Le malattie da disfunzione ciliare

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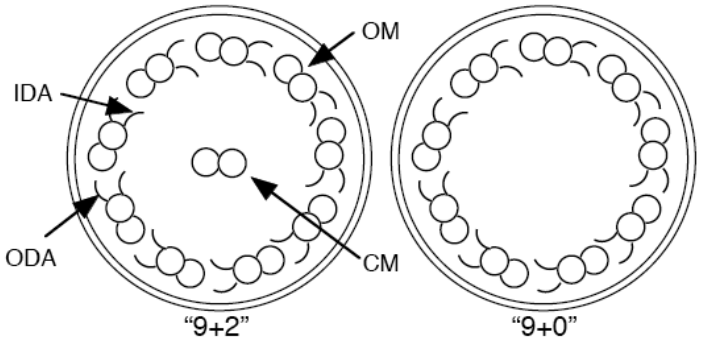
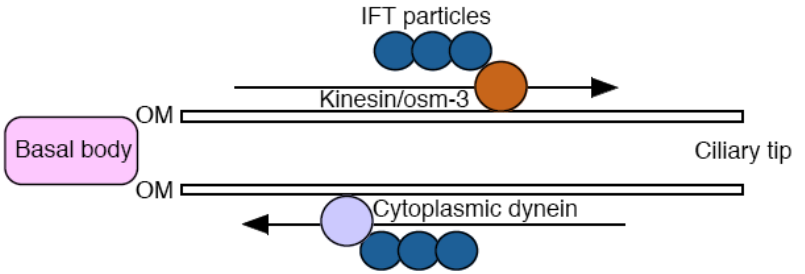
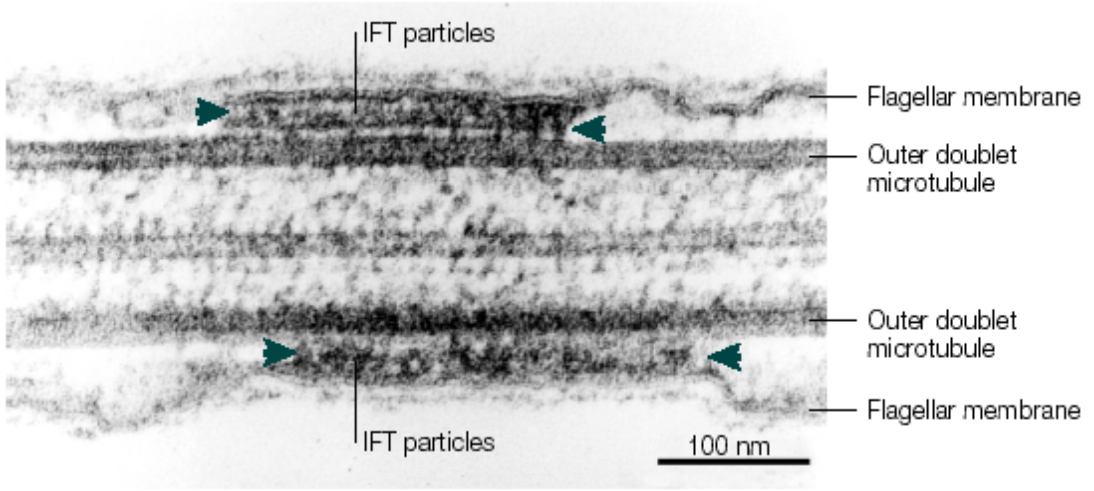
Cilia are devoid of protein synthesis and rely on specialized transport

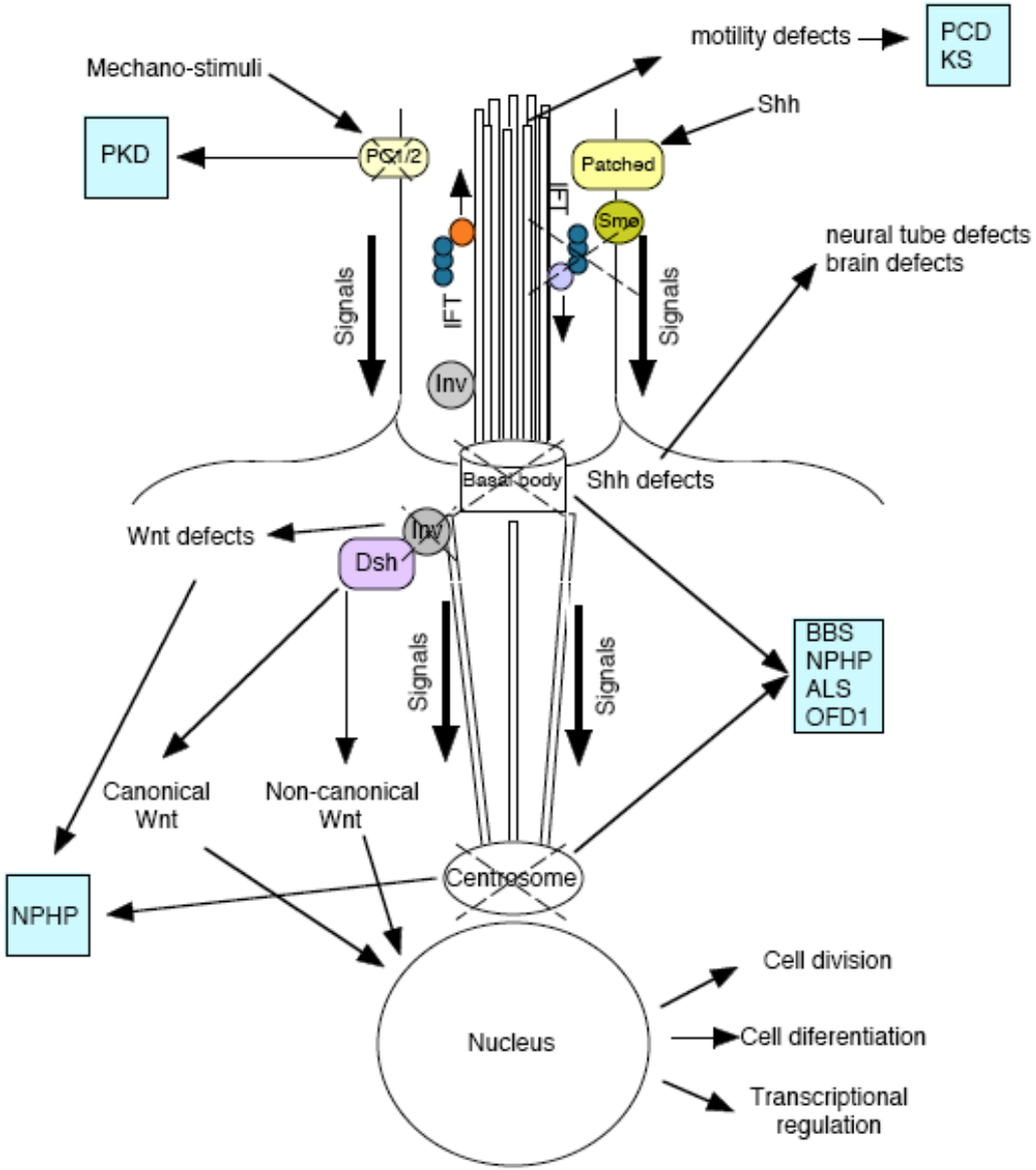


Motile Immotile (primary cilia)





Cilia are involved in a number of complex signaling processes



Badano, Beales, Katsanis Annu Rev Genet Genomics 7 (2006)

Table 1. Ciliary proteins essential for cellular function

Gene and protein	Ciliary localization	Proposed function	Human disease	Disease pathology or developmental defect
Intraflagellar transport				
Kif3a, Kif3a	Cilia	Subunit of the anterograde IFT motor protein kinesin 2	Unknown	Kidney cysts, retinal dystrophy, situs inversus (M)
Kif3b, Kif3b	Cilia	Subunit of the anterograde IFT motor protein kinesin 2	Unknown	Situs inversus (M)
Dnchc2 (M)/ cytoplasmic dynein	Cilia?	Heavy chain subunit of the retrograde IFT dynein motor complex	Unknown	Neural tube defects, polydactyly, situs inversus (M)
Tg737, Polaris/Ift88	Cilia, basal bodies	IFT complex B protein	Unknown	Renal, hepatic and pancreatic cysts, hydrocephalus, polydactyly, situs inversus (M)
Wimple (M), Ift172	Cilia	IFT complex B protein	Unknown	Neural tube defects, polydactyly, situs inversus (M)
Ngd (M), Ift52	Cilia	IFT complex B protein	Unknown	Neural tube defects, polydactyly, situs inversus (M)
hippi (Z), Ift57	Cilia?	IFT complex B protein	Unknown	Hydrocephalus, kidney cysts, situs inversus (Z)
Ciliary motility				
Dnah5, axonemal dynein	Cilia	Heavy chain subunit of ciliary outer dynein arms	PCD	Sinusitus, bronchiectasis, infertility, hydrocephalus, situs inversus
Dnai1, axonemal dynein	Cilia	Intermediate chain subunit of ciliary outer dynein arms	PCD	Sinusitus, bronchiectasis, infertility, hydrocephalus, situs inversus
Dnah11 (*iv/lrd*)(M), left-right dynein	Cilia	Dynein motor protein subunit; required for motility in nodal cilia	PCD?	Situs inversus
Transcription of ciliary genes				
Rfx3 (M), Rfx3	Nucleus	X-box transcription factor; regulates ciliogenic genes	Unknown	Situs inversus (M)
Hfh4/Foxj1 (M), Foxj1	Nucleus	Forkhead transcription factor; regulates ciliogenic genes	Unknown	Situs inversus (M)

Bisgrove BW et al, Development 133, 4131-4143 (2006)

Polycystic kidney diseases

Pkd1, polycystin 1	Cilia, basal bodies	Mechanosensitive and G protein-coupled receptor	ADPKD	Kidney, liver and pancreatic cysts
Pkd2, polycystin 2	Cilia	Mechanosensitive, nonselective cation channel permeable to Ca^{2+}	ADPKD	Kidney, liver and pancreatic cysts; situs inversus (M, Z)
Pkhd1, fibrocystin/ polyductin	Cilia, basal body	Unknown; transmembrane protein	ARPKD	Kidney cysts, liver fibrosis
Cys1, cystin	Cilia, basal body	Unknown	Unknown	Kidney cysts, *cpk* mouse model of PKD
Nphp1, nephrocystin	Cilia, basal bodies, centrosomes	Unknown; interacts with focal adhesion signaling complex elements and nephroretinin	NPHP type I (juvenile)	Kidney cysts, liver fibrosis, retinal dysplasia
Nphp2, *Invs* (M), inversin	Cilia, basal bodies, centrosomes	Interacts with Apc2, N-cadherin calmodulin, nephrocycstin, Dvl; functions in regulation of cell cycle and Wnt pathways	NPHP type II (infantile)	Kidney cysts, situs inversus
Nphp3, *Pcy* (M) , nephrocystin 3	Cilia, basal bodies, photoreceptor connecting cilia	Unknown; interacts with nephrocystin	NPHP type III (adolescent)	Kidney cysts and fibrosis
Nphp4, nephroretinin	Cilia, basal bodies	Unknown; interacts with nephrocystin	NPHP type IV	Kidney cysts, retinitis pigmentosa
Nphp5/Iqcb1i, nephrocystin 5	Cilia, photoreceptor connecting cilium	Unknown; interacts with retinitis pigmentosa GTPase regulator and calmodulin	Senior-Loken syndrome	Kidney cysts, retinitis pigmentosa
Nphp6/Cep290, nephrocystin 6	Centrosomes, photoreceptor connecting cilium	Unknown; interacts with transcription factor Atf4	Joubert sydrome	Kidney cysts, retinitis pigmentosa, cerebellar vermis aplasia

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Table 1. Continued

Gene and protein	Ciliary localization	Proposed function	Human disease	Disease pathology or developmental defect
Cell cycle regulation				
Pdgfrα, Pdgfrα	Cilia	Platelet-derived growth factor receptor; involved in cell-cycle regulation	Malignancies	Mutations associated with gastrointestinal, lung and ovarian tumors
Nek1 (*kat*), Nek1	Cilia, basal bodies, centrosomes	NIMA kinase family member; interacts with PKD proteins, cell cycle regulation?	Unknown	Kidney cysts, male infertility; mouse model of progressive PKD
Nek8, jck (M), Nek8	Cilia	NIMA kinase family member; cell cycle, cytoskeletal regulation?	Unknown	Kidney cysts; mouse model of juvenile cystic kidney disease
Intercellular signaling				
Smo, smoothened	Cilia, cytoplasm	Transmembrane hedgehog receptor, ciliary localization necessary for processing of Gli transcription factors	Unknown; gain of function in some basal cell carcinomas	Neural tube defects, polydactyly (M)
BBS and other disease syndromes				
Bbs1-Bbs11, Bbs1-Bbs11	Basal bodies, centrosome, photoreceptor connecting cilium	Involved in IFT in photoreceptor and olfactory cilia and in intracellular microtubule transport processes	Bardet-Biedl syndrome (BBS)	Kidney cysts, obesity, anosmia, retinal dystrophy, male infertility, situs inversus, diabetes
Alms1, Alms1	Cilia, centrosomes	Unknown	Alstrom syndrome	Retinal degeneration, obesity, diabetes
Ofd1, Ofd1	Basal bodies	Implicated in IFT and intracellular transport processes	Oral-facial-digital syndrome I	Kidney cysts, malformations of the oral cavity, face, and digits
Mks1 and *Mks3*, Mks1 and Mks3	Cilia?	Unknown	Meckel-Gruber syndrome	Kidney and liver cysts, CNS malformations, polydactyly, hydrocephalus

Genes and phenotypes specific to mice (M), zebrafish (Z) are indicated.
ADPKD, autosomal polycystic kidney disease; Alms1, Alstrom syndrome 1; Cys1, cystin 1; Hfh4, hepatocyte nuclear factor/forkhead homolog 4; IFT, intraflagellar transport; Kif3, kinesin superfamily 3; Mks1, Meckel syndrome 1; Nek, NIMA-related kinase; PCD, primary cilia dyskinesia; Pdgfrα, platelet-derived growth factor α; PKD, polycystin; NPHP, nephrocystin; Ofd1, oral-facial-digital type 1 syndrome.

Bisgrove BW et al, Development 133, 4131-4143 (2006)

Diseases due to Primary Cilia dysfunction

Gene	Protein	Disease	Localization
NPHP1	Nephrocystin1	Nephronophthisis 1	Primary Cilia
INV	Inversin	Nephronophthisis 2	Primary Cilia; Basal Body
NPHP3	Nephrocystin 3	Nephronophthisis 3	Primary Cilia
NPHP4	Nephroretinin	Nephronophthisis 4	Primary Cilia
PKD1	PC-1	ADPK Disease	Primary Cilia, elsewhere
PKD2	PC-2	ADPK Disease	Primary Cilia, elsewhere
PKHD1	Polyductin	ARPK Disease	Primary Cilia and Basal Body
BBS1	Bardet-Biedl 1	Bardet-Biedl 1	Centrosome
BBS4	Bardet-Biedl 4	Bardet Biedl 4	Basal Body and centriolar satellite
BBS5	Bardet-Biedl 5	Bardet-Biedl 5	Basal Body
BBS8	Bardet-Biedl 8	Bardet-Biedl 8	Basal Body
OFD1	OFD1	Oral-facial-digital type 1	Basal Body and nucleus
MKS3	meckelin	Meckel-Gruber 3	ciliary localization suggested
MKS1	MKS1	Meckel-Gruber 1	ciliary localization suggested
DNAI1	Dynein	Kartagener	Primary Cilia
RPGR	Retinitis Pigmentosa GTPase Regulator	Retinitis Pigmentosa	Conn. cilia of rods and cones and cilia in airway ep.
IQCB1	Nephrocystin 5	Senior-Loken 5	Primary Cilia
IFT80	IFT80	Jeune syndrome	Basal bodies and selected cilia
DNAI1, DNAH5, DNAH11	DNAI1, DNAH5, DNAH11	Primary ciliary dyskinesia PCD	Axonemes of respiratory primary cilia

Clinical signs shared by ciliopathies

Disease	BBS	OFD1	Senior-Loken	Meckel	Joubert
Retinitis pigmentosa	✓		✓	✓	✓
Renal cystic disease	✓	✓	✓	✓	✓
Polydactyly	✓	✓		✓	✓
Situs inversus/ isomerism	✓		✓	✓	✓
Mental retardation/ developmental delay	✓	✓		✓	✓
Hypoplasia of corpus callosum	✓	✓		✓	✓
Dandy-Walker malformation	✓	✓	✓	✓	✓
Posterior encephalocele	✓*			✓	✓
Hepatic disease	✓		✓	✓	✓
	8	4	5	9	9

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Rene policistico

• Cause non genetiche (acquisito oppure ostruzione urinaria)

• Di origine Genetica

Autosomico dominante

Autosomiche recessive

Legato al cromosoma X

- Autosomico dominante

Rene policistico autosomico dominante (ADPKD) PKD1 e PKD2 (Pc1 e Pc2).

Sclerosi Tuberosa

Malattia di Von Hippel Lindau

Malattia cistica midollare (MCKD1, MCKD2)

Malattia renale glomerulocistica

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- E’ uno dei più comuni disordini genetici con un’incidenza di 1 a 1000 (1/800 nati vivi).
- E’ causa di circa il 10% dei casi di ESRD (end-stage renal disease) ➡ DIALISI.
- Il 60% delle persone affette raggiungono lo stadio ESRD entro i 60 anni.

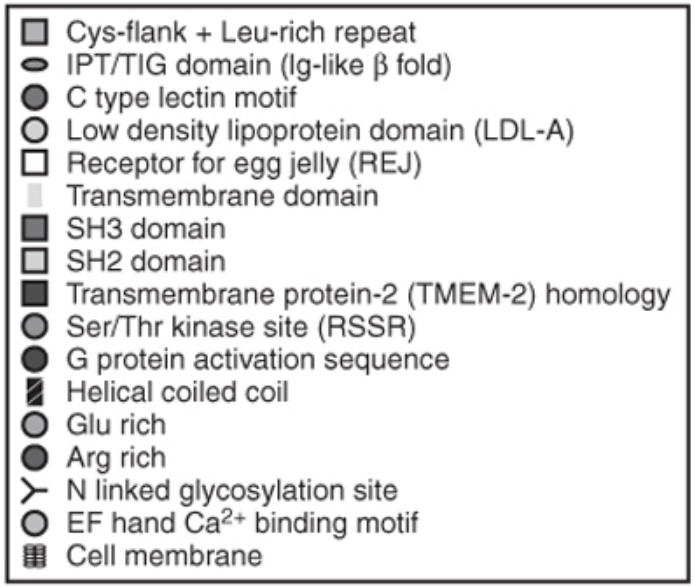
ASPETTI CLINICI

- Numerose cisti a livello dei nefroni e dei dotti collettori.
- Cisti a livello epatico e pancreatico.
- Difetti valvolari cardiaci.
- Aneurismi aortici e cerebrali.
- Eterogeneità fenotipica:
  - gravità della patologia renale
  - numero di manifestazioni extra-renali
  - età di insorgenza.

GENI COINVOLTI ETEROGENEITÀ GENETICA

- **PKD1** (85-90% dei casi)
  - localizzato in 16p13.3
  - 52 kb
  - mRNA di 14 kb
  - 46 esoni

IMPORTANTE RUOLO NELLA INTERAZIONE CELLULA-CELLULA E/O CELLULA-MATRICE

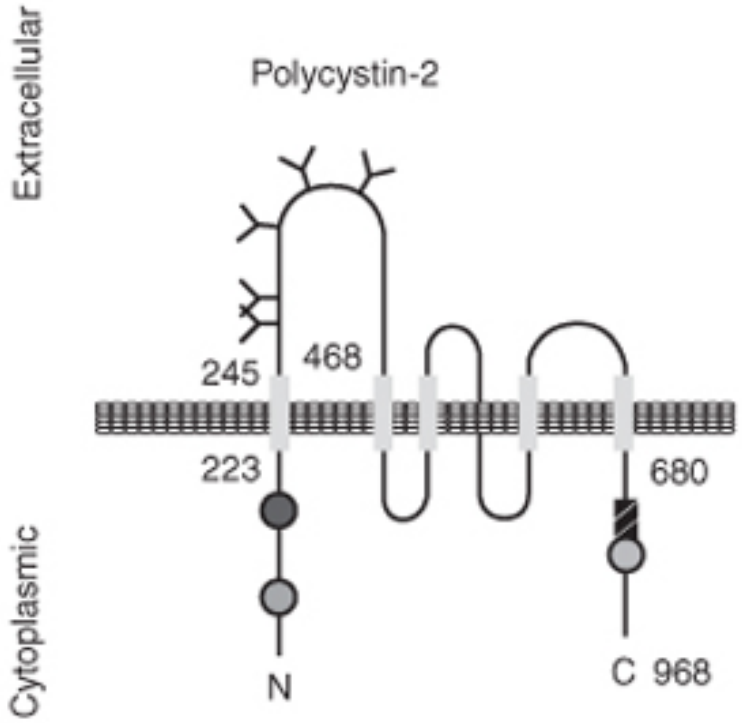


Glicoproteina di 4302 aa

- Vasto dominio extracellulare N-terminale
  leucine rich repeats (adesione cellulare), C-type lectin domain, PKD domain (Ig-like motif), REJ (receptor for egg jelly)
- 11 domini transmembrana
- Dominio intracellulare C-terminale
  Contiene numerosi siti di fosforilazione, Attiva AP-1 (fattore di trascrizione), Interagisce con G-protein, Lega proteine del citoscheletro.

GENI COINVOLTI ETEROGENEITÀ GENETICA

- **PKD2** (15% dei casi)
  - localizzato in 4q22
  - 68 kb
  - mRNA 5.4 kb
  - 15 esoni



PROTEINA INTEGRALE DI MEMBRANA di 400 aa

– 6 domini transmembrana

– Presenta forti omologie di sequenza con TRCP (proteina canale che permette l'ingresso del Ca++ nelle cellule) ed è in grado di legarsi a tale proteina.

– La regione C-terminale presenta una sequenza EF hand che tipicamente si trova nelle proteine che legano il Ca++.

– Lega proteine che interagiscono con actina.

- Autosomiche recessive

Rene policistico autosomico recessivo (ARPKD)

Nefronoftisi (NPHP1-NPHP6) e sindromi correlate (Joubert, Senior-Loken)

Sindromi Bardet-Biedl (BBS1-BBS12)

Sindrome di Jeune (con displasia toracica asfissiante)

Sindromi Meckel-Gruber (MKS1-MKS3)

- Legate al cromosoma X

Sindrome Oro-facio-digitale di tipo I