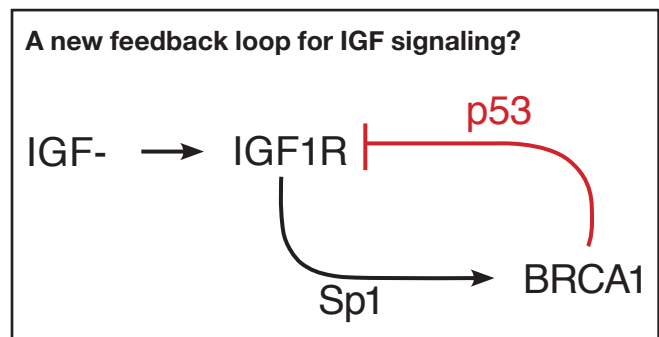
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IGF-I and BRCA1: A New Feedback Loop?

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*.

The authors concluded that BRCA1 is a novel downstream target of IGF1R signaling. IGF1R signaling induces BRCA1 gene expression via the Sp1 transcription factor, and BRCA1 gene silencing stunted IGF-stimulated cell cycle progression. Thus, they inferred that aberrant IGF signaling may lead to dysregulated BRCA1 expression during breast cancer pathogenesis.

Maor S, Papa MZ, Yarden RI, et al. Insulin-like growth factor-I controls BRCA1 gene expression through activation of transcription factor Sp1. *Horm Metab Res.* 2007;39:179-85.

Editor's Comment: *BRCA1 is major tumor suppressor involved in breast carcinogenesis, including both somatic dysfunction and increased familial cancer risk due to germline inactivating mutations. Normally, BRCA1 plays a role in genomic stabilization, inducing cell cycle arrest and DNA repair in response to DNA damage.⁵ BRCA1 acts as transcription factor, interacting with co-repressors and co-activators, to inhibit expression of growth-promoting*

genes and stimulate expression of cell cycle arrest and DNA repair genes, DNA damage inducible genes and interferon inducible genes.⁶ As shown by the same authors as the current paper, one of the genes whose transcription is repressed by BRCA1 is IGF1R.⁷ Thus, their 2 findings may form a feedback loop (Figure), whereby IGF1R signaling induces BRCA1 transcription which in turn represses IGF1R transcription.

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References

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Intrauterine Growth Retardation and Pituitary Gonadal Function

Low birth weight as a consequence of intrauterine growth retardation (IUGR) is associated with an increased risk of disease in adult life. It has been reported to have a detrimental effect on gonadal development in boys, including cryptorchidism and hypospadias. Little is known on the male pituitary-gonadal axis functioning in adulthood. Small for gestational age (SGA) is a result of IUGR during variable periods of gestation, hence a consequence of different adverse events occurring during gestation. This study focused on fetal growth restraint occurring during the third trimester of pregnancy; the authors hypothesized that IUGR in the third trimester of pregnancy would determine the ultimate male reproductive function. Jensen also evaluated the influence of birth weight in relation to gestational age on the pituitary-testicular axis. Participants were recruited from a large prospective study of pregnant women who provided third trimester fetal growth velocity and birth weight. Fifty-two adolescent males participated in the follow-up study and were divided into appropriate for gestational age ([AGA], n=32) and SGA (n=20). The authors were careful to avoid major selection bias. Pubertal stage, testicular size, and reproductive hormones were determined, including overnight LH and FSH profiles.

No significant differences were found in testosterone levels, inhibin B levels and LH/testosterone ratio between AGA and SGA. Neither difference was observed between both groups for testicular size and morphology (determined by ultrasonography and overnight secretory patterns of gonadotropins). Median basal LH secretory rates were two-fold higher in men born AGA but the difference did not reach statistical significance. Fetal growth during the third trimester of pregnancy did not influence any of the reproductive

hormone levels nor their secretory pattern as estimated by deconvolution analysis.

This is the first study to explore the influence of the third trimester fetal growth rate on subsequent adult gonadal function. These results do not rule out the gonadal damage in relation to genital malformations as cryptorchidism and hypospadias which also occur in relation with SGA. The testicular function was not impaired in adolescent males born after compromised fetal growth hormones.

Jensen RB, Vielwerth S, Larsen T, Greisen G, Veldhuis J, Juul A. Pituitary-gonadal function in adolescent males born appropriate or small for gestational age with or without intrauterine growth restriction. *J Clin Endocrinol Metab.* 2007;92:1353-7.

Editor's Comment: *Most IUGR studies have focused on female reproductive function and have suggested that young women born SGA have reduced ovarian volume, decreased ovarian hormones, and increased number of anovulatory cycles.^{1,2} Hyperinsulinemic insulin resistance occurring in these girls is also considered a setting for subsequent development of PCOS in adult women. The rise in FSH levels is greater during infancy in both boys and girls born SGA, whereas inhibin B levels are similar to those in infants born AGA. In adolescent males there is only limited information suggesting impaired spermatogenesis. In only one clinical study³ of males, a significantly decreased testosterone secretion and elevated LH levels were reported, suggesting primary testicular failure in men born SGA. In 54% of those subjects, a mean testicular volume >2 SD below the control mean, with reduced inhibin B was detected; the authors considered that their data supported a link between low birth weight and reduced fertility in males born SGA. The*