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

Panayiotis K. Yiallouros, Panayiotis Koui1,2, Panayiota Pirpa3, Andreas Hadjisavvas3,4, Kyriacos Kyriacou3,4
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 (HSV), axonal 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

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).

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<table>
<thead>
<tr>
<th>Case #</th>
<th>Situs</th>
<th>FVC Z score</th>
<th>FEV1 Z score</th>
<th>Bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY1018*</td>
<td>Solitus</td>
<td>-1.15</td>
<td>-1.19</td>
<td>RML</td>
</tr>
<tr>
<td>CY1043</td>
<td>Solitus</td>
<td>-0.8</td>
<td>-0.37</td>
<td>-</td>
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<td>CY1046</td>
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<td>CY1106*</td>
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<td>-0.58</td>
<td>-0.48</td>
<td>RLL, LLL, Lingula</td>
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<tr>
<td>CY1107</td>
<td>Solitus</td>
<td>-1.31</td>
<td>-1.20</td>
<td>RML, LLL</td>
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<tr>
<td>CY1108</td>
<td>Solitus</td>
<td>-1.57</td>
<td>-1.65</td>
<td>RML</td>
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<tr>
<td>CY1114</td>
<td>Solitus</td>
<td>0.14</td>
<td>0.01</td>
<td>RML, LLL</td>
</tr>
</tbody>
</table>

*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.