Delineation of CCDC39/CCDC40 mutation spectrum and associated phenotypes in primary ciliary dyskinesia

To cite this version:

HAL Id: inserm-00752969
https://www.hal.inserm.fr/inserm-00752969
Submitted on 16 Nov 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Delineation of CCDC39/CCDC40 mutation spectrum and associated phenotypes in primary ciliary dyskinesia

M Legendre1*, S Blanchon1,2, B Copin1, P Duquesnoy1, G Montantin1, E Kott1, F Dastot1, L Jeanson1, M Cachanado3, A Rousseau3, JF Papon4, A Tamalet2, AM Vojtek5, D Escalier1, A Coste4, J de Blic6, A Clément2, E Escudier1, S Amselem1


Background
CCDC39 and CCDC40 genes have recently been implicated in primary ciliary dyskinesia (PCD) with inner dynein arms (IDA) defects and axonemal disorganization; their contribution to the disease is, however, unknown. With the aim to delineate CCDC39/CCDC40 mutation spectrum and associated phenotypes, we screened a large cohort of patients with IDA defects, and accurately described their clinical and ciliary phenotypes.

Methods
All CCDC39 and CCDC40 exons and intronic boundaries were sequenced in 43 patients from 40 unrelated families. We recorded and compared clinical features (sex, origin, consanguinity, laterality defects, ages at first symptoms and evaluation, neonatal respiratory distress, airway infections, nasal polyps, otitis media, bronchiectasis, infertility), ciliary beat frequency and quantitative ultrastructural analyses of cilia and sperm flagella.

Results
Biallelic CCDC39 or CCDC40 mutations were identified in 30/34 (88.2%) unrelated families with IDA defects and axonemal disorganization (22 and 8 families, respectively). Fourteen of the 28 identified mutations are novel. No mutation was found in the 6 families with isolated IDA defects. Patients with identified mutations shared a similar phenotype, in terms of both clinical features and ciliary structure and function. The sperm flagellar ultrastructure, analyzed in 4/7 infertile males, evidenced abnormalities similar to the ciliary ones.

Conclusions
CCDC39 and CCDC40 mutations represent the major cause of PCD with IDA defects and axonemal disorganization. Patients carrying CCDC39 or CCDC40 mutations are phenotypically indistinguishable. CCDC39 and CCDC40 analyses in selected patients ensure to find mutations with high probability, even if clinical or ciliary phenotypes cannot prioritize one analysis over the other.

Author details
1INSERM, UMR_S933, UPMC Univ Paris 06; and AP-HP, Hôpital Armand-Trousseau, Service de Génétique et d’Embryologie Médicales, F-75012, Paris, France. 2AP-HP, Hôpital Armand-Trousseau, Unité de Pneumologie Pédiatrique, Centre National de Référence des Maladies Respiratoires Rares, F-75012, Paris, France. 3AP-HP, Hôpital Saint-Antoine, Unité de Recherche Clinique et d’UPMC Univ Paris 06, Unité Fonctionnelle de Pharmacologie, F-75012, Paris, France. 4AP-HP, Hôpital Inter-Communal et Groupe Hospitalier Henri Mondor-Albert Chenevier, Service d’ORL et de Chirurgie Cervico-Faciale, F-94000, Créteil, France. 5Hôpital Inter-Communal, Service d’Anatomo-Pathologie, F-94000, Créteil, France. 6AP-HP, Groupe Hospitalier Necker-Enfants Malades, Service de Pneumologie et Allergologie Pédiatriques, F-75015, Paris, France.

Published: 16 November 2012