

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.

Adda Grimberg, MD

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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*

presence of cryptorchidism in several cases might have played a role in the data they presented.³ The present study provided no evidence for impaired testicular function. It may mean that whatever its cause, late fetal growth restraint is not associated with testicular dysfunction, hence there is a risk of subfertility. In a recent review⁴ the limitation of information in this area has been stressed, yet many reports have dealt with connected issues such as cryptorchidism, testicular cancer, and hypospadias.

A working hypothesis would be that males with early fetal growth restraint, generally resulting in symmetric SGA, would be at greater risk. Developmental factors would play

a role at this early phase of fetal growth. It would require new prospective studies in a setting similar to that reported in this paper to elucidate this hypothesis.

Raphaël Rappaport, MD

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Jeune Syndrome: Defective Intracellular Flagellar Transport

Major advancements have been made in recent years in identifying gene loci that harbor mutations responsible for human genetic disease. In many, if not most instances, the studies have begun with delineating the disease, then progressing to linkage analysis and other approaches, which eventually lead to the relevant gene locus and the mutations. In the paper discussed here, however, the authors began with a disturbance of gene function and used a bioinformatics approach to find the disease.

More specifically, Beales et al were interested in disturbances of ciliary function, the ciliopathies. Several disorders including Bardet-Biedl, oral-facial-digital type 2, Joubert, Senior-Löken, and Meckel-Grüber syndromes have recently been assigned to this group. The authors questioned if a set of minimum clinical criteria could be used to predict additional ciliopathies. After compiling a list of overlapping features, they queried the London Dysmorphology Database, which yielded a list of 10 features that would potentially predict a ciliopathy. The features included retinitis pigmentosa, polydactyly, renal cystic disease, and situs inversus. When these were ranked and used to query the database again, 25 conditions were identified as possible ciliopathies, among which was Jeune syndrome, often referred to as asphyxiating thoracic dysplasia ([ATD], OMIM 208500).

ATD is an autosomal recessive bone dysplasia characterized by limb shortening, constricted thoracic cage and respiratory insufficiency in infancy. Other features often include polydactyly, cystic renal disease, and retinal degeneration. ATD is known to be genetically

heterogeneous with one locus at chromosome 15q13. The authors ascertained and studied 3 families with linkage to a second locus at chromosome 3q24-3q26. One of the candidate genes in this region encodes WDR56, a protein that has been identified originally as expressed in *C. elegans* ciliary cells. Mutation analysis revealed a single amino acid deletion and 2 missense mutations in the 3 ATD families. Additional mutations were not detected in other patients with ATD and none of the patients with ATD who had WDR56 mutations exhibited extraskelatal manifestations of ATD.

WDR56 is conserved across species and has been renamed IFT80. It encodes a component of intraflagellar transport complex B and is essential for development and maintenance of motile and sensory cilia. To investigate its function further, the authors “knocked down” its expression in developing zebrafish. The treatment disturbed tail, kidney, and heart development and was consistent with a disturbance of hedgehog signaling in the developing fish. The authors suggested that their bioinformatics approach may lead to identification of other ciliopathies.

Beales PL, Bland E, Tobin JL, et al. IFT80, which encodes a conserved intraflagellar transport protein, is mutated in Jeune asphyxiating thoracic dystrophy. Nat Genet. 2007;39:727-9.

Editor's Comment: Clinicians value the London Dysmorphology Database for its diagnostic utility. This paper demonstrates another use that could be applied to other clinical phenotypes.

William A. Horton, MD

Natural History of Noonan Syndrome

One-hundred and fifty-one subjects with Noonan syndrome from 123 families were recruited into the Noonan Syndrome Research Group at St. George's University of London Hospital between 1989 and 1991. Between 2001 and 2003 all families were invited to participate in a follow-up assessment which included clinical examination, echocardiography, three-dimensional

digital facial photography and analysis of the *PTPN11* gene. Of the 151 patients, 34 dropped out of the study and 10 (6.6%) died. The final study cohort comprised 112 individuals (57 males) from 92 families. Seventy of these were fully assessed and 32 partially assessed. The mean age at assessment was 25.3 years and the mean interval for follow-up was 12 years.