Loss-of-function mutations in the axonemal outer dynein arm docking complex gene \textit{CCDC114} cause primary ciliary dyskinesia

\textbf{References}


Onoufriadis et al. (2013)

Exome sequencing identifies mutations in \textit{CCDC114} as a cause of primary ciliary dyskinesia
Knowles et al. (2013)

Cilia, which is Latin for ‘eyelashes’ are highly conserved organelles found almost ubiquitously in eukaryotic cells, with diverse motility and sensory functions. Cilia also have crucial roles in cell signaling pathways and in maintaining cellular homeostasis. They are broadly divided into three types – motile cilia, nodal cilia, and non-motile or primary cilia. Defects in motile cilia cause primary ciliary dyskinesia (PCD, MIM 244400), which is a genetically heterogeneous, rare, usually autosomal recessive disorder affecting 1:15,000 to 1:30,000 individuals.

Ciliary dysfunction was not suspected as the underlying cause when Kartagener first described the triad of sinusitis, bronchiectasis and situs inversus (1). However, individuals with symptoms including respiratory infections, anosmia, male infertility and in approximately 50% of the cases situs inversus totalis, were shown to have defects in ciliary structure and function, and a link between ciliary function and disease was made (2). Symptoms of PCD can include unexplained neonatal respiratory distress, chronic nasal drainage and sinusitis, recurrent otitis media, chronic bronchitis leading to bronchiectasis, and subfertility or increased risk for miscarriage or ectopic pregnancy. In very rare instances, PCD may be associated with hydrocephalus. Individuals with PCD have also been known to suffer from retinal degeneration and cystic kidney disease.

During the forward beating stroke, the tips of cilia engage with respiratory mucous and in the recovery phase, they whip back in the periciliary fluid layer. Thus, loss of ciliary function in the respiratory tract results in impaired mucociliary transport that leads to chronic respiratory infections. Male infertility results when immature sperm fail to move to the vas deferens, owing to either loss of ciliary motility in the efferent ductules, or from a loss of sperm flagellar motility. In females, fertilized ova may fail to reach the uterus if the cilia are unable to move it there, resulting in ectopic pregnancy. Impaired fluid flow in the brain ventricles because of loss of ependymal cilia motility is a possible mechanism underlying hydrocephaly. As for defects in ciliary motility causing situs inversus, in normal mouse embryos, node monocilia rotate in a clockwise direction resulting in an asymmetric leftward flow of extracellular fluid that moves across the node. In inversus viscerum embryos, node cilia are immotile and there is no nodal fluid flow. Thus, cilia-mediated nodal flow is necessary
Table 1. Genes with mutations causing primary ciliary dyskinesia, and the ciliary structure affected by the mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Affected ciliary component</th>
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<tbody>
<tr>
<td>HYDIN</td>
<td>Central pair apparatus proteins</td>
</tr>
<tr>
<td>DNAH5, DNAH11, DNAI12, DNAL1, TXNDC3, CCDC114, DNAI1</td>
<td>Outer dynein arms</td>
</tr>
<tr>
<td>DNAAF1, DNAAF2, DNAAF3, CCDC103, HEATR2, LRRC8</td>
<td>Inner dynein arms</td>
</tr>
<tr>
<td>RSPH4A, RSPH9</td>
<td>Radial spoke head proteins</td>
</tr>
<tr>
<td>CCDC39, CCDC40</td>
<td>Nexin--dynein regulatory complex proteins</td>
</tr>
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</table>

The most recent gene identified causing PCD, CCDC114 is in bold.

for establishing the left/right axis. Taken together, the clinical symptoms of PCD reflect the distribution of motile cilia in affected tissues and organs.

Because the symptoms of PCD overlap with a number of other disorders, diagnosis by clinical symptoms alone is difficult. Although PCD is a genetic disorder, as it is recessive, family history may not provide adequate information for diagnosis. Carrier status can be passed through family members for generations before an individual with disease is observed. Thus, PCD requires a compatible clinical phenotype, and genetic or functional tests for accurate diagnosis. Functional tests consist of specific ciliary ultrastructural defects identified by transmission electron microscopy in biopsies of the respiratory epithelium. The most prevalent of the ultrastructural defects are shortening or absence of dynein arms (∼90%) or absence or disruption of the central apparatus (10%).

Mutations causing PCD have been identified in 17 genes thus far (Table 1). However, mutations in these genes account for only approximately 60% of cases. Biallelic mutations in DNAH5 account for 15–21% of all cases of PCD, whereas mutations in DNAI1 account for 2–9% and mutations in CCDC40 account for 3–8%. Genetic testing will be the best, most reliable method for making the diagnosis, but currently available genetic testing does not pick up all mutations for PCD.

Recently, two groups, Knowles et al. and Onoufriadis et al. sequenced four unrelated individuals with outer dynein arm (ODA) ciliary defects. Only genes with biallelic variants (homozygous or compound heterozygous) were considered, because PCD is a recessive disorder. A homozygous mutation (c.742G>A) in CCDC114 was discovered altering splicing. CCDC114 was sequenced in an additional 104 individuals with PCD, and four individuals with biallelic mutations were identified. In total, four different mutations were identified, three splice-site and one frameshift. The c.742G>A variant was found in all unrelated families, and was homozygous in one family and compound heterozygous in three families. This mutation is found at 0.043% in the exome variant server in non-PCD subjects of European ancestry. CCDC114 is an ODA protein, and nasal scrapes from five biallelic individuals showed complete ciliary immotility in most ciliated cells, confirming that the mutations were dysfunctional. Thus, mutations in CCDC114 were a cause of PCD in 6% of the individuals with PCD and an ODA defect.

The identification in the above two studies of additional genes and mutations proven to cause PCD will increases the success rate of genetic testing as a diagnostic tool in PCD, and may result in genetic tests as the ‘gold standard’ for diagnosing PCD.

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