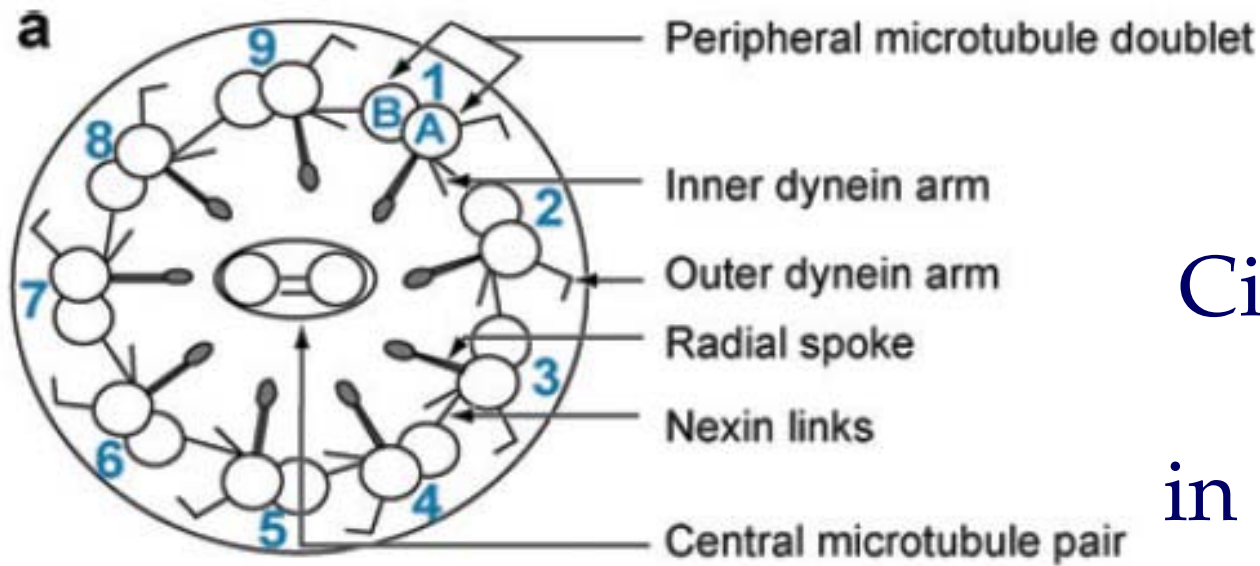
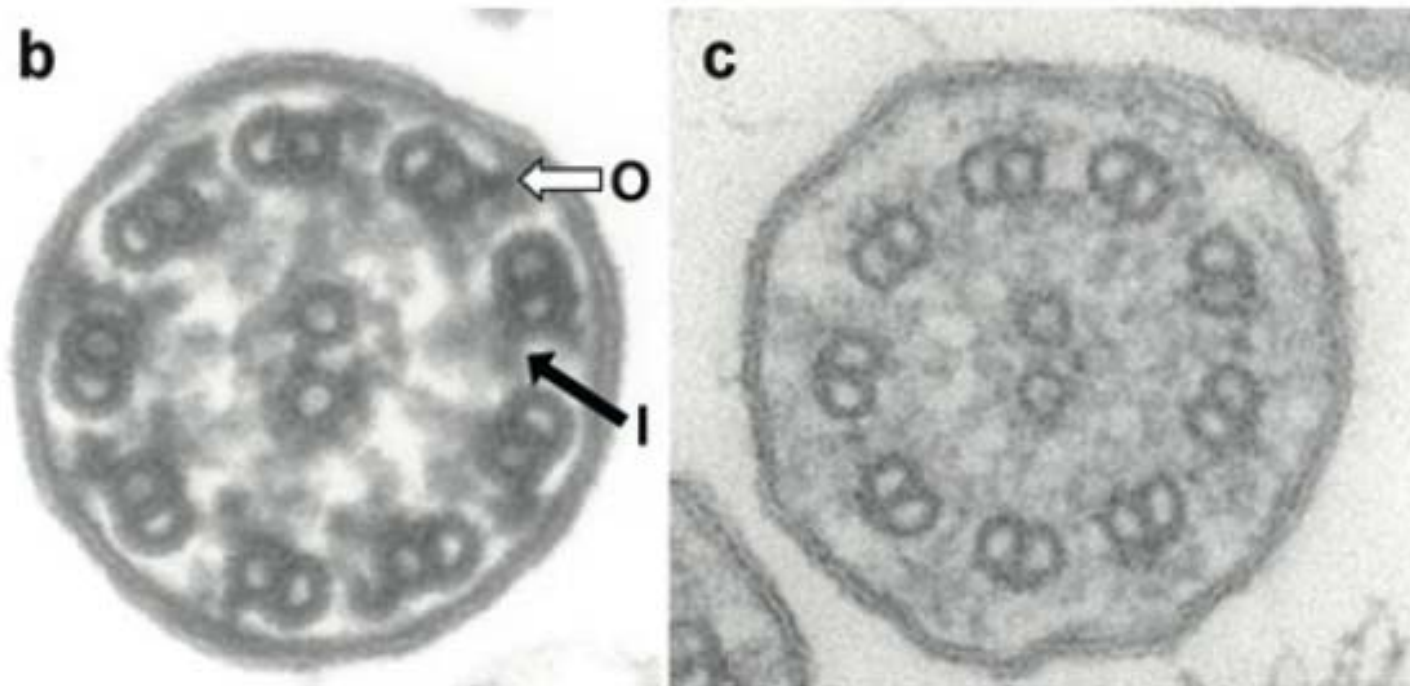


Primary ciliary dyskinesia (PCD)

- PCD is a phenotypically and genetically heterogeneous conditions in which three responsible genes have been identified (DNAH5, DNAI1, DNAH11)
- Prevalence 1:15-30000
- The defect is in the ultrastructure or functions of cilia
- The clinical features include recurrent sinopulmonary infections, subfertility and laterality defects
- It is usually transmitted as an AR trait and includes Kartagener syndrome, Immotile cilia syndrome and ciliary orientation defects.



Ciliary defects
observed
in PCD patients



Zariwala et al. Genetic Defects in Ciliary Structure and Function. Annual Review of Physiology 69:423-450, 2007. O Outer arm, I Inner arm are absent in C (PCD patient)

Quando sospettare una PCD

Prima della nascita

- Eterotassia (Eco durante la gravidanza)

Nel periodo neonatale:

- rinorrea continua fin dal primo giorno di vita
- Problemi respiratori e/o polmoniti neonatali senza apparente causa predisponente
- Eterotassie
- Diagnosi tramite screening effettuata per una anamnesi familiare sospetta e significativa per PCD

Quando sospettare una PCD

Prima della nascita

- Eterotassia (Eco durante la gravidanza)

Nel periodo neonatale:

- rinorrea continua fin dal primo giorno di vita
- Problemi respiratori e/o polmoniti neonatali senza apparente causa predisponente
- Eterotassie
- Diagnosi tramite screening effettuata per una anamnesi familiare sospetta e significativa per PCD

Quando sospettare una PCD

Durante l'infanzia

- Produzione cronica di muco (tosse produttiva). Dx Diff CF
- Asma atipica non responsiva al trattamento
- Bronchiectasie idiopatiche
- Rinosinusiti croniche non responsive a trattamenti medici e chirurgici
- Otite media essudativa non responsiva alla terapia

Quando sospettare una PCD

Nell'adolescenza ed in eta' adulta

- come sopra
- Gravidanze ectopiche e subfertilita' nelle donne
- Infertilita' maschile (motilita' spermatozoi anche se il 50% maschi PCD sono fertili)

Puo' essere spesso trovata in associazione con
rene policistico, degenerazione retinica,
problemi di lateralita', atresia biliare,
idrocefalo

Clinical findings in a PCD patient

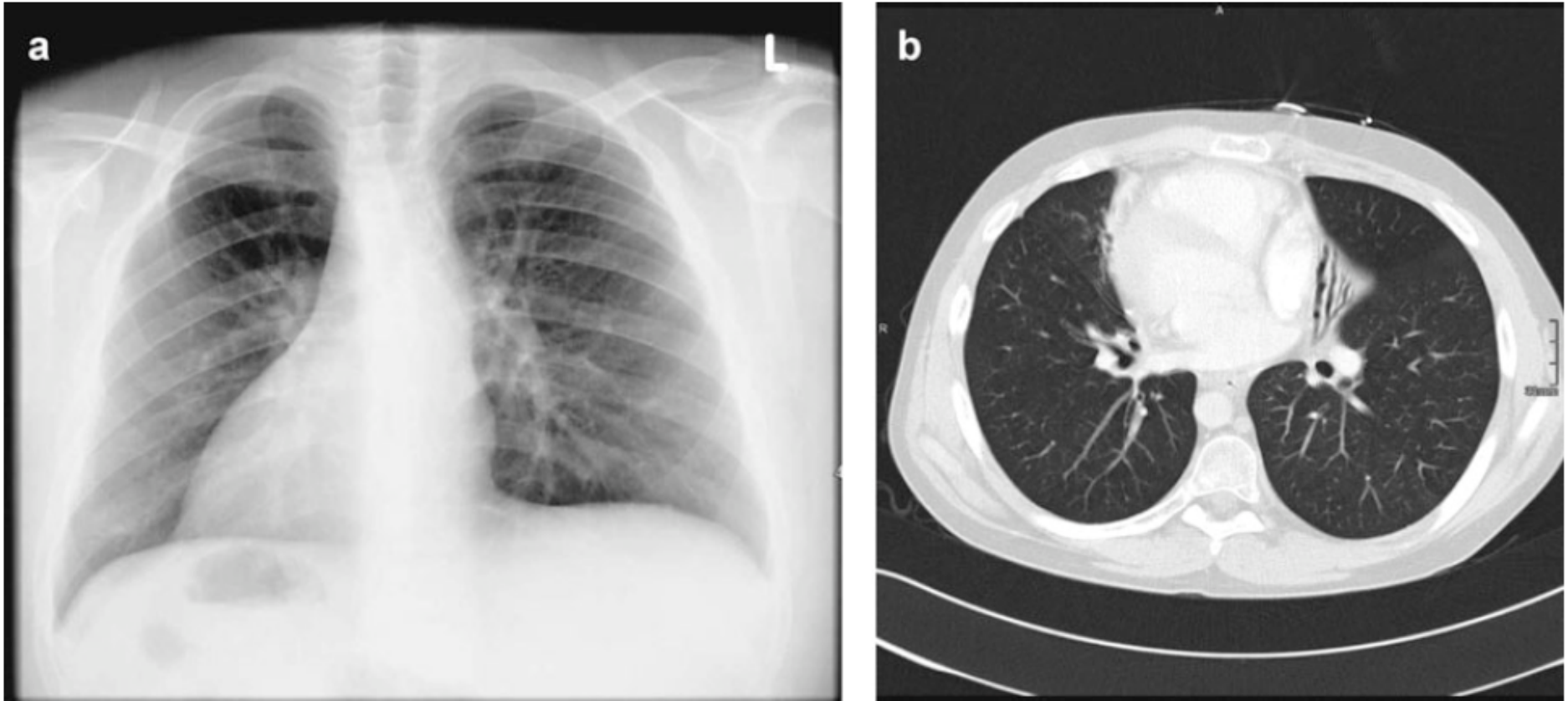


Figure 2

Clinical findings of primary ciliary dyskinesia (PCD). (a) Radiograph of the chest and upper abdomen from a child with PCD and situs inversus. Note the dextroposition of the stomach bubble and the right-sided heart. (b) CT scan of the thorax of a male PCD patient with situs inversus and atelectasis and bronchiectasis caused by recurrent pulmonary infections of the anatomic middle lobe.

Zariwala et al. Genetic Defects in Ciliary Structure and Function. Annual Review of Physiology 69:423-450, 2007.

Sindrome di Bardet-Biedl

- Eredità autosomica recessiva
- Retinite pigmentosa (anomalie e.r.g.)
- Obesità generalizzata
- Polidattilia postassiale
- Rene displasia multicistica
- Ritardo mentale/psicomotorio
- Bassa statura/nanismo
- Ipertensione arteriosa
- Micropene/piccolo pene
- Nistagmo
- Anomalie ovariche
- Pubertà ritardata/ipogonadismo

ORAL-FACIAL-DIGITAL Syndromes (OFDS)

Oral-facial-digital syndromes are a heterogeneous group of developmental disorders characterized by malformation of the face, oral cavities and digits of which at least nine different forms have been described.

Toriello. H. V. “Oral-facial-digital syndromes, 1992”. Clin. Dysmorph. 2, 95-105; 1993.

ORAL - FACIAL- DIGITAL SYNDROMES

- **OFDS Type I: Papillon-Leage-Psaume syndrome**
- **OFDS Type II: Mohr syndrome**
- **OFDS Type III: Sugarman syndrome**
- **OFDS Type IV: Burn-Baraitser syndrome**
- **OFDS Type V: Thurston syndrome**
- **OFDS Type VI: Varadi-Papp syndrome**
- **OFDS Type VII: Whelan syndrome**
- **OFDS Type VIII: Edwards *et al.* (1988)**
- **OFDS Type IX: Gurrieri *et al.* (1992)**
- **OFDS Type X: Figuera**
- **OFDS Type XI: Gabrielli**
- **OFDS Type XII: Moran Barroso**
- **OFDS Type XIII: Degner**

Le diverse forme di OFDS

Findings	OFDS I	OFDS II	OFDS III	OFDS IV	OFDS V	OFDS VI	OFDS VII	OFDS VIII	OFDS IX	OFDS X	OFDS XI	OFDS XII	OFDS XIII
Oral anomalies	Missing teeth tongue clefts frenula	cleft palate frenula tongue nodules and clefts	Cleft uv tongue nod and clefts extra teeth	Cleft palate lobed nod tongue frenula	Frenula (rare)	Cleft palate, lobed nodular tongue, frenula	Cleft palate tongue nodules frenula	Lobed nod tongue, frenula abs teeth	Lobed nod tongue, frenula	cleft palate, vestibul ar fren	cleft palate, frenula	Lobed tonguefren ula	tongue nodules
Facial Anomalies	Telec, hypert median cleft lip alar hypop	Median cleft lip bifid nose tip	Hypert bulbous nose lowset ears	Epicanthal folds micrognathia lowest ears	Median cleft lip	Hypertelorism m cleft lip broad nasal tip	Hypertelorism cleft lip asymmetry	Median cleft lip telec broad/bifid nose	Cleft lip synophrys	telec, flat nasal bridge, retrognathia	hypert median cleft lip alar hypopl	-	Cleft lip
Skin and hair	Alopecia milia skin lesions	Coarse hair	-	-	-	-	-	-	-	-	-	-	-
Hand anomalies	Clino- brachy- syn- dactyly	Clino- brachy-syn- dactyly Pre/ post- axial polydactyly	Postaxial poly- dactyly	Pre-or post- axial polydactyly Clino- brachy-syn- dactyly	Postaxial poly- dactyly	brachy- clino-syn- dactyly central polydactyly	Clinodactyly	Pre- and postaxial polydactyly	Brachy- syn-dacty ly	oligodac tyly, preaxial polydact yly	postaxial polydactyl y	brachy- clino-syn- dactyly	brachy- clino-syn- dactyly
Foot anomalies	Preaxial polydactyl y	Pre- or post-axial polydactyly	Postaxial poly- dactyly	Pre- and post- axial poly-dactyly	Postaxial poly- dactyly	Preaxial poly-syn- dactyly	-	Preaxial polydactyly	Bifid toes	-	postaxial polydactyl y	brachy- clino-syn- dactyly	brachy- clino-syn- dactyly
Heart defects	-	Rare	-	-	-	Rare	-	-	-	-	Hypertrop septum	Heart anomalies	-
Kidney Defects	Adult- onset polycystic	-	-	-	-	Agenesis/ dysplasia	Hydro- nephrosis	-	-	-	-	-	-
Cerebral Anomalies	Callosal agenesis porenceph aly	Porencepha ly hydroceph aly	See-saw winking myoclonic jerks	Porencephal y cerebral atrophy	-	Cerebellar anomalies	-	-	-	-	Dilated ventricles	Myelomen ing Sten acqueduct of Sylvius	leuko- araiosis
Skeletal anomalies	-	-	Short sternum	Pectus excavatum tibial defects	-	-	-	Tibial and radial defects	-	radial short, fibular agen	Cranio- vertebral anomalies	-	-
Miscellaneous	Trembling	-	Hypercon vex nails	Short stature	-	-	Preauricular skin tag	Hypoplastic epiglottis	Retinal anomalies	-	-	-	Neuro-psy symp., epilepsy
Inherit	XLD	AR	AR	AR	AR	AR	AR	XLR	AR/ XLR	AR	AR	AR	AR

ORAL-FACIAL-DIGITAL SYNDROME TYPE I (MIM 311200)

- **OFD type I can be distinguished from the other forms for the presence of polycystic kidneys and for the pattern of inheritance which is X-linked dominant, male lethal.**
- **Occurrence: 1:50.000-250.000**

Clinical features in our cohort of cases

- Limb abnormalities (77.6%)
- Bifid tongue (64.5%)
- Aberrant oral frenuli (59.2%)
- Labio e/o palatoschisis (59.3%)
- Face Milia (59.2%)
- Neurological involvement (46.4%)
- Tongue Amartoma (44.7%)
- Tooth abnormalities (38.1%)
- Cystic kidneys (27.6%)
 - 10% < 18 years
 - 54% > 18 years
- Thin nose (27.4%)
- Hypertelorism (26.2%)
- Broad nasal root (23.8%)
- Micrognathia (21.4%)
- Alopecia (21.1%)
- Frontal bossing (14.3%)

Anomalie delle estremita' 77.6%

- Arti sup. (70%)
- Arti inf. (26%)
 - Brachidattilia (44.7%)
 - Sindattilia (43.4%)
 - Clinodattilia (38.1%)
 - Polidattilia (14.1%)
 - Bifidità dell'alluce (9.2%)

Limb abnormalities >77%
vs 45% in the literature

Cystic kidneys 54% vs 15%
In the literature

Summary

- We generated a conditional *Ofd1*-knockout mouse line which in female mice recapitulates the main feature of the human disease albeit with increased severity possibly due to differences of X-inactivation patterns between the two species
- We demonstrated that *Ofd1* is required for primary cilia formation and left right asymmetry
- We demonstrated altered expression of 5' *Hoxa* and *Hoxd* genes in the limb buds of *Ofd1*-knockout mice presumably due to impairment of Gli3 processing

Conclusions

- Our data definitely places OFDI in the group of disorders ascribed to primary cilia dysfunction
- The floxed line we have generated will allow to study the function of *Ofd1* and primary cilia in different systems in which the *Ofd1* transcripts can be specifically inactivated

The relevance of primary cilia

- Different authors. Primary Cilia:new perspectives.Cell Biology International 28, 2004. The entire issue has been dedicated to primary cilia in different cell types.
- Eley et al. Cilia and disease. Current Opinion in Genetics and Development 15:308-314, 2005.
- Badano et al. The centrosome in human genetic disease. Nature Review Genetics 6:194-205, 2005.
- Hildebrandt et al. Cilia and centrosomes: A unifying pathogenic concept for cystic kidney disease?. Nature Review Genetics 6:928-940, 2005
- Bisgrove et al. The role of cilia in developmental disorders and disease. Development 133, 4131-4143, 2006.
- Satir et al. Overview of Structure and Function of Mammalian Cilia. Annual Review of Physiology 69:377-400, 2007.
- Salathe. Regulation of Mammalian Ciliary Beating. Annual Review of Physiology 69:401-422, 2007
- Zariwala et al. Genetic Defects in Ciliary Structure and Function. Annual Review of Physiology 69:423-450, 2007.