

## **Molecular Testing for *DNAI1* and *DNAH5* mutations associated with Primary Ciliary Dyskinesia / Kartagener Syndrome**

The UNC Hospitals Molecular Genetics Laboratory performs DNA sequencing of the *DNAI1* and *DNAH5* genes to detect mutations that are associated with primary ciliary dyskinesia/Kartagener Syndrome. Selected exons where mutation clusters reside are sequenced. Additional mutation analysis is done under selected circumstances as described below.

### **Biology of the Disease:**

Primary ciliary dyskinesia (PCD) is a genetically heterogeneous disease associated with abnormalities in the structure and function of cilia of the respiratory tract and flagella of the sperm. It is usually inherited as an autosomal recessive trait, although occasionally other modes of inheritance have been observed. It is a rare genetic disorder, with an incidence of approximately 1 in 16,000, which corresponds to a carrier rate of approximately 1 in 63. It is estimated that there are 12-17,000 patients in the USA affected with PCD. Clinically, PCD is associated with recurrent sinusitis and bronchitis, and in severe cases patients may develop end-stage bronchiectasis and require lung transplantation. In addition, the disease affects other organs and patients may exhibit otitis media and infertility. Approximately 50% of patients with PCD present with situs inversus totalis, termed Kartagener syndrome (KS), and at least 6% present with heterotaxy (abnormal placement of organs due to failure to establish the normal left-right patterning during embryonic development.). Diagnosis is made on the basis of clinical criteria and electron microscopic analysis for ultrastructural defects of the cilia. PCD presents with extensive genetic heterogeneity and multiple chromosomal loci have been hypothesized. Mutations in two ciliary outer dynein arm genes, *DNAI1* and *DNAH5*, have been shown to account for 10% and 28% of mutations in PCD, respectively. Despite extensive allelic heterogeneity, mutation clusters have been found to reside in both of these genes.

### **Clinical Indications for Molecular Genetic Testing:**

PCD molecular genetic testing is performed for the purpose of diagnosis of PCD, to determine carrier status, or as confirmatory diagnostic testing. Indications include: 1) patients with clinical disease compatible with PCD, but without a defined etiology such as cystic fibrosis, 2) neonatal respiratory distress in term neonates, 3) suppurative airways disease of unknown etiology, even with normal situs, 4) persistent/chronic cough and sinusitis, 5) non-CF bronchiectasis, 6) severe middle ear disease, 7) situs inversus totalis or situs ambiguus/heterotaxy, 8) congenital heart disease with situs inversus totalis or situs ambiguus 9) non-CF male infertility in conjunction with other features of PCD, for example airway disease or situs defects, 10) airways disease along with congenital heart disease, kidney disease or hydrocephalus, and 11) a family history of PCD/KS. The chance of identifying a mutation in these genes increases if the patient population is selected based on the presence of defined outer dynein arm defects.

### **Laboratory Testing for *DNAI1* and *DNAH5* mutations:**

Requests for testing must be accompanied by a patient consent form and clinical criteria form (available on our website at [http://www.pathology.unc.edu/labs/lablist\\_molpath.htm](http://www.pathology.unc.edu/labs/lablist_molpath.htm)). The preferred sample is ACD anticoagulated blood (pale yellow top) which may be refrigerated up to 48 hours before analysis. The test is performed by sequencing selected coding exons and flanking intronic regions of *DNAI1* (exons 1, 16, 17) and *DNAH5* (exons 34, 50, 63, 76, 77). Mutations in the exons tested have been seen in approximately 23% of the families with confirmed PCD. Results are reported as normal or mutation(s) detected. Any variant that is

identified by sequence analysis is interpreted as a deleterious mutation, a variant of unknown significance, or a benign polymorphism. The detection of two known deleterious mutations in either gene is diagnostic of PCD. The detection of one known deleterious mutation is consistent with being at least a carrier of PCD. Detection of mutations has diagnostic and reproductive implications, while a negative test result does not exclude a diagnosis of PCD. Individuals in whom one or no mutations have been found can be referred for full gene sequence analysis and/or future genetic testing on a research basis (with informed consent). Genetic counseling is recommended; please call 919-966-4380 for a genetic counseling appointment.

**References:**

1. Online Medelian Inheritance in Man (OMIM):  
<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=242650>  
<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=244400>
2. Zariwala et al., Mutations of *DNAI1* in primary ciliary dyskinesia: Evidence of founder effect in a common mutation. *Am. J. Respir. Crit. Care Med.*, 2006; 174: 858-866
3. Hornef et al., *DNAH5* mutations are a common cause of primary ciliary dyskinesia with outer dynein arm defects. *Am. J. Respir. Crit. Care Med.*, 2006; 174: 120-126
4. Noone et al., Primary ciliary dyskinesia: Diagnostic and phenotypic features. *Am. J. Respir. Crit. Care Med.*, 2004; 15: 459-467

**Questions?**

Call the UNC Molecular Genetics Lab at **(919) 966-4408**

Dr. Karen Weck, Medical Director (919-966-4408) or email: [kweck@unch.unc.edu](mailto:kweck@unch.unc.edu)

Dr. Maimoona Zariwala, Research Faculty (919-966-7050).

Ms. Debbie Keelean-Fuller, Certified Genetic Counselor (919-966-4380)

Website: [http://labs.unchealthcare.org/directory/molecular\\_pathology/index\\_html](http://labs.unchealthcare.org/directory/molecular_pathology/index_html)