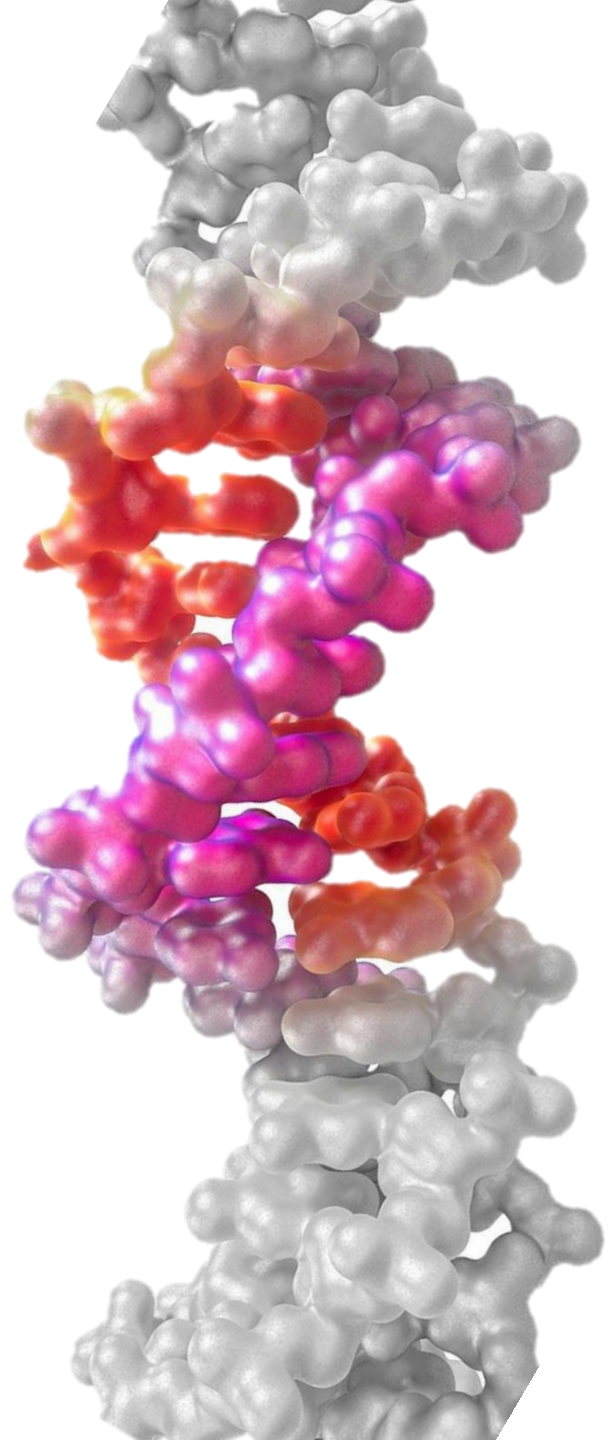

Journée ADCP 24 septembre 2022

association dcp
dyskinésie ciliaire primitive

Nouveautés dans la génétique des DCP

Dr Marie Legendre

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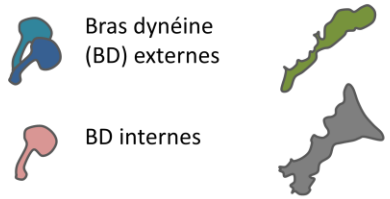
HÔPITAL TROUSSEAU
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

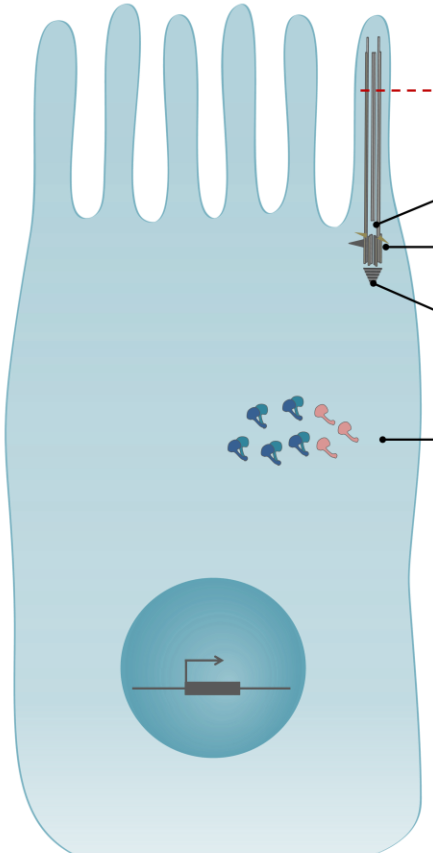
Inserm

Maladies génétiques d'expression pédiatrique

Les 51 gènes de DCP et leur rôle dans la structure du cil



Cellule respiratoire multiciliée



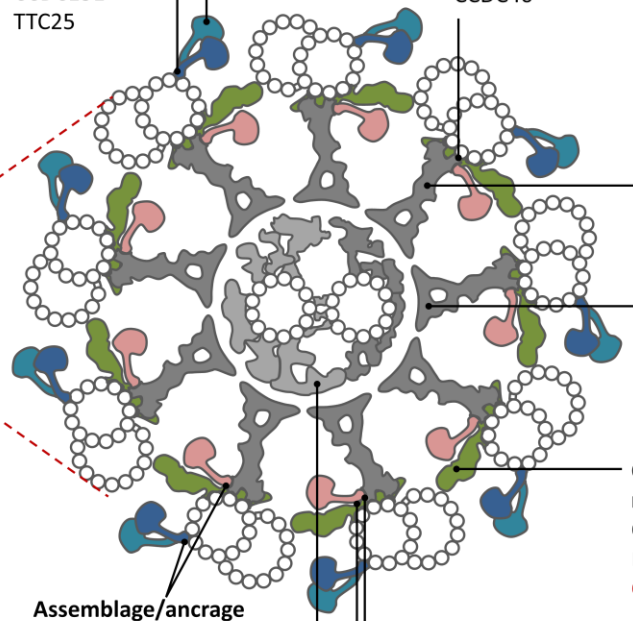
Base de l'axonème
RPGR

Assemblage appendice distal
OFD1

Pied basal, racine
GAS2L2

Assemblage cytoplasmique BD
CFAP298 DNAAF5
CFAP300 DNAAF6
DNAAF1 LRRC6
DNAAF2 SPAG1
DNAAF3 TTC12
DNAAF4 ZMYND10

Multiciliogénèse
CCNO MCIDAS
FOXJ1 NEK10



Bras dynéine (BD) externes
DNAH5 DNAI1
DNAH9 DNAI2
DNAH11 DNAL1

Complexe ancrage BD externes
ARMC4 CCDC151
CCDC114 TTC25

Face interne tubules A
CCDC39
CCDC40

Tige pont radiaire
DNAJB13 NME5
RSPH3

Tête pont radiaire
RSPH1
RSPH4A
RSPH9

Complexe de régulation nexine-dynéine
CCDC65
DRC1
GAS8

Assemblage/ancrage BDs
CCDC103

Gaine centrale
* CFAP74
CFAP221
HYDIN
SPAG6
SPEF2

Assemblage/adressage sous-type BD internes
CFAP57

Modificateur des bras internes (MIA)
* DAW1?

Fonction/localisation exactes à déterminer
LRRC56
NME8
STK36

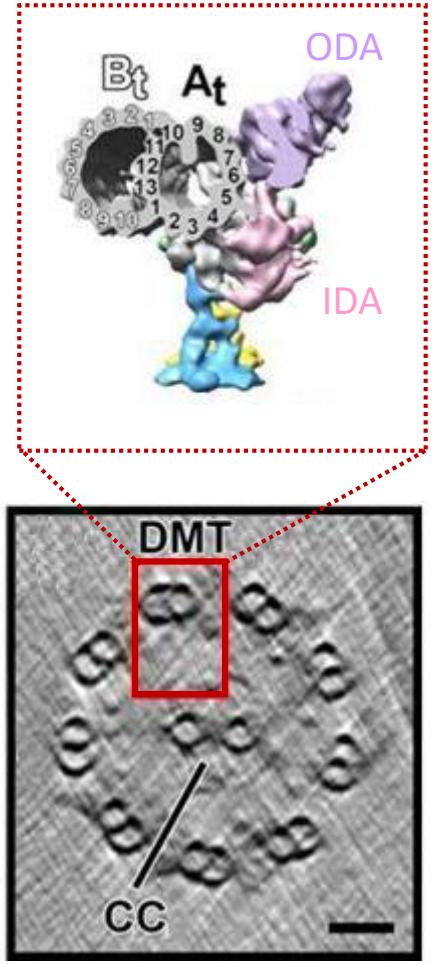
Impliqués par l'équipe

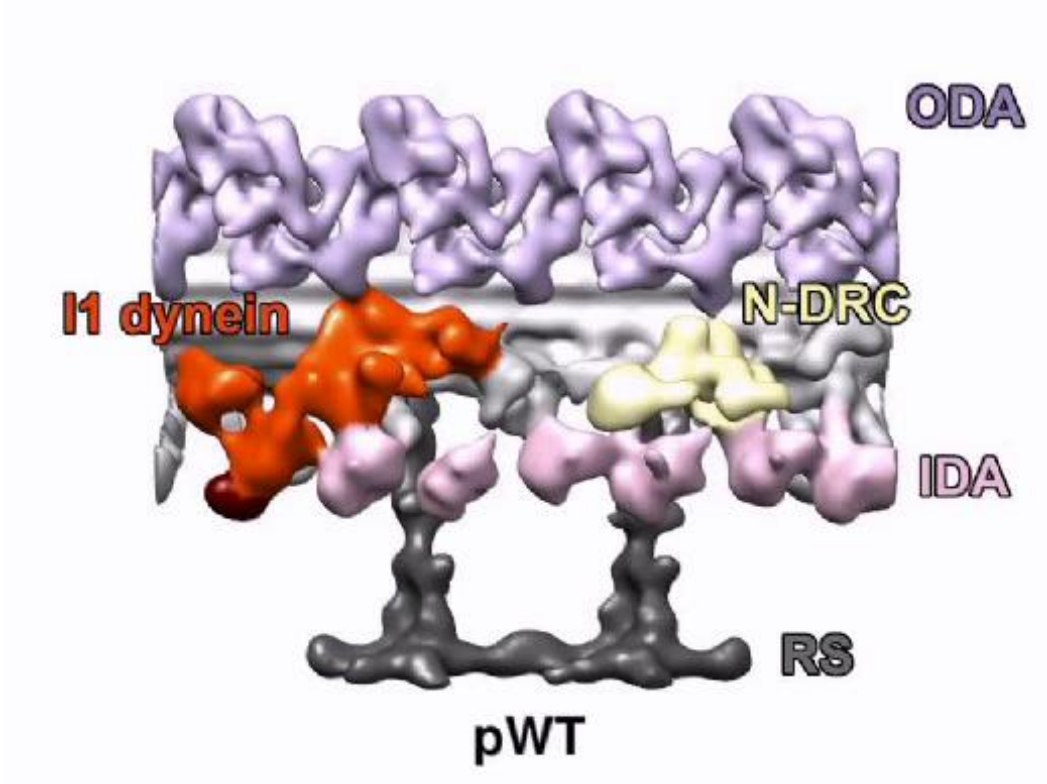
Adapté d'après Legendre et al. *Semin Cell Dev Biol.* 2021

Zoom sur la structure du cil : cryo EM

Chlamydomonas

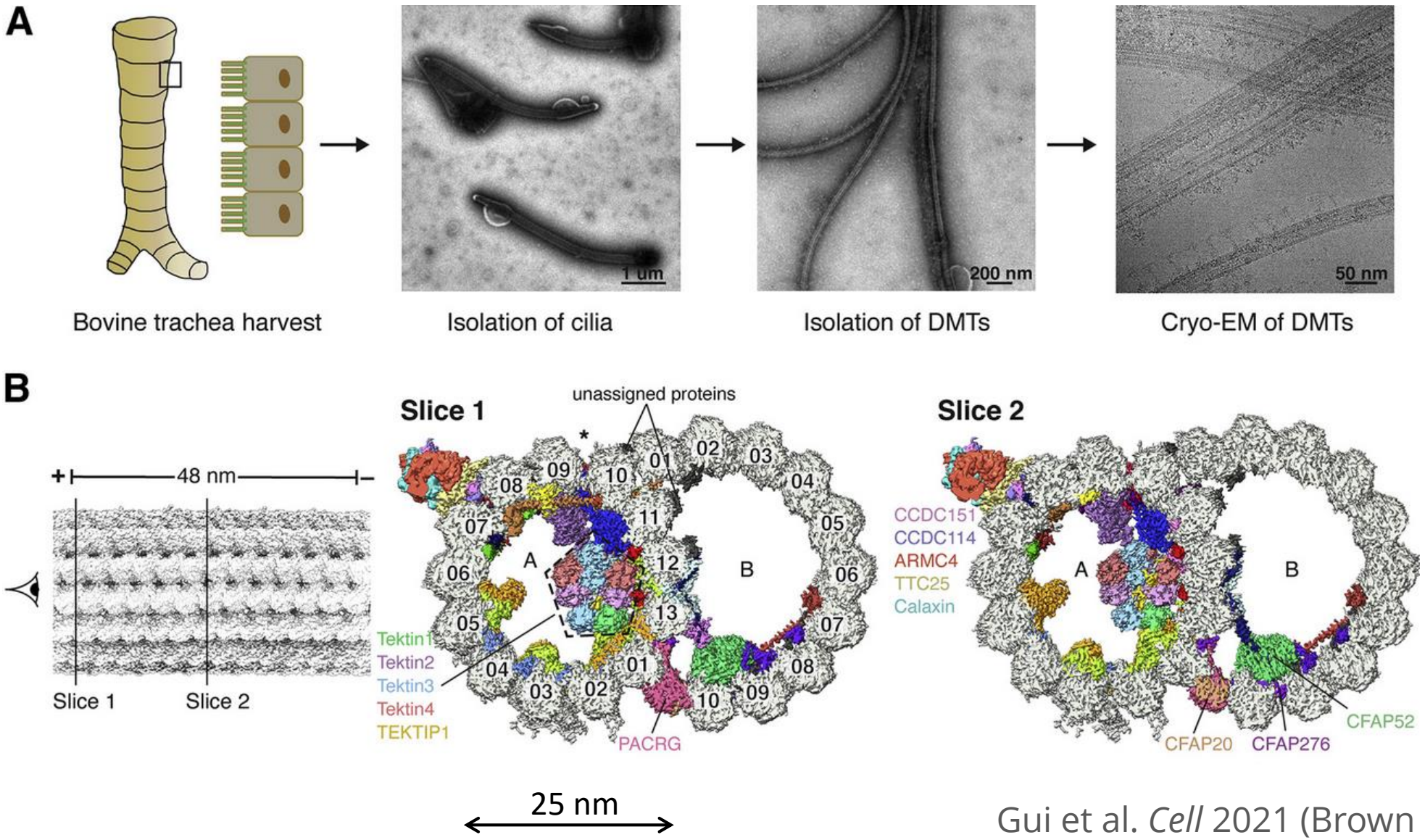
Un des 9 doublets externes





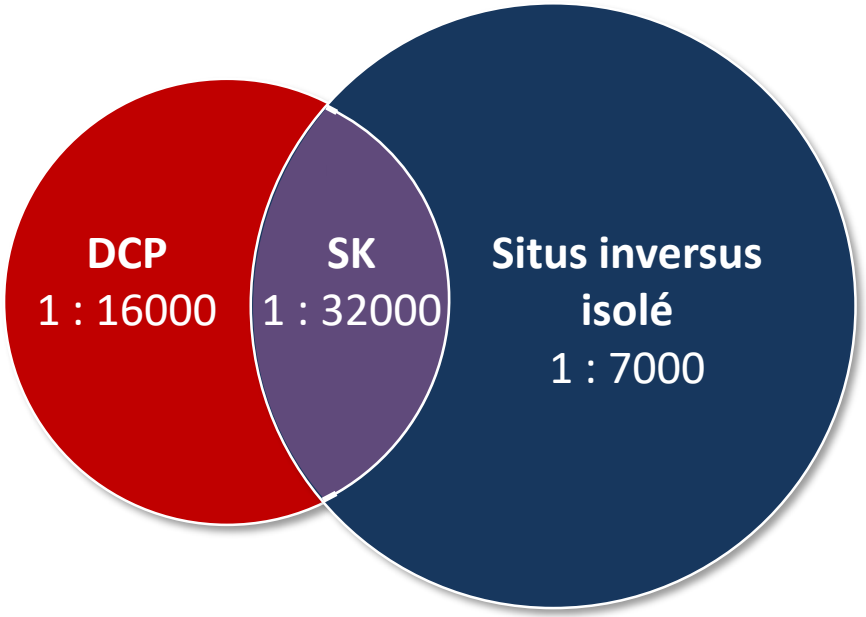
Yamamoto et al. ***J Cell Biol*** 2013

Localisation exacte de protéines à l'intérieur des tubules

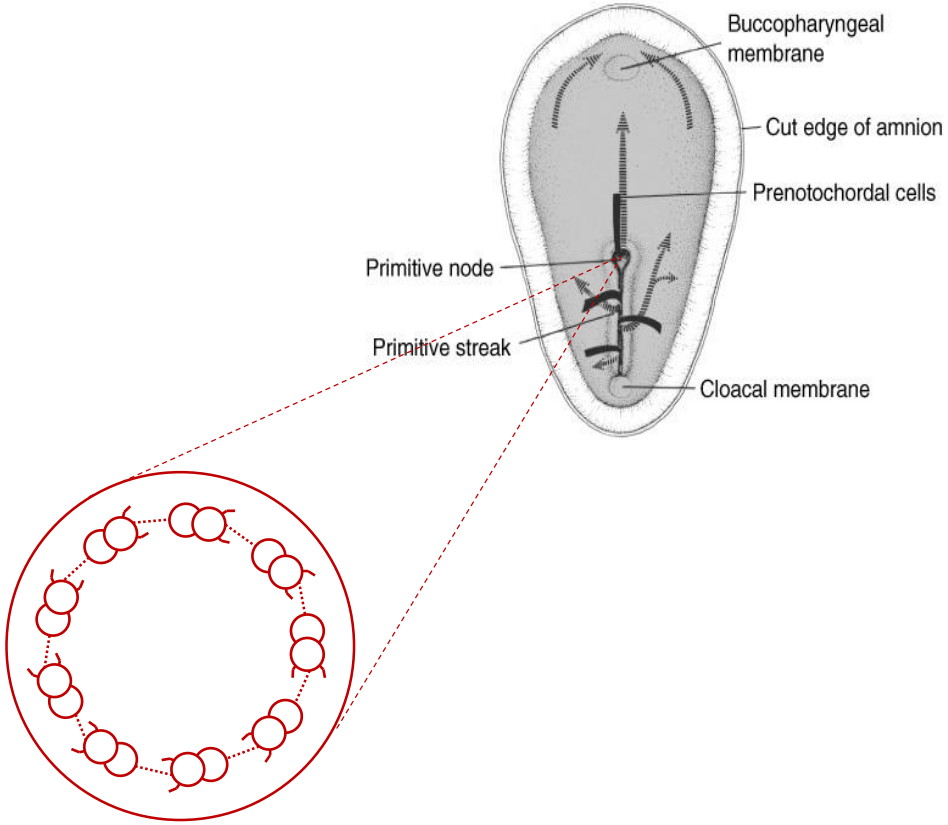


Gui et al. *Cell* 2021 (Brown lab)

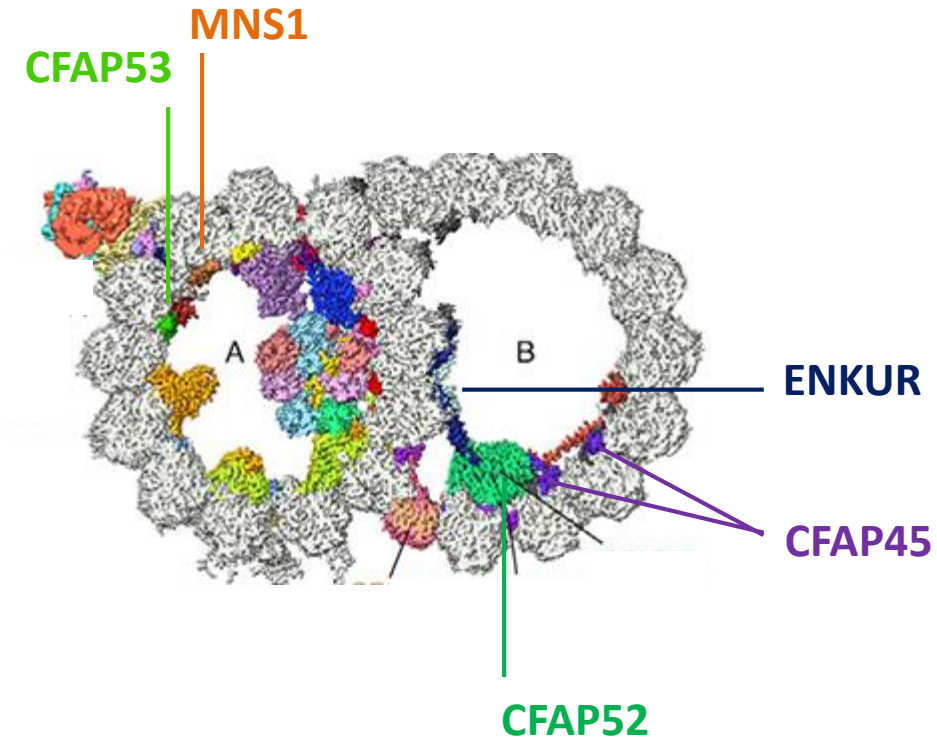
Le situs inversus



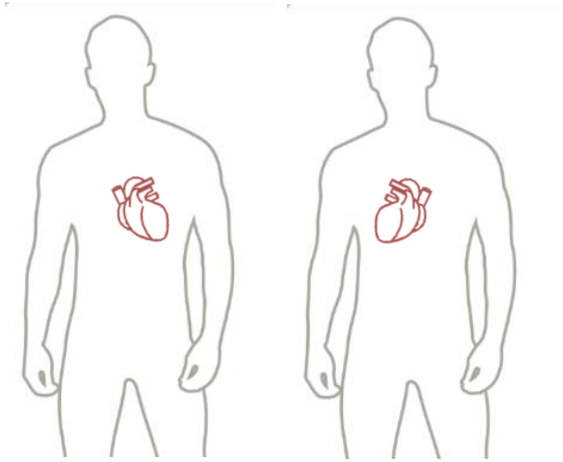
Embryon et cil mobile



Implication de 3 gènes de protéines à l'intérieur des tubules dans des hétérotaxies isolées



Situs inversus sans atteinte respiratoire



Gui et al. *Cell* 2021 (Brown lab)

Trouver la variation causale parmi des milliers

2 variations pathogènes dans un gène de DCP

Une mutation probable hétérozygote dans un gène de DCP

Une variation de signification incertaine (**VSI**) hétérozygote dans un gène de DCP

Une variation pathogène hétérozygote dans un autre gène de DCP

2 VSI dans un bon gène candidat

Une variation pathogène hétérozygote dans un gène de fonction inconnue

2 VUS dans un autre gène de maladie respiratoire

Une variation pathogène hétérozygote dans un gène de DCP controversé

Une variation hétérozygote potentiellement pathogène dans un bon gène candidat

Equipe CiliaVar, BEAT-PCD European Respiratory Society Clinical Reasearch Collaboration

Amelia Shoemark

Myrona Goutaki

Suzanne Crowley

Marie Legendre

Mafalda de Ameida Gomes

Rahma Mani

Muxiao Sun

CRC Chairs
Amelia Shoemark
Myrona Goutaki

WP2 Leads
Suzanne Crowley (Chair)
Marie Legendre (co-Chair)
Bernard Maitre (co-Chair)

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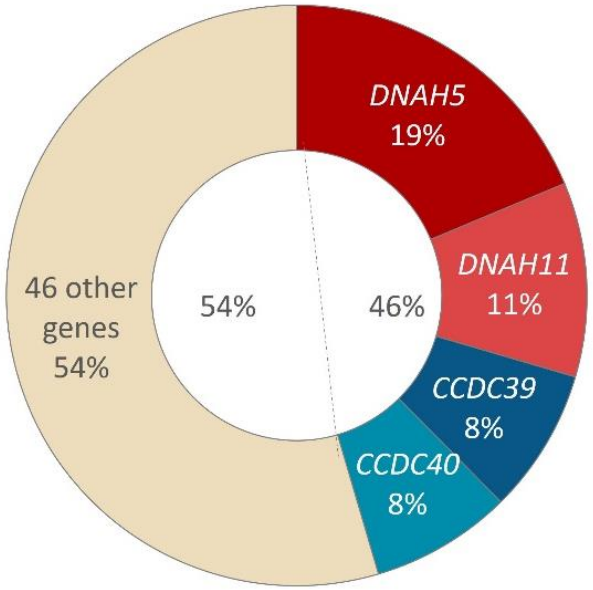
Mahmoud Fassad
Rahma Mani
Hannah Mitchison
Adrian Rodriguez Gonzalez
Muxiao Sun

Software development
Jack Gilmore
Martin Groves
Pete Marshall
Leandro Tramma
CFTR-France team

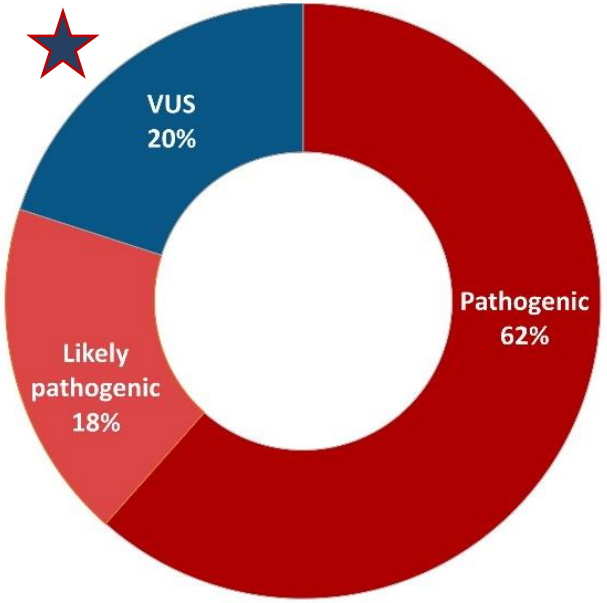
Collaborations
Claire Hogg
Jane Lucas
Deborah Morris-Rosendahl
Nisreen Rumman

CiliaVar : base de données de mutations de la DCP

1 551 patients DCP indépendants
Gènes les plus fréquents



1 267 mutations distinctes
identifiées chez les patients



Rahma Mani

Analyse de la literature :

651 articles identifiées
262 analysés

Data by Rahma Mani & Marie Legendre
Sorbonne Université and Inserm,
Hôpital Armand-Trousseau

CiliaVar : beta - testing

CiliaVar BEAT-PCD CiliaVar Home Users Records Privacy

Gene: CCDC39 | Chromosome: 3 | Format: hg19 hg38 | Variant 1: NC_000003.11:g.180337717_180337718del | Variant 2: NC_000003.11:g.180377547_180377548del | Search

Welcome to CiliaVar

This website is designed to provide information about variants in genes which cause the motile ciliopathy primary ciliary dyskinesia (PCD).

For each variant or combination of variants entered the website will provide information on:

1. Detailed annotation including allelic frequency in controls, conservation through evolution, potential effect on splicing and basic ACMG pathogenicity classification.
2. If the variant has been previously described in someone with clinical symptoms of PCD.
3. Information about associated clinical symptoms for that gene or variant where it has been described in >10 other people.

If you would have specific questions, would like to submit data to CiliaVar or wish to be involved in data curation please email beatpcd@ers.net

Saisie des données

PCD diagnosis

PCD diagnosis

PCD confirmed or highly likely

Certainty of genetic diagnosis (add features to categorise some)

Age at diagnosis (ERS guideline) (yrs)

Clinical information

Biological sex

Affected siblings

Ancestry

BMI

Height (cm)

Fev1_z at diagnosis

Neonatal respiratory distress

Productive/wet cough at time of diagnosis

Chronic rhinitis at time of diagnosis

Otitis media

Cardiac situs

Situs

Abnormal heart morphology

Infertility

Diagnostic information

NO over 5 years measured by chemiluminescence (nl/min)

Other NO

Electron microscopy findings

High speed video: Ciliary beat pattern

Pseudomonas aeruginosa chronic infection of lower airways

Other test results/ symptoms/ ciliopathy features/ comments

CiliaVar

Données agrégées par mutations (> 10 fois) et par gène

Variant 1:

NC_000003.11:g.180337717_180337718del

1/1655 of individuals with PCD had this mutation

Because less than 5 individuals had this mutation there is no information provided on clinical symptoms.

Variant 2:

NC_000003.11:g.180377547_180377548del

5/1655 of individuals with PCD had this mutation

Symptoms at time of diagnosis		
Neonatal Respiratory Distress		60%
Productive/Wet Cough		100%
Chronic Rhinitis		100%
Otitis Media		60%
Cardiac Situs		
	Levocardia	80%
	Dextrocardia	20%
Situs		
	Inversus	25%
	Solitus	75%
	Ambiguous	<5%
Abnormal Heart Morphology		100%
Infertility		100%
Brochiectasis		60%
Lobectomy		<5%

<5 individuals had this combination of variants

Symptoms at time of diagnosis		
Neonatal Respiratory Distress		<5%
Productive/Wet Cough		100%
Chronic Rhinitis		100%
Otitis Media		<5%
Cardiac Situs		
	Levocardia	100%
	Dextrocardia	<5%
Situs		
	Inversus	<5%
	Solitus	100%
	Ambiguous	<5%
Abnormal Heart Morphology		<5%
Infertility		<5%
Brochiectasis		<5%
Lobectomy		<5%

Gene:

CCDC39

140/1655 individuals with PCD had other variants in this gene

Symptoms at time of diagnosis		
Neonatal Respiratory Distress		68%
Productive/Wet Cough		96%
Chronic Rhinitis		79%
Otitis Media		52%
Cardiac Situs		
	Levocardia	42%
	Dextrocardia	58%
Situs		
	Inversus	53%
	Solitus	40%
	Ambiguous	7%
Abnormal Heart Morphology		18%
Infertility		100%
Brochiectasis		75%
Lobectomy		6%

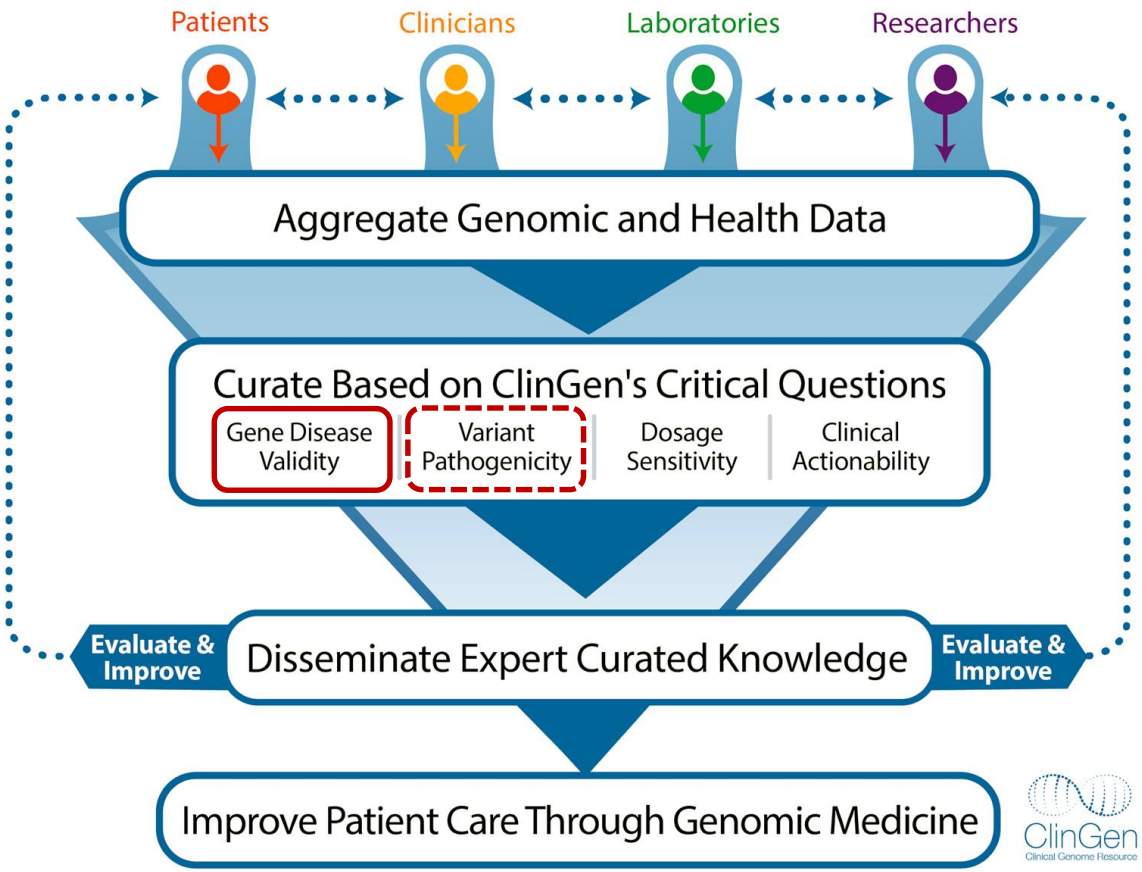
CiliaVar

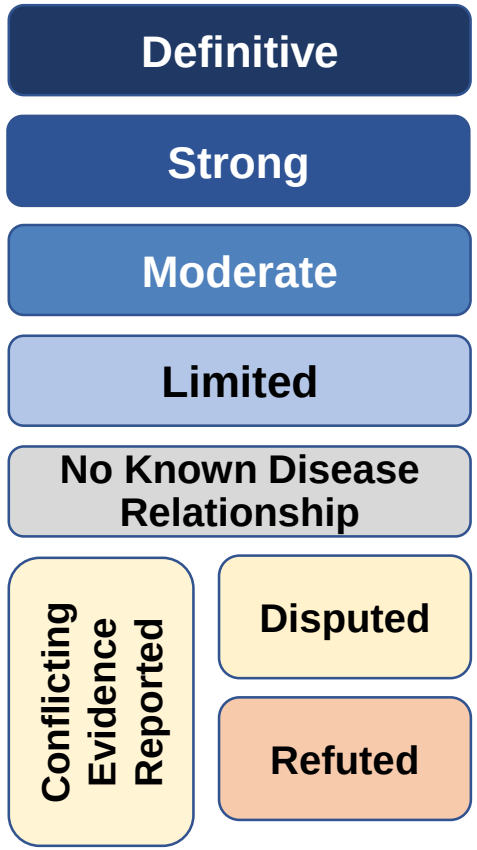
The Clinical Genome Resource (ClinGen, NIH/NHGRI)

ClinGen
Clinical Genome Resource

Ressource publique qui définit la **pertinence clinique** de **gènes** et de **variants** pour la médecine personnalisée et la recherche.

Méthodologie semi-quantitative pour évaluer le niveau de preuve de l'implication d'un gène dans une maladie





Courtesy of L. Milko, Ph.D and C. Thaxton, Ph.D

ClinGen Motile Ciliopathy Gene Curation Expert Panel

(DCP, situs inversus isolé, infertilité masculine isolée par anomalie du flagelle)

Coordinatrice : Marwa Elnagheeb
Modératrices : Hannah Mitchison, Marie Legendre

Canada
Sharon Dell
Catrina Loucks

France
Estelle Escudier
Marie Legendre

Allemagne
Bernd Dworniczak
Johanna Raidt

Norvège
Suzanne Crowley

Pologne
Ewa Zietkiewicz

UK
Mahmoud Fassad
Robert Hirst
Hannah Mitchison
Deborah Morris-Rosendahl
Amelia Shoemark
Simon Thomas

USA
Stephanie Davis
Benjamin Gaston
William Hannah
Margaret Leigh
Keith Nykamp
Courtney Thaxton
Maimoona Zariwala

Tunisie
Rahma Mani

Evaluation de l'implication des gènes :
Evaluer le niveau de preuves en faveur de l'implication d'un gene dans la DCP

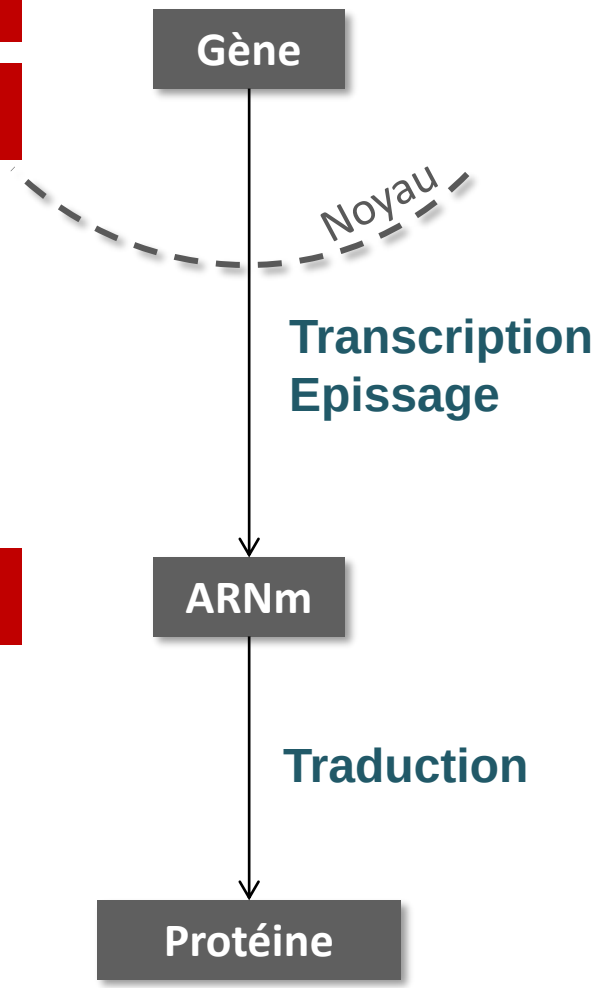
Evaluation de la pathogénicité des variants :
Rassembler un groupe d'expert pour évaluer rigoureusement la pathogénicité de variations d'un gène

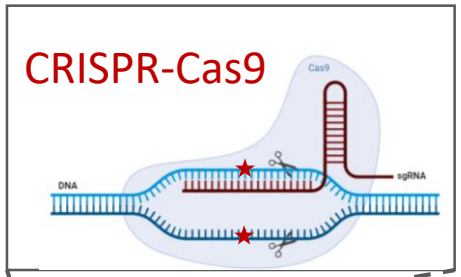
Nouvelles thérapies en développement (recherche)

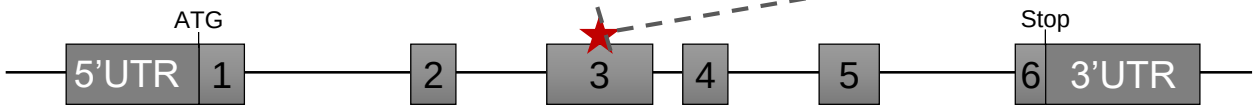
Thérapie génique

Thérapie cellulaire

Thérapie ARN

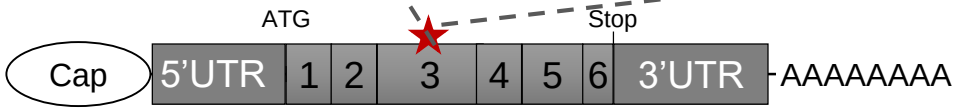


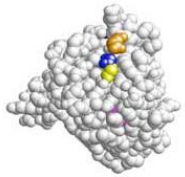




Oligonucléotides anti-sens (ASO)
ARNm de remplacement

Read-through





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Inserm & Sorbonne Université

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Lucie Thomas

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Marie Legendre, AP-HP

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Guy Montantin
Valérie Nau
William Piterboth
Sylvie Tissier

https://geneticdiseases-lab.fr

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Catherine Faucon

Inserm U955, Bruno Louis
Biomécanique et appareil respiratoire, Créteil

Emilie Bequignon
Mathieu Bottier
Sylvain Blanchon
André Coste
Jean-François Papon

Pneumologues, ORLs & Généticiens

Patients & ADCP support group

Inserm
SORBONNE UNIVERSITÉ
LABORATORY OF CHILDHOOD GENETIC DISEASES
HÔPITAL TROUSSEAU
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
RaDiCo Rare Disease Cohorts
BEAT-PCD
RespiFil Filière Maladies Respiratoires Rares
association dcp dyskinésie ciliaire primitive