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Kartagener syndrome occurring simultaneously in a Filipino child with 5p- (Cri du chat) syndrome

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Kartagener syndrome is a genetic disease caused by defects of the structure and function of the cilia that leads to abnormal mucociliary clearance causing disease of the sinus and pulmonary regions. Kartagener syndrome is characterized by the triad of bronchiectasis, paranasal sinusitis and situs inversus totalis. The most common gene affected is *DNAH5* which encodes ciliary dynein axonemal heavy chain. *DNAH5* is linked to chromosome 5p which is the primary chromosome affected in Cri du chat syndrome. Here, we report a 7 month old Filipino female presenting with the common features of Cri du chat syndrome as well as situs inversus totalis, recurrent respiratory infections and bronchiectasis which point to a concomitant Kartagener syndrome. Kartagener syndrome can be caused by hemizygous *DNAH5* mutation in combination with a 5p segmental deletion which can be attributed to Cri du chat syndrome on the opposite chromosome. The patient presented here had a partial deletion in chromosome 5p13-5p15.3 causing deletion of one allele of *DNAH5* which resides on chromosome 5p15-p14. A biallelic mutation of *DNAH5* must occur to manifest features of Kartagener syndrome. Immunoflourescent staining done showed complete absence of *DNAH5* and the transmission electron microscopy of nasal cilia also confirmed the absence of the outer dynein arms; hence, we conclude that there was a mutation in the remaining allele of *DNAH5*.

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Exome, genome and RNA sequencing for diagnosis of pediatric mitochondrial disease: Integration of NGS strategies and functional analysis for in both mitochondrial DNA and nuclear genes encoding mitochondrial proteins

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Molecular diagnostic testing is commonly used to confirm clinical suspicion of mitochondrial diseases and has been greatly facilitated by the advent of next generation sequencing, including whole genome and exome sequencing (WGS/WES). Many factors make WGS/WES attractive, including the cost-effectiveness, the ability to identify patients with a typical clinical presentation, as well as the identification of novel disease genes. One group of conditions especially amenable to WGS/WES is mitochondrial diseases, which collectively represent a significant source of morbidity and mortality in children, with a conservative estimate for prevalence being 1 in 5000 live births. The diverse clinical presentation of mitochondrial disease in conjunction with the large number of both nuclear and mitochondrial gene disease targets make the molecular diagnosis of mitochondrial diseases challenging. At least 265 disease genes have been identified to date, with up to 20 new disease genes described every year. We have been offering WES since 2011 as part of an undiagnosed disease program at The Center for Pediatric Genomic Medicine at Children's Mercy Hospital. Like many other centers, we have published diagnostic yields of ~50%. However, challenges remain in diagnosing the remaining half of these patients with rare disorders, which may harbor variants refractory to standard diagnosis. An important adjunct to WES/WGS is transcriptomics (RNA-seq.), which is emerging as a powerful tool to examine the impact of genomic variants on transcript expression, identify the potential pathways involved in pathogenesis, and assess the impact of a disease-causing variant on transcripts in other genes. In the last year, we have collectively published the identification of four novel causal genes for mitochondrial disorders, and provided insight into the molecular pathogenesis leading to mitochondrial dysfunction. Currently, we have 6 additional putative novel genes. Characterization of the impact of variants by biochemical and/or functional studies will lead to a better understanding of the process of mitochondrial dysfunction, shedding light on potential therapeutic strategies that could potentially be applicable to the more common acquired mitochondrial diseases.

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