Clinical Spectrum of Primary Ciliary Dyskinesia patients with *RSPH9* gene mutations: a case series

Panayiotis K. Yiallouros[1], Panayiotis Kouis[1,2], Panayiota Pirpa[3], Andreas Hadjisavvas[3,4], Kyriacos Kyriacou[3,4]

[1] Medical School, University of Cyprus

[2] Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus

[3] Department of Electron Microscopy and Molecular Pathology, Cyprus Institute of Neurology and Genetics, Nicosia Cyprus

[4] Cyprus School of Molecular Medicine, Cyprus Institute of Neurology and Genetics, Nicosia Cyprus

Introduction

Mutations in radial spoke head subunit 9 (*RSPH9*) gene result in Primary Ciliary Dyskinesia (PCD) characterized by rotational ciliary beat pattern (CBP) and 9+0 ultrastructure. To date, the clinical variability in *RSPH9* PCD patients has not been described. In this study, we applied Whole Exome Sequencing (WES) to

a) investigate the genetic diagnosis in patients from Cyprus with ciliary ultrastructure and ciliary motility findings similar to those described previously in PCD patients bearing pathogenic *RSPH9* mutations and

b) describe the phenotypic and clinical manifestations in the confirmed cases.

Methods

The records of all PCD patients in Cyprus were retrospectively reviewed to obtain diagnostic information and clinical data. Diagnostic evaluation included nasal Nitric Oxide measurement (nNO), ciliary motility assessment with High Speed Video Microscopy (HSVM), axonemal ultrastructural assessment with Transmission Electron Microscopy (TEM) and genetic testing by WES.

Basic demographic data and history information was obtained through a standardized questionnaire and the clinical findings at the time of diagnosis were recorded.

Results

Diagnostic characteristics:

Among 38 PCD patients in Cyprus, seven individuals belonging to two families that originate from the same area of South-East Cyprus, were found harboring a homozygous splice site mutation on *RSPH9* (c670+2T>C). Detailed diagnostic information for all cases is presented below.

Case #	NO (nl/min)	CBF	CBP	TEM
CY1018*	41.7	9.35	rotational	CP (40%)
CY1043	86.6	7.74	rotational	CP (30%)
CY1046	113	10.3	rotational	CP (33%)
CY1106*	25.5	11.7	rotational	CP (35%)
CY1107	57.9	10.9	rotational	CP (33%)
CY1108	43.8	11.2	rotational	CP (20%)
CY1114	87.43	10.4	rotational	CP (60%)

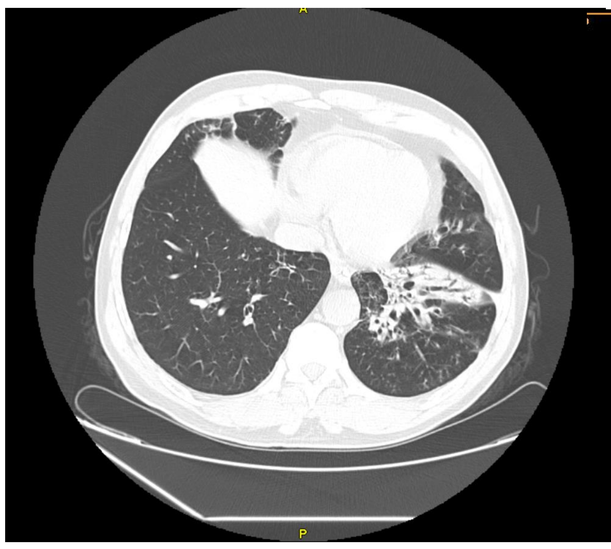
*Index Case, CBF: Ciliary Beat Frequency, CBP: Ciliary Beat Pattern, CP: Central Pair

Results

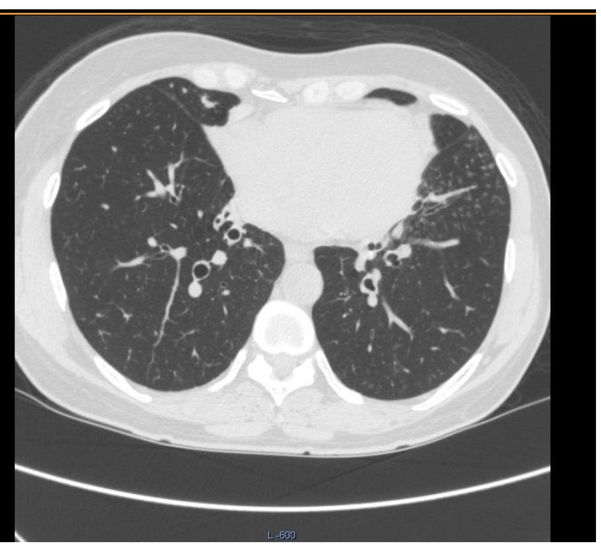
Clinical Picture:

Index case 1, CY1018 (family 1) experienced recurrent pneumonias at an early age and developed mild bronchiectasis while her siblings have only mild respiratory symptoms and normal auscultatory findings.

Index case 2, CY1106 (family 2) presented with severe bronchiectasis and recurrent hemoptysis as opposed to his siblings (CY1107, CY1108) that have only mild bronchiectasis and no history of hemoptysis. First cousin (CY1114) of these three patients presented with double sided bronchiectasis (RML and LLL) and a history of lobectomy at age 44 (see table below).



CY1106, Chest CT, Age 51



CY 1107, Chest CT, Age 49

Case #	Situs	FVC Z score	FEV1 Z score	Bronchiectasis
CY1018*	Solitus	-1.15	-1.19	RML
CY1043	Solitus	-0.8	-0.37	-
CY1046	Solitus	-2.01	-1.79	-
CY1106*	Solitus	-0.58	-0.48	RLL, LLL, Lingula
CY1107	Solitus	-1.31	-1.20	RML, LLL
CY1108	Solitus	-1.57	-1.65	RML
CY1114	Solitus	0.14	0.01	RML,LLL

*Index Case, FEV1: Forced Expiratory Volume – 1 second, FVC Forced Vital Capacity

Conclusions

Significant clinical variability was observed among PCD patients with the same homozygous *RSPH9* mutation. Studies from larger cohorts of RSPH9 patients are required to confirm these findings.

CYPRUS INTERNATIONAL INSTITUTE FOR ENVIRONMENTAL AND PUBLIC HEALTH

BESTCILIA

SEVENTH FRAMEWORK PROGRAMME

PK, SP, KK and PY are members of EU-funded COST Action BEAT-PCD (BM1407)