**A novel homozygous nonsense *HYDIN* gene mutation p.(Arg951\*) in two siblings from Southern**

**India with primary ciliary dyskinesia**

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disorder that disrupts the structure and function of motile cilia thereby resulting in impaired muco-ciliary clearance. In PCD, cilia are immotile or dyskinetic. Clinical phenotype includes term neonate with respiratory distress, early onset persistent wet cough, purulent nasal discharge, otitis media and later bronchiectasis and fertility issues. Around one-half of PCD patients have situs inversus. In a patient with typical phenotype the diagnosis of PCD is made using a combination of tests.1We report for the first time a novel loss of function *HYDIN* gene mutation in two siblings with PCD.

An 18-month girl and her elder sibling, a 5-year-old boy, born out of consanguineous marriage, presented with persistent productive cough and recurrent respiratory infections since infancy. Both of them were born at term and had neonatal respiratory distress. They were thriving with no digital clubbing, had purulent nasal discharge and chest examination revealed occasional crackles. There was no family history of atopy. Chest X-rays and immunoglobulin profiles were within normal limits.

Their PICADAR predictive score was 7.2 High speed video microscopy (HSVM) analysis of nasal brushings showed motile dyskinetic cilia with uncoordinated and stiff motility. An additional observation of rotational ciliary movement was observed in elder sibling. Targeted NGS of 38 genes

known to be associated with PCD was perfomed and homozygous *HYDIN* c.2851C>T p.(Arg951\*) nonsense mutation were identified in both siblings **(Figure 1).**3

*HYDIN* (hydrocephalus-inducing protein homolog) gene encodes for axonemal central pair apparatus protein considered important for coordinated ciliary motility. Olbrich et al identified a PCD associated locus on chromosome 16q21-q23 which includes the *HYDIN* gene and published on a series of PCD patients with *HYDIN* mutations.4 Individuals with PCD harboring mutations of *HYDIN* have normal situs and had normal ciliary ultrastructure.5 Our patients also had normal situs. We hereby document novel HYDIN mutation from siblings with PCD with clinical phenotype of neonatal respiratory distress, early onset persistent wet cough/nasal discharge with consistently abnormal HSVM and a confirmed novel homozygous nonsense *HYDIN* mutation. PCD should be considered even with normal body symmetry if there are other features.

**References:**

1. Lucas JS, Barbato A, Collins SA, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J. 2017;49.

2. Behan L, Dimitrov BD, Kuehni CE, et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. Eur Respir J. 2016;47: 1103-12.

3. Paff T, Kooi IE, Moutaouakil Y, et al. Diagnostic yield of a targeted gene panel in primary ciliary dyskinesia patients. Hum Mutat. 2018;39: 653-65.

4. Olbrich H, Schmidts M, Werner C, et al. Recessive HYDIN mutations cause primary ciliary dyskinesia without randomization of left-right body asymmetry. Am J Hum Genet. 2012;91: 672-84. 5. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med. 2013;188: 913-22.