

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.

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References

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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.

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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.