Joubert syndrome

Enza Maria Valente
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University of Salerno
The first description by Dr Marie Joubert in 1969...

Family Agenesis of the Cerebellar Vermis: A Syndrome of Episodic Hyperpnea, Abnormal Eye Movements, Ataxia, and Retardation

Marie Joubert, MD; Jean-Jacques Eisenring, MD; J. Preston Robb, MD; Frederick Andermann, MD

- Autosomal recessive condition (three affected siblings)
- Hypotonia and ataxia (++ axial)
- Oculomotor apraxia
- Developmental delay
- Neonatal breathing abnormalities
- Mental impairment
- Behavioural problems
The “Molar Tooth Sign”: revolutioning the diagnosis

- dysplastic small vermis situated abnormally high
- thickened and mal-oriented superior cerebellar peduncles
- deep interpeduncular fossa, abnormally narrow isthmus
- midline clefting
- umbrella-shaped fourth ventricle

“molar tooth sign”

Maria et al, 1999
Differential diagnosis with Dandy-Walker malformation

**Normal**

**MTS**
- fourth ventricle slightly increased
- superior cerebellar peduncle well visible and horizontalised
- tentorium normal or mildly elevated

**DWM**
- cystic dilatation of the fourth ventricle
- superior cerebellar peduncle hardly visible
- abnormal position of tentorium
Besides the MTS: neuroanatomy and tractography of JS

Table 1. Joubert Syndrome: Neuropathology

<table>
<thead>
<tr>
<th>Friede and Boltshauser’s Case</th>
<th>Current Case</th>
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<tbody>
<tr>
<td><strong>Patient age: 2 Years</strong></td>
<td><strong>Patient age: 31 Years</strong></td>
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<tr>
<td>Aplasia of vermis</td>
<td>Aplasia of vermis</td>
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<td>Large cerebellar hemispheres</td>
<td>Small cerebellar hemispheres</td>
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<tr>
<td>Cortical cytoarchitecture normal</td>
<td>Neuronal loss and gliosis of Purkinje cell layer</td>
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<td>Fragmented dentate nucleus</td>
<td>Fragmented dentate nucleus</td>
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<td>Heterotopias of roof nuclei</td>
<td>No apparent heterotopias</td>
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<tr>
<td>Abnormal elongation of locus coeruleus</td>
<td>Abnormal elongation of locus coeruleus</td>
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<tr>
<td>Dysplasia of inferior olives</td>
<td>Hypoplasia of inferior olives</td>
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<tr>
<td>Absence of pyramidal decussation</td>
<td>Absence of pyramidal decussation</td>
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<tr>
<td>Anomalies of dorsal column nuclei, solitary tract, and cranial nerve V tract</td>
<td>Anomalies of dorsal column nuclei, solitary tract, and cranial nerve V tract</td>
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<td>Apparent reduction in reticular formation neurons</td>
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**Diffusion Tensor Imaging in Joubert Syndrome**

**BACKGROUND AND PURPOSE:** Neuropathologic findings and preliminary imaging studies demonstrated the absence of pyramidal tract and superior cerebellar peduncular decussation in individual patients with Joubert syndrome (JS). We hypothesized that functional-structural neuroimaging findings do not differ between the genetic forms of JS.

**MATERIALS AND METHODS:** MR imaging was performed with a 3T MR imaging unit. Multiplanar T2- and T1-weighted imaging was followed by diffusion tensor imaging (DTI). Isotropic diffusion-weighted images, apparent diffusion coefficient maps, and color-coded fractional anisotropy maps, including tractography, were subsequently calculated.

**RESULTS:** In all 6 patients studied, DTI showed that the fibers of the superior cerebellar peduncles did not decussate in the mesencephalon and the corticospinal tract failed to cross in the caudal medulla. The patients represented various genetic forms of JS.

**CONCLUSION:** In JS, the fibers of the pyramidal tract and the superior cerebellar peduncles do not cross, irrespective of the underlying mutation.
Spectrum of disorders sharing the MTS: the JSRD


Molar Tooth Sign of the Midbrain–Hindbrain Junction: Occurrence in Multiple Distinct Syndromes

Joseph G. Gleeson,1* Lesley C. Keeler,1 Melissa A. Parisi,2 Sarah E. Marsh,1 Phillip F. Chance,2 Ian A. Glass,2 John M. Graham Jr,3 Bernard L. Maria,4 A. James Barkovich,5 and William B. Dobyns6**

TABLE I. JS and Related Disorders (JSRD) of Midbrain/Hindbrain Formation

<table>
<thead>
<tr>
<th></th>
<th>Classical Joubert</th>
<th>Joubert + LCA or retinal dystrophy</th>
<th>Dekaban–Arima syndrome</th>
<th>Senior–Löken syndrome</th>
<th>COACH/Gentile syndrome</th>
<th>Váradi–Papp syndrome (OPD VI)*</th>
<th>Joubert + Polymicrogyria*</th>
<th>Malta syndrome*</th>
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<td>MTS</td>
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<td>Clinical features of MTS</td>
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<td>+ (Late)</td>
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A more descriptive nosology for JS

- pure JS:
  - hypotonia/ataxia
  - developmental delay
  - oculomotor apraxia
  - breathing abnormalities

- JS+retina:
  - Leber amaurosis
  - other retinopathy

- JS+retina+kidney (COR):
  - nephronophthisis
  - cystic dysplastic kidneys
  - kidney (COR)

- JS+kidney:
  - colobomas
  - congenital heart defects

- JS+liver:
  - congenital liver fibrosis

- JS+L+K:
  - median line defects (tongue tumours, cleft lip/palate etc)

- brain (MTS):
  - dysmorphic features

- OFD VI:
  - situs inversus

- JS+

- eye:
  - Hirschsprung disease

- liver:
  - congenital liver fibrosis

- colobomas:

- congenital heart defects

- other SNC malformations (encephalocele, DW-like, PMG ecc)
Additional features in Joubert syndrome

typical facies
LCA

situs inversus

PMG

occipital encephalocele

optic nerve coloboma

cystic kidneys
Oro facio digital features in Joubert syndrome

- Polydactylies
- Cleft palate
- Tongue amartoma
- Multiple frenuli
- Notched upper lip
Cognitive abnormalities in JS

Normal Cognitive Functions in Joubert Syndrome

- 14 Italian patients
- mean age: 8.7yrs (2.2-29)
- variable phenotypes

<table>
<thead>
<tr>
<th>COGNITIVE:</th>
<th>LANGUAGE:</th>
<th>MOTOR:</th>
<th>BEHAVIOR:</th>
<th>ADAPTIVE:</th>
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<tbody>
<tr>
<td>Griffith / Leiter-R; Wechsler (&gt;4yrs)</td>
<td>Verbal comprehension Peabody</td>
<td>ABC movement / GMFM</td>
<td>CBCL</td>
<td>Vineland</td>
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</table>

- full scale IQ: 93
- only minor difficulties in some executive functions and visual-spatial organization
- homozygous mutations in the INPP5E gene, marked intrafamilial variability!

- 20yr old lady
- 2 affected brothers with severe cognitive impairment
- all had confirmed MTS

Language: comprehension relatively preserved, worse on the expressive side (also in pts with normal QI)

Attention, memory, adaptive abilities: in line with mental age

Motor abilities: overall more compromised

Behavior: 2 pts with autistic traits and severe MR, 1 pts with psychiatric disturbance and borderline QI
Basic diagnostic algorithm

- Careful **family history** (consanguinity)

- Detailed **neurological and neuropsychological** evaluation, dysmorphisms

- **Kidney**
  - renal ultrasound, renal function, blood count, urinary specific gravity
  - (urinary concentration test)

- **Eye**
  - careful visual testing, fundus oculi
  - (electroretinogram, slit lamp exam for colobomas)

- **Liver**
  - palpate for hepatosplenomegalgy, transaminases, abdominal ultrasound
  - (liver MRI, liver biopsy)

- Careful examinations for **polydactyly, tongue/mouth abnormalities, heart defects, situs inversus**...

- Detailed **review of MRIs** for other CNS abnormalities

*Romani et al, Lancet Neurol 2013*
<table>
<thead>
<tr>
<th>locus</th>
<th>gene/protein</th>
<th>JSRD</th>
<th>MKS</th>
<th>NPH/SLS</th>
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<td>1q42</td>
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Genetic heterogeneity in JS: all genes encode for proteins of the primary cilium.
The primary cilium

- Membrane-enclosed antenna-like structure with a ring-shaped skeleton (9+0 doublets of mt), a basal body (triplets of mt) and a transition zone.
- Up to 3000 proteins involved.
- Mutations identified in over 50 disease-genes.
- About 100 disorders may be driven by cilia abnormalities.
- Minimal estimated collective incidence: 1/1000 conceptuses.
In many tissues, primary cilia link mechanosensory, visual and osmotic stimuli to cell-cycle control and epithelial cell polarity.

In the embryonic node (a transient structure during gastrulation), motile nodal cilia generate a leftward nodal flow that is essential for L-R axis determination.
Primary cilia control neural and limb patterning, by modulating:
- Sonic Hedgehog pathway
- Wnt / beta-catenin pathway
- planar cell polarity pathway

Valente et al, Nat Rev Neurol 2013
Common features of ciliopathies

- Disorders caused by genes encoding for proteins of the primary cilium and its apparatus (basal body, centrosome)
- Variable severity and multiorgan involvement
- Clinical and genetic overlap among distinct conditions

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<tr>
<th></th>
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<th>JBTS</th>
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Arts & Knoers, Ped Nephrol 2012
Overlap with other ciliopathies: Meckel syndrome

- cystic dysplastic kidneys
- occipital encephalocele, other posterior fossa abn
- liver fibrosis (ductal plate malformation)
- postaxial polydactyly

- other: ocular/retinal abn, CHD, genital abn

- in utero / early lethality
- autosomal recessive inheritance
Isolated Nephronophthisis and Senior-Loken syndrome

Isolated juvenile NPH is the most common genetic cause of ESRF in childhood

Asymptomatic in the first decade of life

Symptoms at onset (late first decade):
- polyuria, polydypsia
- anemia, growth retardation
- urinary concentration defect
- acute renal failure!!!!

Kidney ultrasound (variable): small kidneys, cortico-medullary hyper-echogenicity, isolated small cysts

Kidney biopsy: thickening of the tubular basal membrane, interstitial fibrosis

DDAVP test: deficit of urinary concentration ability after Desmopressin stimulation (positive from 3-4 years of age!!)
Bardet-Biedl syndrome

- obesity, hypogenitalism
- retinal dystrophy
- renal dysplasia (including cysts)
- polydactyly
- congenital heart defects
- hepatic fibrosis
- (cognitive impairment, ataxia, deafness, neural tube defects)
Hydrolethalus and acrocallosal syndromes

**Hydrolethalus syndrome**
- postaxial polydactyly of hands
- preaxial polydactyly of feet
- micrognathia
- hydrocephaly / anencephaly
- occipital bone defect

**Acrocallosal syndrome**
- postaxial polydactyly of hands
- preaxial polydactyly of feet
- corpus callosum agenesis
- hypertelorism
- (MTS??)

Joubert patients:
- MTS, neurological signs
- retinitis pigmentosa
- postaxial polydactyly

Putoux et al, Nat Genet 2011
Orofaciodigital type 1 (OFDI) syndrome

X-linked dominant, male lethality

Facial and oral abnormalities
• tongue anomalies, frenula
• cleft palate/lip
• abnormal teeth and hair
• dysmorphic features

Skeletal abnormalities
• brachydactyly, polydactyly, other

Other organs
• cystic kidneys
• CNS malformations

Joubert patients:
- also male patients!
- PMG, hydrocephalus
- retinitis pigmentosa
- postaxial polydactyly
- polycystic kidneys
- OFDVI phenotypes
Jeune Asphyxiating Thoracic Dystrophy (JATD)

Co-Occurrence of Joubert Syndrome and Jeune Asphyxiating Thoracic Dystrophy

AJMG, 2010

A.M. Lehman,1 P. Eydox,2 D. Doherty,3 I.A. Glass,3 D. Chitayat,4 B.Y.H. Chung,4 S. Langlois,1 S.L. Yong,1 R.B. Lowry,5 F. Hildebrandt,6 and P. Trnka7*

- long narrow thorax, short ribs
- short long bones, short stature
- cone-shaped epiphyses
- trident-staped acetabulum
- Occasionally:
  - polydactyly
  - renal cystic dysplasia (similar to NPH)
  - retinal degeneration
  - liver involvement

TTC21B
- recessive mut in Jeune
- het mut in JS
IFT80, which encodes a conserved intraflagellar transport protein, is mutated in Jeune asphyxiating thoracic dystrophy

Philip L Beales¹, Elizabeth Bland¹, Jonathan L Tobin¹, Chiara Bacchelli¹, Beyhan Tuysuz², Josephine Hill¹, Suzanne Rix¹, Chad G Pearson³, Masatake Kai¹, Jane Hartley⁵, Colin Johnson⁶, Melita Irving¹, Nurset Elcioglu¹, Mark Winey⁵, Masazumi Tada⁴ & Peter J Scambler¹

Nat Genet 2007

Mutation in IFT80 in a fetus with the phenotype of Verma-Naumoff provides molecular evidence for Jeune-Verma-Naumoff dysplasia spectrum

Denise P Cavalcanti¹,² Celine Huber,² Kim-Hanh Le Quan Sang,² Geneviève Baujat,² Felicity Collins,³ Anne-Lise Delezoide,⁴ Nathalie Dagoneau,² Martine Le Merrer,² Jelena Martinovic,⁵ Marcos Fernando S Mello,⁶ Michel Vekemans,² Arnold Munnich,² Valerie Cormier-Daire²

Verma-Naumoff sdr

- prenatal/early lethality
- same radiological features as Jeune sdr
- variable malformations (cleft lip/palate, cystic kidneys, other GI, urinary, heart, CNS anomalies)

IFT80: intraflagellar transport protein

DYNC2H1 Mutations Cause Asphyxiating Thoracic Dystrophy and Short Rib-Polydactyly Syndrome, Type III

Nathalie Dagoneau,¹,⁷ Marie Goulet,¹,⁷ David Geneviève,¹ Yves Sznajer,² Jelena Martinovic,¹ Sarah Smithson,³ Céline Huber,¹ Geneviève Baujat,¹ Elisabeth Flori,⁴ Laura Tecco,⁵ Denise Cavalcanti,¹ Anne-Lise Delezoide,⁶ Valérie Serre,¹ Martine Le Merrer,¹ Arnold Munnich,¹ and Valérie Cormier-Daire¹,*

AJHG 2009

DYNCH1: dynein2 heavy chain 1
OFDIV: overlap between OFD, SRP, JS and MKS

**OFD-related abnormalities**
- tongue anomalies, frenula
- cleft palate/lip
- postaxial polydactyly

**Skeletal abnormalities**
- tibial hypoplasia and thickening
- bowing of long bones
- trident aspect of the acetabular margin
- NO SHORT RIBS

**Other organs**
- (cystic dysplastic kidneys)
- (liver ductal plate proliferation)
- CNS malformations

Mutations in **TCTN3** also found in a family with Joubert syndrome
Co-Occurrence of Distinct Ciliopathy Diseases in Single Families Suggests Genetic Modifiers

Maha S. Zaki,1* Shifteh Sattar,2 Rustin A. Massoudi,2 and Joseph G. Gleeson2

AJMG 2012

<table>
<thead>
<tr>
<th>Ciliopathy-672</th>
<th>Ciliopathy-1491</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-1</td>
<td>IV-1</td>
</tr>
<tr>
<td>IV-2</td>
<td>IV-2</td>
</tr>
<tr>
<td>IV-3</td>
<td>IV-3</td>
</tr>
<tr>
<td>IV-4</td>
<td></td>
</tr>
</tbody>
</table>

NPH                  | BBS             |
polydactyly          | pure JS         |
mild CVA             | JS              |

polydactyly          | pure JS         |
corneal opacity      | JS              |

JSRD + MKS
- TMEM67 mut
- TMEM216 mut

JSRD + ACLS
- KIF7 mut
Genetic overlap between JSRD and other ciliopathies

Several genes cause distinct ciliopathies with variable clinical overlap. Not all genes have been tested for all phenotypes → further associations to come soon.

Zaghloul & Katsanis, Trend in Genet 2010
Ciliopathies: the concept of «splitting and lumping»

**LUMPING**
- distinct phenotypes ➔ same gene

**SPLITTING**
- same phenotype ➔ distinct genes
Splitting...
Ciliary proteins interact in complex, integrated networks

Families of ciliary proteins with distinct functions may associate with specific phenotypes:

• BBS → BBSome
• Skeletal dysplasias → IFT complex
• NPH → NPH complex at the transition zone
• JSRD/MKS → Tectonic complex at the transition zone

Zaghloul & Katsanis, Trends Genet 2010; Garcia-Gonzalo et al, Nat Genet 2011
The B9D1 (or Tectonic) complex at the ciliary transition zone encloses the vast majority of proteins mutated in JS and MKS.

The transition zone represents a diffusion barrier forming a ‘gating system’ that actively regulates movement of proteins into and out of the cilium, in order to maintain the cilium as highly compartmentalized organelle.
... but lumping?
Genotype-phenotype correlates

**RPGRIPL1 – TMEM67 – CC2D2A**

- 2 truncating mutations
  - MKS
- at least 1 missense mutation
  - JSRD

**MKS1**

**NPHP3**

**CEP290**

Wide phenotypic spectrum:
- LCA – NPH – SLS – JSRD – MKS
- Founder hypomorphic mutation → isolated LCA;
- Otherwise, no obvious correlation between mutation type and phenotype

**NPHP1**

- 95% cases: same homozygous 250kb deletion encompassing the gene → variable phenotypes (NPH – SLS – JSRD)

Garcia-Gonzalo et al, Nat Genet 2011
Oligogenic inheritance and mutational load in ciliopathies

Mutations or rare variants at a second locus influence the phenotypic expression of recessive mutations at the main disease locus

<table>
<thead>
<tr>
<th>Gene mutated</th>
<th>None</th>
<th>AHI1</th>
<th>INPP5E</th>
<th>CEP290</th>
<th>NPHP1</th>
<th>NPHP1+AHI1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>Normal</td>
<td>JBTS</td>
<td>JBTS</td>
<td>LCA, SLS, NPHP, JBTS, BBS, MKS</td>
<td>NPHP</td>
<td>NPHP+RD</td>
</tr>
</tbody>
</table>

= Normal chromosome  = Mutated chromosome

Severity

Novarino and Gleeson, Cell 2011
Oligogenic inheritance and mutational load in ciliopathies

The oligogenic properties of Bardet–Biedl syndrome

Nicholas Katsanis*

*Human Molecular Genetics, 2004, Vol. 13, Review Issue 1
DOI: 10.1093/hmg/ddh692
Advance Access published on February 19, 2004

Evidence of Oligogenic Inheritance in Nephronophthisis

Julia Hoebeke,*+ Matthias T.F. Wolf,* John F. O'Toole,* Edgar A. Otto,* Ulla Schultheiss,* Georges Dêschenes,* Massimo Attanasio,* Boris Utsch,* Corinne Antignac,* and Friedhelm Hildebrandt*++

JASN Express. Published on April 4, 2007 as doi: 10.1681/ASN.2006101164

High NPHP1 and NPHP6 Mutation Rate in Patients with Joubert Syndrome and Nephronophthisis: Potential Epistatic Effect of NPHP6 and AHI1 Mutations in Patients with NPHP1 Mutations

Kalman Tery,*† Tiphaine Lacoste,*† Lydia Burglen,* Vincent Morinico,*† Nathalie Boddaert,* Marie-Alice Machet,* Brigitte Llanas,† Hubert Nivot,*+ Albert Bensman,*† Patrick Niaudet,* Corinne Antignac,* and Sophie Saunier*+†

TTC21B contributes both causal and modifying alleles across the ciliopathy spectrum

IFT139

Nat Genet 2011

in several patients, only one heterozygous mutation is identified instead of the expected two
(e.g. het TSGA14 mut + het mut in other genes in half mutated pts)

TTC21B recessive mutations:
- isolated NPH / NPH plus / JATD

TTC21B heterozygous mutations:
-2.5% pts with ciliopathies (some mutated in other genes) vs 0.06% controls
**Even common variants may act as genetic modifiers**

A common allele in *RPGRIPL1* is a modifier of retinal degeneration in ciliopathies

Hemant Khanna¹,², Erica E Davis³,², Carlos A Murga-Zamalloa¹, Alejandro Estrada-Cruzcano¹, Irma Lopez³, Anneke I den Hollander¹, Marijke N Zonneveld¹, Mohammad I Othman¹, Naushin Waseem⁵, Christina F Chakarova³, Cecilia Maubaret⁵, Anna Diaz-Font⁶, Ian MacDonald⁷, Donna M Muzny⁸, David A Wheeler³, Margaret Morgan⁸, Lora R Lewis⁸, Clare V Logan⁹, Perciliz L Tan², Michael A Beer⁴,¹⁰, Chris F Inglehearn⁴, Richard A Lewis¹¹-¹⁴, Samuel G Jacobson¹⁵, Carsten Bergmann¹⁶, Philip L Beales³, Tania Attie-Bitach¹⁷, Colin A Johnson⁹, Edgar A Otto¹⁸, Shomi S Bhattacharya⁵, Friedhelm Hildebrandt¹⁶,¹⁹, Richard A Gibbs⁸, Robert K Koenekoop¹, Anand Swaroop¹,²¹ & Nicholas Katsanis²,²¹

*Nat Genet 2009*

**AHI1 p.R830W**
- controls: 2.8%
- ciliop. non RP: 0%
- ciliop + RP: 4.5% (p<0.001)

**RPGRIPL1 p.A229T**
- controls: 2.8%
- isolated NPH: 1.8%
- SLS: 25% (p<0.001)
- other ciliopathies: ns

*Nat Genet 2010*

AH11 is required for photoreceptor outer segment development and is a modifier for retinal degeneration in nephronophthisis

Carrie M Louie¹, Gianluca Caridi², Vanda S Lopes³,⁴, Francesco Brancati⁵,⁶, Andreas Kispert⁷, Madeline A Lancaster¹, Andrew M Schlossman¹, Edgar A Otto⁸,⁹, Michael Leitges¹⁰, Hermann-Josef Gröne¹¹, Irma Lopez¹², Harini V Gudiseva¹³, John F O’Toole⁶,⁹, Elena Vallespin¹⁴, Radha Ayagari¹⁵, Carmen Ayuso¹⁴, Franz P M Cremer¹⁵, Anneke I den Hollander¹⁶, Robert K Koenekoop¹², Bruno Dallapiccola¹⁷, Gian Marco Ghigeri², Friedhelm Hildebrandt⁵,⁹, Enza Maria Valente⁵,¹⁸, David S Williams⁵,⁶ & Joseph G Gleeson¹

*Nat Genet 2010*

**NEXT GENERATION SEQUENCING:**
- targeted gene resequencing
- whole exome sequencing

[Diagram of the sequencing process]
Ciliopathy genes targeted resequencing project @ Mendel Inst.

NGS-based target resequencing of **all known** plus **few candidate primary ciliopathy-related genes**, to better define:
- the spectrum of JS-causative genes
- the correlations between genes/genotypes and phenotypes
- the role of genetic modifiers

**Experimental design:**
- ~100 genes in two panels (exons+splice junctions+UTR): ~ 750Kb
- Solid 5500xL (LifeTechnologies)
- pools of 24 samples per lane: up to 288 samples in a single run
- costs: ~400 € per sample
- mean coverage: 300x
- mean % of bases with at least 20x coverage: 95%
- mean % of not covered bases: <1.5%
Proportion of pathogenic mutations in each gene

- **non mutated**: 54%
- **others**: 4%
- **TMEM67**: 6%
- **AHI1**: 6%
- **CEP290**: 7%
- **CC2D2A**: 7%
- **C5Orf42**: 7%
- **TMEM216**: 2%
- **RPGRIP1L INPP5E**: 3%
- **OFD1**: 2%
- **INPP5E**: 2%
- **TMEM216**: 2%
Genotype-phenotype correlates

**JS with liver involvement**
- TMEM67
- INPP5E
- CC2D2A
- RPGRIP1L
- others

**JS pure or with retinal involvement**
- AHI1
- TMEM216
- C5Orf42
- INPP5E
- CC2D2A
- others

**cerebello-oculo-renal phenotype**
- CEP290
- others

**OFDVI**
- C5Orf42
- OFD1
- others
Peculiar cases: coexistence of hom mutations in 2 distinct genes

**COR322**
- CEP290 p.R1622C hom (predicted deleterious by 3 software)
- OFD1 p.Q870Lfs*1 hemi (truncating mutation)

- polydactyly of four hands and feet
- cleft palate
- situs inversus
- dysmorphisms (hypertelorism, low set ears)
- neonate, no information regarding retina or kidney involvement

**COR072**
- AHI1 p.W443D hom (predicted deleterious by 4 software)
- BBS4 p.V202G hom (predicted deleterious by 3 software)

- leber congenital amaurosis
- mild dysmorphic features
- no other reported organ abnormalities
Heterozygous rare variants and frequency comparison

Selection criteria:
- MAF <0.01 or absent
- nonsense, splicing, frameshift, missense non synonymous predicted as pathogenic by at least one prediction software
- not present in internal controls

Heterozygous rare variants (novel or with MAF < 0.01) were found in several JS and non-JS genes → do they contribute to the mutational load in JS?
A final word on JS nomenclature...

Visual Diagnosis

Molar Tooth Sign Is Not Pathognomonic for Joubert Syndrome

Mehmet Alp Dirik MD a, Uluç Yiş MD b,*, Eray Dirik MD c

patient with OFDVI!!!

disease. Molar tooth sign is not pathognomonic for Joubert syndrome and may be seen in cerebello-oculo-renal syndrome, Dekaban-Arima syndrome, COACH syndrome, Malta syndrome, Senior Loken syndrome, and Varadi-Papp syndrome. Clinical and neuroradiologic findings in our pa-
Acronyms of JSRD

**Joubert syndrome (JS)**
- neurological features, MTS
- ± postaxial polydactily
- ± encephalocele
- ± posterior fossa cyst

**Dekaban-Arima syndrome (DAS)**
- neurological features, MTS
- Leber congenital amaurosis
- cystic dysplastic kidneys
- ± coloboma
- ± postaxial polydactily

**COACH and Gentile syndromes**
- neurological features, MTS
- hepatic fibrosis
- ± coloboma
- ± renal disease

**Varadi-Papp syndrome (OFD VI)**
- neurological features, MTS
- midline orofacial dysplasia
- polydactyly, Y-shaped central metacarp
- ± hypothalamic hamartoma
- ± periventricular nodular heterotopia
- ± congenital heart disease

**Senior-Loken syndrome**
- Leber congenital amaurosis
- nephronophthisis
- ± neurological features, MTS

**MALTA syndrome**
- neurological features, MTS
- encephalocele
- hydrocephalus
- renal cystic disease
- ± coloboma
- ± retinal dystrophy

**JS + polymicrogyria**
- neurological features, MTS
- cortical polymicrogyria

**MARSH syndrome**
- neurological features, MTS
- white matter cysts
- renal cysts

**JS + nephronophthisis**
- neurological features, MTS
- nephronophthisis

**Gleeson et al, AJMG 2004**
a first attempt to reclassify JS based on clinical features

<table>
<thead>
<tr>
<th>Clinical subtypes</th>
<th>Mandatory features</th>
<th>Preferentially associated features*</th>
<th>Previously used nosology</th>
<th>Major gene(s)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Joubert syndrome (JS)</td>
<td>MTS</td>
<td></td>
<td>JS</td>
<td></td>
</tr>
<tr>
<td>JS with ocular defect (JS-O)</td>
<td>MTS</td>
<td>Retinal dystrophy (including LCA)</td>
<td>JS type B</td>
<td>AHI1</td>
</tr>
<tr>
<td>JS with renal defect (JS-R)</td>
<td>MTS</td>
<td>NPH</td>
<td></td>
<td>NPHP1</td>
</tr>
<tr>
<td>JS with oculorenal defects (JS-OR)</td>
<td>MTS</td>
<td>Retinal dystrophy (often LCA)</td>
<td>SLS plus MTS</td>
<td>CEP290</td>
</tr>
<tr>
<td>JS with hepatic defect (JS-H)</td>
<td>MTS</td>
<td>Colobomas</td>
<td>COACH s.</td>
<td>TMEM67</td>
</tr>
<tr>
<td>JS with orofaciiodigital defects (JS-OFD)</td>
<td>MTS</td>
<td>Lobulated/bifid tongue (incl. hamartomas) Polydactyly</td>
<td>Váradi-Papp s.</td>
<td>TMEM216 (2 patients only)</td>
</tr>
</tbody>
</table>

Brancati et al, Orphanet J Rare Dis 2010
Shall we simply call «Joubert syndrome» all MTS-related disorders?

However, increasing evidence suggests that the variable clinical manifestations associated with the molar tooth sign do not comprise distinct clinical syndromes, but are rather part of the wide phenotypic range that is characteristic of Joubert syndrome. In view of the emerging genetic complexity of this disorder, the distinction between Joubert syndrome and “Joubert syndrome and related disorders” now seems to be blurred and does not contribute to the diagnostic definition of patients (which is simply based on the presence of the molar tooth sign), and simultaneously creates confusion, especially for families. For these reasons, we propose to abandon the term “Joubert syndrome and related disorders” in favour of the classic term “Joubert syndrome” to encompass all molar tooth sign-related disorders, and to adopt a descriptive classification that defines the disease’s clinical subgroups on the basis of the extent of organ involvement (figure 3).