Bardet-Biedl syndrome

Prof. Hélène Dollfus

Service de Génétique Médicale,
Hôpital de Hautepierre,Strasbourg

France

ERKNet
The European
Rare Kidney Disease
Reference Network

Dr. Jens König

Pediatric Children‘s hospital
Münster

Germany

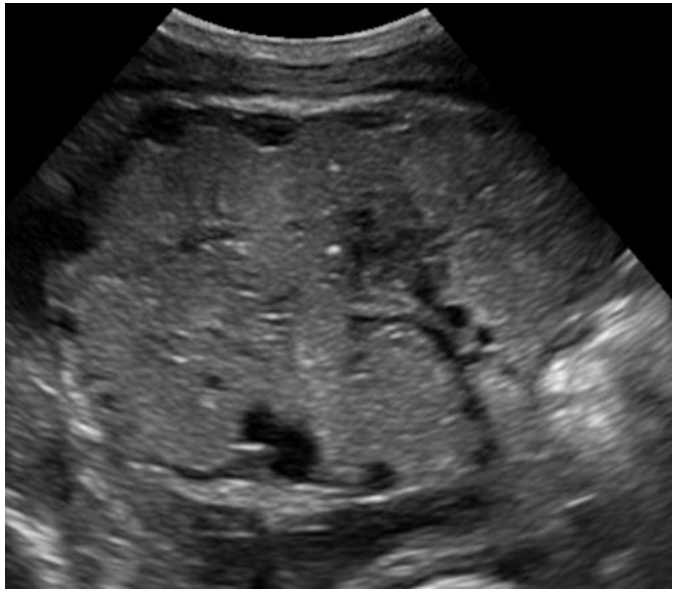
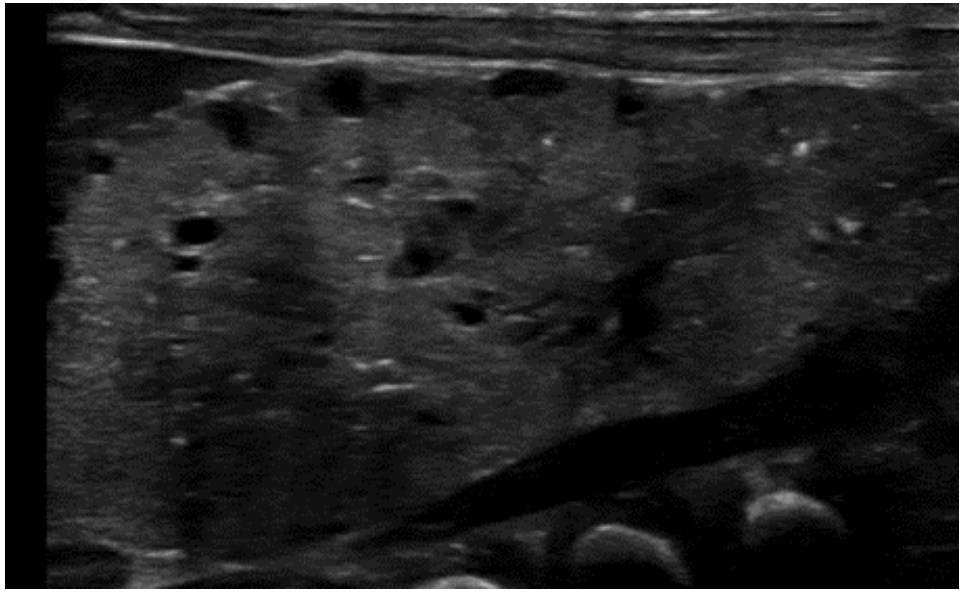
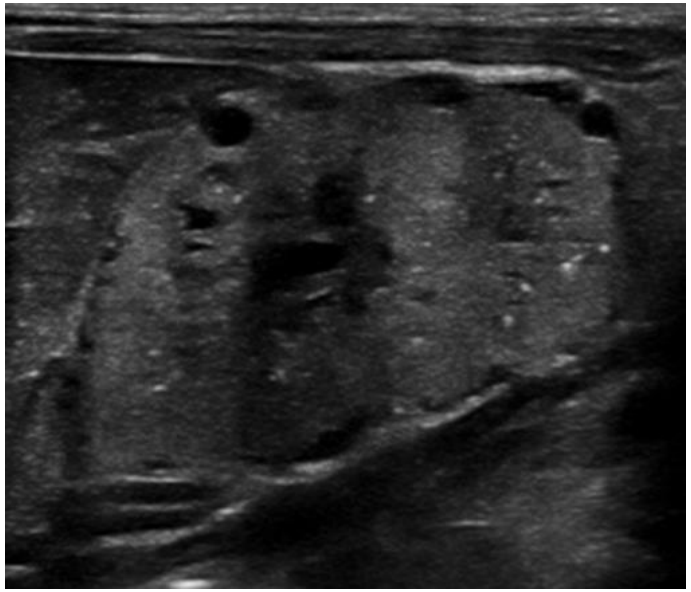
„Referral of the day“

- Early born boy out of 36+0 gestational weeks
  - birth weight 2275 g, length 44 cm
  - APGAR 5/6/10
  - oligoahydramnious since 26th week of gestation
  - polycystic kidneys

- original plan: palliative care owing to an expected lung hypoplasia caused by early oligohydramnious and polycystic kidney disease

- referral after 15 hours of life:
  - no need for ventilation
  - first urine production observed after 22 hours of life, spontanously increasing to 2.5 ml/kg/h

Ultrasound presentation – „most likely ARPKD“

- bilateral enlarged hyperechogenic kidneys: volume 21ml/ 23ml
- blurred medullo-cortical differentiation
- multiple macro- and microcystic lesions in the cortex and medulla

First doubts arising after a few days

- no arterial hypertension
- ultrasound appearance not quite ARPKD-typical

- …and then there was this additional hint →

hexadactyly on right foot

← homozygous truncating variant in BBS12 gene (p.Arg386*)

Ali, 2.5 years of age

- CKD IV
  - eGFR 24 ml/min/1.73 m^2
  - polydipsia of >1500 ml/day
- reduced vision. 0.3-0.4 binocular
- BMI 19.5 kg/m^2 (+2.2 SDS_{LMS})
- muscular hypotonia
- delayed motoric and speech development

Bardet Biedl syndrome – etiology

- Rare inherited disorder
- Autosomal recessive inheritance
- Affecting multiple organs and systems
- Frequency varies
  - 1:120.000-1:160.000 in North America and Europe *
  - 1:13.500 - 1:36.000 in Bedouins and mixed Arab population **
  - 1:3.700 in Faroe Islands ***

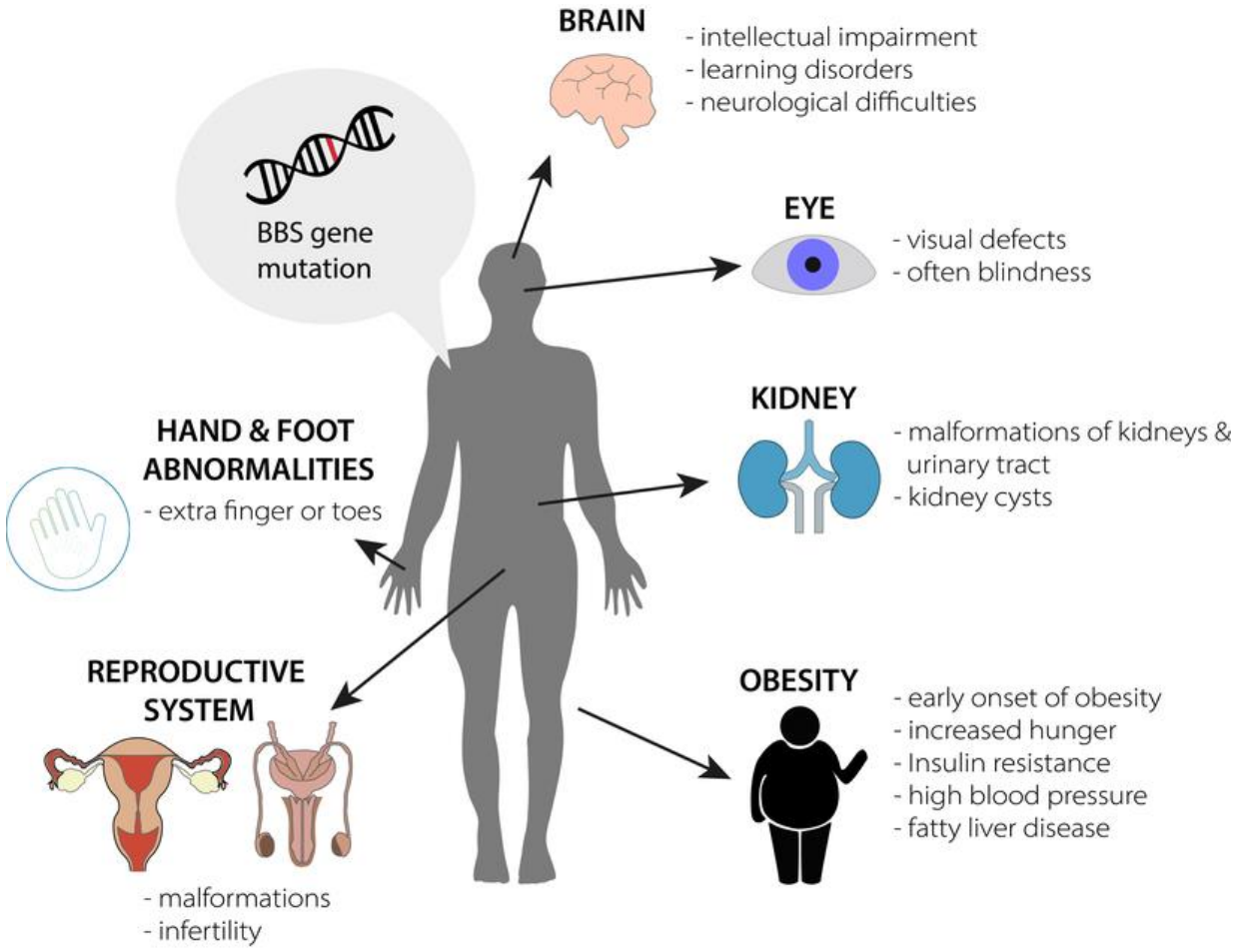
Arthur Biedl
(1869-1933)

George Bardet
(1885-1966)

Clinical diagnosis

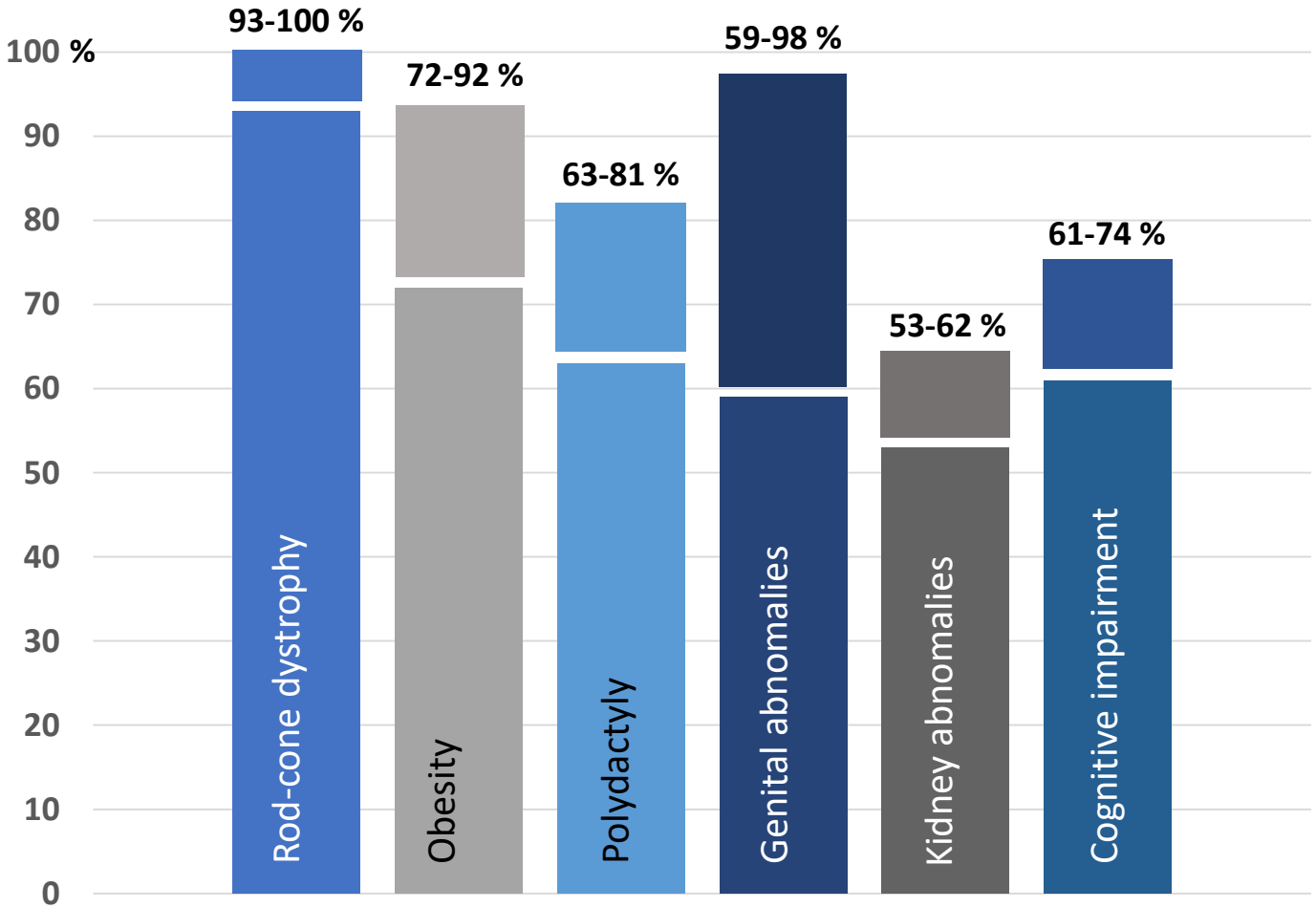
- Clinical criteria published by *Beales et al.*
- Diagnosis requires the presence of either at least 4/6 primary features or 3 primary and two secondary features

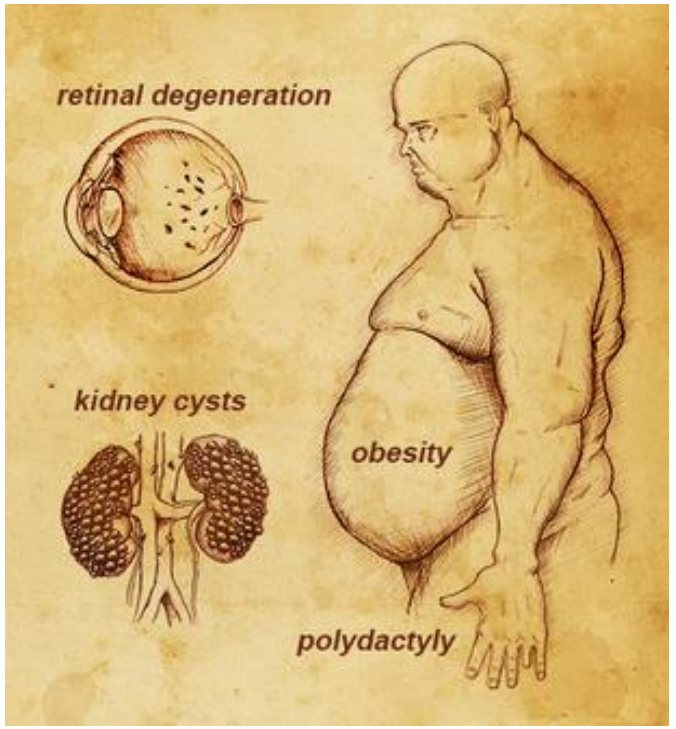
Primary Diagnostic Features	Secondary Diagnostic Features	Described BBS Features Non Included in the Diagnostic Criteria
Retinal Degeneration	Strabismus, cataracts, and astigmatism	Cutaneous Dermatoses
Obesity	Metabolic/endocrine abnormalities (metabolic syndrome, subclinical hypothyroidism, polycystic ovary s.)	Hearing loss
Postaxial polydactyly	Brachydactyly/syndactyly	Asthma
Renal Anomalies	Anosmia/olfactory dysfunction	Dysregulated immune and hematopoietic systems
Learning Disabilities	Neurodevelopmental abnormalities (developmental delay, speech delay, epilepsy, behavioral disturbances, ataxia/poor coordination, mild spasticity)	Musculoskeletal abnormalities
Hypogonadism and Genitourinary Abnormalities	Liver and other gastrointestinal diseases (Hirschsprung disease, inflammatory bowel disease, celiac disease)	
	Cardiovascular and thoraco-abdominal abnormalities	



Beales PL, et al.J Med Genet. 1999 Jun;36(6):437-46.

Frequency of primary features in BBS

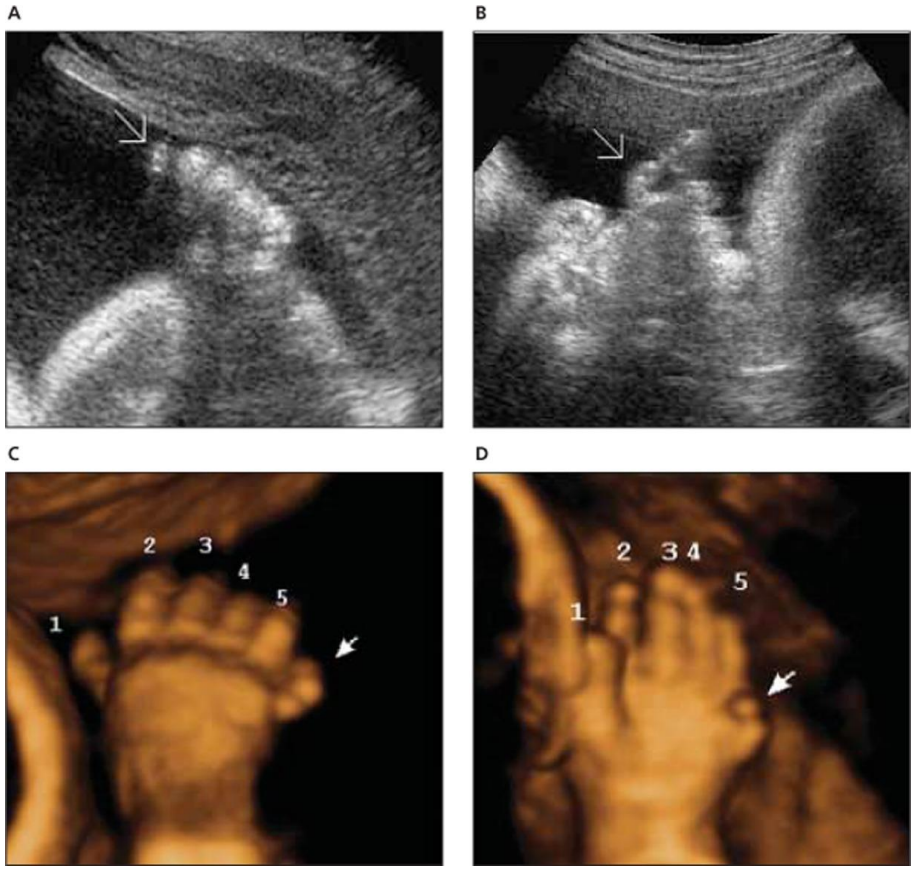




Forsythe, Beales, European Journal of Human Genetics (2013) 21, 8–13

Early signs/ suspicion for BBS

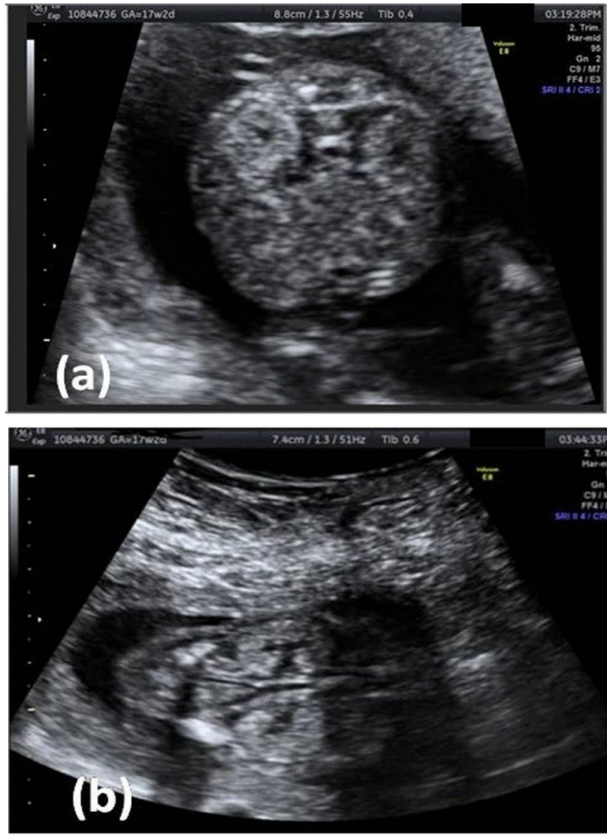
prenatal polydactyly



Hun Zun et al.; JUM 2007.26.4.529

&

hyperechogenic kidneys +/- cysts



Sablok et al.; Journal of Fetal Medicine 2020

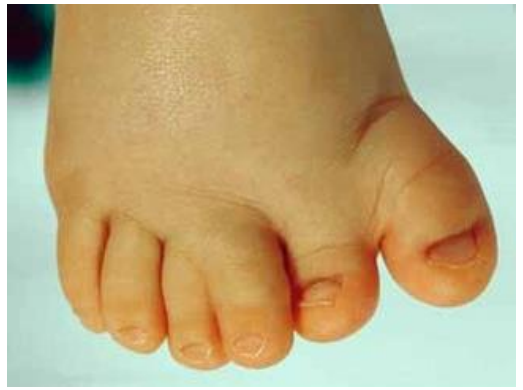
Sceletal abnormalities

- polydactyly overall 63-81%
  - all 4 limbs 21%
  - only hands 8%
  - only feet 21%
- brachydactyly 46%
- syndactyly 8%

  (usually 2. &3. toe)

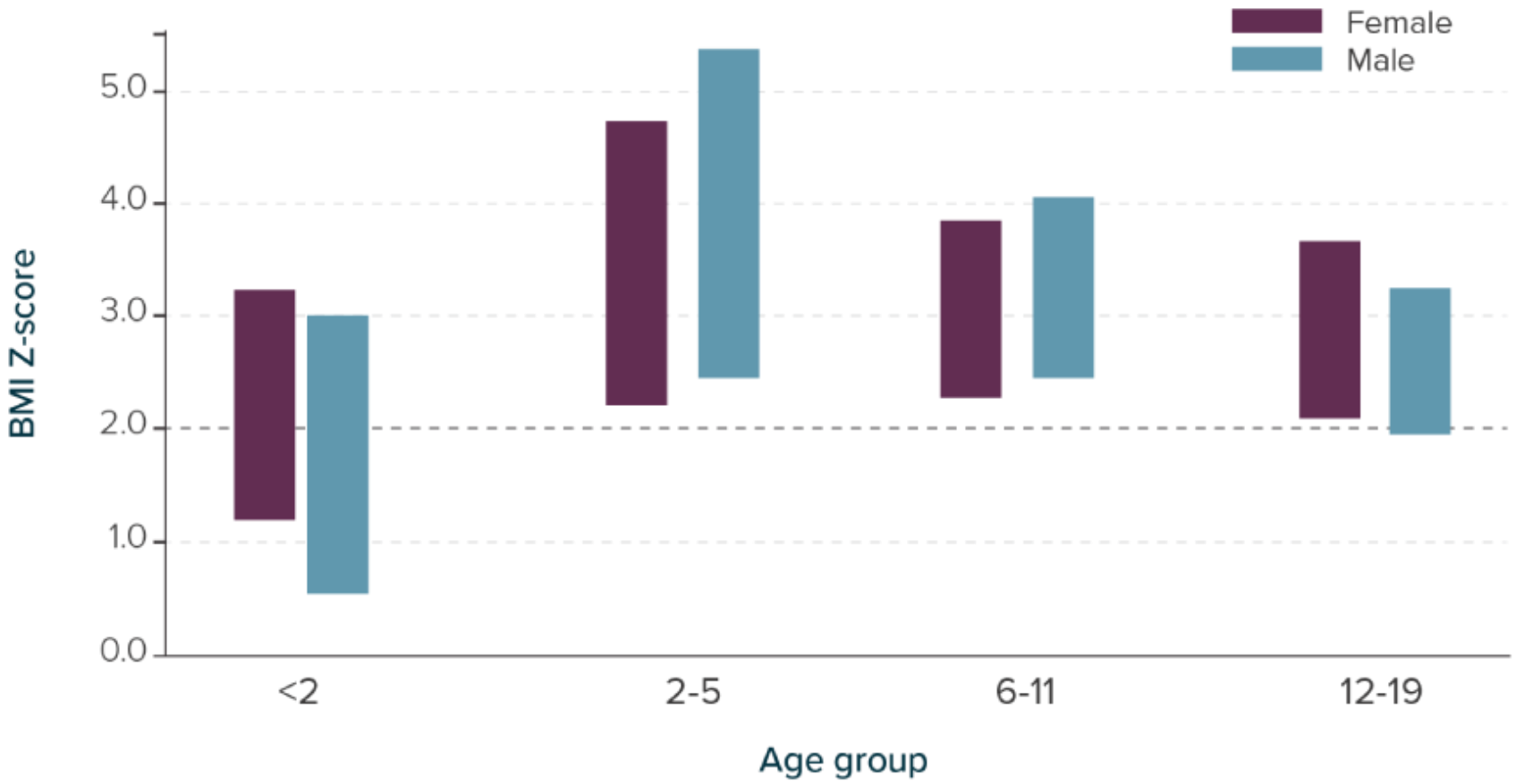
polydactyly

brachydactyly

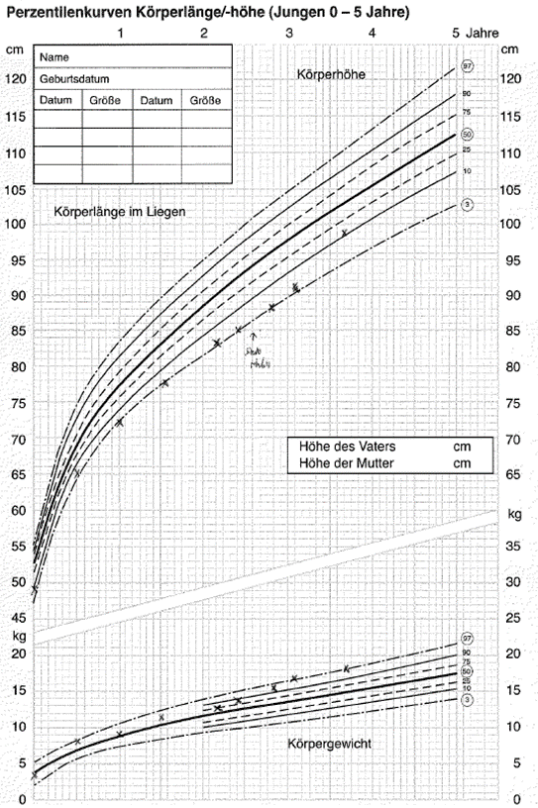


syndactyly

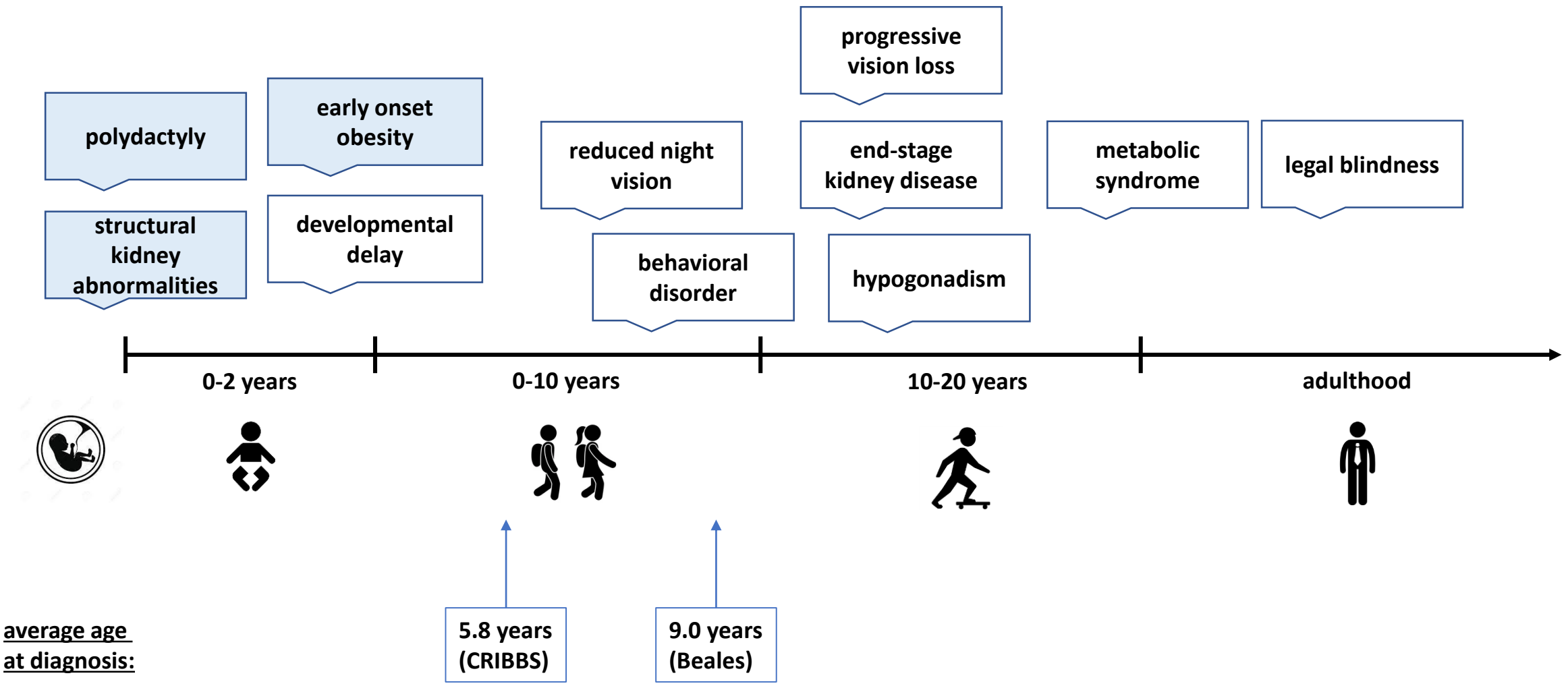
Early developing obesity



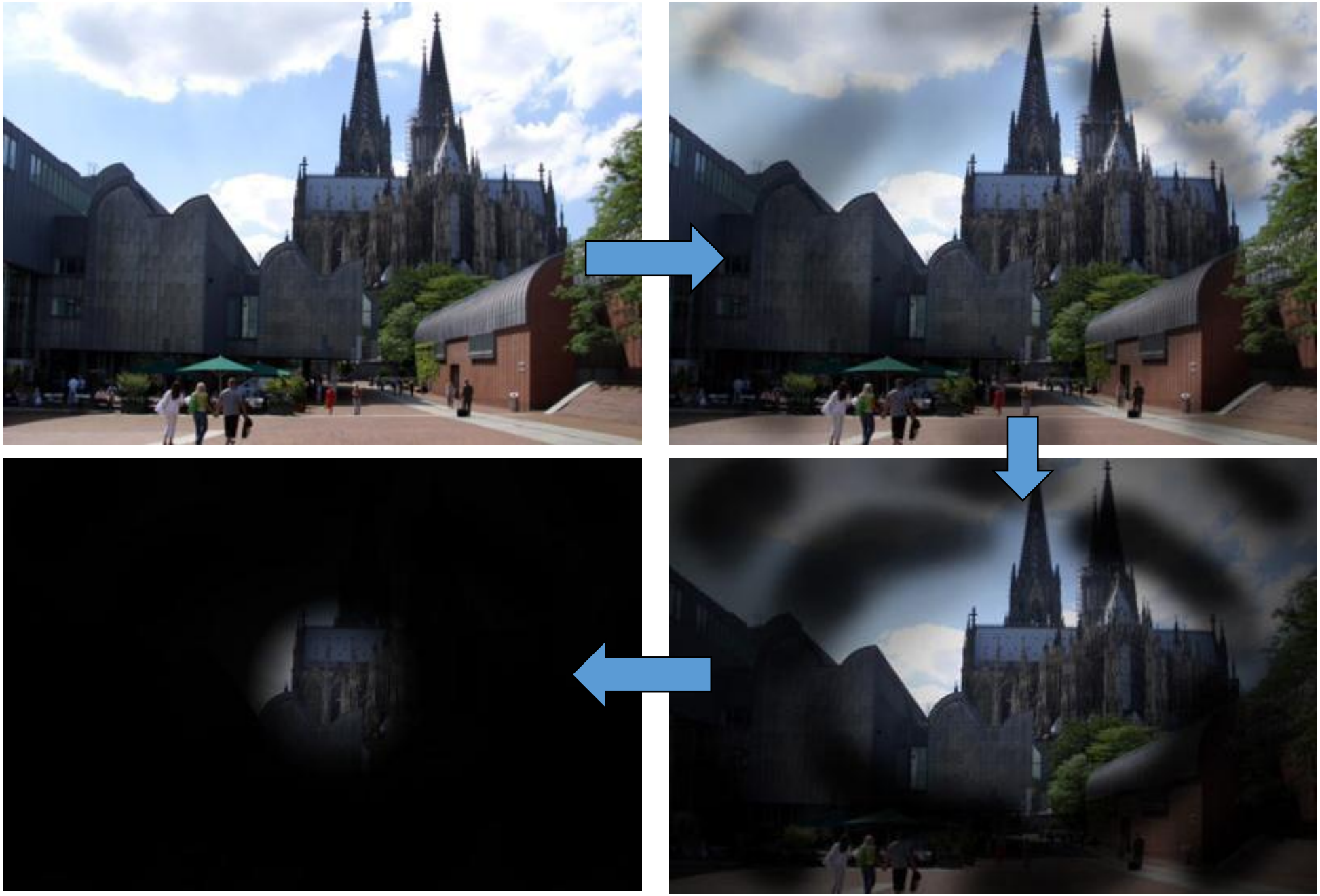
Adapted from Pomeroy et al. *Pediatric Obesity*. 2020.



Full clinical spectrum develops over time



Retinopathy (100%)



(http://www.pro-retina.de
/simulation/retinitis-pigmentosa)

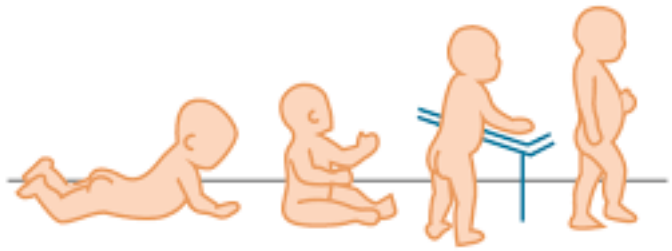
Developmental delay (66%) & behavioral abnormalities (33%)

Developmental delay:

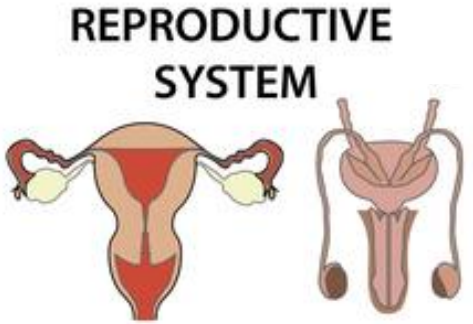
- often global
- sometimes specific for some areas
  - motor
  - language
- speech delay usually responds well to speech therapy

Behavioral abnormalities:

- obsessive, compulsive and ritualic behaviour
- anxiety
- emotional immaturity
- disinhibition
- hyperactivity
- depression



Reproductive system (59%)



males: ♂

- cryptorchism
- micropenis
- small volume testes

females: ♀

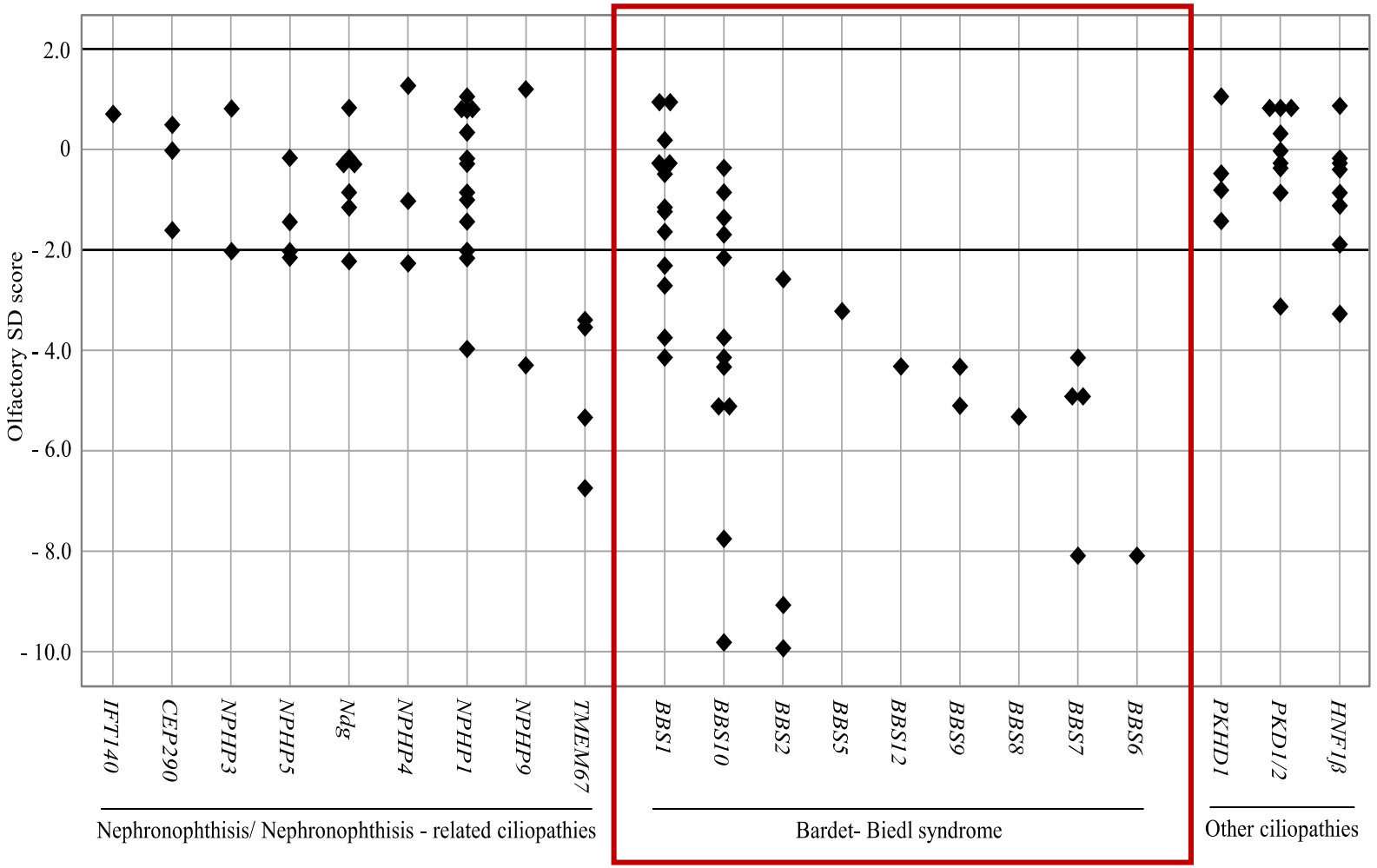
- malformed uterus
- irregular menstrual cycle
- polycystic ovaries

reproduction

- generally difficult, but reports of some who gave birth to children

(♀ >♂)

Hyposmia/Anosmia (50%)

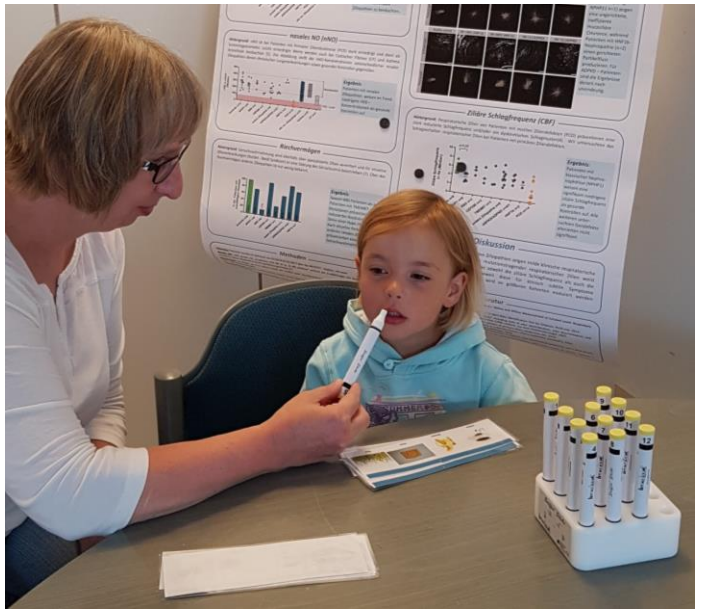


ORIGINAL RESEARCH

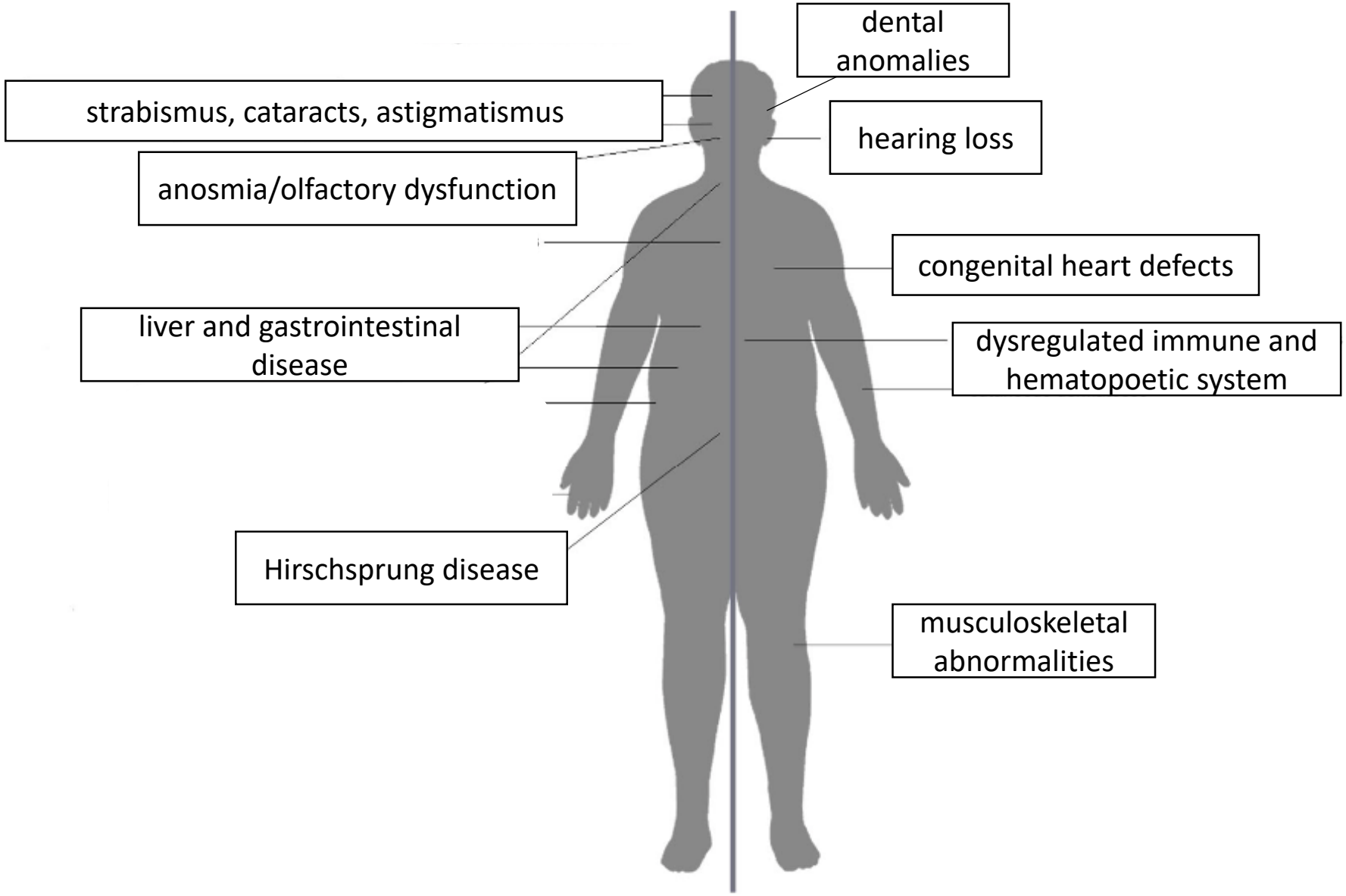
Systematic evaluation of olfaction in patients with hereditary cystic kidney diseases/renal ciliopathies

Mareike Dahmer-Heath,[1] Valentin Schriever,[2] Sabine Kollmann,[1] Carolin Schleithoff,[1] Andrea Titieni,[3] Metin Cetiner,[4] Ludwig Patzer,[5] Burkhard Tönshoff,[6] Matthias Hansen,[7] Petra Pennekamp,[1] Joachim Gerß,[8] Martin Konrad,[1] Jens König [1]

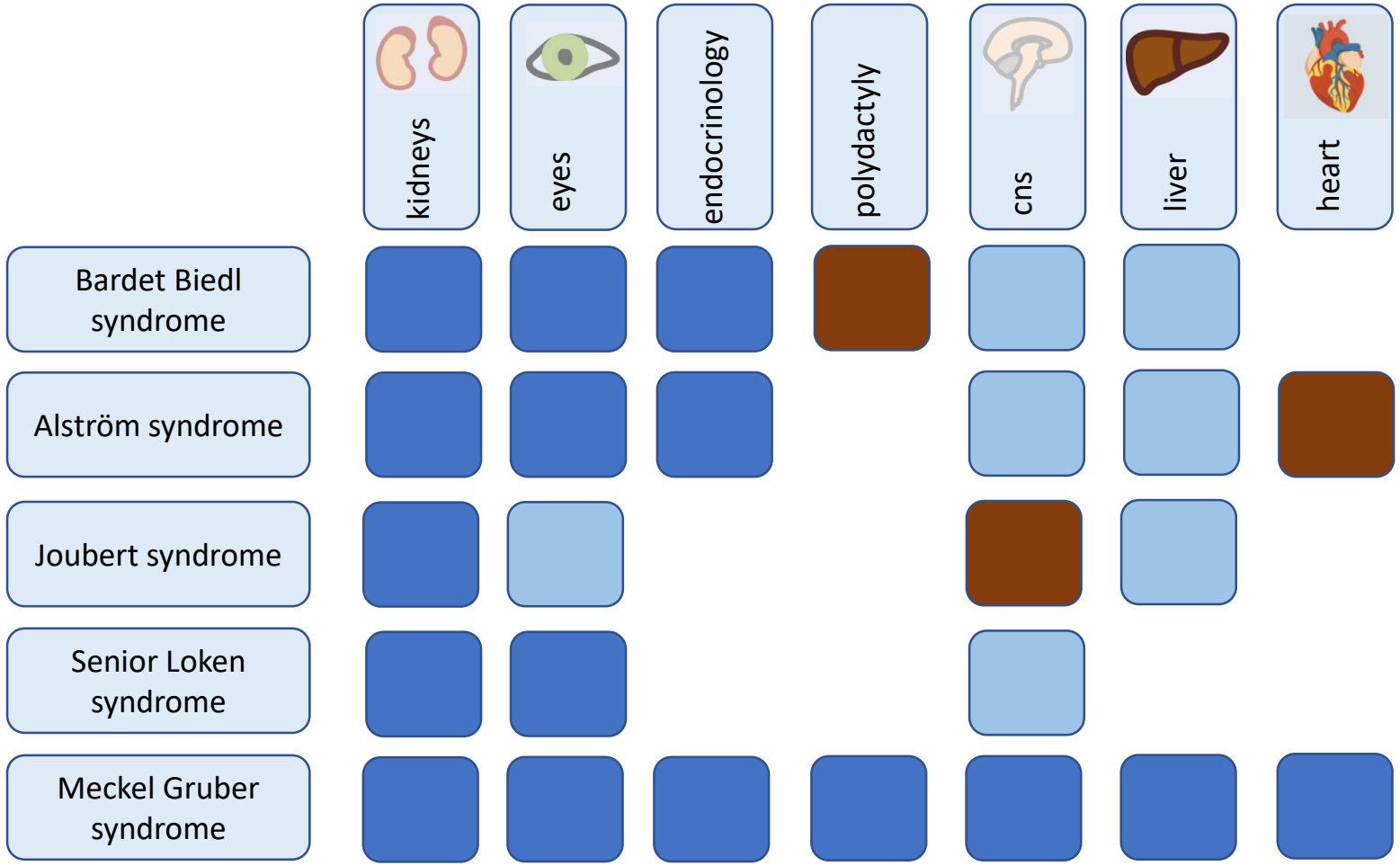
(J Med Genet. 2020 Sep 11;jmedgenet-2020-107192.)



Secondary features (59%)



Clinical overlap with other syndroms



modified Titieni, König; Med. Genetik 2018

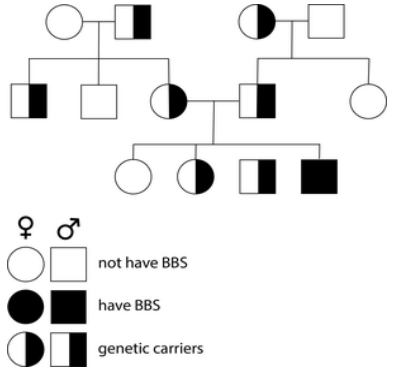
Genetic confirmation required

Genetic background

variants in up to least 26 BBS genes

Gene	Name	Chromosomal Coordinate	Localization of the Protein in the Cell	Tissue Specificity	Protein Function
BBS1	Bardet-Biedl syndrome 1	11q13.2	Cilium and basal body	Low	Component of BBSome complex
BBS2	Bardet-Biedl syndrome 2	16q13	Cilium and basal body	Low	Component of BBSome complex
BBS3/ARL6	Bardet-Biedl syndrome 3/ ADP ribosylation factor like GTPase 6	3q11.2	Cilium, basal body, transition zone and cytosol	Low	GTP-binding protein involved in ciliary trafficking[146]
BBS4	Bardet-Biedl syndrome 4	15q24.1	Cilium and basal body	Low	Component of BBSome complex
BBS5	Bardet-Biedl syndrome 5	2q31.1	Basal body	Low	Component of BBSome complex
BBS6/MKKS	Bardet-Biedl syndrome 6/ MKKS centrosomal shuttling protein	20p12.2	Cilium and basal body	Low	Chaperonin like protein assisting BBSome formation
BBS7	Bardet-Biedl syndrome 7	4q27	Cilium and basal body	Low	Component of BBSome complex
BBS8/TTC8	Bardet-Biedl syndrome 8/ tetratricopeptide repeat domain 8	14q31.3	Cilium, IFT and basal body	Low	Component of BBSome complex
BBS9	Bardet-Biedl syndrome 9	7p14.3	Cilium	Low	Component of BBSome complex
BBS10	Bardet-Biedl syndrome 10	12q21.2	Basal body	Low	Chaperonin like protein assisting BBSome formation
BBS11/TRIM32	Bardet- Biedl syndrome 11- tripartite motif containing 32	9q33.1	Intermediate filaments	Low	E3 ubiquitin ligase; it promotes degradation of several targets[147]
BBS12	Bardet-Biedl syndrome 12	4q27	Basal body	Low	Chaperonin like protein assisting BBSome formation
BBS13/MKS1	Bardet-Biedl syndrome 13/MKS transition zone complex subunit 1	17q22	Basal body	Low	Component of the tectonic-like complex localized at the transition zone of primary cilium[148]
BBS14/CEP290	Bardet-Biedl syndrome 14/centrosomal protein 290	12q21.32	Basal body and centrosome	Low	Centrosomal protein involved in primary cilium formation[149]
BBS15/WDPCP	Bardet-Biedl syndrome 15/WD repeat containing planar cell polarity effector	2p15	Cytosol, axoneme and plasma membrane,	Low	Controls ciliogenesis[150]

Gene	Name	Chromosomal Coordinate	Localization of the Protein in the Cell	Tissue Specificity	Protein Function
BBS16/SDCCAG8	Bardet-Biedl syndrome 16/SHH signaling and ciliogenesis regulator SDCCAG8	1q43-q44	Basal body, transition zone and centriole	Low	Involved in ciliogenesis and Sonic Hedgehog signaling pathway
BBS17/LZTFL1	Bardet-Biedl syndrome 17/leucine zipper transcription factor like 1	3p21.31	Cilium and basal body	Mainly in lymphoid tissue	Regulator of BBSome trafficking and Sonic Hedgehog signalling[151]
BBS18/BBIP1	Bardet-Biedl syndrome 18/BBSome interacting protein 1	10q25.2	Cytosol	Mainly in testis	Component of BBSome complex
BBS19/IFT27	Bardet-Biedl syndrome 19/intraflagellar transport 27	22q12.3	Cilium, IFT and basal body	Low	Intraflagellar trafficking (IFT-B) component[151]
BBS20/IFT172	Bardet-Biedl syndrome 20/ intraflagellar transport 172	2p23.3	Vesicles	Low	Intraflagellar trafficking (IFT-B) component[152]
BBS21/ CFAP418/ C8orf37	Bardet-Biedl syndrome 21/ cilia and flagella associated protein 418	8q22.1	Basal body and ciliary root	Low	Unknown[153]
BBS22/IFT74	Bardet-Biedl syndrome 22/ intraflagellar transport 74	9p21.2	Cilium, IFT and basal body	Low	Intraflagellar trafficking (IFT-B) component[152]
CEP19	Centrosomal protein 19	3q29	Centrosome	Low	Recruits the RABL2B GTPase to the ciliary base and intraflagellar transport (IFT) complex B[154]
NPHP1	Nephrocystin 1	2q13	Transition zone	Mainly in skeletal muscle	Cell-matrix signaling at focal adhesions[155]
SCAPER	S-phase cyclin A associated protein in the ER	15q24.3	Endoplasmic reticulum and ciliary tip	Low	Ciliary dynamics and disassembly[156]
SCLT1	Sodium channel and clathrin linker 1	4q28.2	Centriole	Low	Component of distal appendages which anchor the cilium to the plasma membrane, involved in ciliogenesis[157]



- *BBS1-BBS18* account for 70-80% of cases
- *BBS1, BBS2* and *BBS10* make up for 50% in western countries

Genetic background

BBS1, BBS2 and BBS10 most frequently effected

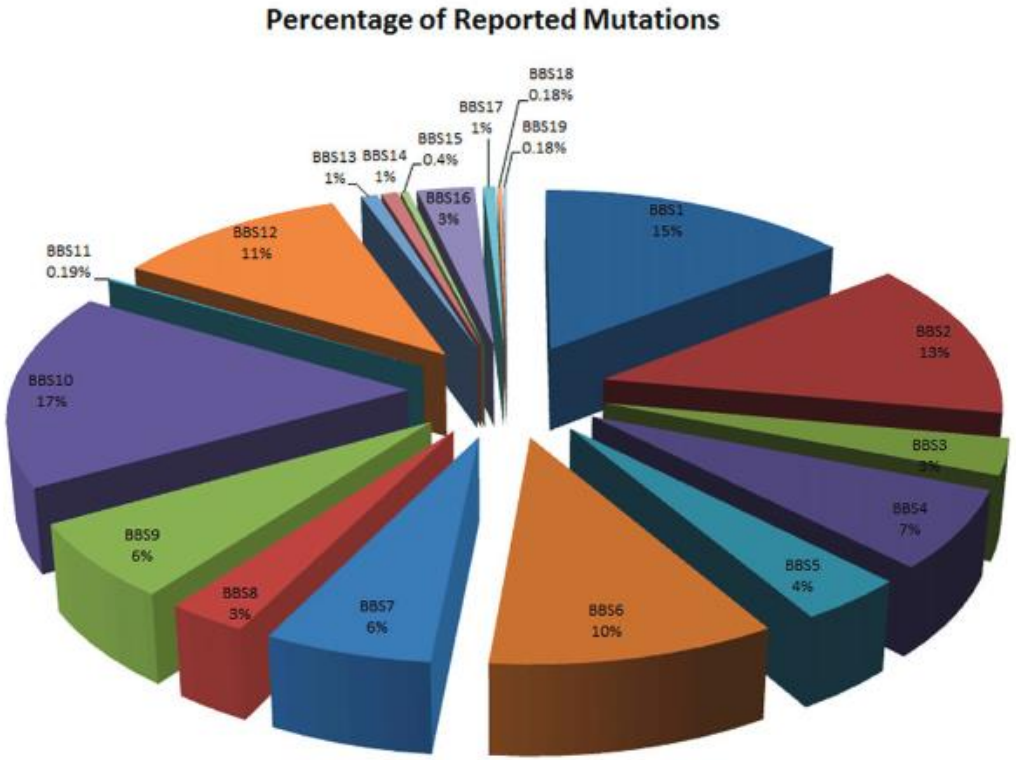


Table 2. Number of reported mutations in BBS genes causing BBS phenotypes

			Type of mutation			
BBS gene	OMIM	Reported mutations	Missense/ nonsense	Splicing	Deletions and insertions	Complex rearrangements
BBS1	209901	76	37	19	18	2
BBS2	606151	70	42	13	15	–
ARL6	608845	16	11	2	3	–
BBS4	600374	35	19	5	11	–
BBS5	603650	20	12	2	6	–
MKKS	604896	53	44	1	8	–
BBS7	607590	31	16	4	10	1
TTC8	608132	15	4	5	6	–
PTHB1	607968	34	16	6	11	1
BBS10	610148	87	53	1	43	–
TRIM32	602290	1	1	–	–	–
BBS12	610683	57	36	–	21	–
MKS1	609883	4	3	–	1	–
CEP290	610142	4	1	–	3	–
WDPCP	613580	2	1	1	–	–
SDCCAG8	613524	14	5	2	7	–
LZTFL1	606568	3	2	–	1	–
BBIP1	613605	1	1	–	–	–
IFT27	615870	1	1	–	–	–

Khan SA, et al. Clin Genet. 2016 Jul;90(1):3-15.

Dominating genotypes: BBS1, BBS10, BBS2

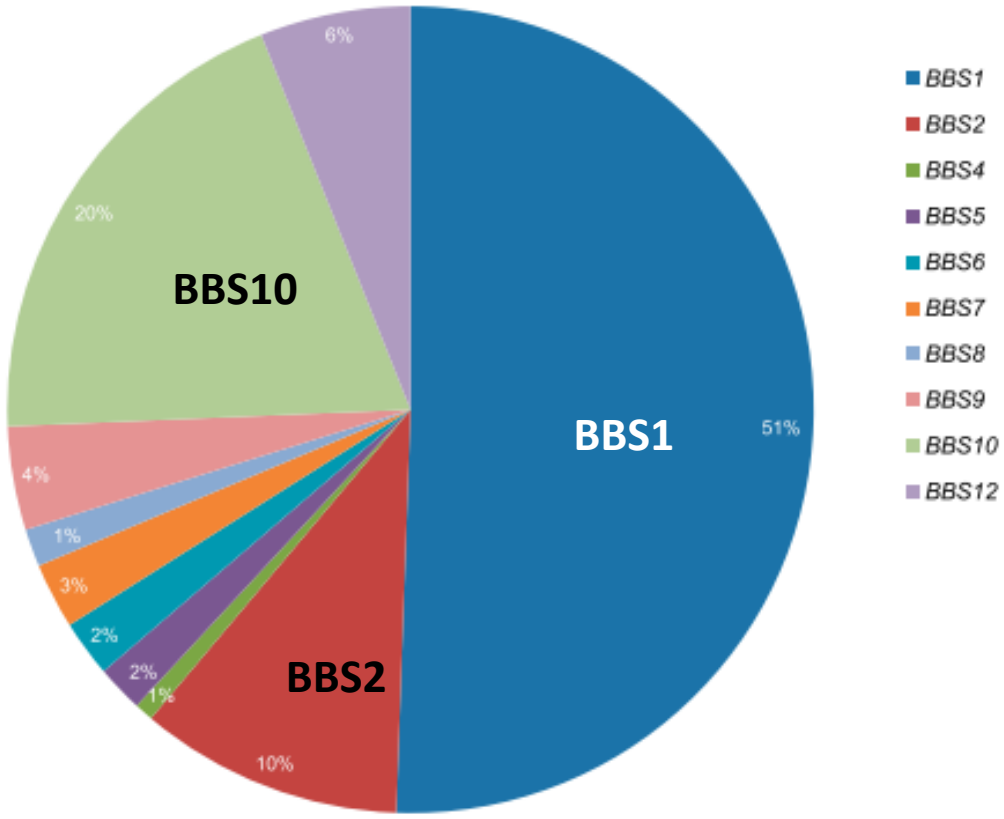


Figure 1. The *BBS1* genotype predominates in the UK population of patients with Bardet-Biedl syndrome followed by mutations in *BBS10* and *BBS2*. Distribution of genotypes.

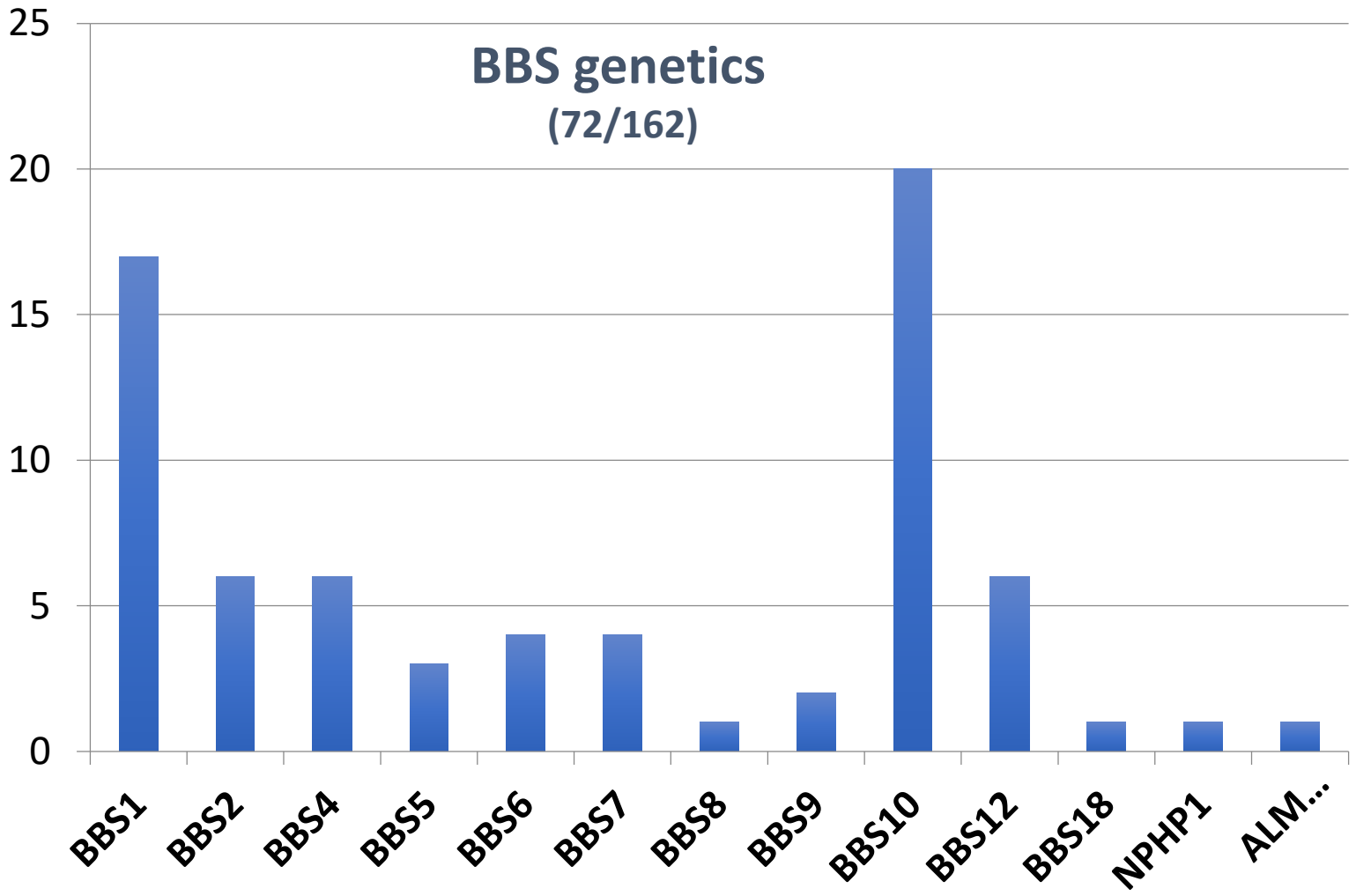
350 BBS patients from the UK (2010-2014)

- 54% male
- 46% female

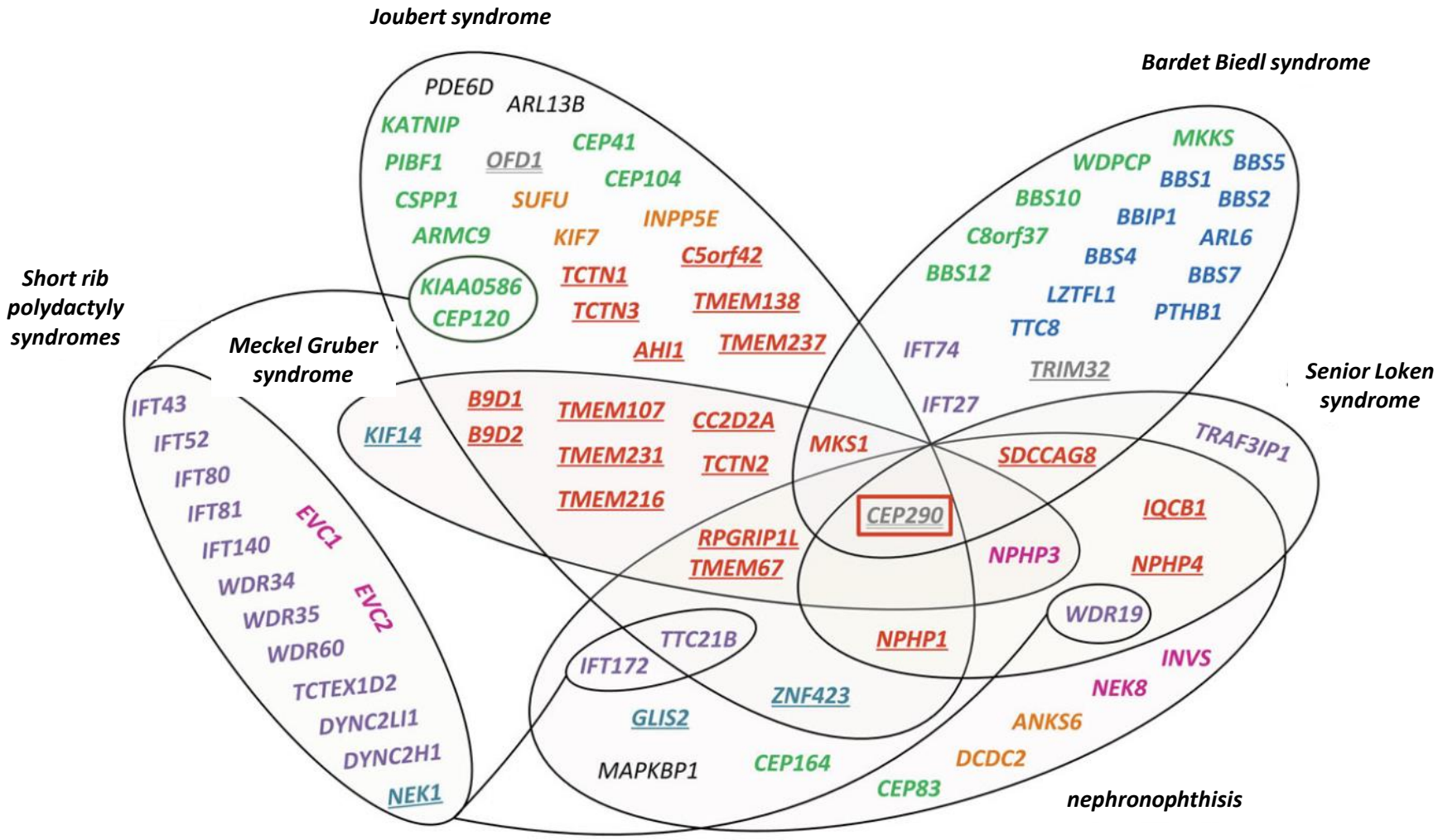
- genetic diagnosis in 256/350 patients

Forsythe E et al. J Am Soc Nephrol. 2017 Mar;28(3):963-970.

German NEOCYST cohort



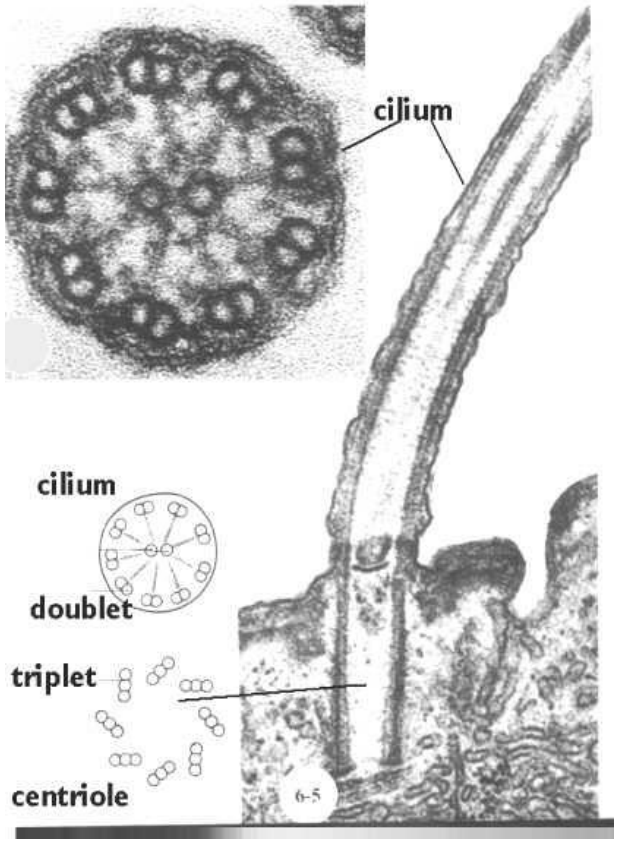
Also significant genetic overlap with other complex syndromes

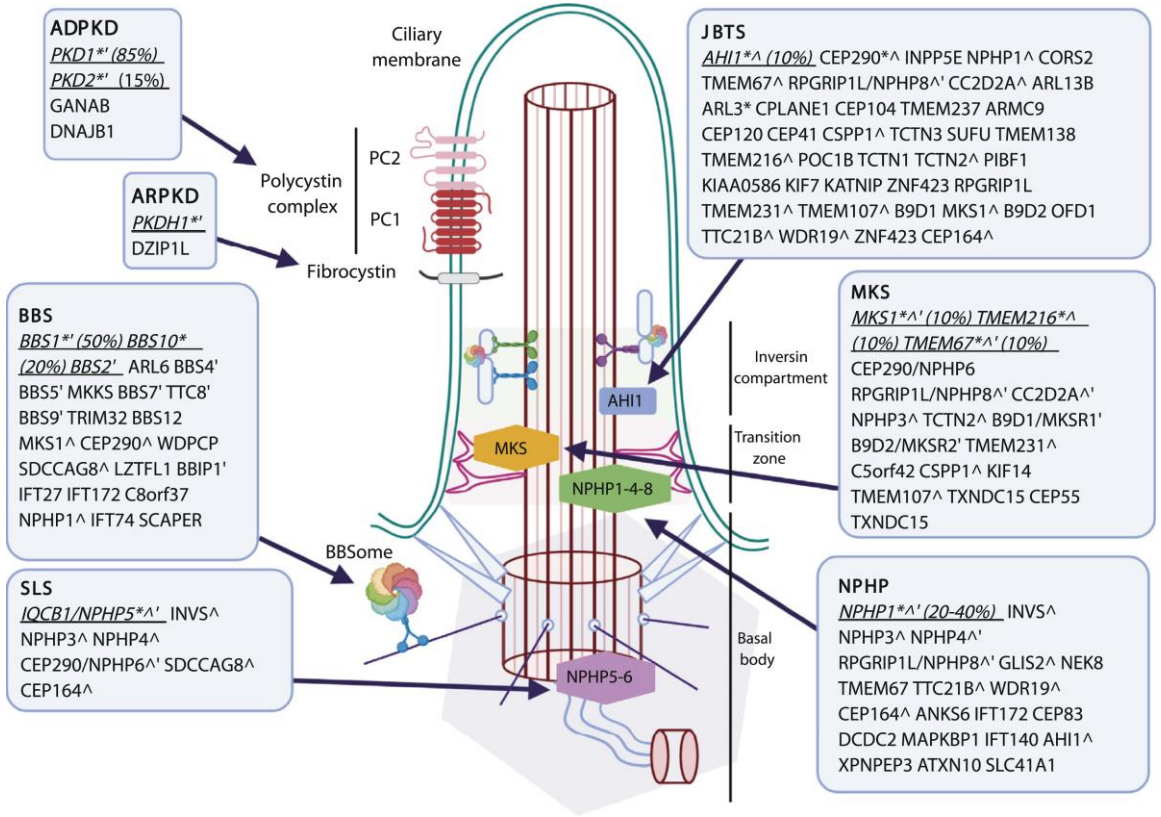


Titieni, König; Med. Genetik 2018

BBS – a model of non-motile ciliopathy

It has been shown that the genes involved in BBS encode proteins, that are responsible for the function or development of cilia.





McConnachie DJ, et al.. Am J Kidney Dis. 2021 Mar;77(3):410-419.

Physiological role of primary cilia (PC)

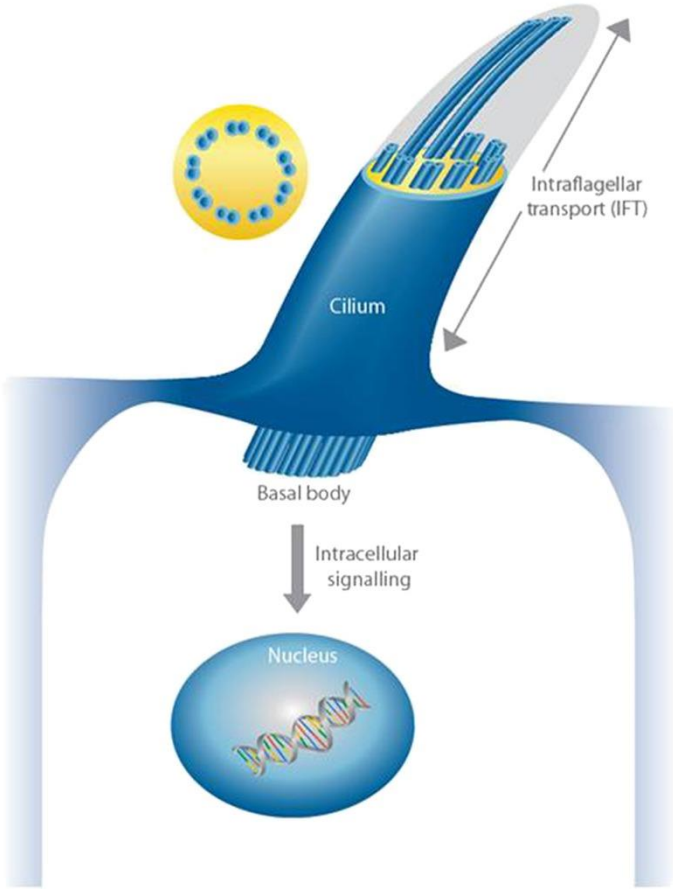
- PC transfer different stimuli from the extracellular milieu into the cell

- PC play a crucial role in several vital cellular functions including
  - cell division
  - polarity and
  - Metabolism

- PC structure consists of an microtuble-based axonema surounded by a ciliary membrane

- PC contains >600 proteins

- No evidence of protein synthesis within the cilia, thus…
- … ciliary proteins need to be transported into and out of the cilium by sophisticated transport mechanims

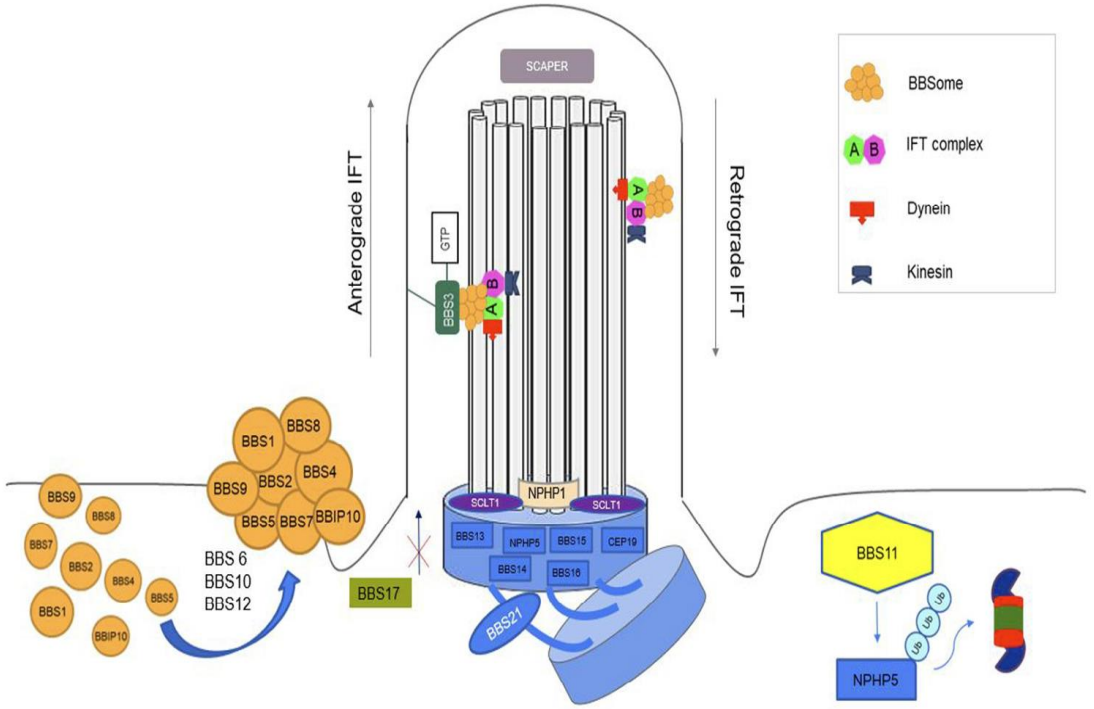


Melluso A, et al. Ther Clin Risk Manag. 2023 Jan 30;19:115-132.

Bergmann C; Pediatrics 2012

Role of BBS proteins for ciliary integrity

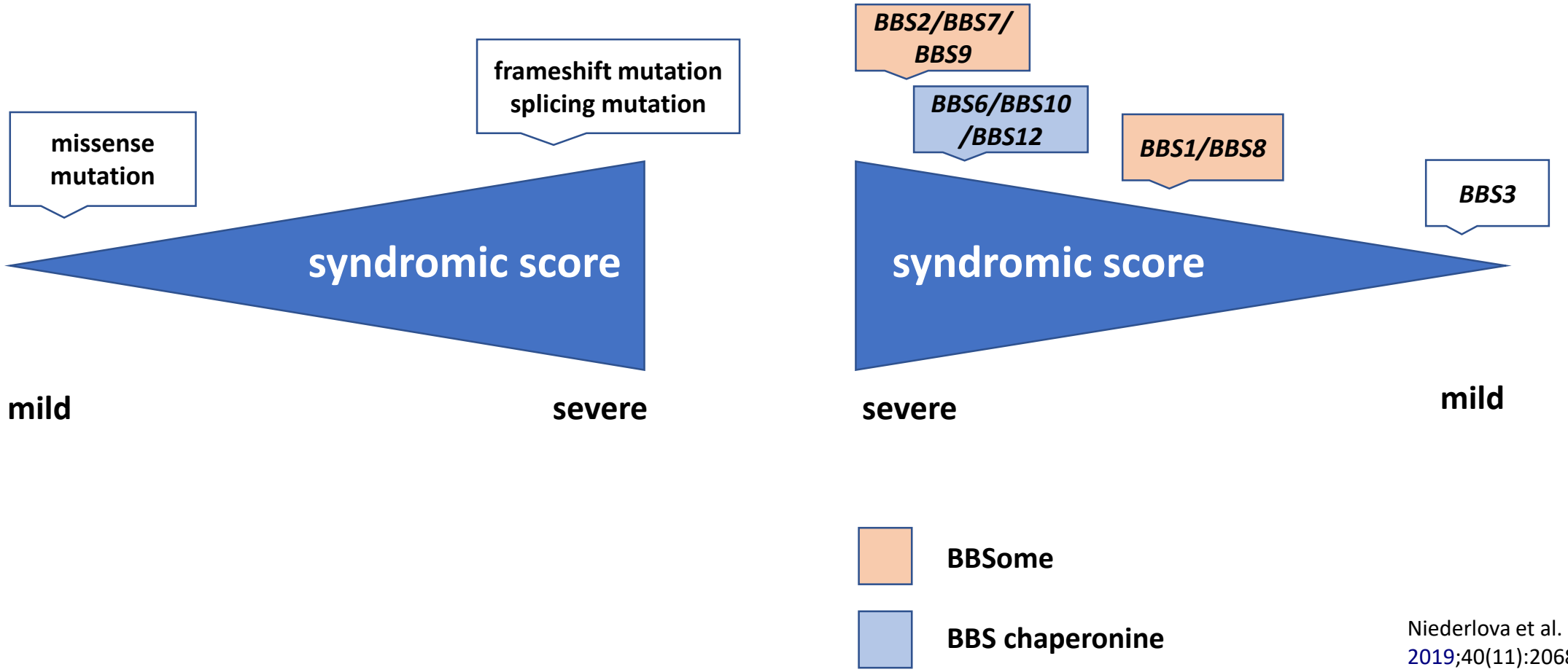
- **BBSome** complex is constituted by BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, BBIPI1.
- **BBSome regulates** molecule **traffiking to the ciliary membrane.**
- **Chaperone like proteins** BBS6, BBS10 and BBS12 assist in the assembly of the BBSome.
- **BBS3-GTPase** links the BBSome to intraflagellar transport.
- Link to **BBS17** keeps BBSome at the basal body level.
- Retrograde transport from tip to base mediated by IFT-A.
- Antegrade transport (base to tip) mediated by IFT-B complex including **BBS19 and BBS20.**
- **BBS11** favours protein ubiquitination.



- Melluso A, et al. Ther Clin Risk Manag. 2023 Jan 30;19:115-132.
- Novas R et al. FEBS Lett. 2015 Nov 14;589(22):3479-91.

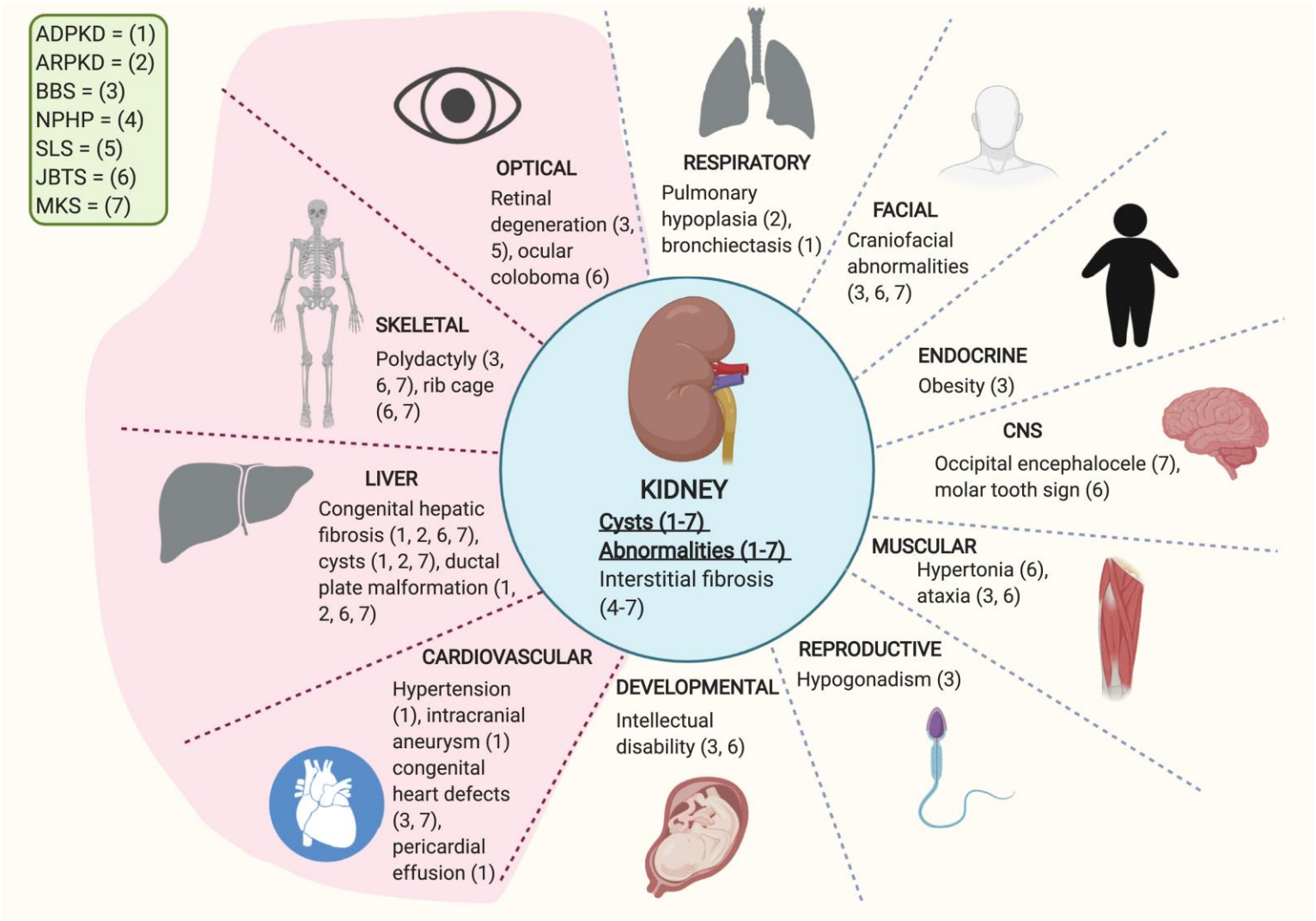
Genotype-phenotype correlation

Metaanalysis using data from 899 individuals from 85 articles



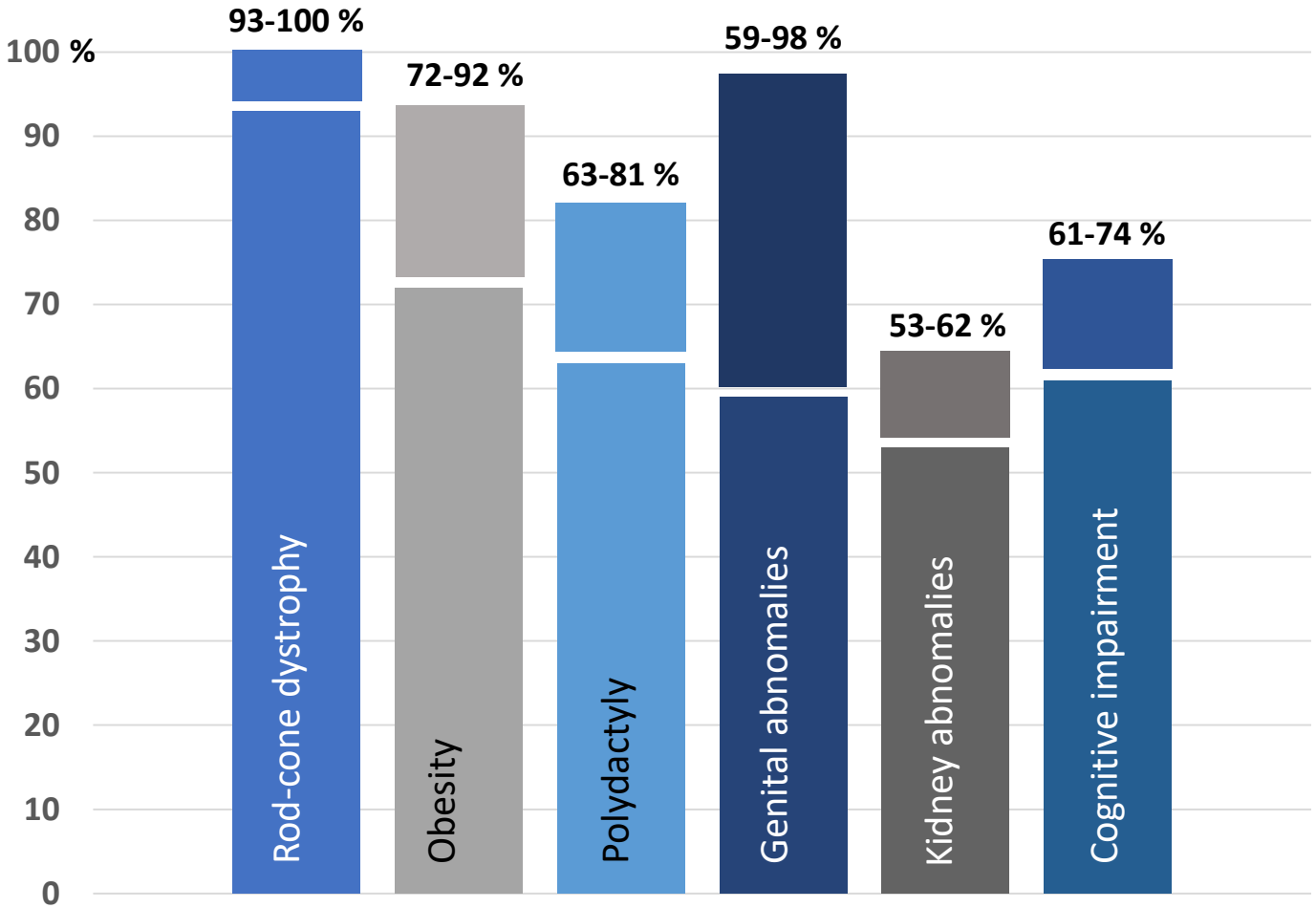
Niederlova et al. Hum Mutat. 2019;40(11):2068–2087

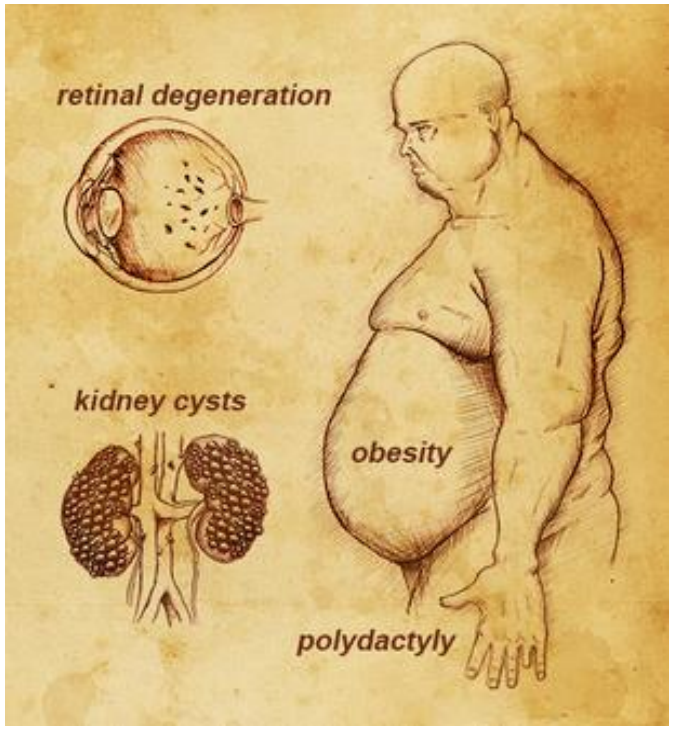
Primary ciliopathies affect several organ systems – and kidney involvement as a typical feature



McConnachie DJ, Stow JL, Mallett AJ. Ciliopathies and the Kidney: A Review. Am J Kidney Dis. 2021 Mar;77(3):410-419.

Kidney involvement as a primary feature in BBS





Forsythe, Beales, European Journal of Human Genetics (2013) 21, 8–13

Kidney involvement differs between genotypes

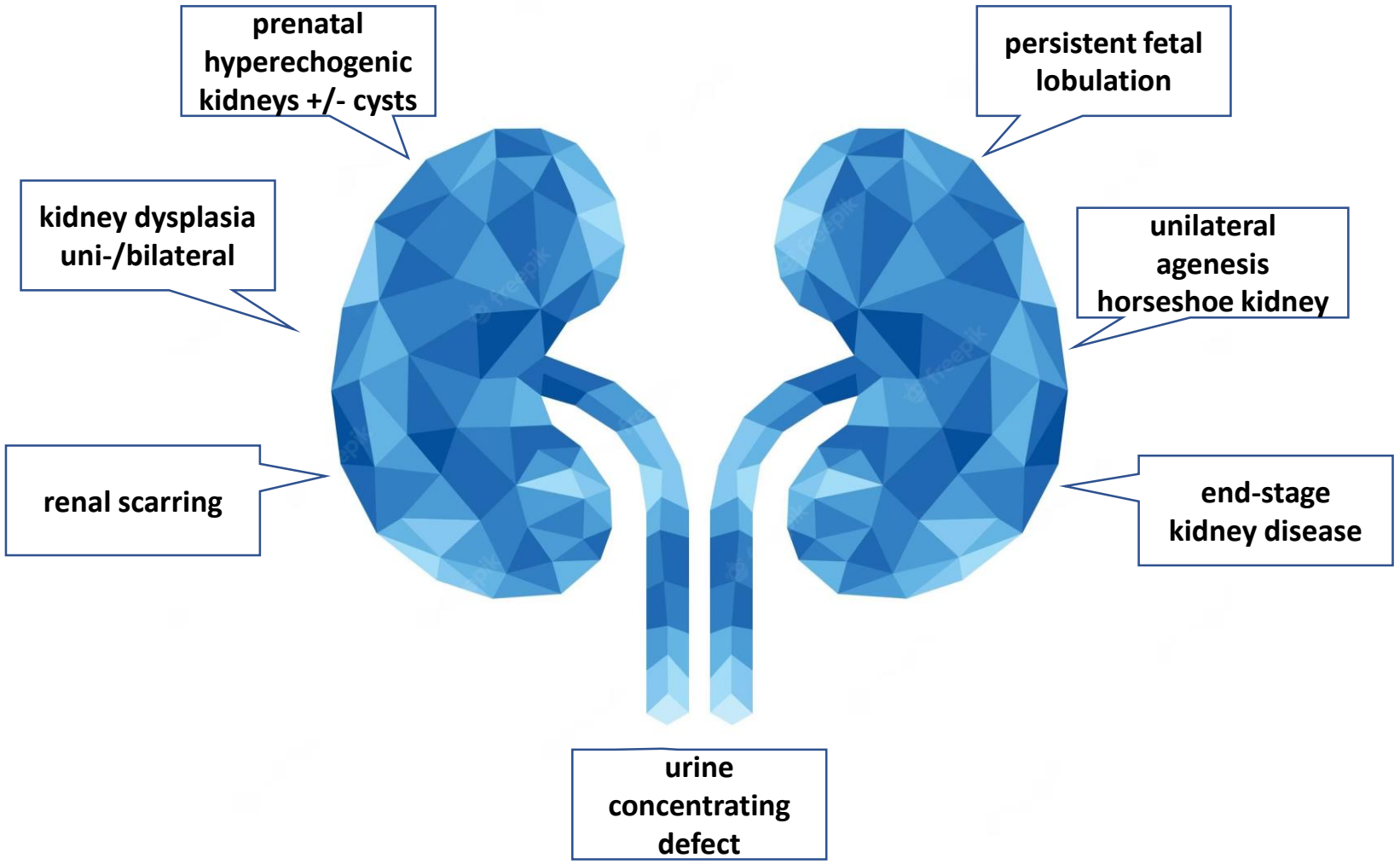
Table 3 Global frequencies of the six BBS primary features found in our cohort. Detailed percentages for each *BBS* gene and data for chaperonin-like genes as a whole are shown

Clinical features	*BBS1* (n=33)	*BBS10* (n=9)	*BBS12* (n=8)	Chaperonin-like BBS genes (n=19)
Retinal dystrophy	100% (33/33)	100% (9/9)	100% (7/7)	100% (18/18)
Obesity	84% (27/32)	88% (7/8)	100% (8/8)	94% (17/18)
Polydactyly	70% (23/33)	100% (9/9)	88% (7/8)	95% (18/19)
Cognitive impairment	53% (17/32)	57% (4/7)	75% (6/8)	71% (12/17)
Urogenital anomalies	25% (4/16)	83% (5/6)	63% (5/8)	69% (11/16)
Renal abnormalities	18% (4/22)	57% (4/7)	60% (3/5)	62% (8/13)

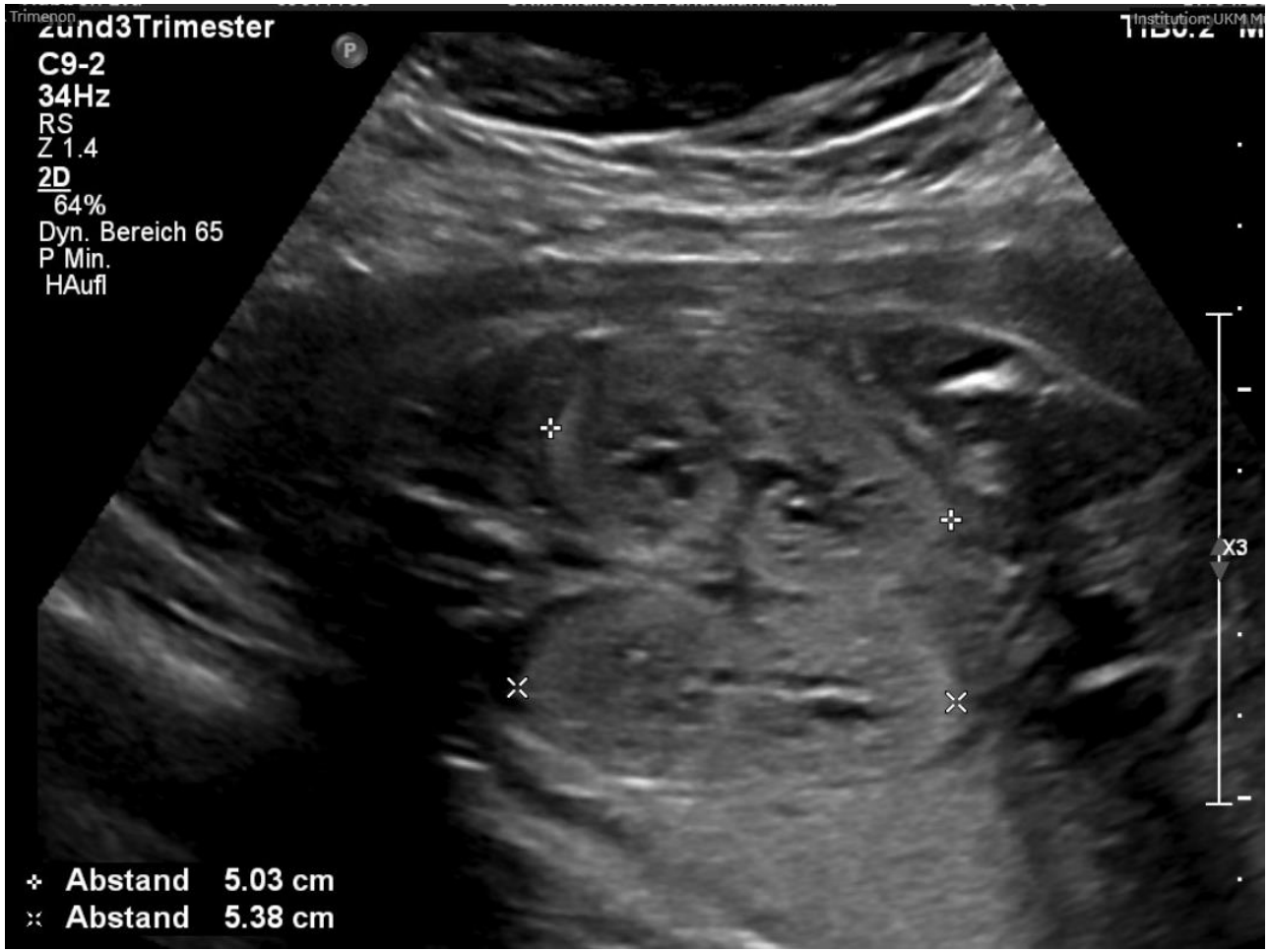
Percentages were calculated based on number of patients for which data were available. 'Chaperonin-like BBS genes' includes *BBS6*, *BBS10* and *BBS12* data.
BBS, Bardet-Biedl syndrome.

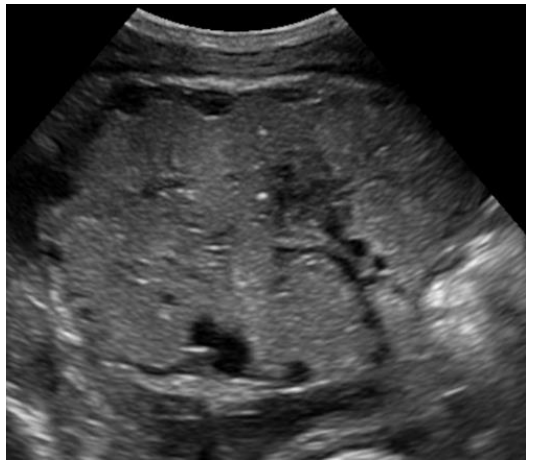
Castro-Sánchez S, *et al*. *J Med Genet* 2015;**0**:1–11. doi:10.1136/jmedgenet-2015-103099

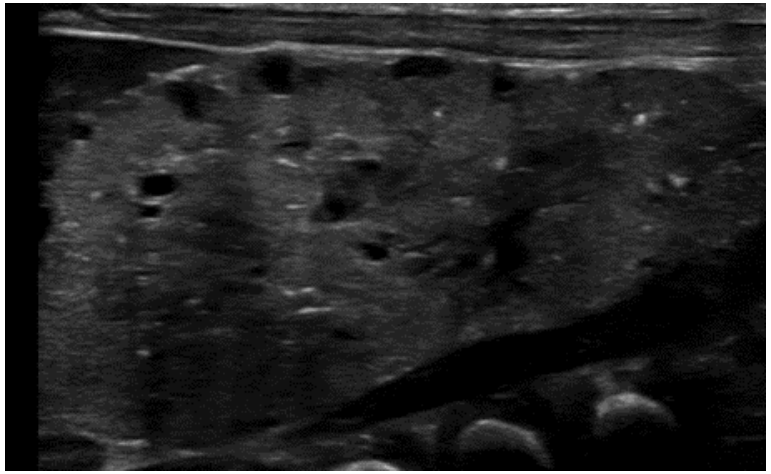
Clinical spectrum of kidney disease in BBS (53-62%)



Prenatal hyperechogenecity +/- parenchymal cysts



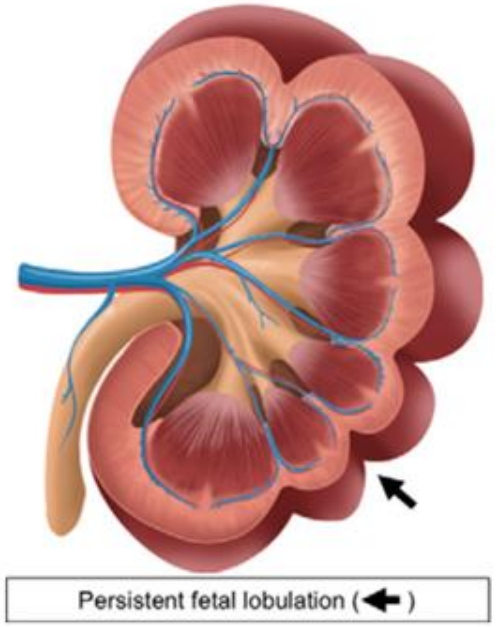


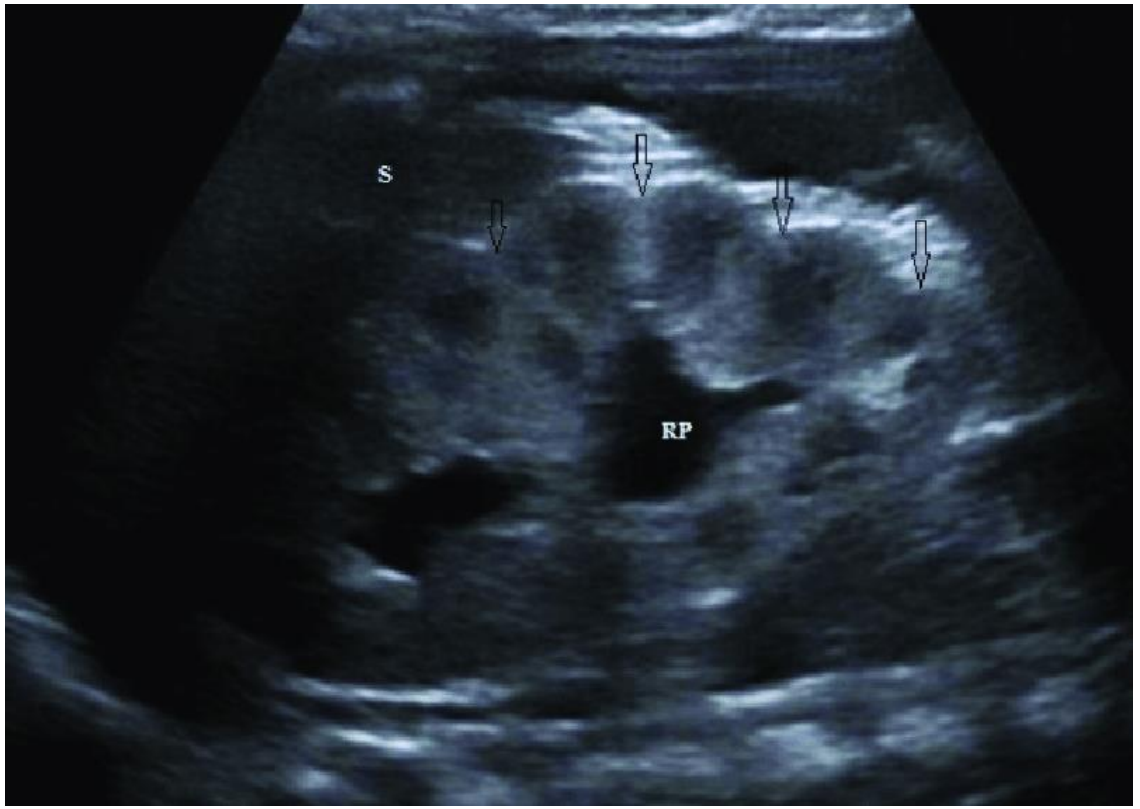


cortical & medullary cysts (persistent or temporary)

Persistent fetal lobulation of the kidney

- benign kidney abnormality with no consequences for kidney survival

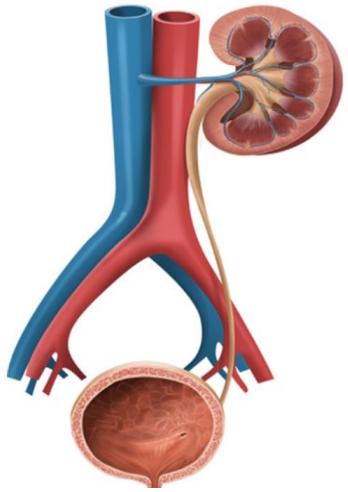




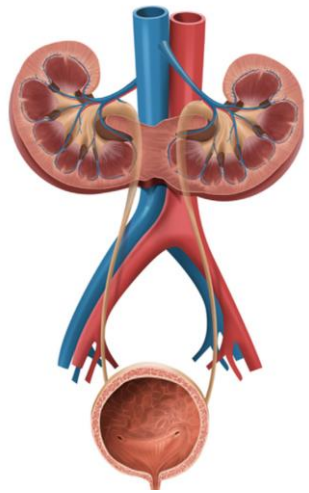
Structural genito-urinary anomalies (CAKUT)

common in BBS:

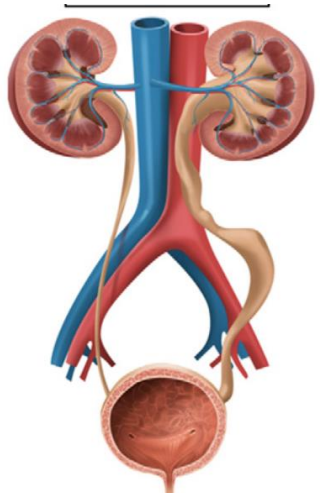
- parenchymal and calyceal cysts
- hydronephrosis
- renal agenesis
- horseshoe kidney,
- vesicoureteral reflux,
- vaginal atresia,
- urogenital sinus



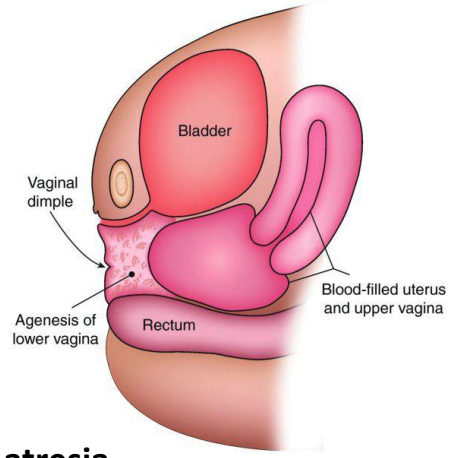
renal agenesis



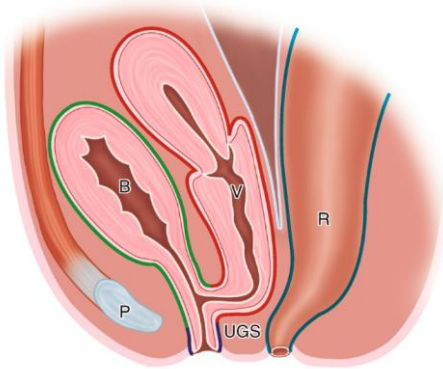
horseshoe kidney



megaureter



vaginal atresia



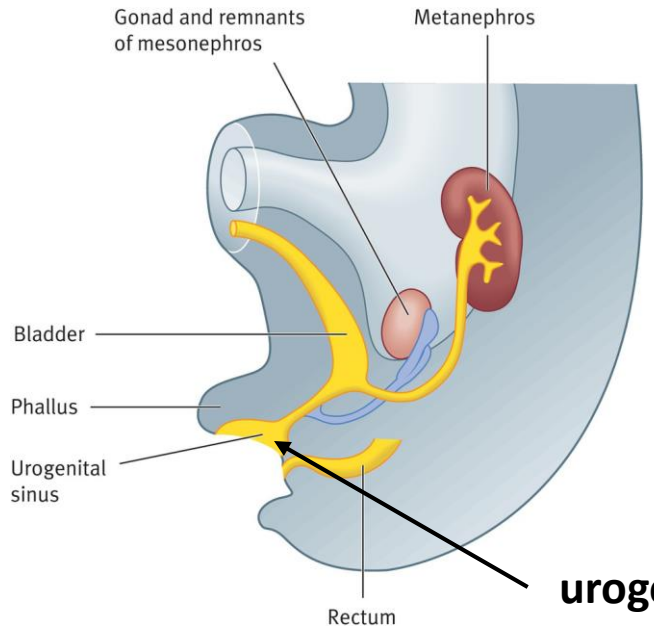
urogenital sinus

Indian J Pediatr (July 2014) 81(7):719–721
DOI 10.1007/s12098-013-1147-z

CLINICAL BRIEF

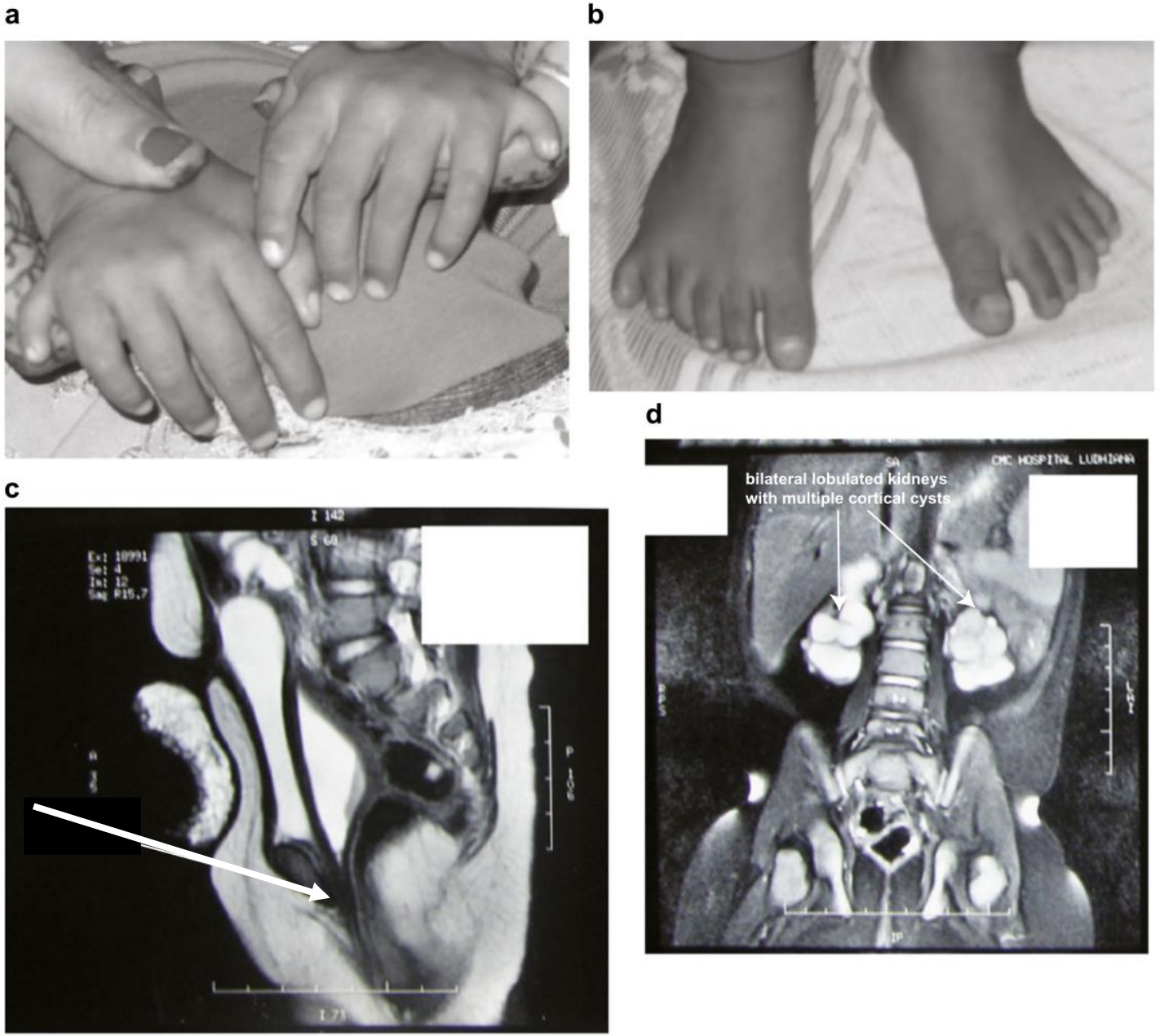
Bardet-Biedl Syndrome with Urogenital Sinus Presenting with Acute Renal Failure in a Neonate

Nandini K. Bedi · Dhruv Grover



urogenital sinus

MRCOG Part One *Your Essential Revision Guide*
DOI: https://doi.org/10.1017/CBO9781107587519.012



Renal scarring

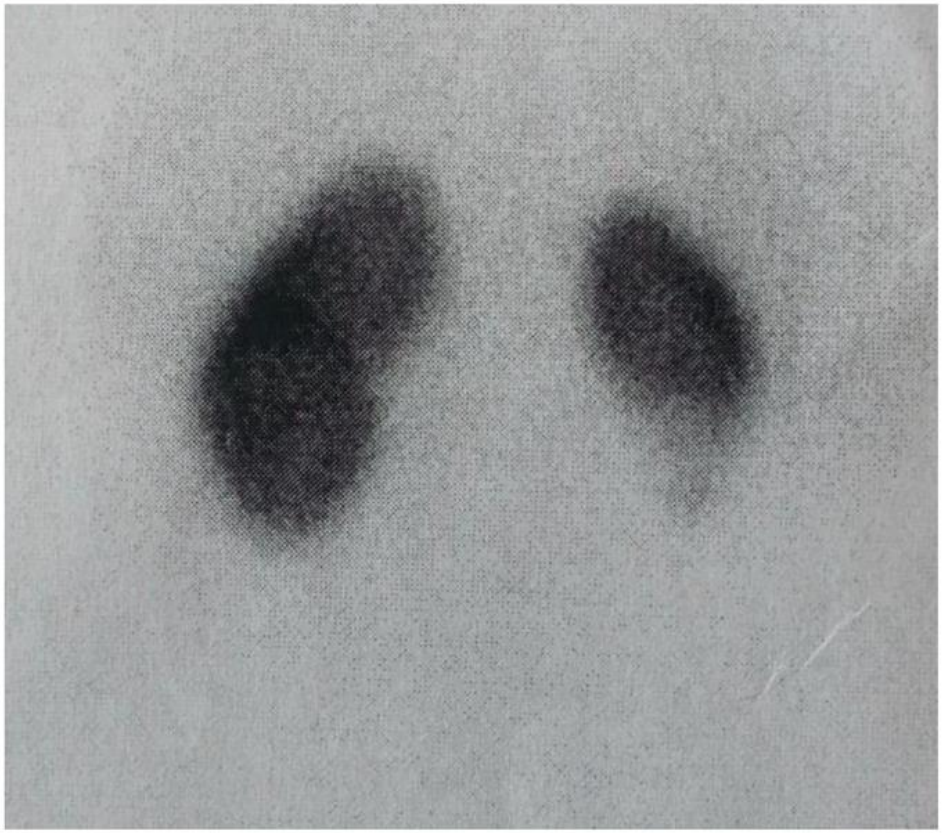


Figure 2 – Tc99m-DMSA scan in a child with Bardet Biedl syndrome and focal scarring in the lower pole of the right kidney

- **Focal dysplasia** in one kidney without a medical history of recurrent urinary tract infections reported in 4 children (2 male/ 2 female) with BBS

10.1515/prilozi-2015-0048

ISSN 1857-9345
UDC: 616.61-007.1-056.7-053.2

CASE REPORT

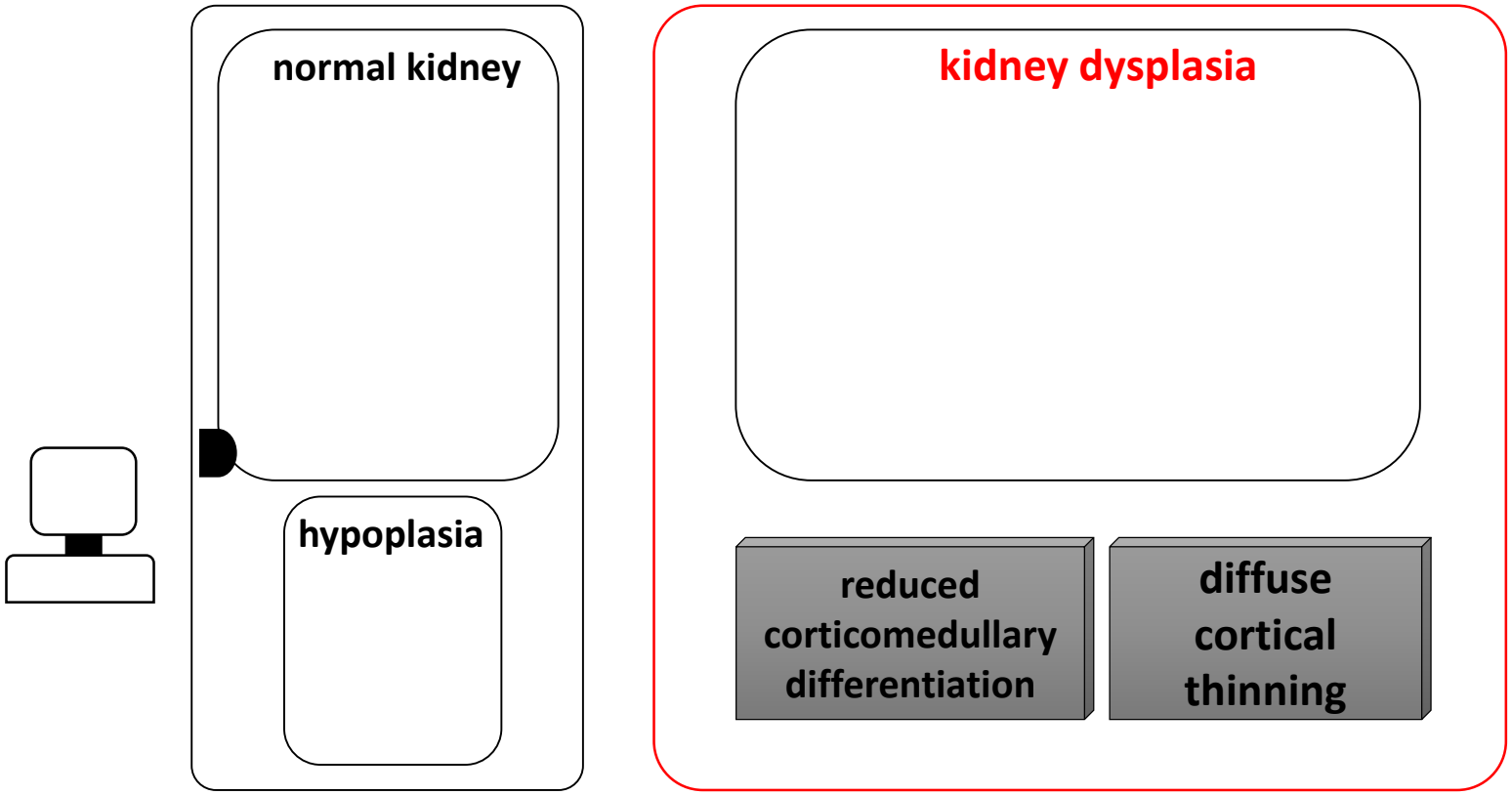
RENAL DYSPLASIA IN BARDET-BIEDL SYNDROME

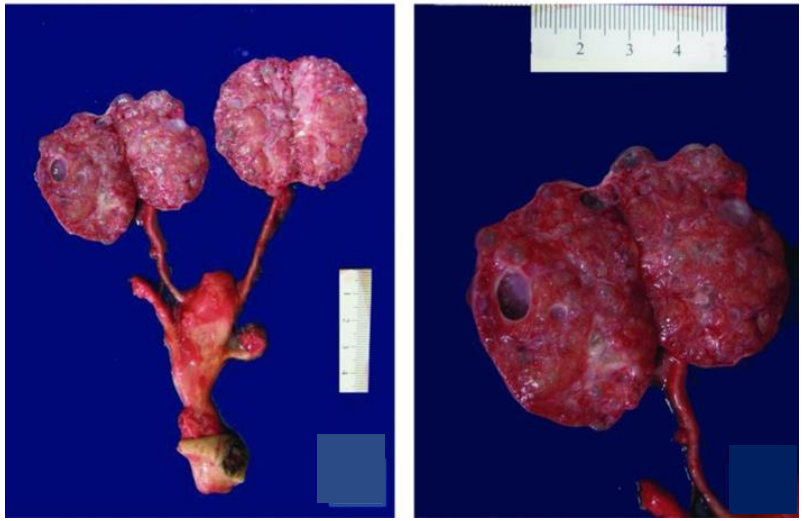
Nadica Ristoska Bojkovska[1], Lidvana Spahiu[2], Aleksandra Janchevska[1], Zoran S. Gucev[1], Velibor Tasic[1]

Clinical features of the Bardet Biedl patients

Patient	Age*	Gender	Retino-pathy	Polydactyly	Obesity	Learning disabilities	Hypogo-nadism	Renal status
1	6	M	+	+	+	+	+	Bill. dysplasia
2	3	M	+	+	+	+	+	Bill. dysplasia
3	7	F	+	+	+	+	NA	Focal scarring
4	6	F	+	+	+	+	NA	Focal scarring

Kidney (Hypo-) Dysplasia

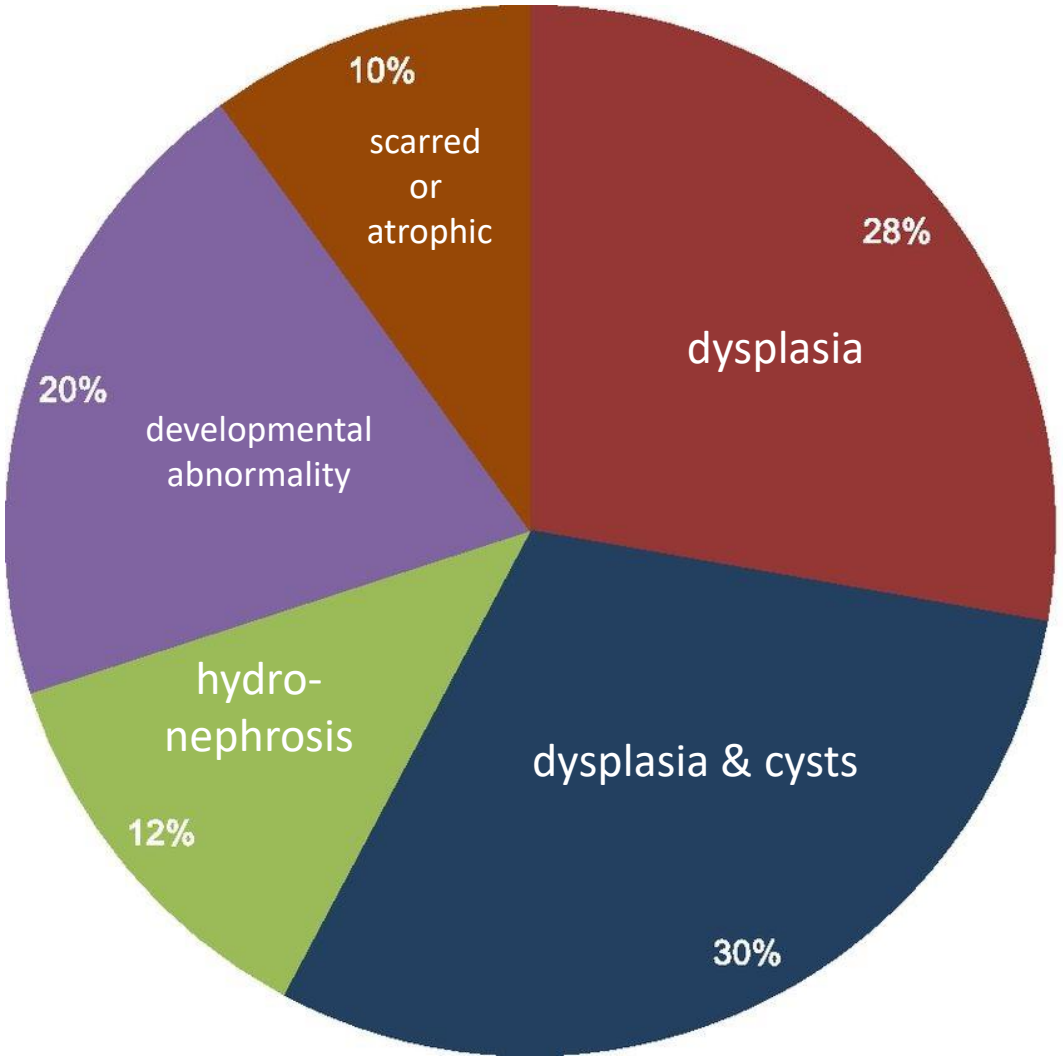




Rodriguez MM. Fetal Pediatr Pathol. 2014 Oct-Dec;33(5-6):293-320.

Kohl et al, *NDT* 2022

50% of BBS patients with „structural kidney defects“



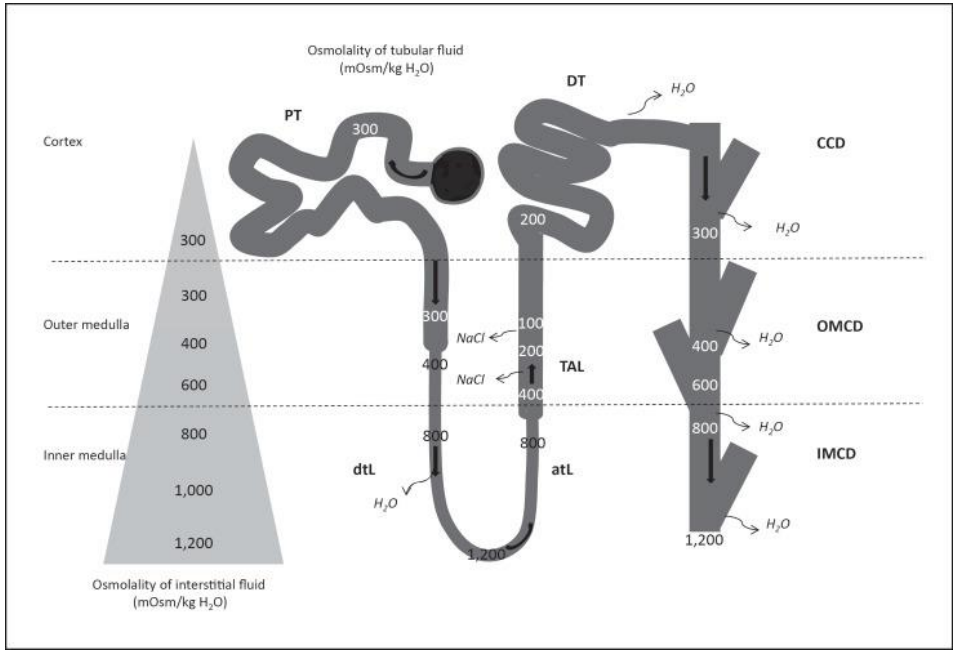
177 ultrasound reports on BBS patients

- 49% unremarkable
- **51% structural defects**

Forsythe E et al. Risk Factors for Severe Renal Disease in Bardet-Biedl Syndrome. J Am Soc Nephrol. 2017 Mar;28(3):963-970.

Urine concentrating defect

- Urine concentrating defect is a common dysfunction in many (renal) ciliopathies
- Precise underlying mechanisms are largely unknown
- Clinically resulting in hyposthenuria, polyuria and polydipsia
- **Hyposthenuria is the most common kidney defect in BBS**



Urine concentrating defect leading to polyuria/polydipsia
– a well known phenomenon

THE CARDINAL MANIFESTATIONS OF BARDET–BIEDL SYNDROME, A FORM OF LAURENCE–MOON–BIEDL SYNDROME

JANE S. GREEN, M.Sc., PATRICK S. PARFREY, M.D., JOHN D. HARNETT, F.R.C.P.(C.), NADIR R. FARID, M.D., BENVON C. CRAMER, F.R.C.R.(C.), GORDON JOHNSON, M.D., OLGA HEATH, M.Sc., PATRICK J. MCMANAMON, F.R.C.R.(C.), ELIZABETH O'LEARY, AND WILLIAM PRYSE-PHILLIPS, M.D.

Table 5. Renal Abnormalities in Patients with Bardet–Biedl Syndrome.

ABNORMALITY	NO. WITH ABNORMALITY	NO. TESTED	%
Structural			
Abnormal calyces	20	21	95
Communicating cysts or diverticulae	13	21	62
Fetal-type lobulation	20	21	95
Diffuse cortical loss	6	21	29
Focal scarring	5	21	24
Functional			
Hypertension	18	29	62
End-stage renal disease	3	32	9
Partial defect in urine concentration	14	17	82
Renal tubular acidosis			
Incomplete	5	19	26
Complete	1	19	5

82%

n=32

International Urology and Nephrology 25 (5), pp. 509–514 (1993)

Clinical Aspects of Renal Involvement in Bardet–Biedl Syndrome

A. ANADOLIISKA, D. ROUSSINOV

Department of Paediatric Nephrology and Haemodialysis, Higher Medical Institute, Paediatric University Hospital, Sofia, Bulgaria

Table 2
Symptoms of renal involvement

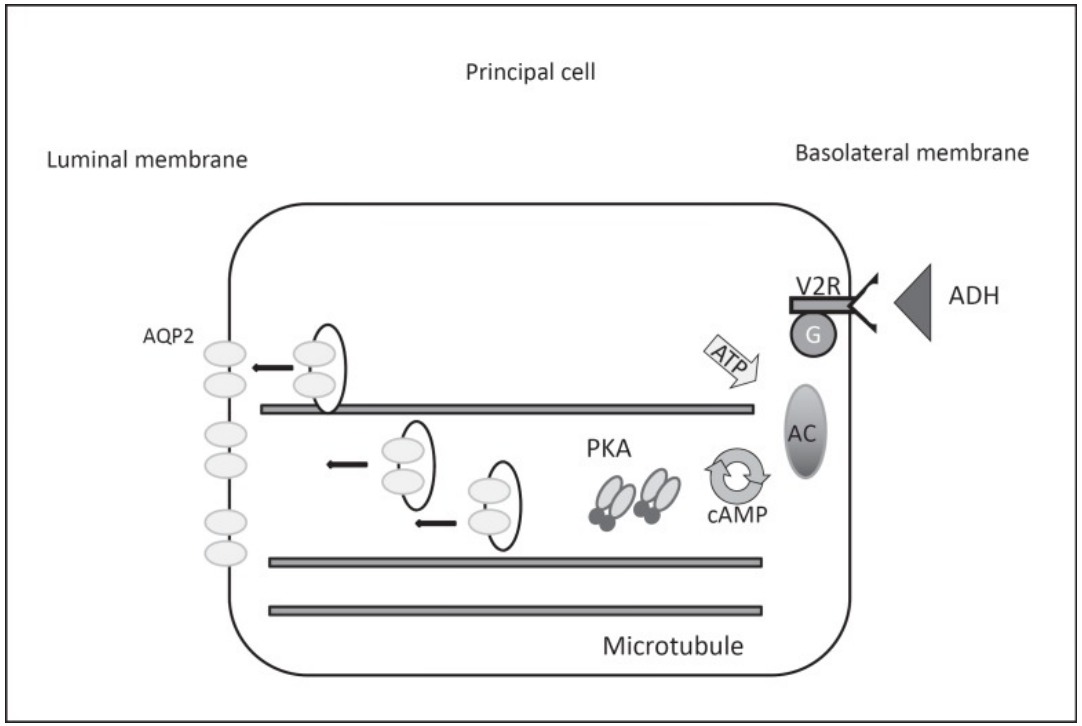
Patient	Polydypso-polyuria	Reduced concen-trating ability	Proteinuria	Renal failure
1. D.K.	+	+	–	ESRD
2. M.K.	+	+	+	CRF
3. P.K.	+	+	–	–
4. A.K.	+	+	–	ESRD

ESRD = End-stage renal disease
CRF = Chronic renal failure

Pathophysiology of urine concentrating defect

- Some studies suggested AQP2 mistraffiking as the putative mechanism of hyposthenuria in BBS.

- Reduced urinary uromodulin excretion in BBS also suggested a pathophysiologic link of the thick ascending limb (TAL)



Zacchia M et al. Kidney Dis 2017. Jul;3(2):57-65.

Urine concentrating defect

ckj OXFORD era edta

Clinical Kidney Journal, 2021, vol. 14, no. 6, 1545–1551

doi: 10.1093/ckj/sfaa182
Advance Access Publication Date: 6 December 2020
Original Article

ORIGINAL ARTICLE

Urine concentrating defect as presenting sign of progressive renal failure in Bardet–Biedl syndrome patients

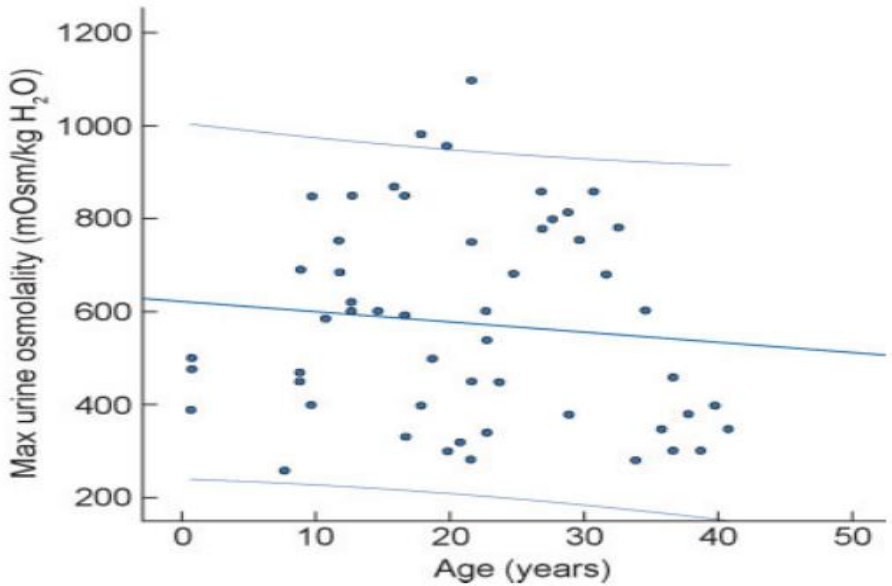
Miriam Zacchia[1], Francesca Del Vecchio Blanco[2], Annalaura Torella[2], Raffaele Raucci[1], Giancarlo Blasio[2], Maria Elena Onore[2], Emanuela Marchese[3,4], Francesco Trepiccione[1,5], Caterina Vitagliano[1], Valentina Di Iorio[6], Perna Alessandra[1], Francesca Simonelli[6],

Study in a cohort of 54 Bardet-Biedl individuals

- 41 adults, 13 children
- GFR:
  - <90 ml/min/1,73m^2 61%
  - 60-90 ml/min/1,73m^2 22%
  - <60 ml/min/1,73m^2 16%

Mean **max. Uosm** after overnight dehydration = **581.8 +/-215 mOsm/kg**.

- after excluding patients with eGFR <60 ml/min/1,73m^2 **rate of hyposthenuria 56%** (24/43 patients).



Zacchia M et al. Clin Kidney J. 2020 Dec 6;14(6):1545-1551.

Urine concentrating defect

Clinical Kidney Journal, 2021, vol. 14, no. 6, 1545–1551
doi: 10.1093/ckj/sfaa182
Advance Access Publication Date: 6 December 2020
Original Article

ORIGINAL ARTICLE

Urine concentrating defect as presenting sign of progressive renal failure in Bardet–Biedl syndrome patients

Miriam Zacchia[1], Francesca Del Vecchio Blanco[2], Annalaura Torella[2], Raffaele Raucci[1], Giancarlo Blasio[2], Maria Elena Onore[2], Emanuela Marchese[3,4], Francesco Trepiccione[1,5], Caterina Vitagliano[1], Valentina Di Iorio[6], Perna Alessandra[1], Francesca Simonelli[6],

1. **Truncating mutations** correlated with **max-Uosm**

Table 4. Mann–Whitney test shows that biallelic truncating and mixed mutation (truncating plus any type of mutations) significantly correlate with max-Uosm

Variable	Truncating/mixed mutation	Missense mutation	P-value (Mann–Whitney)
eGFR (ml/min/1.73 m2), mean ± SD	85.3 ± 41 (n = 21)	132.1 ± 3(n = 6)	0.1
Max-Uosm (mOsm/kg), mean ± SD	490.9 ± 158 (n = 18)	654 ± 181 (n = 6)	0.05

2. **Hyposthenuria** significantly correlated with **baseline eGFR** as well as decline of eGFR (**ΔeGFR**)

Table 3. 24 BBS patients with a median follow-up period of 6.5 years were divided by the base of the mean annual decline of the eGFR

Variables	Patients with mean ΔeGFR <−1.5 mL/min/year	Patients with mean ΔeGFR >−1.5 mL/min/year	P-value
Total number	19	9	–
Age (years)	22.68 ± 12.5	20.3 ± 5.9	0.5
Baseline eGFR (mL/min/1.73 m^2)	98.9 ± 35.3	113.5 ± 15.1	0.22
ACR (mg/g)	282.3 ± 613	7.7 ± 6.6	0.17
BMI (kg/m^2)	33.17 ± 6.3	28.7 ± 5.2	0.14
U-osm (mOsm/L)	506.3 ± 171	737.8 ± 216.7	<0.005
SBP (mmHg)	121 ± 18	112 ± 18	0.3
DBP (mmHg)	80 ± 9.2	78.6 ± 13	0.8

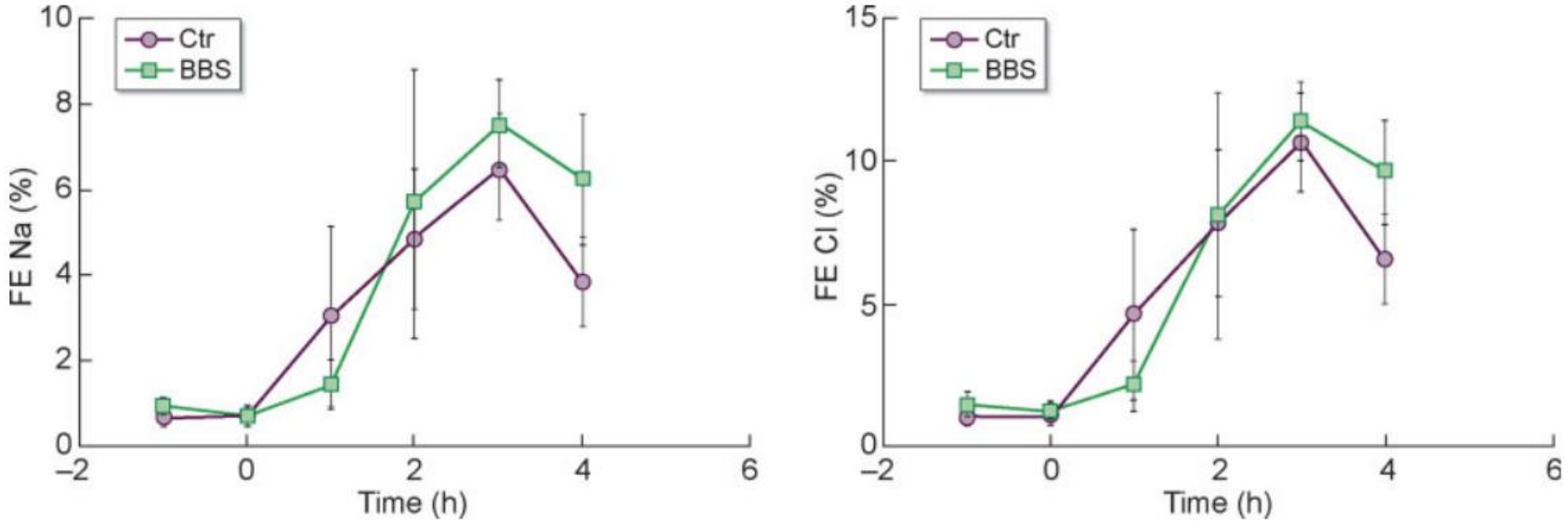
Values presented as mean ± SD unless stated otherwise.
Patients with more severe reductions did not differ for any basal parameter of the table but max-Uosm.

Pathophysiology of urine concentrating defect

- Normal-high urine aquaporine 2 levels and
- normal NaCl absorption in furosemide test

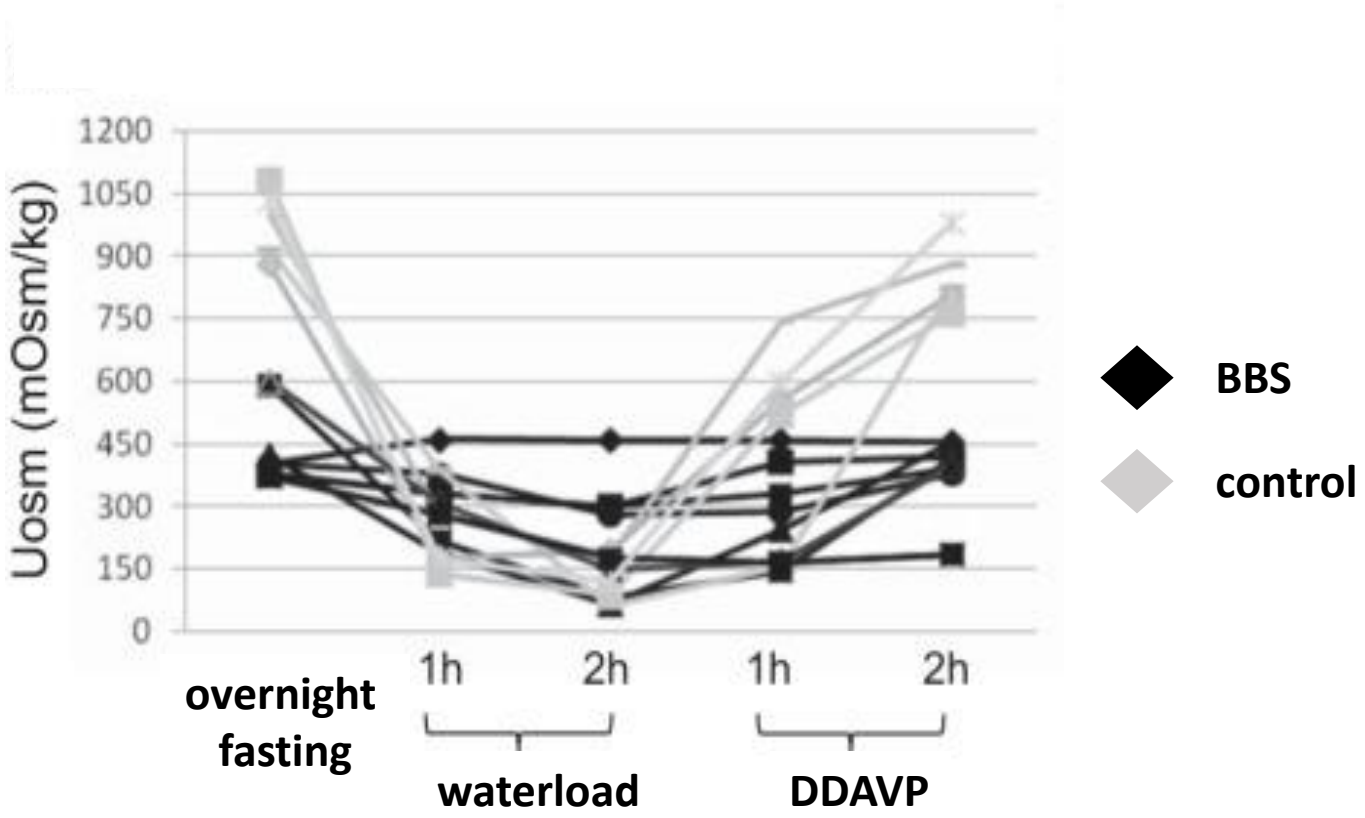
suggested that neither a specific collecting duct nor a thick ascending limb dysfunctions are likely to play a central role in the pathogenesis of hyposthenuria.

Furosemide test



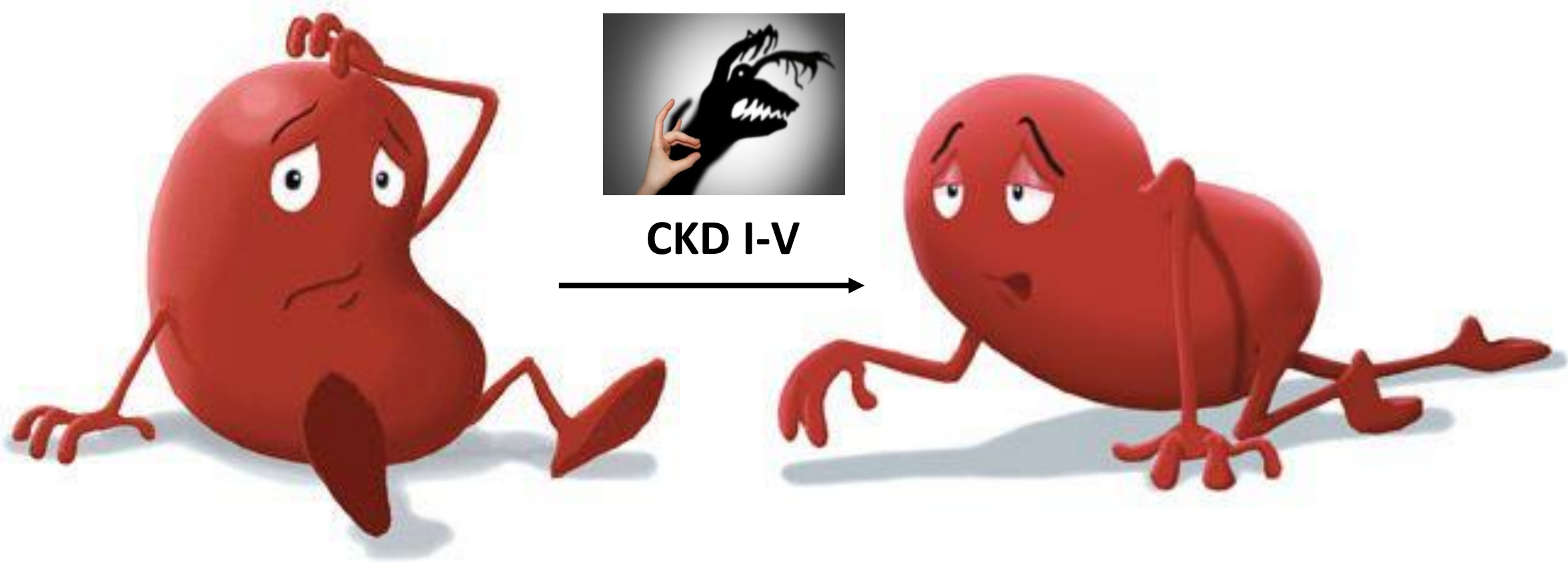
Zacchia M et al. Clin Kidney J. 2020 Dec 6;14(6):1545-1551.

BBS patients also showed a deficiency in dilution of urine



Zacchia M et al. Am J Physiol Renal Physiol. 2016 Oct 1;311(4):F686-F694.

Chronic kidney disease



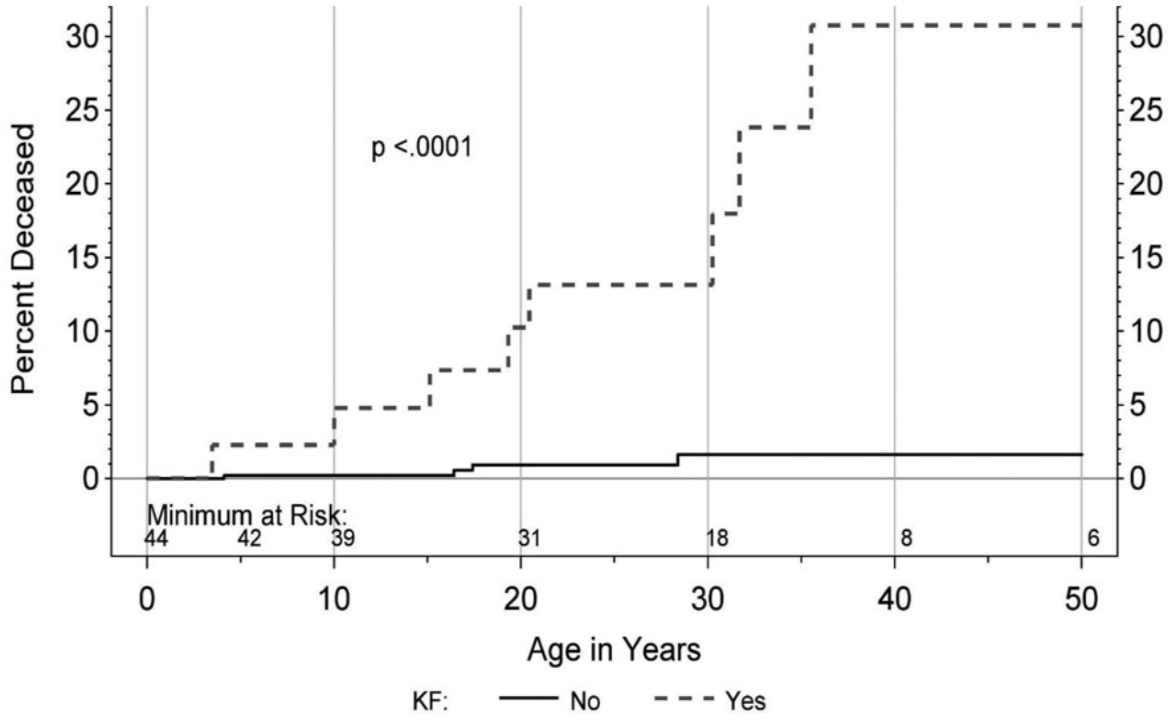
Impact of CKD on BBS overall morbidity

ESKD contributes majorly to overall mortality in BBS patients.

- median survival of BBS patients = 63 years
- 25% die before the age of 44 years
- 72% die because of renal impairment

Table 3 Causes of Death of BBS Patients

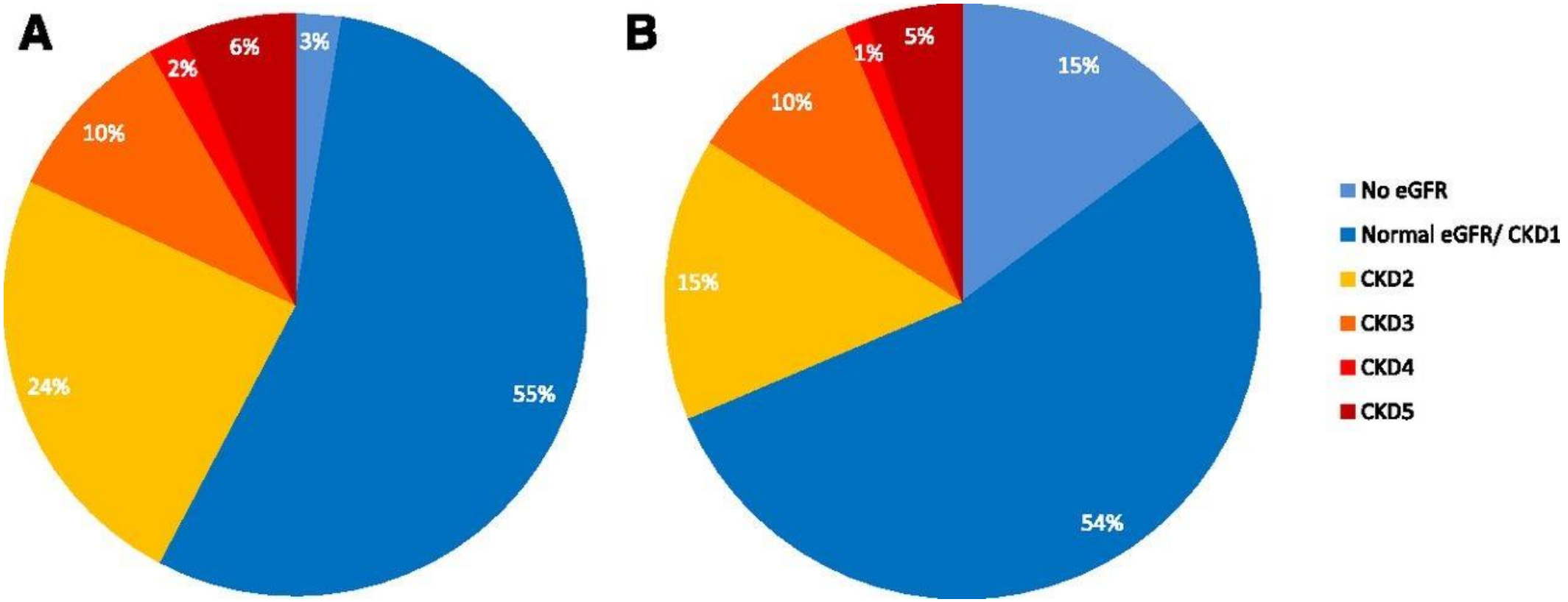
Age at Death (Years)	Primary Cause of Death	Source
40, 48, 50, 53, 54	Myocardial infarction	Moore et. Al (2005)[4]; Riise (1996)[114]
67	Valvulopathy	Riise (1996)[114]
63, 37	Cerebrovascular disease	Moore et. Al (2005)[4]; Riise (1996)[114]
19, 27, 53, 35, 60, 24, 37	Renal disease	Moore et. Al (2005)[4]; Riise (1996)[114]
63	Renal carcinoma	Moore et. Al (2005)[4]
62	Septicemia secondary to urinary tract infection	Moore et. Al (2005)[4]
1.5	Hirschsprung disease	Moore et. Al (2005)[4]
45	Gastro-intestinal hemorrhage after colonic resection	Moore et. Al (2005)[4]
32, 34	Embolism/thrombosis	Moore et. Al (2005)[4]; Riise (1996)[114]
52	Aspiration pneumonia (seizure due to a meningioma)	Moore et. Al (2005)[114]



Melluso A, et al. Ther Clin Risk Manag. 2023 Jan 30;19:115-132.

Meyer JR, et al. Clin Genet. 2022 Apr;101(4):429-441.

Overall CKD in BBS patients (n=350)



Adults 41% CKD
(n=194)

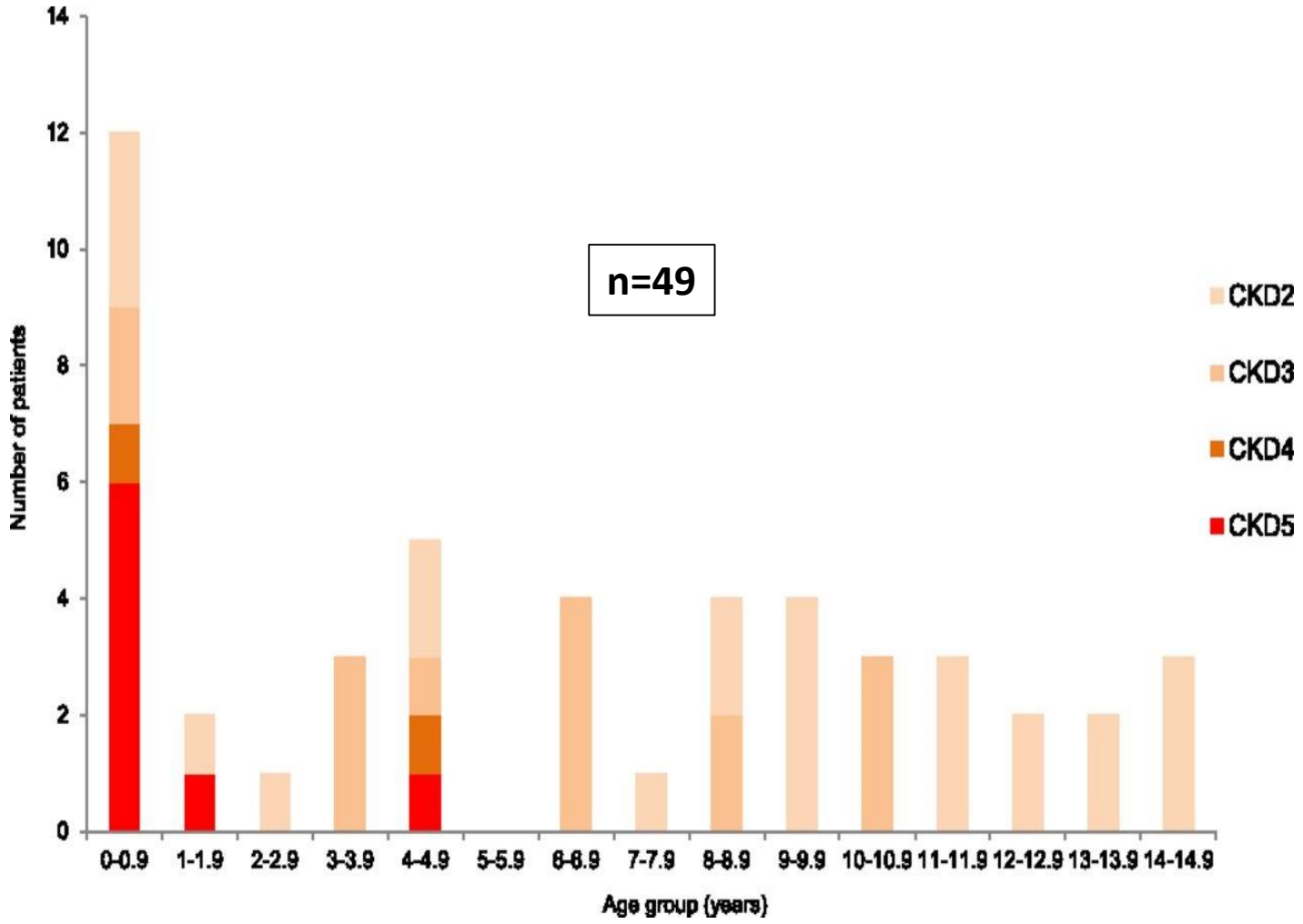
Children 31% CKD
(n=156)

Forsythe E et al. Risk Factors for Severe Renal Disease in Bardet-Biedl Syndrome. J Am Soc Nephrol. 2017 Mar;28(3):963-970.

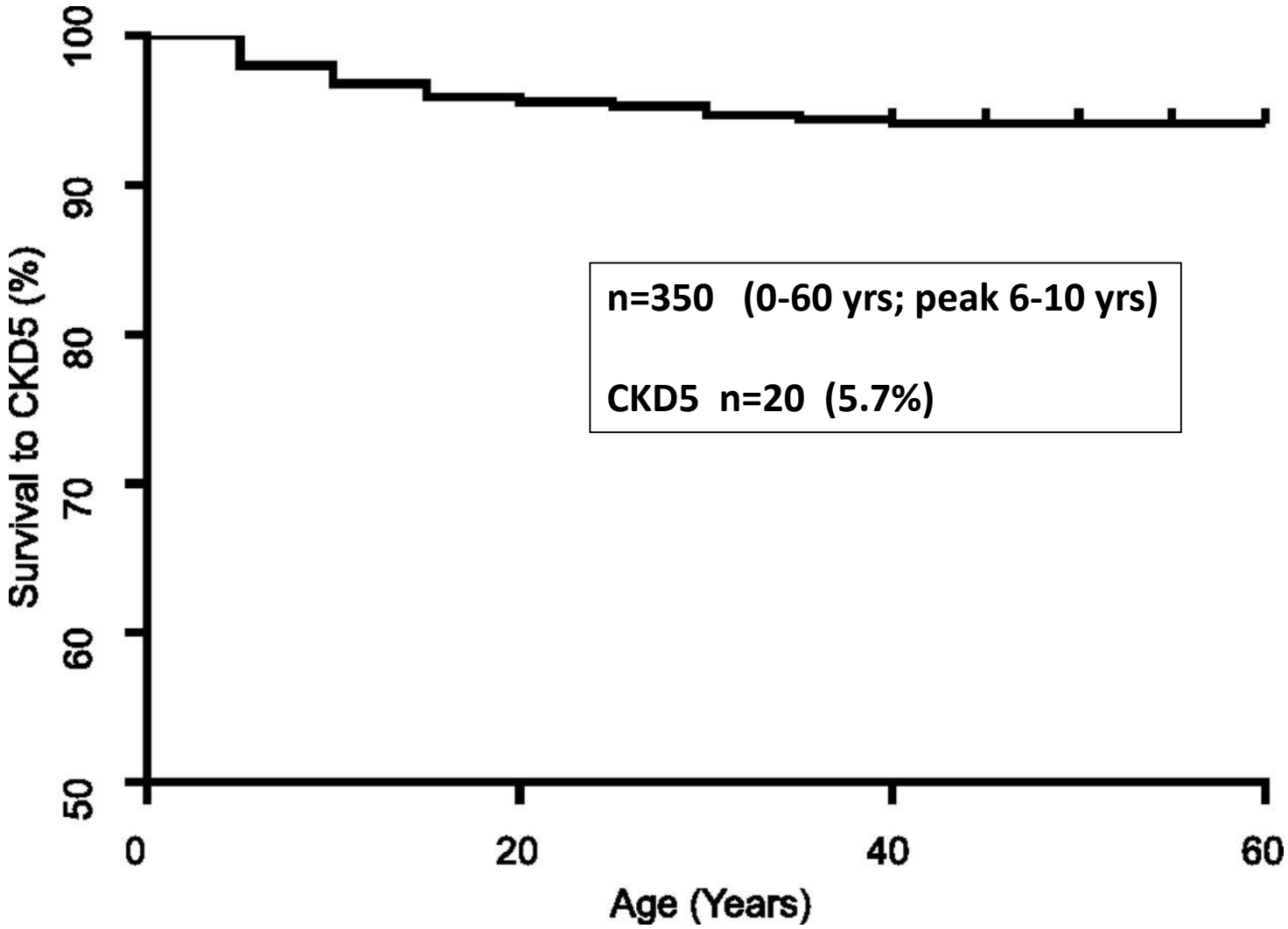
Age at diagnosis of CKD in pediatric BBS

Table 2. - Prevalence of CKD in adults and children, according to age group

Age Group, yr	Normal/CKD1/No eGFR	CKD2	CKD3	CKD4	CKD5	Total
Pediatric patients, *n*						
0–5	22	2	7	0	5	36
6–10	42	7	5	2	1	57
11–15	29	6	2	0	1	38
16–18	14	9	1	0	1	25
Total (% of total)	107 (69%)	24 (15%)	15 (10%)	2 (1%)	8 (5%)	156
Adult patients, *n*						
16–20	27	0	3	0	2	32
21–25	29	5	1	1	3	39
26–30	17	5	1	1	1	25
31–35	14	4	1	1	3	23
36–40	6	7	5	0	1	19
41–45	5	8	2	1	1	17
46–50	6	5	2	0	1	14
51–55	6	8	3	0	0	17
56–60+	2	5	1	0	0	8
Total (% of total)	112 (58%)	47 (24%)	19 (10%)	4 (2%)	12 (6%)	194

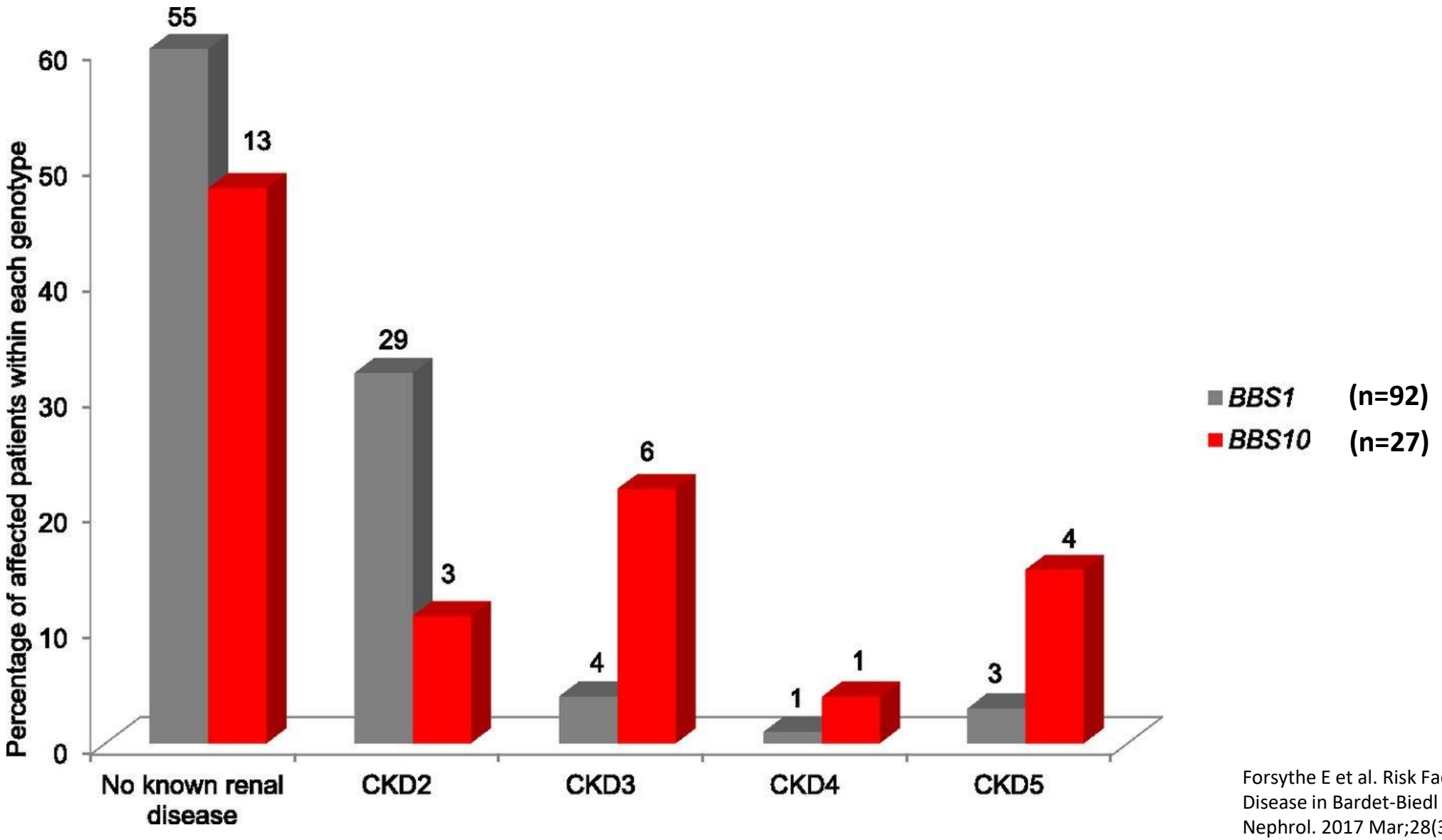


Kidney survival



Forsythe E et al. Risk Factors for Severe Renal Disease in Bardet-Biedl Syndrome. J Am Soc Nephrol. 2017 Mar;28(3):963-970.

BBS10 with a more severe kidney phenotype compared to BBS1



Forsythe E et al. Risk Factors for Severe Renal Disease in Bardet-Biedl Syndrome. J Am Soc Nephrol. 2017 Mar;28(3):963-970.

Type of mutation rather than affected gene determine the risk for severe kidney disease

Table 3. Univariable logistical regression analysis of risk factors for severe renal disease (eGFR<45 ml/min per 1.73 m^2) in adults with known common genotypes

Risk Factor	Odds Ratio	Confidence Interval		*P* Value
		2.5%	97.5%	
Genetic factors				
Genotype (*n*=154)				
BBS1 mutation (*n*=90)	(Reference)			
BBS2 mutation (*n*=22)	4.4	1.28	15.19	0.02[a]
BBS9 mutation (*n*=6)	2.4	0.12	17.74	0.46
BBS10 mutation (*n*=26)	7.4	2.49	23.32	<0.01[a]
BBS12 mutation (*n*=10)	5.9	1.08	28.39	0.03[a]
Mutation type (*n*=149)				
Missense/missense (*n*=76)	(Reference)			
Truncating/truncating (*n*=40)	11.4	3.9	41.8	<0.01[a]
Missense/truncating (*n*=33)	6.3	1.5	28.6	0.01[a]
Diabetes (*n*=137)	0.62	0.14	0.99	0.47
Hypertension (*n*=137)	5.43	2.21	14.29	<0.01[a]
Body mass index (*n*=93)	1.04	0.96	1.10	0.32
Age (*n*=154)	1.02	0.99	1.96	0.15

[a]Statistically significant result.

Meyer JR, et al. Clin Genet. 2022 Apr;101(4):429-441.

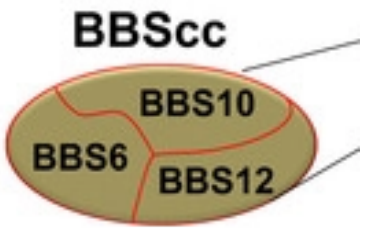
Genotype-phenotype correlation

In contrast in a French cohort > 16 years of age (n=33) *BBS6*, *BBS10* and *BBS12* (chaperone like proteins) genotype associated with a „more severe renal disease“ (CKD 2-3) .

Table 6. **Renal and cardiovascular genotype-phenotype relationship; BBSome genes compared with other genes**

Signs/Symptoms	Mutations in BBS1 through BBS11 Gene (Excluding BBS6 and BBS10) (n = 20/33)	Mutations in BBS6, BBS10, or BBS12 Gene (n = 10/33)	Unknown (n = 3/33)
CKD (stages 2 and 3) (n = 12/33)	15% (3/20)	70% (7/10)	66% (2/3)
Proteinuria (n = 10/30)	25% (5/20)	20% (2/10)	100% (3/3)
Abnormal urine concentration (n = 19/30)	55% (11/20)	70% (7/10)	33% (1/3)
Renal cysts (n = 6/26)	20% (4/20)	20% (2/10)	0% (0/3)
Caliectasis (n = 13/26)	35% (7/20)	50% (5/10)	33% (1/3)
Hypertension (n = 10/28)	25% (5/20)	20% (2/10)	100% (3/3)
Diabetes (n = 2/33)	10% (2/20)	0% (0/10)	0% (0/3)
Dyslipidemia (n = 17/32)	45% (9/20)	50% (5/10)	100% (3/3)
Obesity (n = 23/33)	60% (12/20)	80% (8/10)	100% (3/3)
Metabolic syndrome (n = 13/29)	35% (7/20)	40% (4/10)	66% (2/3)
LVH (n = 5/29)	5% (1/20)	10% (1/10)	100% (3/3)

CKD stage 2: eGFR <90 ml/min per 1.73 m^2 and markers of kidney damage (proteinuria, hematuria, or morphological abnormalities). CKD stage 3: eGFR <60 ml/min per 1.73 m^2.



Chaperone like BBS proteins

Imhoff O, et al. Clin J Am Soc Nephrol. 2011

Lessons from the CRIBBS registry

CRIBBS registry:

(Clinical Registry Investigating BBS) = global patient self-reporting registry

- overall 607 patients registered (12/21)
- females 300, males 307
- 364 registrants molecularly confirmed
  - BBS10 26,6%
- 44 patients with ESKD (7.2%)

Lessons from the CRIBBS registry (02/21)

- ESKD in 37/364 genetically confirmed patients (10.1%)
- Median age of ESKD 12.5 years
- 86,7% ESKD before 30 years of age
- Females over-represented (77,3%) in ESKD group
- Presence of uropathies and presence of diabetes mellitus did not have a significant impact on the occurance of ESKD (0.67)

- <u>Risk factors:</u>
  - Female sex
  - Truncating variants
  - Genes other than BBSome/chaperon-like genes

Received: 19 October 2021 | Revised: 29 January 2022 | Accepted: 30 January 2022
DOI: 10.1111/cge.14119

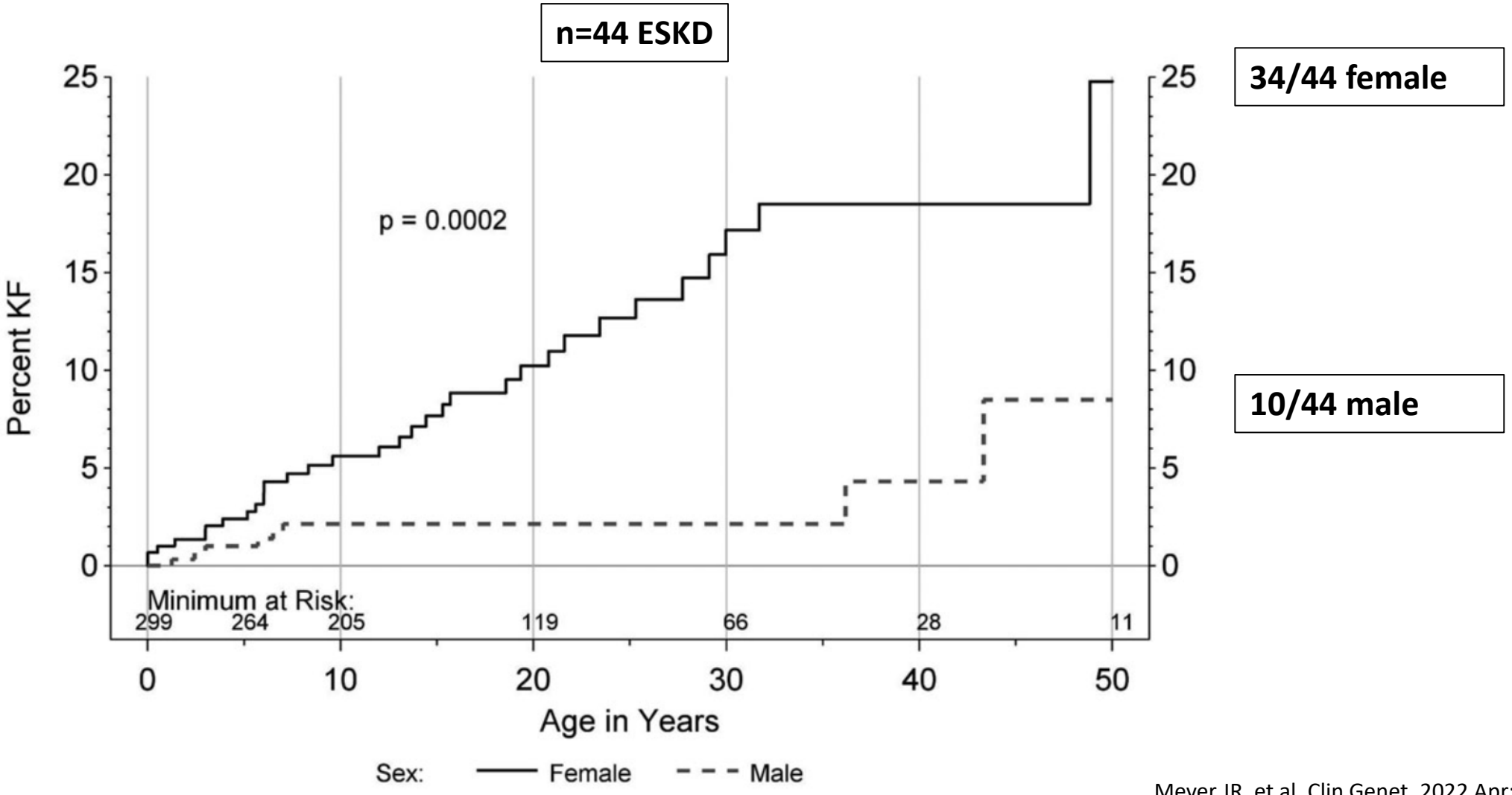
ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Kidney failure in Bardet–Biedl syndrome

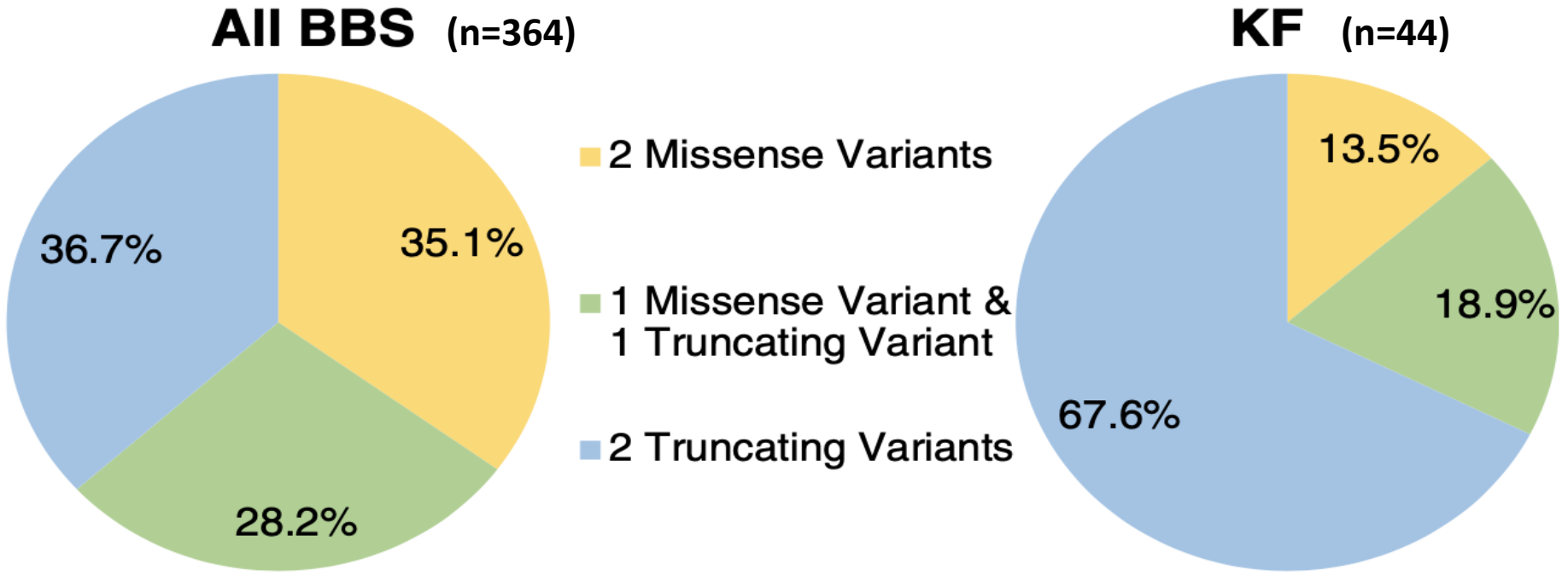
Jennifer R. Meyer[1] | Anthony D. Krentz[2] | Richard L. Berg[3] | Jesse G. Richardson[3] | Jeremy Pomeroy[4] | Scott J. Hebbring[5] | Robert M. Haws[4,6]

Female sex associated with an increased risk for ESKD



Meyer JR, et al. Clin Genet. 2022 Apr;101(4):429-441.

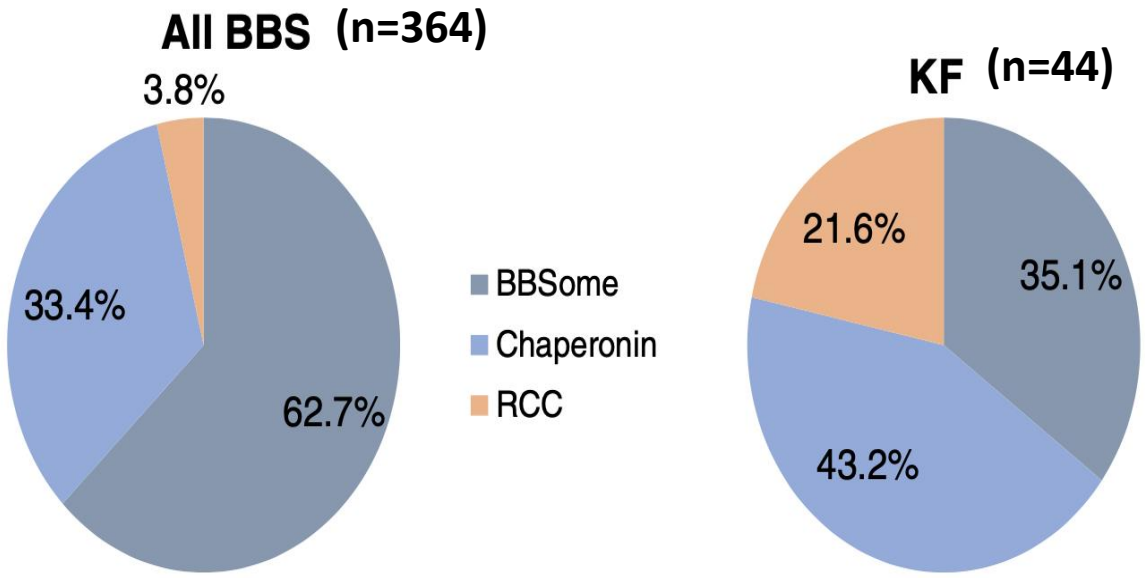
Influence of variant severity

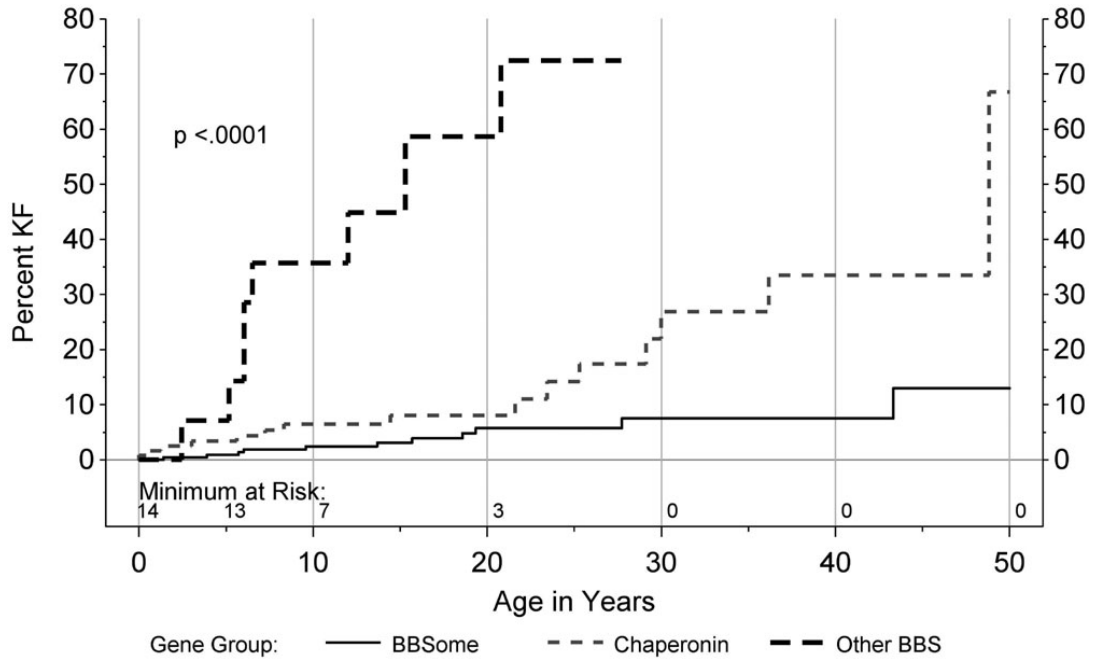


Onset of ESKD earlier in individuals with two truncationg variants.

Meyer JR, et al. Clin Genet. 2022 Apr;101(4):429-441.

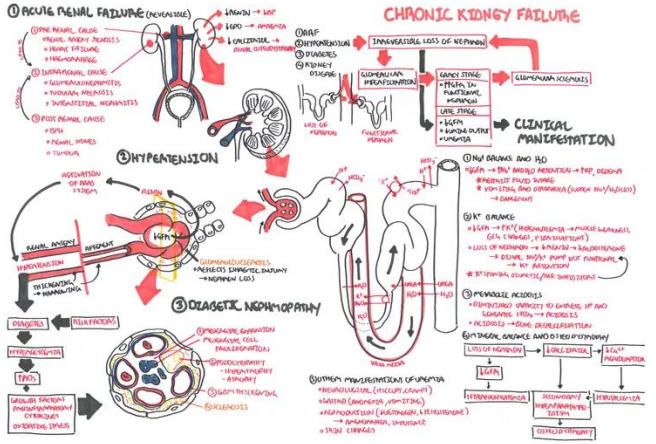
Influence of gene group





Meyer JR, et al. Clin Genet. 2022 Apr;101(4):429-441.

Pathogenesis of kidney disease in BBS



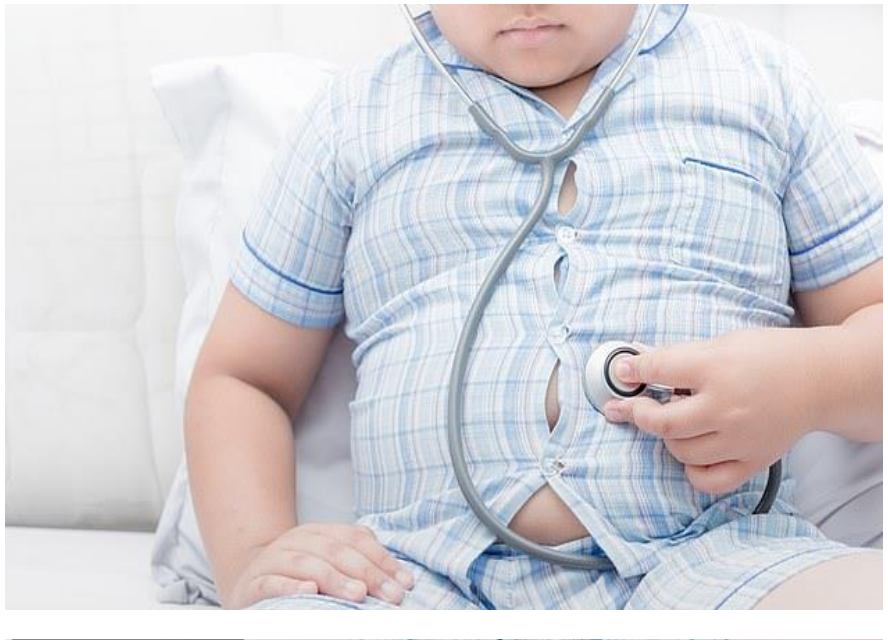
- pathogenesis of progressing CKD in BBS unclear
- hypertension, obesity and diabetes II are known risk factors
- renal hyposthenuria seems to be associated with faster decline of eGFR

- in vitro data suggest metabolic aberrations in the absence of BBS10
  - increased aerobic glycolysis
  - abnormal cytoplasmic lipid accumulation
  - mitochondrial dysfunction

- Marchese E. et al. Int J Mol Sci. 2022;23(16):9420.
- Zacchia M. Kidney Blood Press Res. 2017;42(5):784–793

Kidney Transplantation

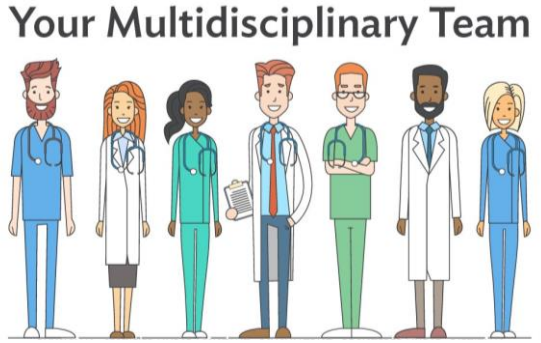
- Kidney transplantation can be considered and has been shown to result in favorable outcomes for patients with BBS.
- In fact, outcomes are comparable to those of the general population.
- However, obesity should be a limit, especially for adult subjects.
- Increase of the median BMI of the renal transplant cohort compared to the non-transplant cohort is reported….
- …Yet, obesity was not disproportionately severe in renal transplant recipients with BBS compared to the CRIBBS cohort.



Haws RM, et al. Renal transplantation in Bardet–Biedl syndrome. Pediatr Nephrol. 2016;31 (11):2153–2161.

Management –
many hand are required

Proposal for assessment



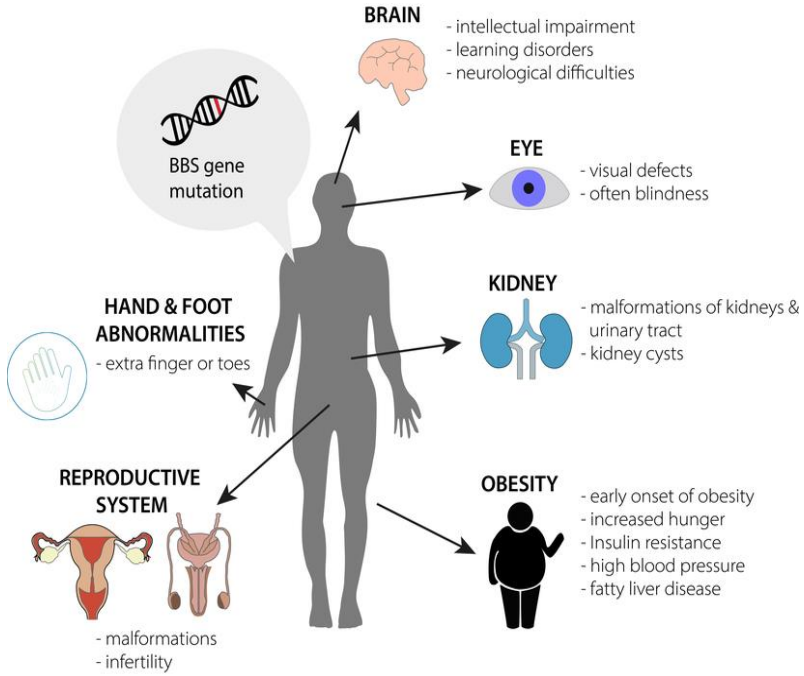
- Family history
- Anthropometric assessment, vital signs and accurate clinical examination
- Neuropsychological testing adapted to age and low vision
- Ophthalmological evaluation: complete eye examination, visual acuity, visual field testing, fundus examination, ERG (generally from 4–5 years of age) and, if necessary, visually evoked responses and optical coherence tomography (OCT)
- Orodental assessment
- Audiometry
- Echocardiogram, electrocardiogram (ECG)
- Abdominal ultrasound
- Analysis of renal function,including estimation of GFR,albuminuria, electrolytes and acid base balance; urine osmolality
- If neurological abnormalities are present, consider brain magnetic resonance (MRI)
- Laboratory tests: liver function tests, complete blood count, electrolytes, creatine, urea, lipid panel, blood glucose (HbA1c, oral glucose tolerance test for older children/adults), gonadotropins and sex hormones (if in age of puberty), thyroid hormones
- Genetic analysis and counseling.

Melluso A et al. Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook. Ther Clin Risk Manag. 2023

Summary

„When children drink lots and often eat plenty,
when their fingers and toes add up to higher than twenty,
when speech is delayed and the penis is burried,
when parents and doctors are equally worried,
when night vision is blurred or even a mess,
than go for genetics – it might be BBS. “

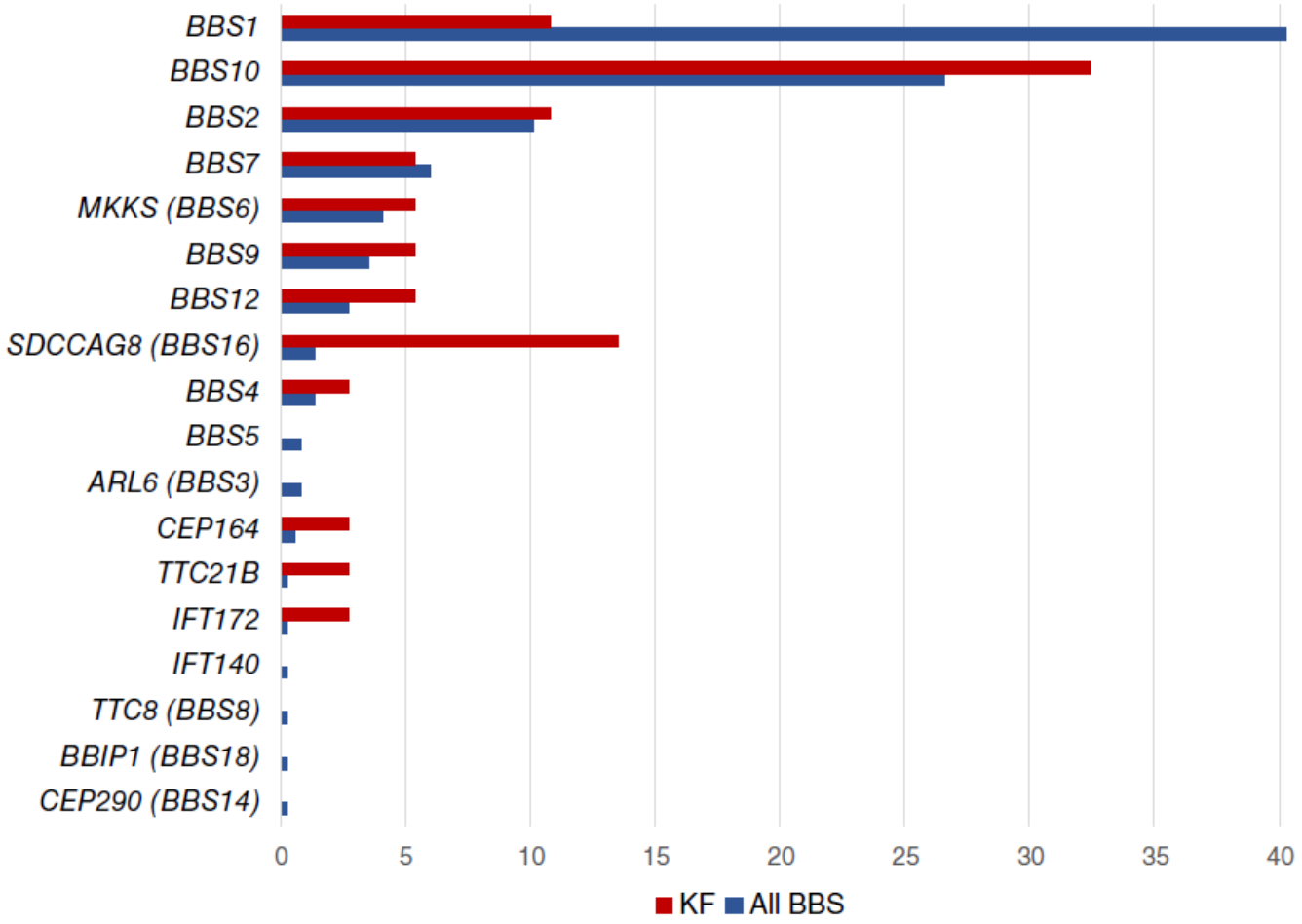
J.K.



Thank you for your attendance!

Genotypes associated with ESKD

	overall CRIBBs	ESKD
BBS1	*40,3%*	*10,8%*
BBS10	*26,6%*	*32,4%*
SDCCAG8	*<1,4%*	*13,7%*



Meyer JR, et al. Clin Genet. 2022 Apr;101(4):429-441.

WEBINAR

16/05/23

Welcome to

ERKNet/ERN-Eye/ESPN Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Syndromic Ciliopathies (Bardet Biedl)

Speaker: Jens König (ERKNet) &

Hélène Dollfus (ERN-Eye)

Moderator: Elena Levtchenko (Amsterdam, Netherlands)

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

European Reference Network ERN-EYE

Bardet-Biedl Syndrome and the eye

Hélène Dollfus

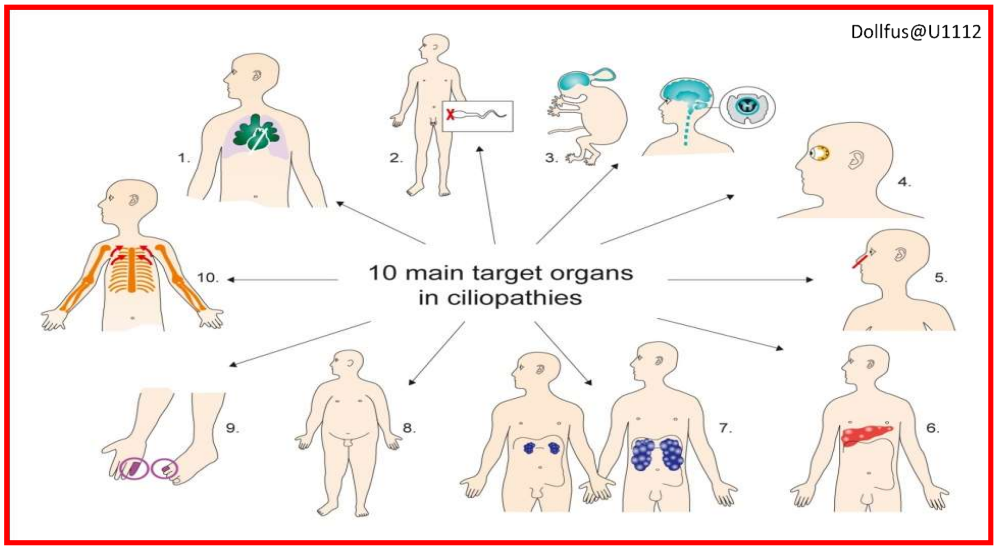
Strasbourg University Hospital

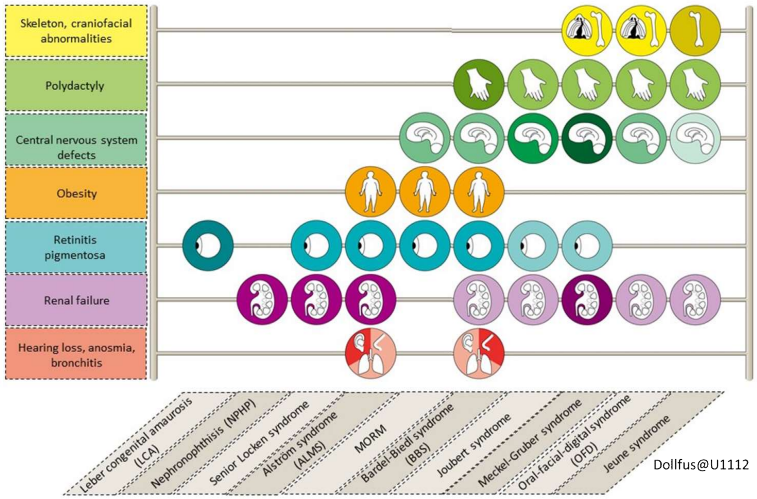
ERN-EYE

Disclosures

- Novartis
- Janssens & Janssens
- Meira-GTx
- Rhythm Pharmaceuticals
- SparingVision

Ciliopathies = a vast group of rare diseases

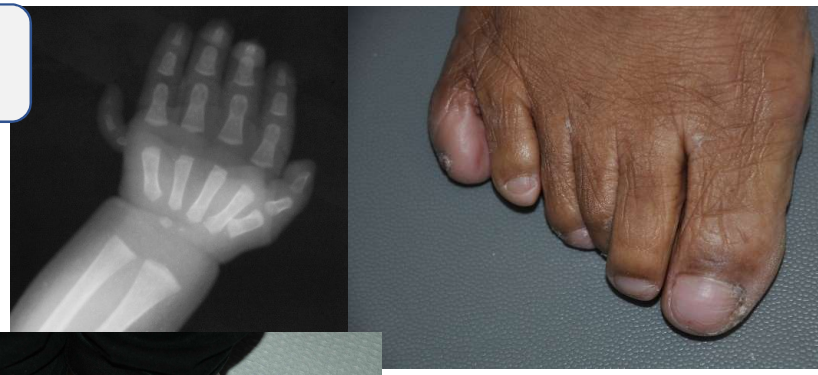


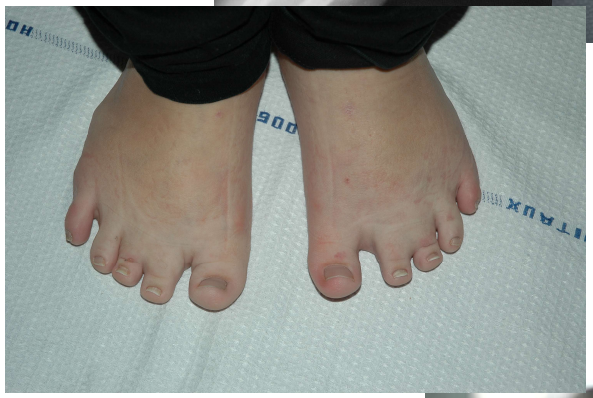


Developmental anomalies

- **Hands & feet +++**
- Kidney development
- Genital malformations
- Heterotaxia (situs inversus)
- Hirschprung
- Congenital Heart Disease
- Oro-dental anomalies
- Cranio facial
- Scoliosis

Polydactyly, brachydatyly





Neurodevelopmental features :
Intellectual disability, speech delay, hyper emotivity, anxiety, autistic features ASD , dvp psychiatric traits , …
Anosmia !

Main manifestations

- Kidney Disease: not obligatory ! reduced urinary concentration, end-stage kidney remains quite rare structural anomalies + (incl. urinary tract), HBP, voiding dysfunction
- Hypogonadism (central & peripheral) : delayed puberty, genital anomalies and abnormal testing of sexual hormones - No defect in spermatogenesis
- Endocrine : **OBESITY** (« *truncal* »)[20-86%] rapidly occuring, eating disorder reported by parents/family (hyperphagia), hypothyroidism (20%), insulin resistance & Diabetes type 2, metabolic disorders >standard obese population, HBP
- Sleeping disorder non specific but has to to be explored

Obesity in BBS can begin in childhood and increase in severity with age [1]

Although birth weight is normal, weight gain may rapidly occur in the first year of life[2]

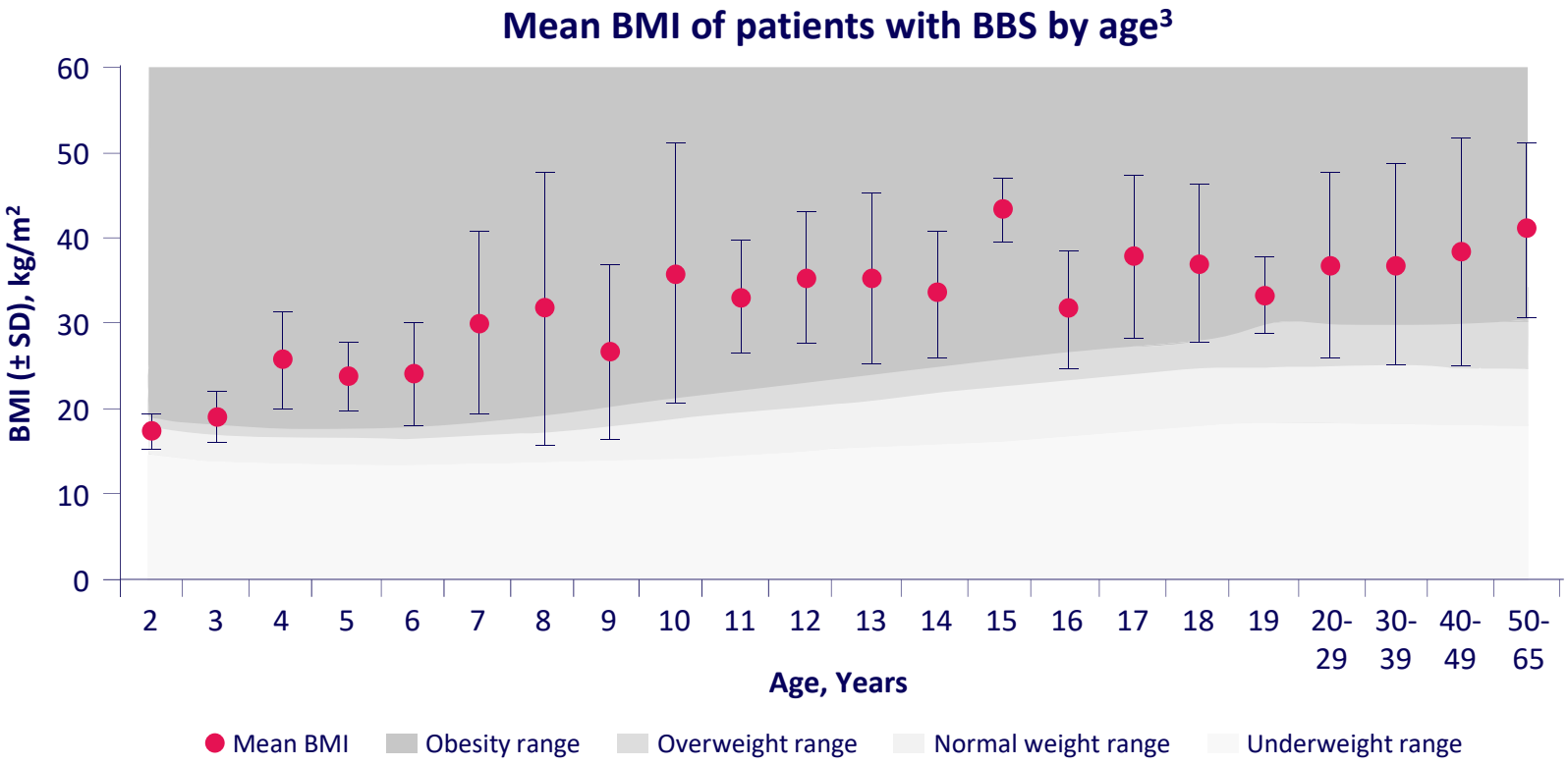


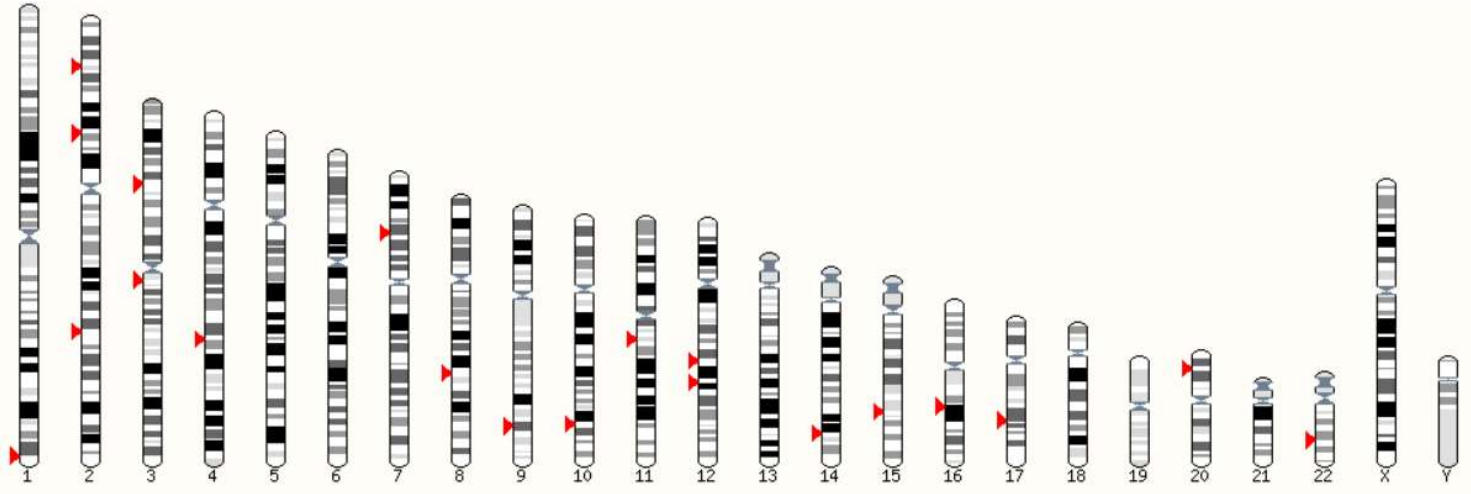
Figure adapted with permission from Marshfield Clinic Research Institute, the research division of Marshfield Clinic Health System.
BBS, Bardet-Biedl syndrome; BMI, body mass index.

1. Katsanis N, et al. *Hum Mol Genet*. 2001;10(20):2293-2299. 2. Forsythe E, Beales PL. *Eur J Hum Genet*. 2013;21(1):8-13. 3. Marshfield Clinic Research Foundation. Accessed April 24, 2020. https://www.bbs-registry.org/bbs-news/body-mass-index-patterns-in-bbs.

Bardet-Biedl Syndrome genetics

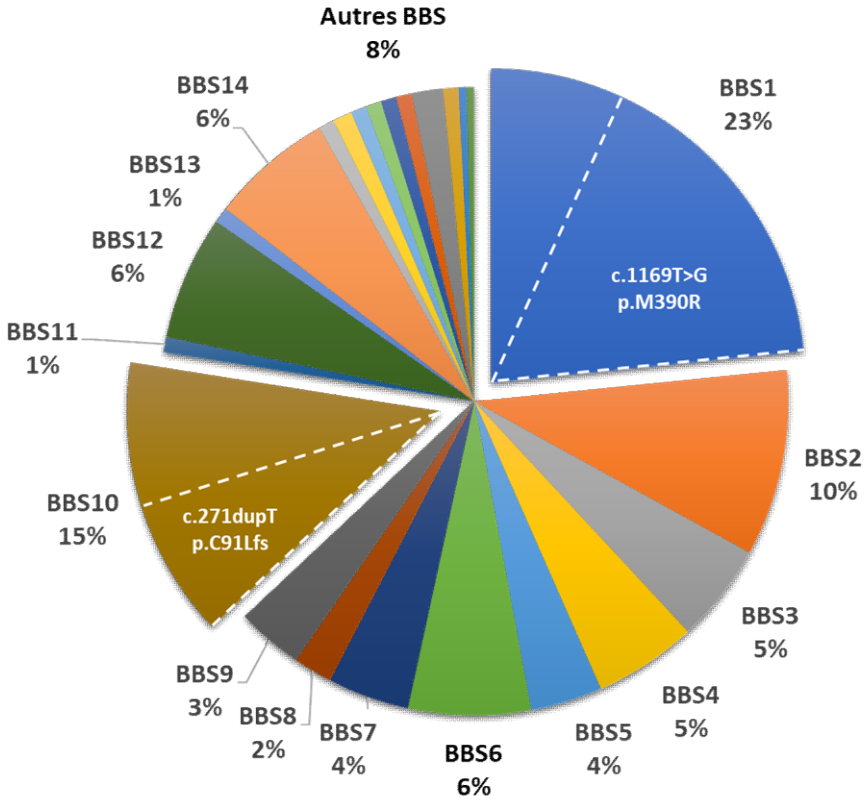
- Rare ~1/100000 - ~1/150000
- Autosomal recessive (digenic , oligogenic , triallelic)
- **High level genetic heterogenity**
- **> 24** genes BBS (> **417 exons, ~53kb CDS, > 16879 aa**)
- Clinical heterogeneity

- SANGER => PANELS => WES =WGS



Genetic diagnosis

- > 25 genes
- 2 most frequent : BBS1 & BBS10



(adapted from GeneReviews)

HGNC Gene Symbol	BBS	Synonyms
BBS1	BBS1	
BBS2	BBS2	BBS2L1
ARL6	BBS3	RP55
BBS4	BBS4	
BBS5	BBS5	
MKKS	BBS6	
BBS7	BBS7	
TTC8	BBS8	RP51
BBS9	BBS9	PTHB1
BBS10	BBS10	
TRIM32	BBS11	HT2A, TATIP
BBS12	BBS12	
MKS1	BBS13	
CEP290	BBS14	NPHP6, CEP290, MKS4, JBTS5, SLSN6
WDPCP	BBS15	fritz, hFrtz
SDCCAG8	BBS16	CCCAP, NPHP10, NY-CO-8, SLSN7
LZTFL1	BBS17	
BBIP1	BBS18	BBIP10
IFT27	BBS19	RAYL
IFT172	BBS20	NPHP17
CFAP48	BBS21	FLJ30600, CORD16, RP64, FAP418, MOT25, C8orf37
IFT74	BBS22	CCDC2
CEP19	BBS23	C3orf34
SCAPER	BBS24	ZNF291
SCLT1	BBS25?	Candidate
CEP164	BBS26?	Candidate
NPHP1	?	

FBN3, …

BBS Genetic diagnosis

- BBS is autosomal recessive

- Genetic tests:
  - Sanger (recurrent mutations BBS1 &10)
  - PANELS (variable , Kidney, RP, cilio, ect)
  - WES
  - WGS (in first intention in France –PFMG)

Biallelic pathogenic variants (class 4 or 5) for positive molecular diagnosis…

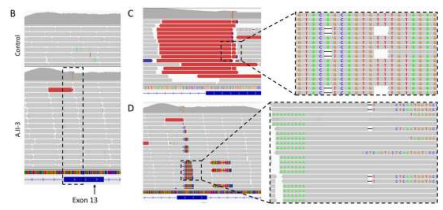
Resolving class III

Unsolved heterozygotes

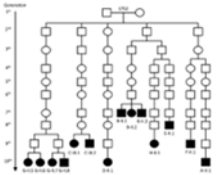
Unsolved < 10%

Prenatal or preimplantory diagnosis

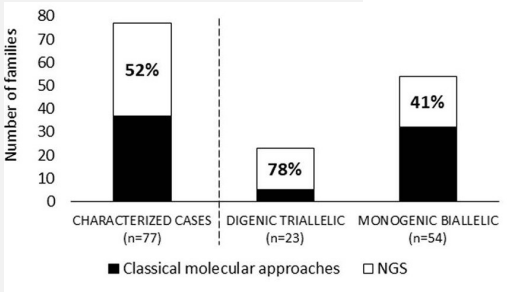
- NGS has helped to solve cases
  Example: SVAF BBS1
  Retrotransposon insertion
  (Tavares 2019, Delvallée 2021)



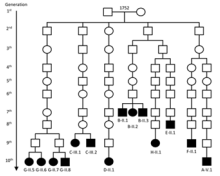
- Founder variants such as La Réunion Island for BBS3
  (Gouronc et al, 2021)



- Oligogenic inheritance : triallelism, second-site modifiers – third modifier alleles
  (Perea-Romero et al, 2022)



Funder effect
La réunion Island *BBS3*



Île de la Réunion

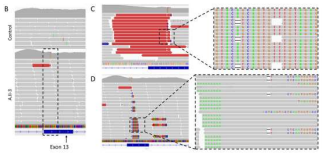
SHORT REPORT

CLINICAL GENETICS WILEY

High prevalence of Bardet-Biedl syndrome in *La Réunion* Island is due to a founder variant in *ARL6/BBS3*

Aurélie Gouronc[1] | Vincent Zilliox[2] | Marie-Line Jacquemont[3] | Françoise Darcel[4] | Anne-Sophie Leuvrey[1] | Elsa Nourisson[1] | Manuela Antin[1] | Jean-Luc Alessandri[5] | Bérénice Doray[6] | Paul Gueguen[6] | Frédérique Payet[6] | Hanitra Randrianaivo[3] | Corinne Stoetzel[7] | Sophie Scheidecker[1,7] | Hugues Flodrops[8] | Hélène Dollfus[7,9,10] | Jean Muller[1,2,7]

New mutationnal mechanism



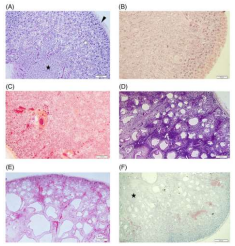
HHS Public Access
Author manuscript
Clin Genet. Author manuscript; available in PMC 2021 July 02.

Published in final edited form as:
Clin Genet. 2021 February ; 99(2): 318–324. doi:10.1111/cge.13878.

A *BBS1* SVA F retrotransposon insertion is a frequent cause of Bardet-Biedl syndrome

Clarisse Delvallée[1], Samuel Nicaise[1], Manuela Antin[2], Anne-Sophie Leuvrey[2], Elsa Nourisson[2], Carmen C. Leitch[3], Georgios Kellaris[3], Corinne Stoetzel[1], Véronique Geoffroy[1], Sophie Scheidecker[1,2], Boris Keren[4,5], Christel Depienne[4,6], Joakim Klar[7], Niklas Dahl[7], Jean-François Deleuze[8], Emmanuelle Génin[9], Richard Redon[10], Florence Demurger[11], Koenraad Devriendt[12], Michèle Mathieu-Dramard[13], Christine Poitou-Bernert[14], Sylvie Odent[15,16], Nicholas Katsanis[3,17], Jean-Louis Mandel[2,18], Erica E. Davis[3,17], Hélène Dollfus[1,19,20], Jean Muller[1,2]

Large series of Fœtus BBS

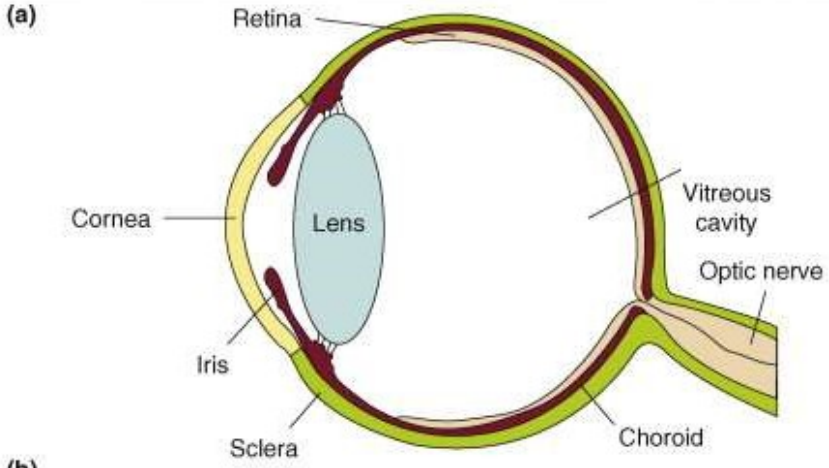


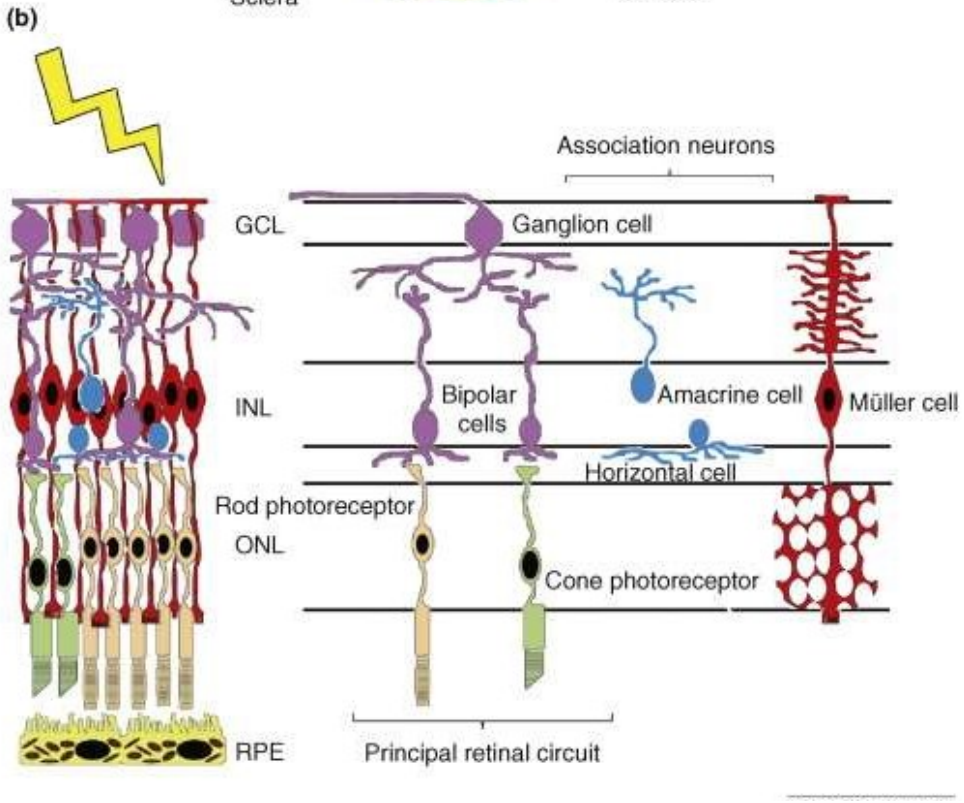
WILEY CLINICAL GENETICS

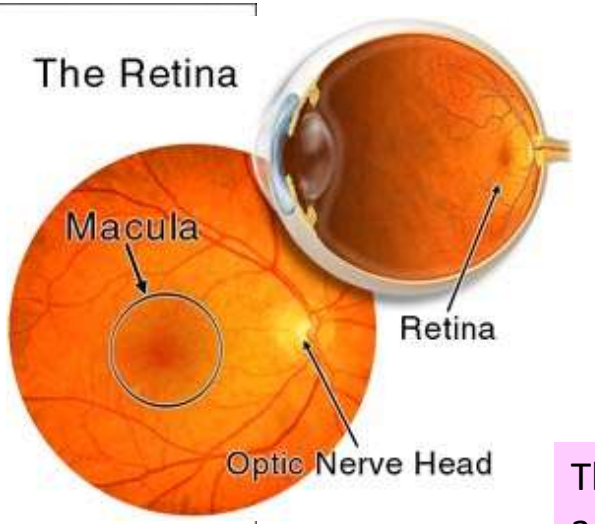
ORIGINAL ARTICLE

Bardet-Biedl syndrome: Antenatal presentation of forty-five fetuses with biallelic pathogenic variants in known Bardet-Biedl syndrome genes

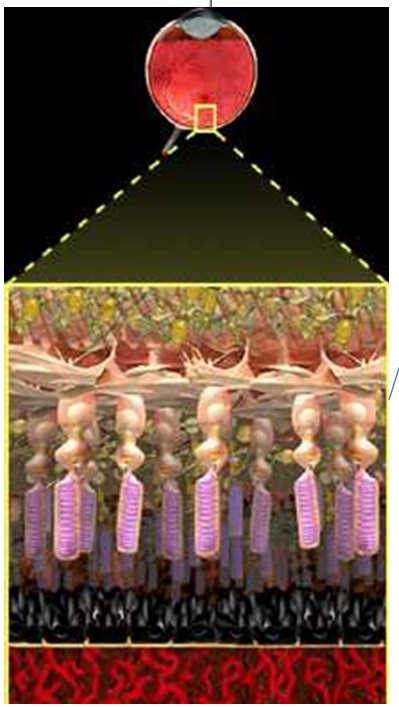
Laura Mary[1,2] | Kirsley Chennen[2,3] | Corinne Stoetzel[2] | Manuela Antin[1] | Anne Leuvrey[1] | Elsa Nourisson[1] | Elisabeth Alanio-Detton[4] | Maria C. Antal[5,6] | Tania Attié-Bitach[7,8] | Patrice Bouvagnet[9] | Raymonde Bouvier[10] | Annie Buenerd[10] | Alix Clémenson[11] | Louise Devisme[12] | Bernard Gasser[13] | Brigitte Gilbert-Dussardier[14,15] | Fabien Guimiot[16] | Philippe Khau Van Kien[17] | Brigitte Leroy[18] | Philippe Loget[19] | Jelena Martinovic[20] | Fanny Pelluard[21,22] | Marie-Josée Perez[23] | Florence Petit[24] | Lucile Pinson[25] | Caroline Rooryck-Thambo[26] | Olivier Poch[3] | Hélène Dollfus[2,27,28] | Elise Schaefer[2,27] | Jean Muller[1,2]

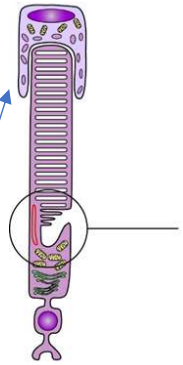


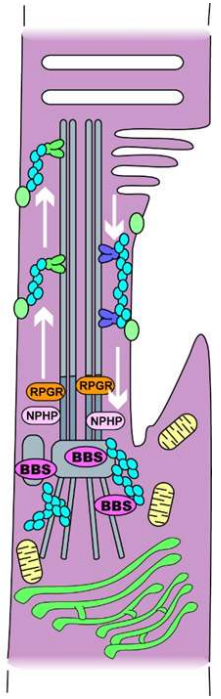




The photoreceptor is a modified cilia







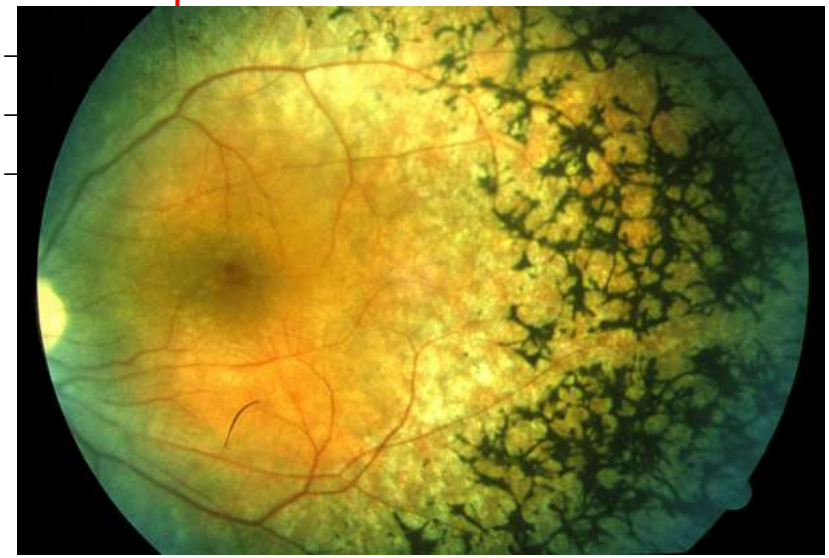
Typical Retinitis Pigmentosa

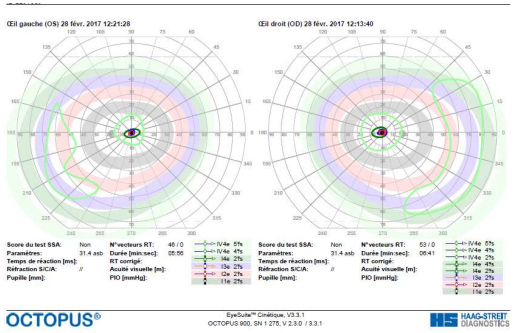
- Nyctaploia
- Visual field progressive constriction
- Loss of central vision

- Imaging & Functional evaluation :

BCVA, AERG, OCT, Autofluorescence, ect …

- Fundus aspect :





Visual handicap & BBS

- **Visual impairement:** the best eye is not more then 3/10 and/or the Visual Field not more then 20°
- **Legal Blindness:** better eye is not more then 1/20 and/or the visual field is not more then 10°
- WHO 3 categories
- Category I : Severe visual impairement « counting fingers at 1m »
- Category II : almsot blind : « see hand move at 1m » En pratique, le sujet voit bouger la main à 1 mètre.
- Catégory III : Total blindness no percpetion of ligth

ICD-9-CM RANGES		EQUIVALENT NOTATIONS		TRUE SNELLEN FRACTIONS (numerator = test distance)					Visual Angle Notations		VISUAL ACUITY SCORE
		Deci-mal	US	6.3 m	*6 m*	5 m	4 m	1 m	MAR (1/V)	Log MAR	
(Near-) Normal Vision	Range of Normal Vision	1.6	20/12.5	6.3/4	*6/3.8*	5/3.2	4/2.5	1/0.63	0.63	-0.2	110
		1.25	20/16	6.3/5	*6/4.8*	5/4	4/3	1/0.8	0.8	–0.1	105
		1.0	**20/20**	**6.3/6.3**	***6/6***	**5/5**	**4/4**	**1/1**	**1.0**	**0**	**100**
		0.8	20/25	6.3/8	*6/7.5*	5/6.3	4/5	1/1.25	1.25	+0.1	95
	Near-Normal Vision	0.63	20/32	6.3/10	*6/9.5*	5/8	4/6.3	1/1.6	1.6	0.2	90
		0.5	20/40	6.3/12.5	*6/12*	5/10	4/8	1/2	2.0	0.3	85
		0.4	20/50	6.3/16	*6/15*	5/12.5	4/10	1/2.5	2.5	0.4	80
		0.32	20/63	6.3/20	*6/19*	5/16	4/12.5	1/3.2	3.2	0.5	75
Low Vision	Moderate Low Vision	0.25	20/80	6.3/25	*6/24*	5/20	4/16	1/4	4	0.6	70
		0.20	20/100	6.3/32	*6/30*	5/25	4/20	1/5	5	0.7	65
		0.16	20/125	6.3/40	*6/38*	5/32	4/25	1/6.3	6.3	0.8	60
		0.125	20/160	6.3/50	*6/48*	5/40	4/32	1/8	8	0.9	55
	Severe Low Vision	**0.10**	**20/200**	**6.3/63**	***6/60***	**5/50**	**4/40**	**1/10**	**10**	**+1.0**	**50**
		0.08	20/250	6.3/80	*6/75*	5/63	4/50	1/12.5	12.5	1.1	45
		0.063	20/320	6.3/100	*6/95*	5/80	4/63	1/16	16	1.2	40
		0.05	20/400	6.3/125	*6/120*	5/100	4/80	1/20	20	1.3	35
	Profound Low Vision	0.04	20/500	6.3/160	*6/150*	5/125	4/100	1/25	25	1.4	30
		0.03	20/630	6.3/200	*6/190*	5/160	4/125	1/32	32	1.5	25
		0.025	20/800	6.3/250	*6/240*	5/200	4/160	1/40	40	1.6	20
		0.02	20/1000	6.3/320	*6/300*	5/250	4/200	1/50	50	1.7	15
(Near-) Blind-ness	Near-Blindness	0.016	20/1250	6.3/400	*6/380*	5/320	4/250	1/63	63	1.8	10
		0.0125	20/1600	6.3/500	*6/480*	5/400	4/320	1/80	80	1.9	5
		0.01	**20/2000**	**6.3/630**	***6/600***	**5/500**	**4/400**	**1/100**	**100**	**+2.0**	**0**
		---	---	---	---	---	---	---			---
	Blindness	No Light Perception (NLP)									

Ciliopathies can lead to retinal degeneration

- Bardet-Bield : 100% penetrance for retinal dystrophy
- Usually occurs in childhood with early onset retinal degeneration
- Most common syndromic RP (with Usher syndrome)

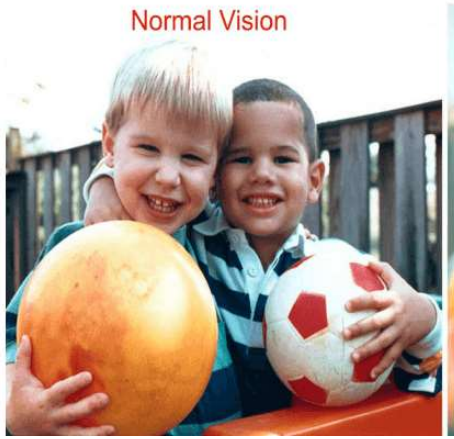
- **Early onset retinal dystrophy** : Diagnosis around 5-10 years old , starts around 4-5 years old
- **Nyctalopia**, **photophobia, visual field defects , nystagmus**, low vision
- Legal blindness around age 15
- Diagnosis relies on : retinal **imaging** and Electroretinogramm (**ERG**)

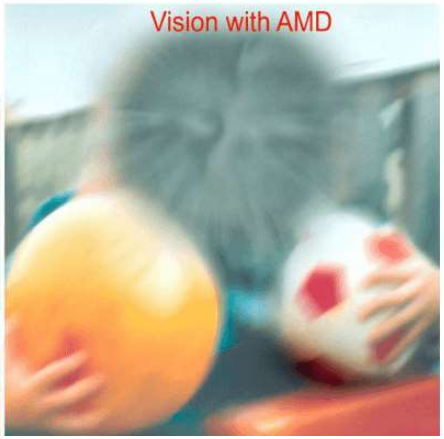
Manifestations

- (early onset photophobia and nystagmus => Alström syndrome)
- Difficult night /dim light vision (nyctalopia)
- Visual field progressive restriction => clumsiness – bumping , …
- Central vision can be affected early => playing – reading –color impairement , …
- Secondary : nystagmus, strasbismus ,

Normal vision

As seen by a person with retinitis pigmentosa





Electroretinogramme ERG

- Test retinal cells with ligth stimulus
- Alteration detectable even if fundus seems normal

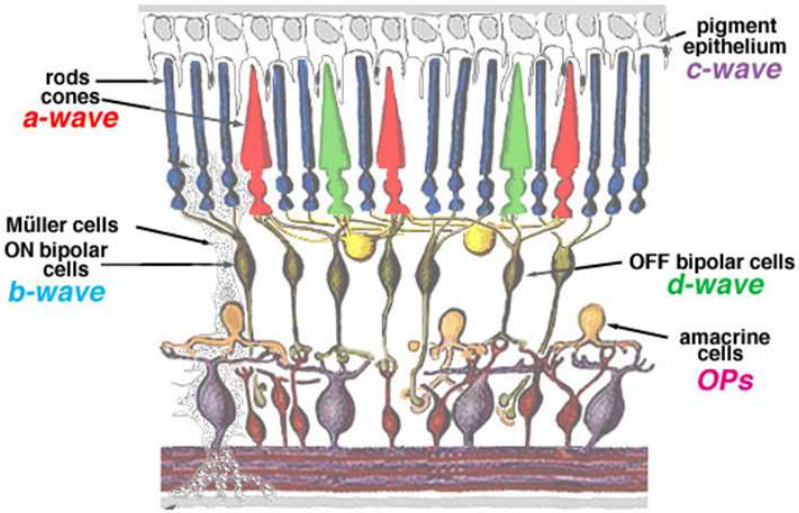


Fig.3 Cartoon of the retina to show where the major components of the ERG originate.

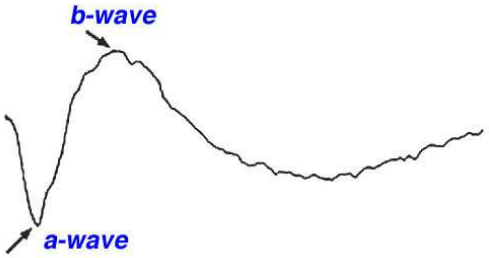


Fig.1 The biphasic waveform of the ERG of a normal patient.

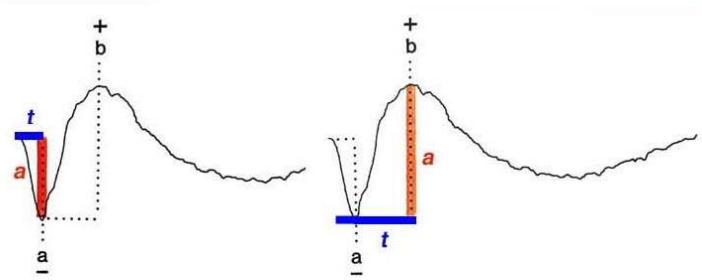
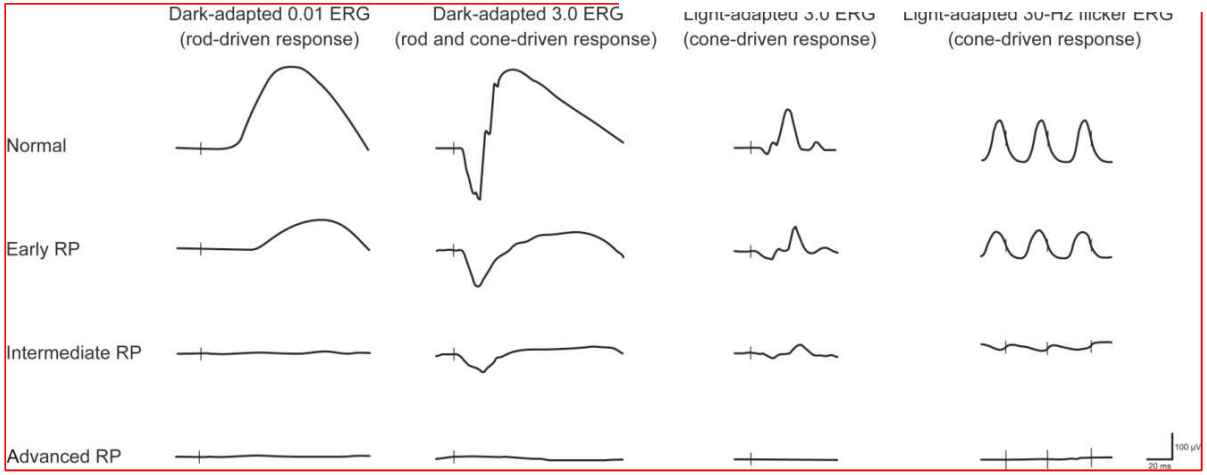
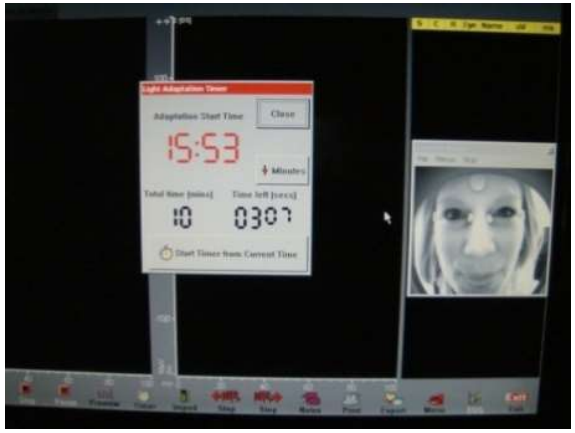
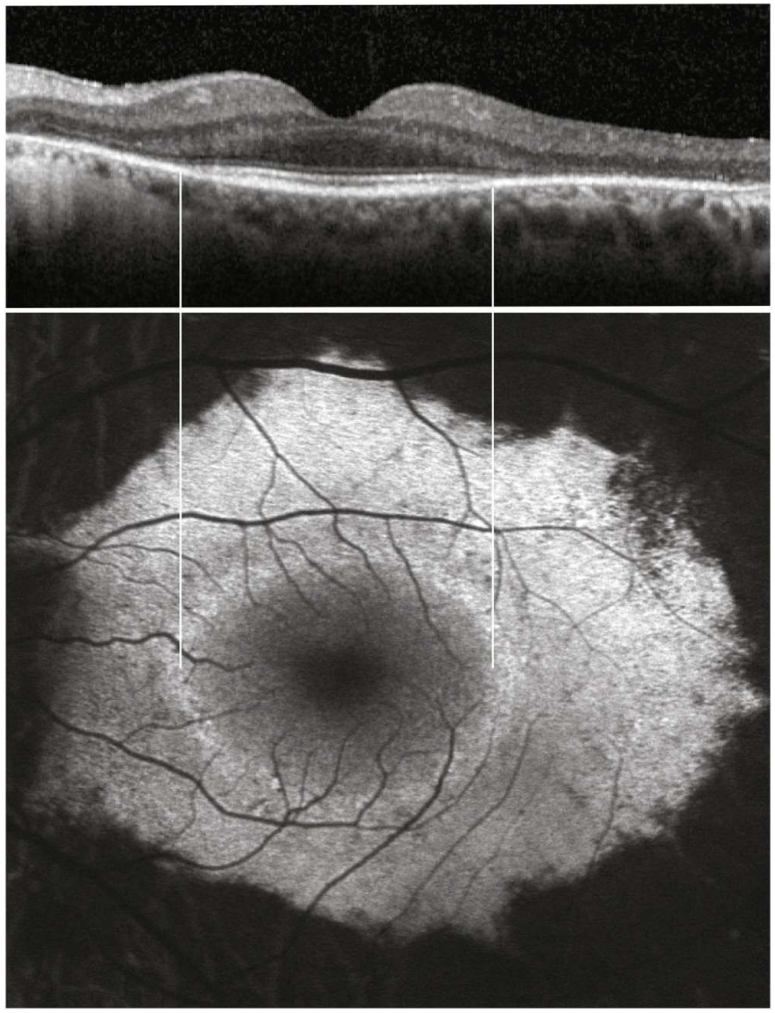
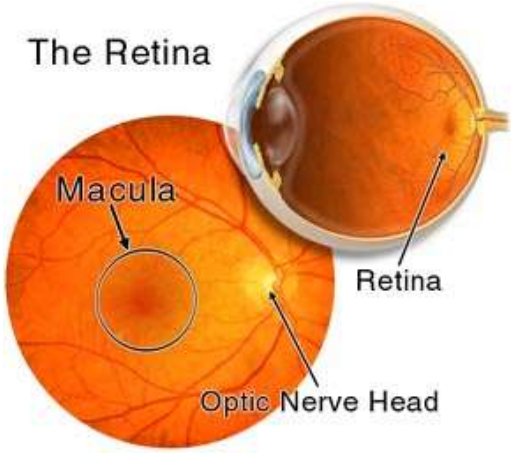


Fig.2 Amplitude and implicit time measurements of the ERG waveform.




Light Adaptation Timer
Adaptation Start Time
Close
15:53
Minutes
Total time [min:s]
Time left [sec:s]
10
0307
Start Timer from Current Time





OCT et autofluorescence d'un patient avec une rétinopathie pigmentaire:

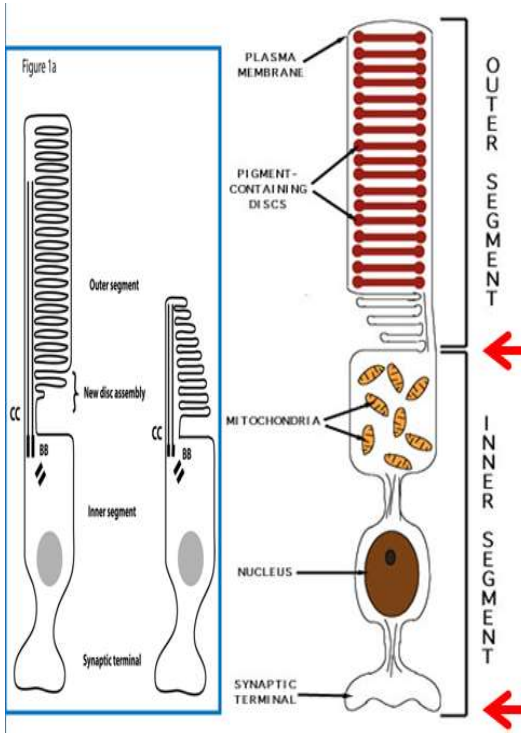
-Perte des couches externe de la rétine périmaculaire

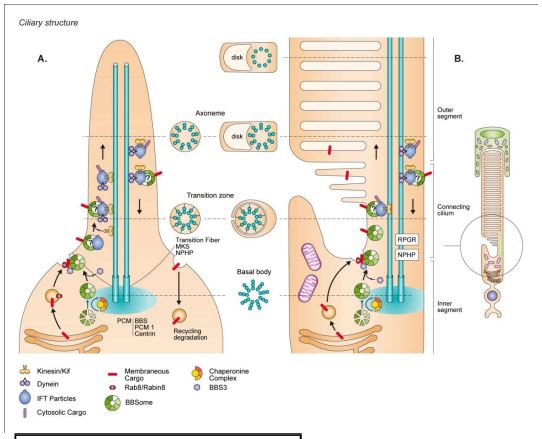
-Zone ellipsoïde

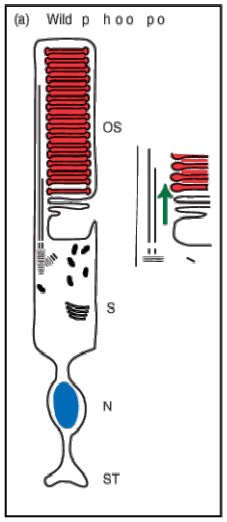
-=> correspondance avec anneau hyperfluorescent

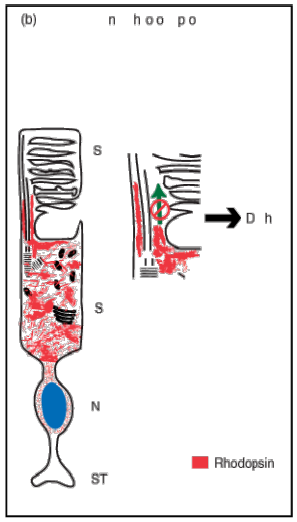
Verbakel SK, et al, Prog Retin Eye Res. 2018

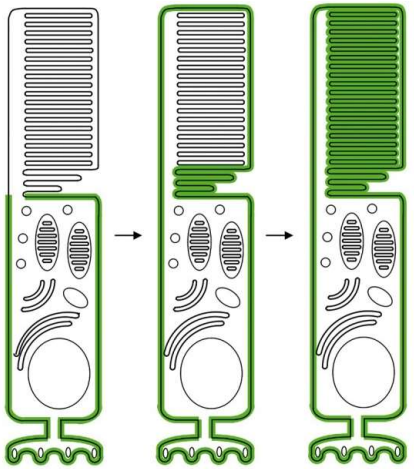
Retinal degeneration in ciliopathies











Seo and Datta 2017

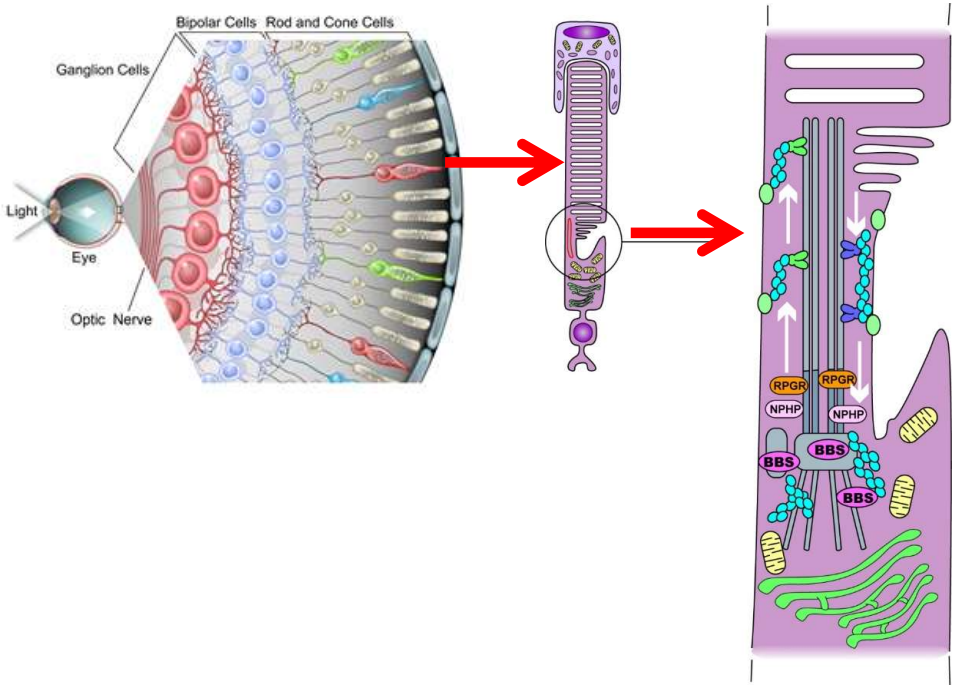
Photoreceptors have a ciliary structure

Many animal models for BBS : *Paramecium, Chlamydomonas Reinardtii, Trypanosoma brucei, Caenorhabditis elegans, Dario, mouse, Rhesus macaque*

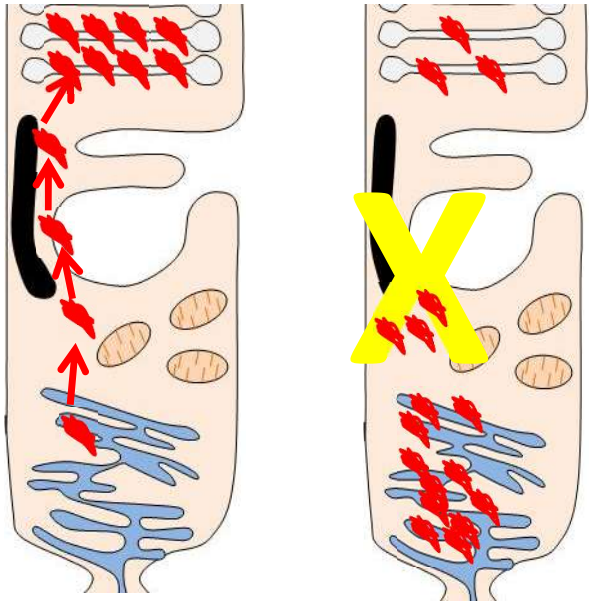
Mecanism 2 X : accumulation of proteins in the Inner Segment and/or accumulation of unwanted proteins in the Outer Segment that cannot return in the Inner Segment machinery

(Review Delvallee & Dollfus, in press)

RETINAL DEGENERATION



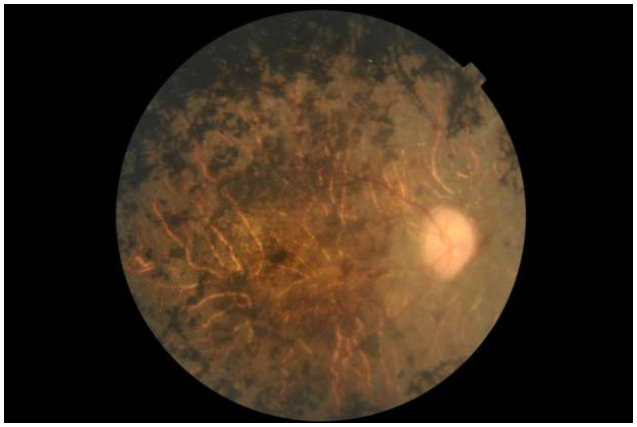
Intra Flagellar Traffic (IFT)

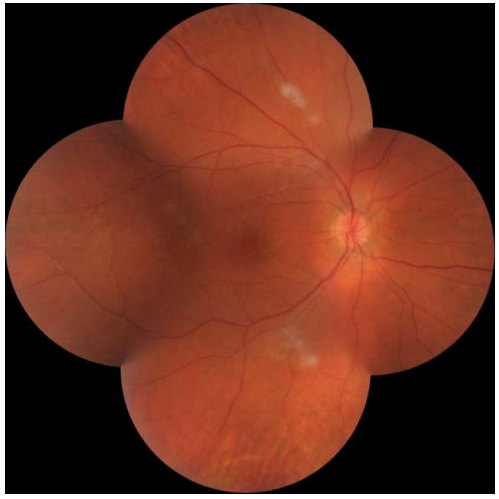


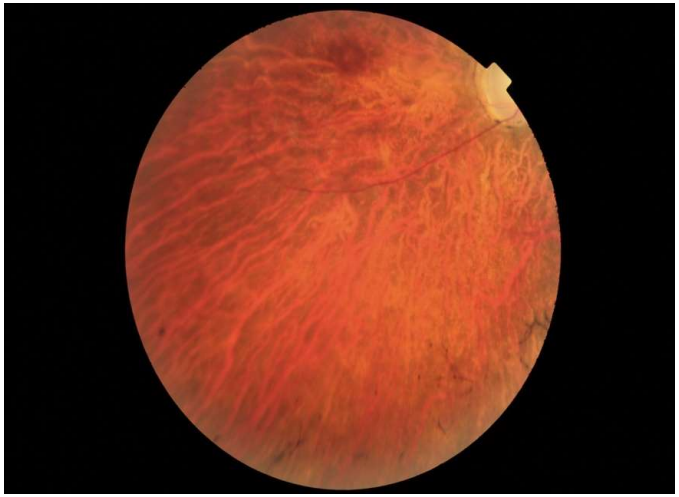
1° PROTEIN OVERLOAD
2° ER STRESS
3° UPR *Unfolded protein response*
4° APOPTOSIS

Clinical variability i.e the Retina

- Early onset RP
- Visual symptoms before the age of 5
- ERG early defects => flat
- Poorly sighted education
- Legal blindness around 15
- Adults are usuallly highly handicaped



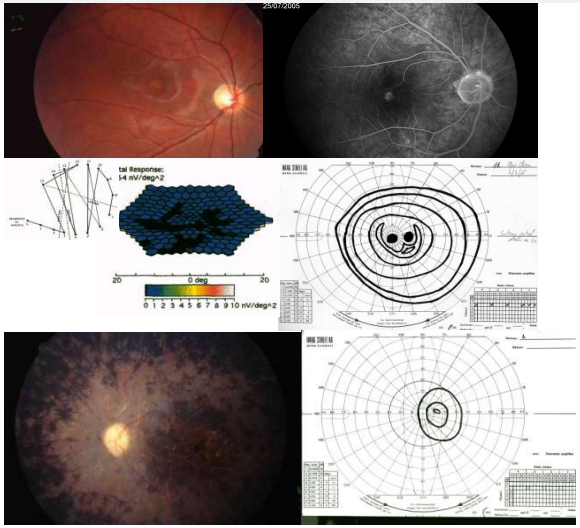


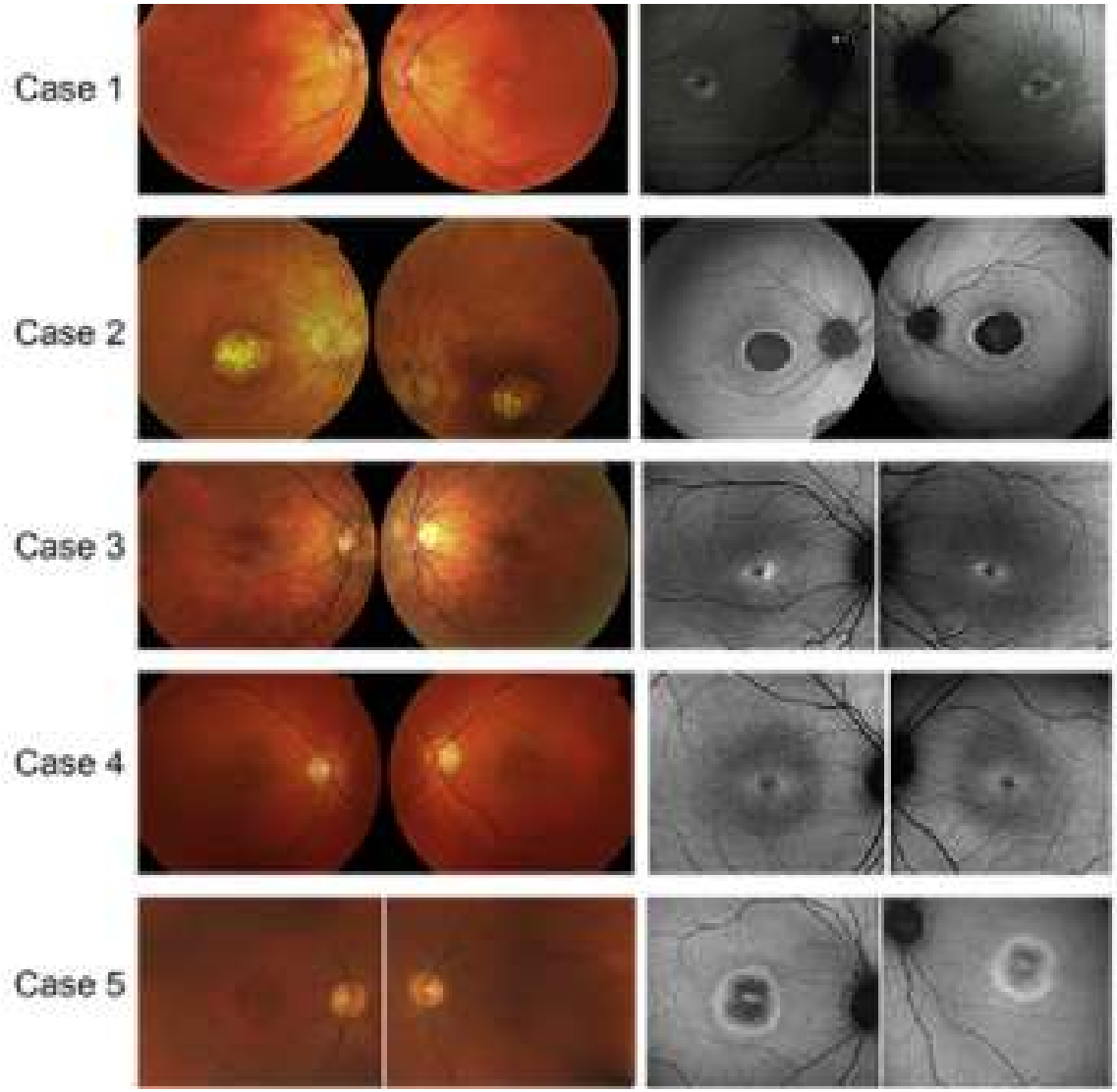


Retinal dystrophy

- *Rod-Cone* & *Cone–Rod* most often « global »
- Late onset possible
- Major central forms exists

Predominantly Cone-System Dysfunction as Rare Form of Retinal Degener
Molecularly Confirmed Bardet-Biedl Syndrome.
Scheidecker S et al Am J Ophtalmol 2015

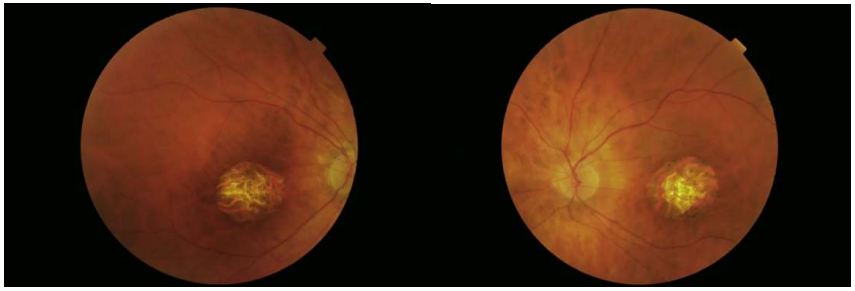


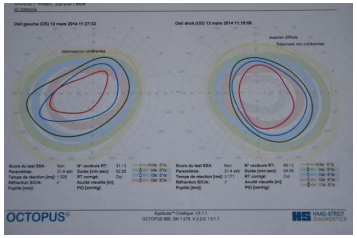


Extreme phenotype: Maculopathy

(Scheidecker et al, 2015)

- *Polydactyly*
- *Mild learning difficulties*
- *Retinal degeneration since the age of 8*
- *Notion of nivaquine intake for a few months*
- ***BBS12* p.[P159L];[I346T]**

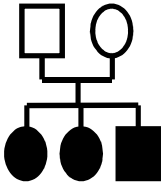




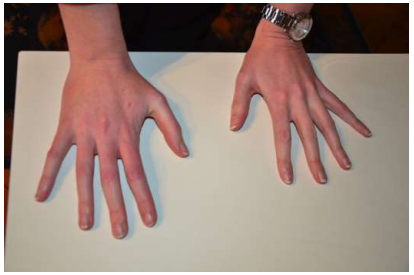
Extreme phenotype: late onset….

(Scheidecker et al, 2015)

HOMOZYGOTE for Mutation
p.[M390R];[M390R]
BBS1 gene
Polydactyly
Obesity
Slowness of mind
Psychiatric problems



RETINA :
VA diminishes at 9 years old
Normal fundus at 10
ERG normal at 14
At 31 yo: AV OD 1/13ème P4 et OG 2,4/10ème P4



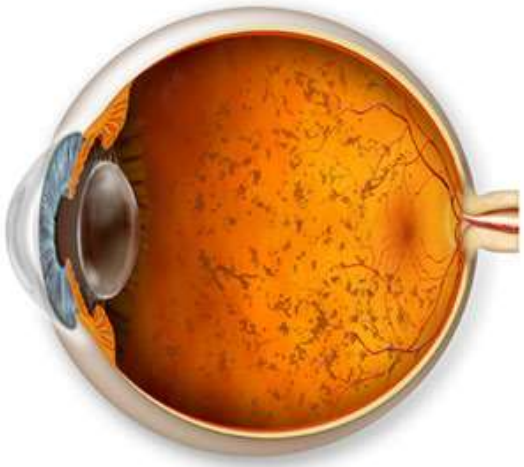
ISOLATED and SYDNROMIC IRD's: identical genes ?

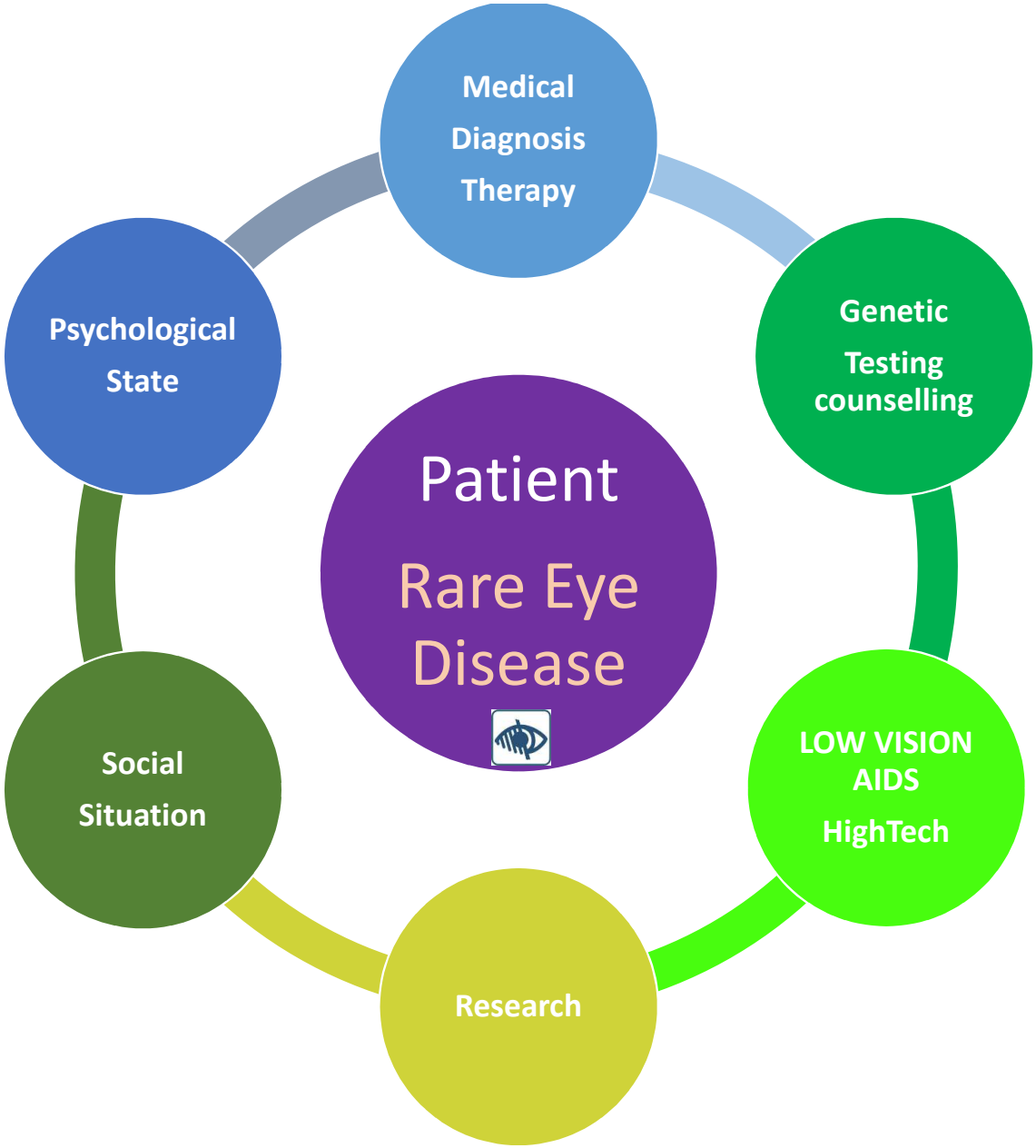
USHER SYNDROME

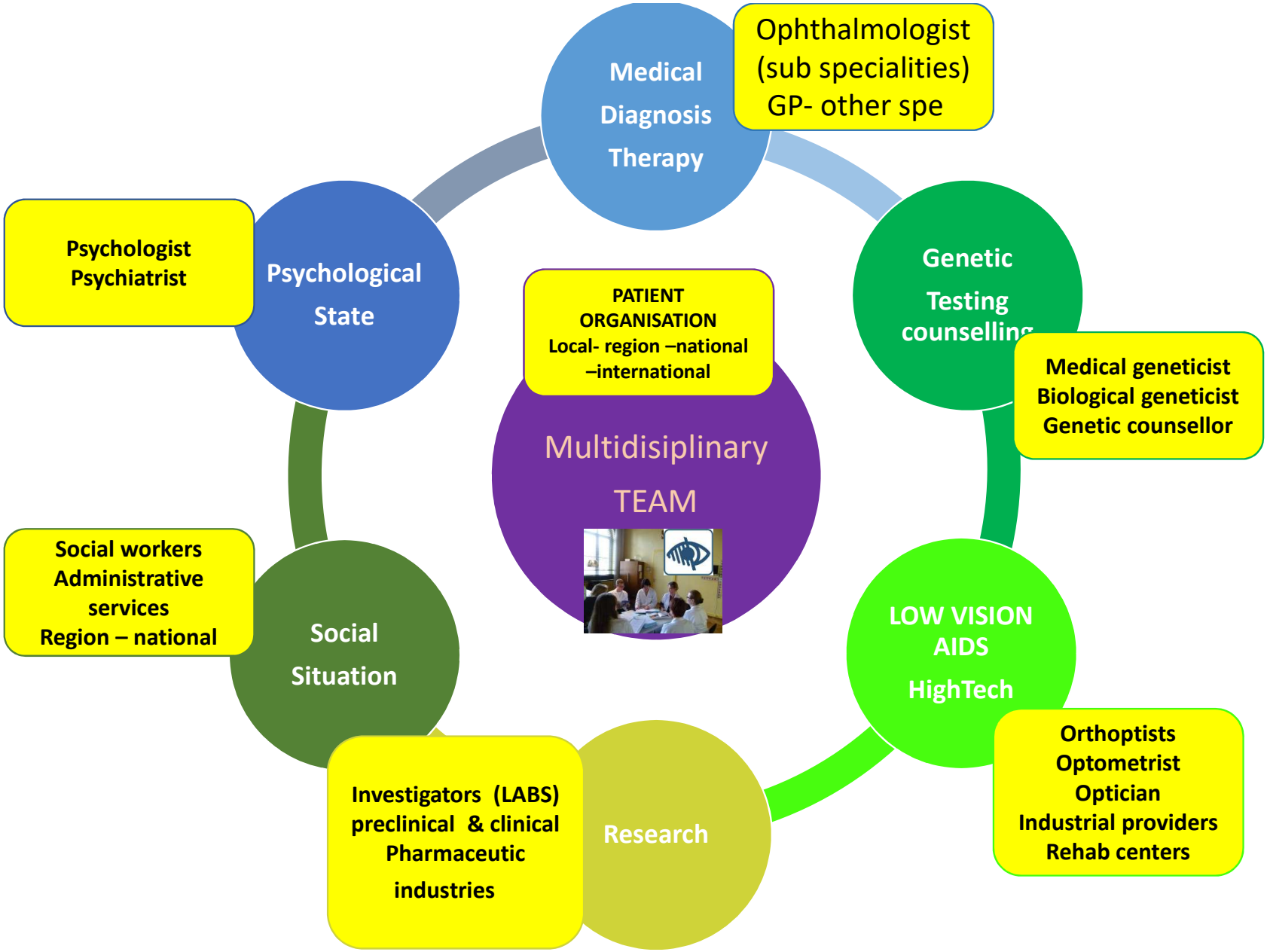
- USH2A: Isolated RP or Usher syndrome (Seydahami et al, 2004)

CILIOPATHIES

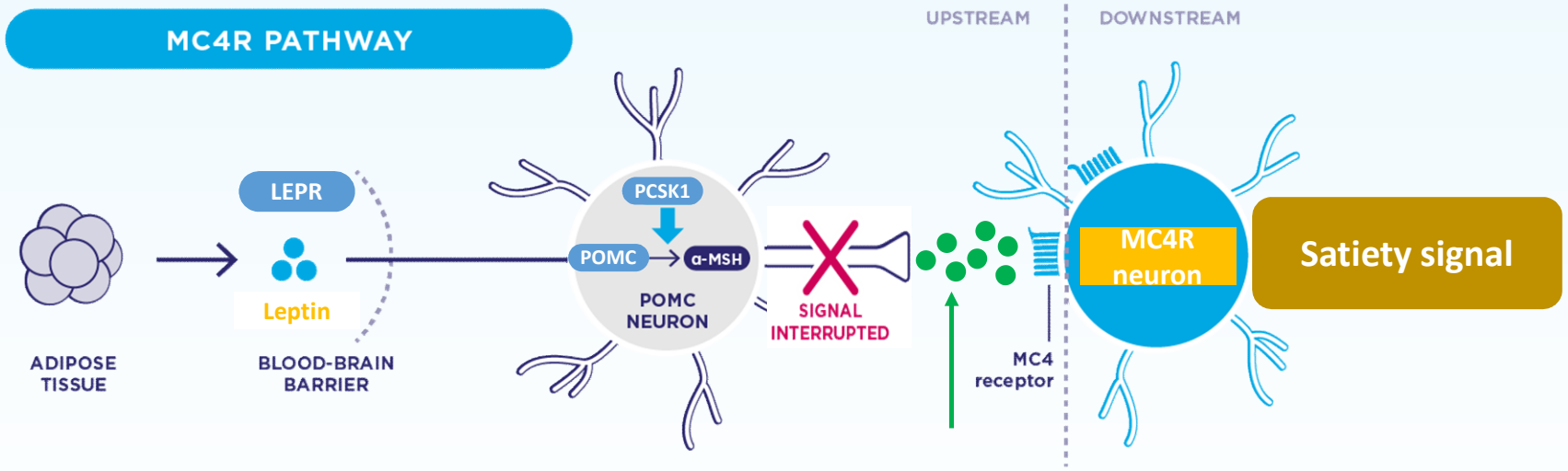
- **CEP290/NPHP6** (Den Hollander et al, 2006)
- **BBS3** (Aldahmesh, 2009)
- **BBS8** (Riazzudin et al, 2010)
- **BBS1** (Estrada- Cuzanao et al, 2012)
- **BBS10** (Grudzinka Pechhacker,2021)
- **BBS21** (Kahn et al, 2016)
- **IFT 172** (Bujakowska et al, 2015)
- **IFT140** (Hull S, 2016)
- **AHI1** (N'Guyen et al, 2017)




Medical
Diagnosis
Therapy
Genetic
Testing
counselling
LOW VISION
AIDS
HighTech
Research
Social
Situation
Psychological
State
Patient
Rare Eye
Disease


Medical
Diagnosis
Therapy
Ophthalmologist
(sub specialities)
GP- other spe
Genetic
Testing
counselling
Medical geneticist
Biological geneticist
Genetic counsellor
LOW VISION
AIDS
HighTech
Orthoptists
Optometrist
Optician
Industrial providers
Rehab centers
Research
Investigators (LABS)
preclinical & clinical
Pharmaceutic
industries
Social
Situation
Social workers
Administrative
services
Region – national
Psychological
State
Psychologist
Psychiatrist
PATIENT
ORGANISATION
Local- region –national
–international
Multidisiplinary
TEAM

Setmelanotide:
MC4R agonist that restores the signal at the hypothalamic level

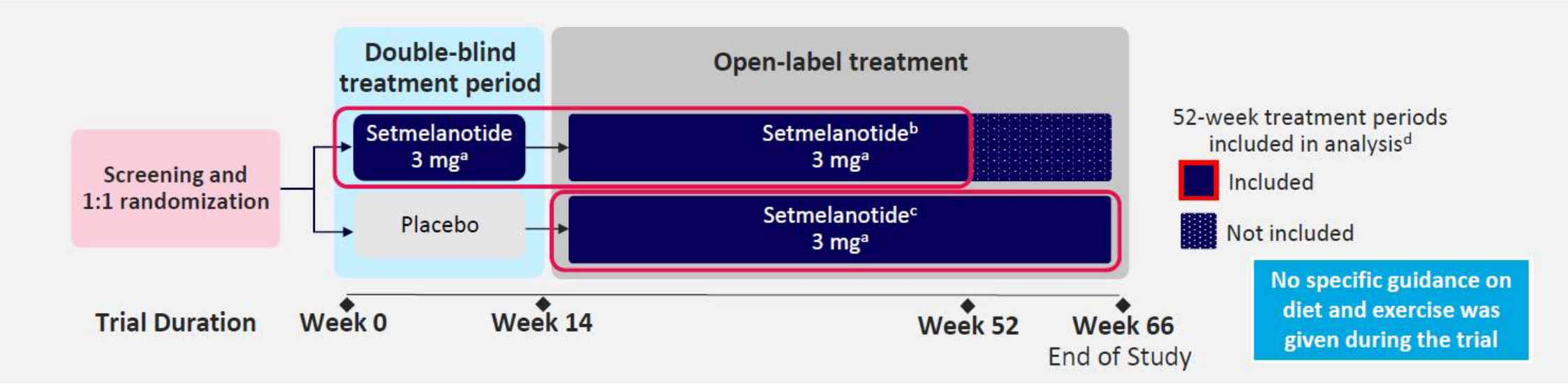


- Reduction of hyperphagia
- Increased energy expenditure

- Weight and BMI reduction
- Improved quality of life

Setmelanotide MC4R agonist, mimics the action of α-MSH

Phase 3 SETMELANOTIDE



In patients with BBS and obesity, after 1 year of treatment with setmelanotide:

- A clinically and statistically significant weight loss in adults
- an improvement in BMI z-score in children and adolescents
- a clinically significant reduction in hunger scores
- an increase in QoL scores

Setmelanotide was well tolerated in accordance with the profile established in previous trials

IMCIVREE® (setmelanotide)

Treatment of obesity and hunger control associated with genetically confirmed **biallelic pro-opiomelanocortin (POMC) loss of function,** including PCSK1 deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children aged 6 years and older

November 2020
FDA approval

July 2021
EMA approval

January 2022
Early access approval
in France

BBS indication extension - FDA and EMA
Treatment of obesity and hunger control associated with **Bardet-Biedl Syndrome (BBS)** in adults and children aged 6 years and older

BBS indication - Early Access France
Treatment of obesity and hunger control associated with genetically confirmed **Bardet-Biedl syndrome (BBS)** in adults and children aged 6 years and older

June 2022
FDA approval

September 2022
EMA approval

July 2022
Early access approval
in France

Setmelanotide clinical development

	Diseases	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	Registration	Market authorization
SETMELANOTIDE	POMC / PCSK1 deficiencies					US EU	US EU
	LEPR deficiency					US EU	US EU
	Bardet-Biedl Syndrome					US EU	US EU
	Alström						
	EMANATE trial: - Heterozygous POMC/PCSK1 & LEPR deficiencies - - Heterozygous or homozygous NCOA1 / SH2B1 deficiencies						
	Pediatrics trial (2 – 5 years)						
	Hypothalamic obesity						
	Weekly trial						
	DAYBREAK trial: Genes involved in MC4R pathway						

European Market Access: IMCIVREE® available in 8 european countries

Germany Monogenic obesity + BBS	▪ IMCIVREE® commercial availability since June 2022 for monogenic obesity and April 2023 for BBS 
France Monogenic obesity + BBS	▪ Early access since January 2022 for monogenic obesity and since July 2022 for BBS 
Italy, NL,UK, Austria, TK, Spain Monogenic obesity	▪ IMCIVREE® commercial availability since Q3-Q4 2022 since Q1 2023 

BBS Early Access Program IMCIVREE® in France: 7th July 2022

HAUTE AUTORITÉ DE SANTÉ

Indication:

IMCIVREE® (setmelanotide) is indicated for the treatment of obesity and hunger control associated with Bardet-Biedl Syndrome (BBS), in adults and children aged 6 years and older

Conditions for prescription and supply:

- Hospital prescription.
- Initial prescription and renewal reserved for specialists in endocrinology-diabetology-nutrition, pediatrics and medical genetics.
- IMCIVREE should be prescribed and monitored by a doctor specializing in obesity with underlying genetic etiology.
- Contact with the expert centers is recommended.

Eligibility criteria:

- Adult: BMI ≥ 30 kg / m² and/or hyperphagia
- Child ≥ 6 years old / Adolescent: obesity with weight ≥ 97e percentile (BMI-Z score ≥ + 2DS) and/or hyperphagia

Non-eligibility criteria:

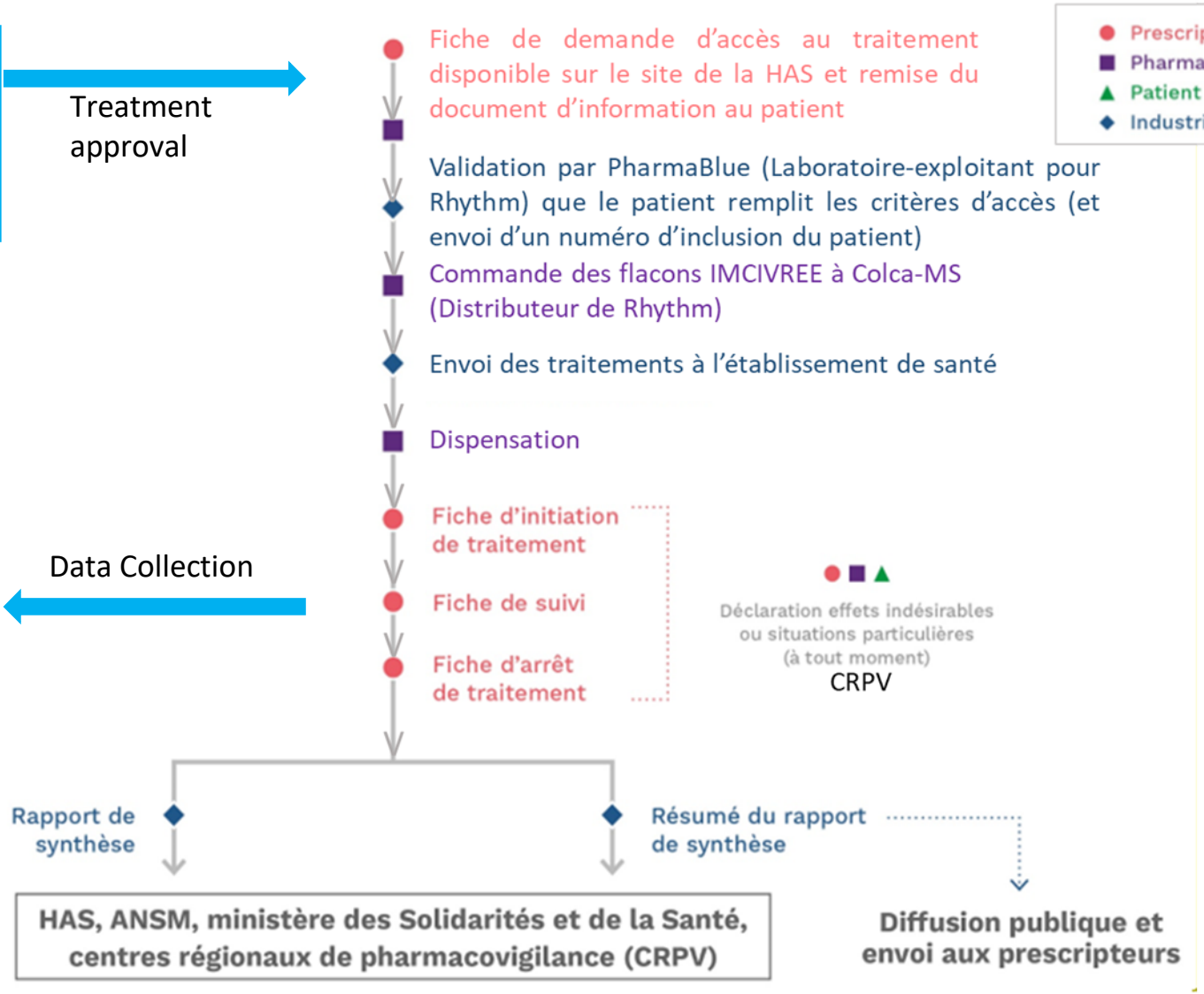
- Hepatic impairment
- End-stage renal disease
- Significant hypersensitivity to study drug
- Suicidal ideation

Practical modalities of treatment and follow-up of patients in France

Centre de Référence pour les Affections Rares en Génétique Ophtalmologique

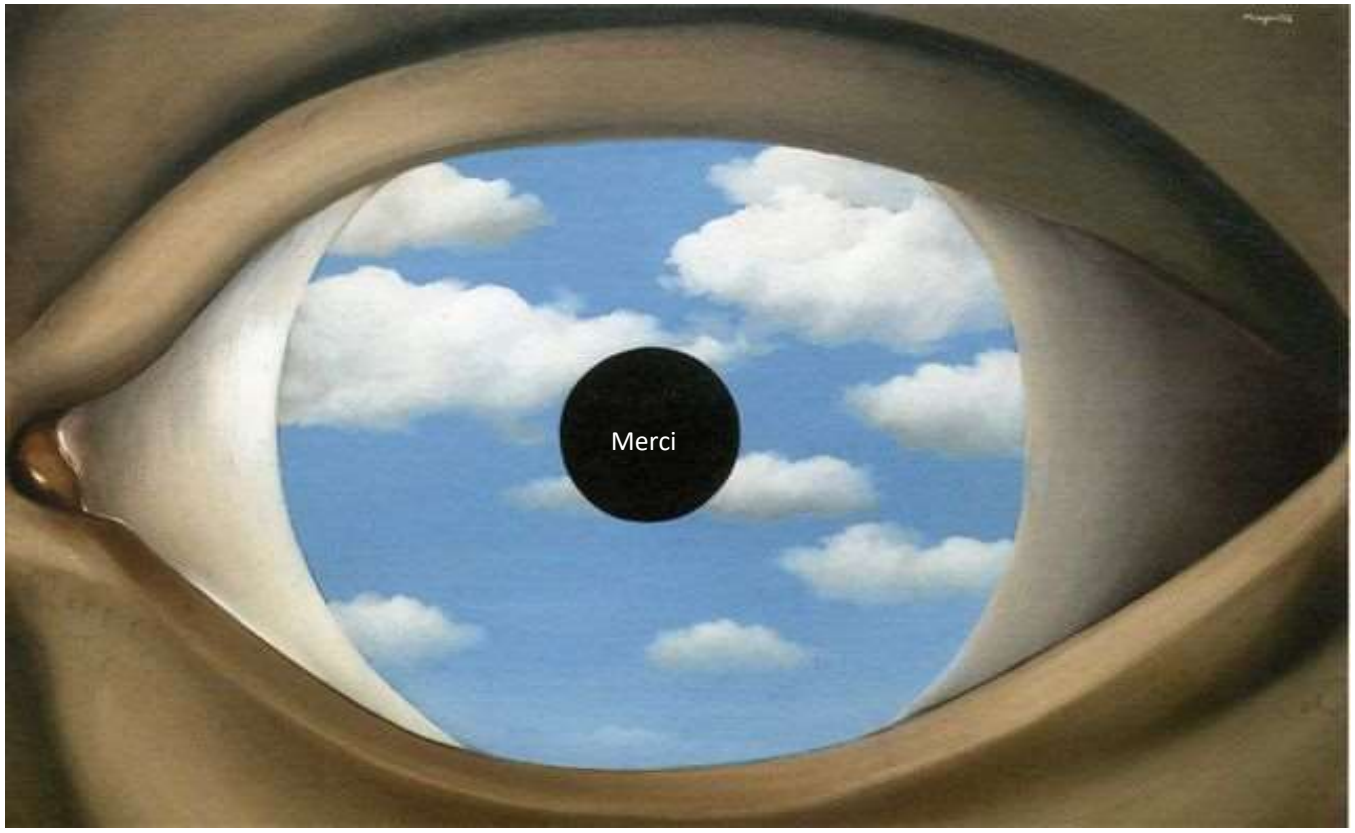
Multidisciplinary meeting: joint committee of centers of reference (PRADORT + CARGO)

Treatment approval



Data Collection

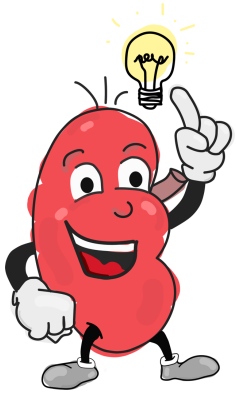
Centers of reference



www.ern-eye.eu

ERKNet Disease Information Brochures

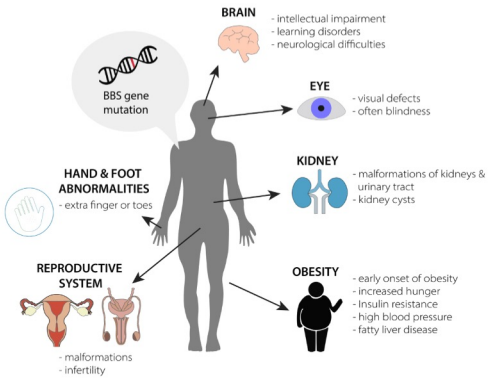
ERKNet
The European Rare Kidney Disease Reference Network



ERKNet
The European Rare Kidney Disease Reference Network

INFORMATION
FOR PATIENTS

BARDET-BIEDL SYNDROME



What do you need to know about Bardet Biedl Syndrome?

The aim of this booklet is to explain which organs can be affected by Bardet-Biedl syndrome, and how the prognosis and quality of life of BBS patients can be improved. Early diagnosis is important for quality of life and patients with BBS generally require multi-specialised care.

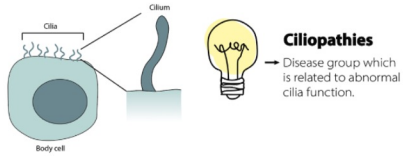
Kidney problems can cause serious complications of the disease and later in this leaflet we will explain how medication and lifestyle changes can delay the onset of kidney failure.

History of the disease

The disease was first described independently in 1920 by a French doctor, Georges Bardet, and in 1922 by Hungarian-Austrian

DISEASE DEFINITION

Bardet-Biedl syndrome (BBS) is a rare disease affecting several organs, including the kidneys. BBS is caused by an abnormally functioning cell component called a cilium (or cilia, plural) which is present on many cell types from different organs. Cilia are long, thin, hair-like projections that enable the cell to receive signals from outside and inside the cell. Bardet-Biedl syndrome is therefore categorized as a 'ciliopathy' (to find out more about cilia and their function please see pages 4 and 7).



Ciliopathies
→ Disease group which is related to abnormal cilia function.

Have you heard of this before?

As recently shown BBS patients have also a higher prevalence of certain autoimmune diseases:

- inflammatory bowel diseases as Crohn´s disease
- diabetes Typ 1
- rheumatoid arthritis
- hypothyroidism and Hashimoto's thyroiditis

Altered red blood cell and platelet compartments, as well as elevated white blood cell levels have been found in BBS patients. Some study reveals a connection between a ciliopathy and dysregulated immune and hematopoietic systems and immunity. Some of these alterations are associated with BBS-induced obesity which leads to elevated concentration of white blood cells in BBS patients. Obesity can induce the state of low-grade metabolic inflammation and one of the major players in obesity-associated inflammation is leptin, an adipocyte-derived hormone which acts as a pro-inflammatory cytokine. It has been shown that leptin signalling in the central nervous system regulates immune responses. Thus, it is possible that defective leptin signalling in the nervous system directly contributes to high prevalence of autoimmunity in BBS patients.

NEXT WEBINARS

06/06/23

27/06/23

07/23 – 08/23

19/09/2023

Subscribe our Newsletter
Or follow us on Twitter
@EuRefNetwork

Physiology of Podocytophathies
Tobias Huber (Hamburg, Germany)

Immune glomerulopathies: a pathogenesis and treatmentoriented approach for clinical management
Paola Romagnani (Florence, Italy)

SUMMERBREAK

Galloway-Mowat Syndrome
Guillaume Dorval (Paris, France)

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

WGIKD Working Group on Inherited Kidney Disorders

IPNA