HNF1B-related disease : a paradigm of developmental disorder eligible for ADTKD

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Agenda

- Epidemiology
- HNF1B-related nephropathy : a tubulointerstitial disease? pro/con
- How to diagnose HNF1B-related disease?
  - Extra-renal findings
  - Family history
  - Genetic testing is mandatory
- The HNF1B score as a tool for pre-genetic screening
- Specific management
  - Electrolyte disorders
  - Transplantation in HNF-1 related disease
  - Genetic counselling

Prevalence of HNF-1B disease : study cohorts of ≥50 patients with renal presentation and/or MODY

Presentation Age at testing	Kidney cysts or CAKUT Fetuses[1] (2007-2013)	Kidney cyst or dysplasia Pediatric[2] (2006-2011)	Kidney (unexplained) Any[3] (2008-2010)	CAKUT familial Any[5] (2014)	MODY Any[4] (2013)
N. Studies	2	4	3	1	1
N. Subjects	165	343	587	749/ 650 fam	?
N. HNF1B (%)	30 (18%)	57 (17%)	118 (20%)	6 (6.3%)	- 1%

Data from [1]Decramer (2007) and Madariaga (2013) [2] Ulinski (2006), Weber (2006), Adalat (2009) and Thomas (2011) [3]Edghill (2008), Nakayama (2010) and Heidet (2010) [4]Edghill (2013) [5]Hwang DY Kidney Int (2014)

Prevalence of HNF1B disease in general population ?

- Areas where pediatric and adult nephrologists have a long-standing interest for HNF1B disease
- To evaluate prevalence in two independent areas (internal control)
- To estimate simultaneously the prevalence of others orphan renal diseases (Alport syndrome, Fabry disease and nephronopthisis) (external control)

Prevalence of HNF1B in general population ?

Identification of cases

1) All Renal Units
2) Regional Registries for Rare Renal Diseases & Renal Transplantation
3) Genetic Lab

Inclusion criteria

- Being a permanent resident in the studied regions
- Established diagnosis of one of the 4 diseases (biochemistry, pathology or genetic test)

Prevalence of HNF-1B disease : descriptive epidemiology in South-West of France, and comparison to rare inherited renal disorders

Area	*Midi Pyrénées*	*Limousin*	*All*	*Prevalence (pmh)*	
N. Inhabitants (INSEE, 2010)	2,929 M	0,746	3,675	*South-West France*	*Other studies*
N. diagnosed					
Alport	47	8	55	15	19-25
Fabry	10	3	13	3.7	≈4.0
Nephronopthisis	15	2	17	4.6	?
HNF1B	43	12	55	15	?

Midi-Pyrénées 14.7

Limousin 16

Chambaraud et al, in preparation)

Limitations

This figure likely is an underestimation

- Ascertainement bias (kidney, not diabetes-MODY)

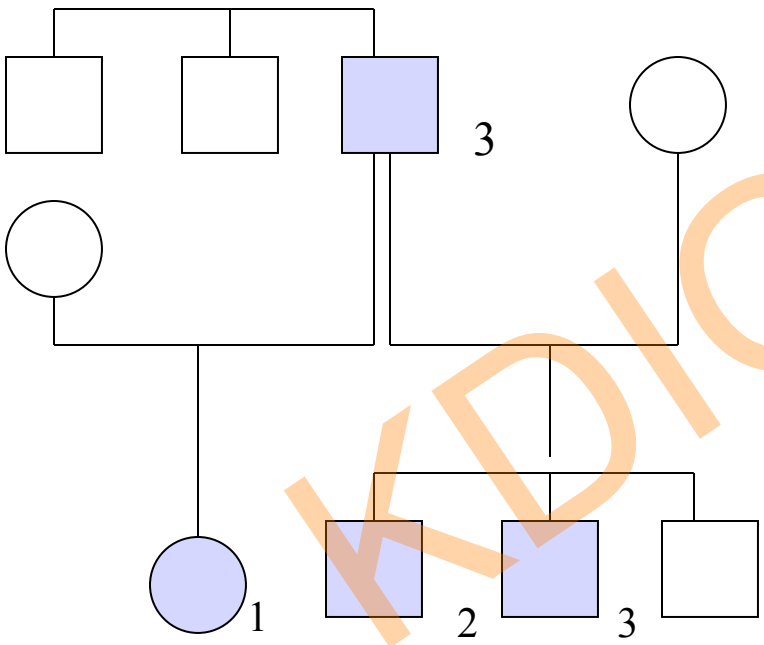
- Undiagnosed cases (wide variability and mild phenotype in adults)

Renal involvement in HNF1B disease

Most frequently affected target-organ

Almost complete penetrance, if correctly detected

Extreme variability among and within families



I-3, born 1956
2006 : S creat 119, GFR 60
Poor corticomedullary differentiation
Few renal cysts, bilateral
No reflux
Hypokalemia 3,2 - Ku = 50/d
Magnesium : 0,52
Proteinuria 0,1g/d
No diabetes mellitus
1 liver cyst

II-1
« Polycystic »
kidney disease

II-2, born 1977
Neonatal RHD + reflux
Right Nx 1978
ESRD 1999 K+ =2,6
No diabetes

II-3, born 1979
S creat 140, GFR 65
Single left kidney, and cysts

HNF1B point mutation

« … the renal phenotype in adults with *HNF1B* disease is clearly one of chronic tubulointerstitial nephritis… »

Faguer S et al, Kidney Int 2011, 80, 7:768-76

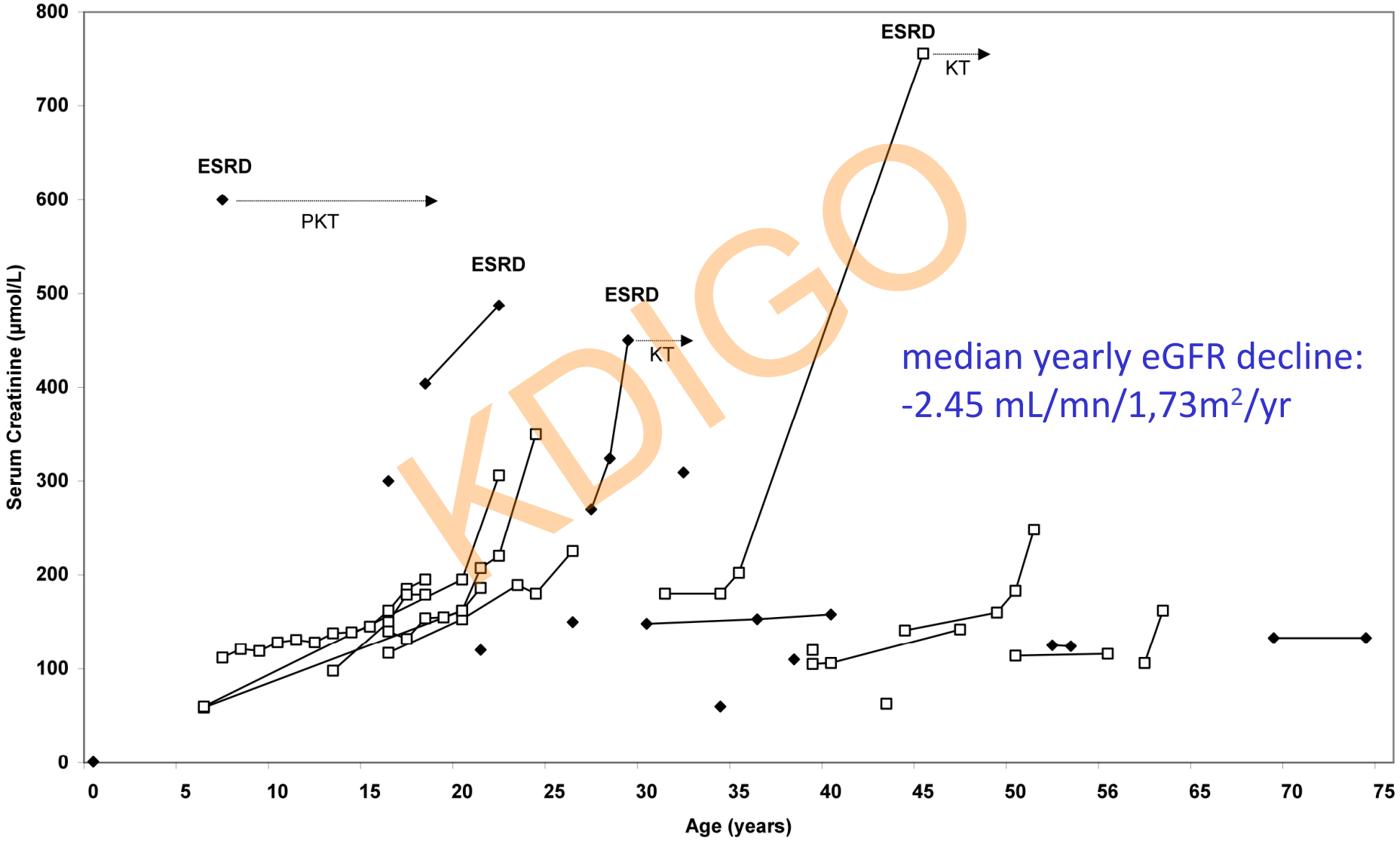
27 adults from 20 families,
median age at last FU = 35 years (16-74)

Hematuria	0
No proteinuria	74%
Low-grade proteinuria (<1 g/d)	26%
Hypertension	7%

Polyuria was not a finding

« … and slowly progressive kidney failure »

Faguer S et al, Kidney Int 2011, 80, 7:768-76



In addition, in adults with *HNF1B* disease, additional features point to defective tubular transport

Faguer S et al, Kidney Int 2011, 80, 7:768-76

- Tubular leak of either of 2 cations is a very suggestive finding
  - Hypomagnesaemia (Mg^{++}< 0.75 mmol/) in 62%

    resulting from renal wasting (FE_{Mg}: 7-22 %, N<0.5%)

  - Hypokalaemia (< 3.5 mmol/L) in 46%

    Despite renal decline: 10 individuals with CKD 3-5 had K^{+}< 3.5 mmol/L

    1 patient started on dialysis with K^{+} = 2.6 mmol/L

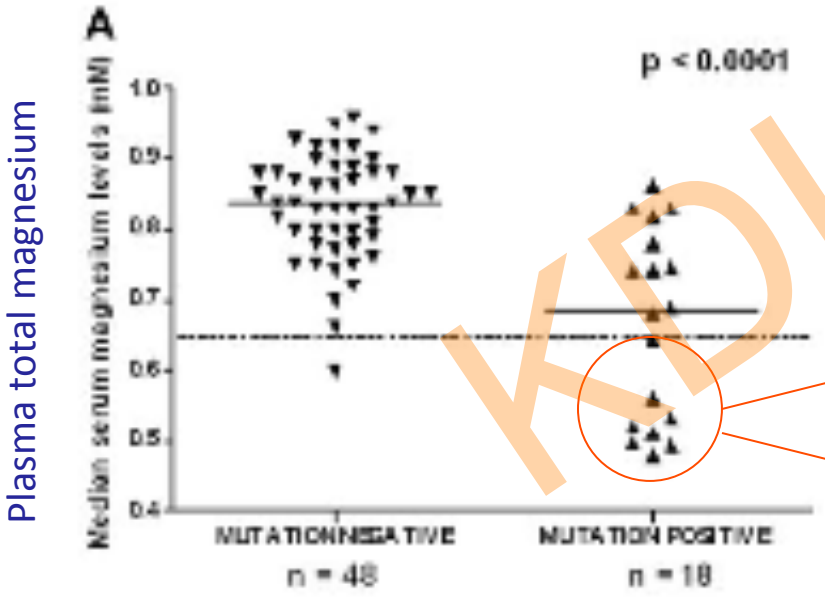
→ hypokalemia or hypomagnesemia were detected in 15 patients (62%)

- 2 unrelated patients presented with generalized defects of proximal and distal tubular function

Hypomagnesemia (< 0.65 mmol/L) is a frequent finding in children with HNF1b disease

… and is related to renal leak

Adalat S et al. JASN 2009;20:1123-1131



Plasma total magnesium

Fractional magnesium excretion = 6.5%
(4.5-14.3, N< 4%)

Target genes HNF1B (2012)?

Tubulogenèse	Différenciation néphronique	Homéostasie epithéliale & transport tubulaire
Socs3	*Umod*	*Fxyd2°*
Pax2	*Pkhd1*	*Kif12*
LHX1	*Pkd2*	
Wnt9b		

°gène cible chez l'homme

Homodimère (ou hétérodimère *HNF-1α/HNF-1β)*

However, some aspects are disputable for *typical* TKD

1. Small sized kidneys is not a frequent finding

2. Renal pathology is equivocal

3. (Unexplained acute kidney deterioration may occur (3/27, 11%)

4. (in contrast to *UMOD* and *MUC1* diseases, but alike *REN* disease, renal involvement in HNF1B is not restricted to adulthood)

Renal imaging in *HNF1B* adult patients

Renal imaging (24/27 individuals) demonstrates extreme heterogeneity and escapes easy classification

Faguer S et al, Kidney Int 2011, 80, 7:768-76

Kidney size at last FU	
Normal	13 (61%),
Small	7 (30%)
bilateral	5
unilateral	2
Massively enlarged	2 (9%)

A cystic disease? Not a universal finding - possible overlap

Normal kidney	12% normal size and shape, no cyst
Renal cysts	62%, the majority with few (≤ 5) cortical or medullary cysts per kidney
Solitary kidney	21%
Diverse abnormalities	16% (nephrocalcinosis, kidney stone, hydronephrosis or hydroureter, and vesicoureteric reflux)

9 patients (38%) had no detectable renal cyst between age 16 and 48
in 6 cystic pts with sequential imaging, no progressive increase of cysts number

To summarize renal imaging in young adults with HNF1B disease

- ≈ 60% have normal sized kidneys with regular shape,
  ≈ 60% harbor a small number of bilateral renal cysts

- Imaging studies is not a diagnostic clue for HNF1B disease but is mandatory to rule out
  - ADPKD/ARPKD
  - obstructive uropathy (irregular shape)

Additional imaging studies at older age would be useful

Renal phenotype in children with *HNF1b* disease

Imaging (N= 21)[2]

Bilateral disease	76%
Large K, echogenic, no cyst	43%
Large K, echogenic, with cysts	24%
Hydronephrosis	14%
Unilateral MCKD	19%

Uncommon [1-2]	
Single kidney	≈5%
Normal US	< 5%

Clinic findings at last FU

	series Adalat	Heidet
N.	21	75
Age	8.0 yr	8.5 yr
Early gout	?	5%
eGFR	63 (8-113)	?
> 80		68%
CKD stage 5	2 (21%)	?
ESRD	0	0

[1]*Heidet & Decramer, CJASN 2010, 5:1079*
[2]*Adalat S, JASN 2009, 20:1123*

[1]*Decramer S, J Am Soc Nephrol, 2007*
[2]*Ulinski T, J Am Soc Nephrol, 2006*

Renal course in childhood : data from 43 individuals - no sequential study

Series	Toulouse[1]	France[2]
N.	18	25
Age at diagnosis	Antenatally	0,2
Median FU (years)	6	2,5
GFR at last FU		
> 80	-	14 (56%)
> 70	7 (39%)	-
40-80		10 (40%)
40-70	8 (45%)	-
< 40	2 (10%)	1 (4%)
ESRD	1 (5%)	0

However, some aspects are disputable for *typical* TKD

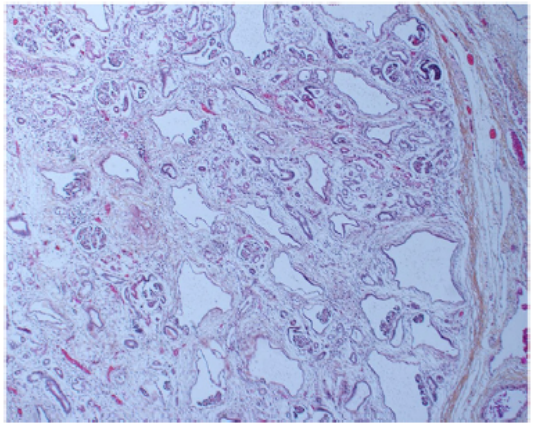
1. Small sized kidneys is not a universal finding
2. Renal pathology is equivocal in HNF1B-disease
3. Unexplained acute kidney deterioration may occur (3/27, 11%)
4. (in contrast to *UMOD* and *MUC1* diseases, but alike *REN* disease, renal involvement in HNF1B is not restricted to adulthood)

Renal pathology: is HNF1B-disease really a tubulointerstitial nephritis ?

1. Very few data
   - Practical reasons : small or cystic kidneys = risk of complication
   - So far, diagnostic value not established

2. ≈ 20 individual reports in the literature, mostly in children (or fetus)
   - Glomerulocystic disease (n=6)
   - Oligomeganephronia (n=3)
   - Cystic renal dysplasia (n=2)

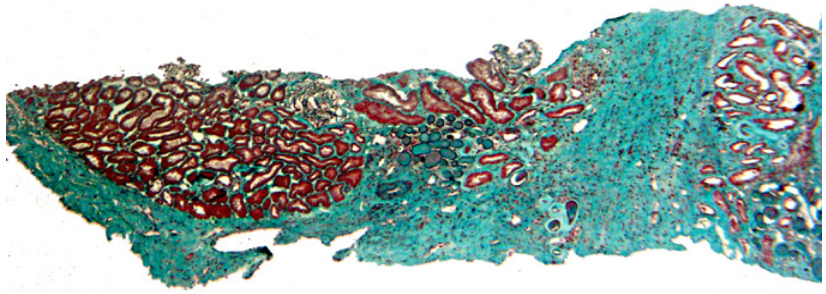
3. Tubulointerstitial findings
   - No specific assessment
   - Neither TBM lamelation, nor increased width
   - No specific study of HNF1B by IHC

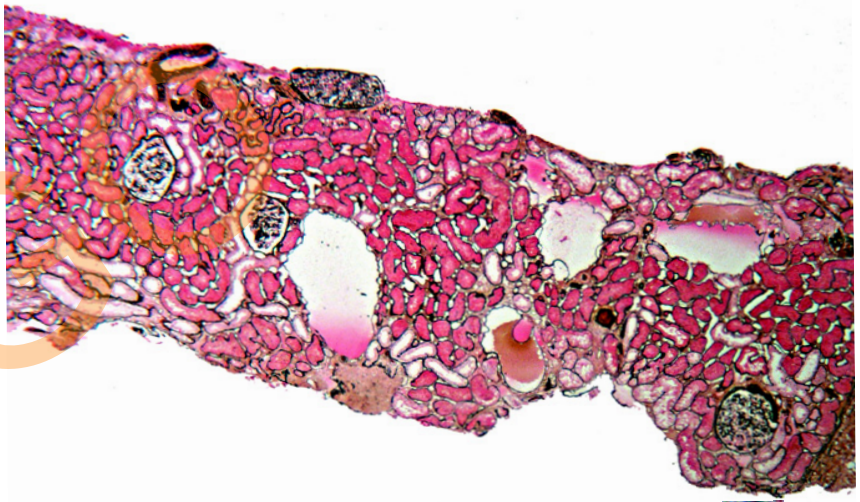


Madariaga, CJASN, 2013

Pathological findings on kidney biopsy in 6 adults with HNF-1B mutation

Bellanné, Chauveau et al., Ann Intern Med 2004

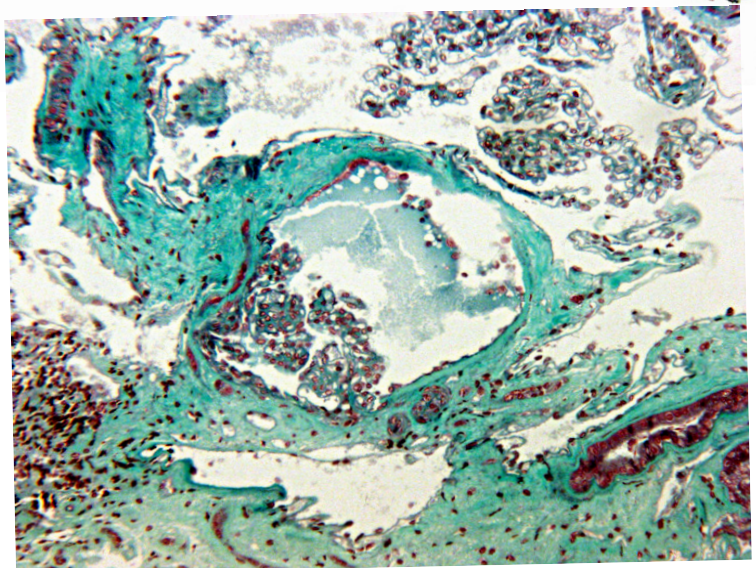




- Enlarged glomeruli 4/6
- Glomerular cysts 2/6
- Oligomeganephronia 1/6

None is specific

- Interstitial fibrosis 6/6



- Diabetic GN 0/6

As compared to *UMOD* nephropathy

- Due to scarce data, renal pathology is still of limited value to diagnose HNF1B-related disease
- Whether kidney biopsy should be routinely performed in adults with suspected HNF1B-related disease is not yet clear
- We need to better delineate the pathological characteristics, and to develop biomarkers that could help in establishing the diagnosis of HNF1-related kidney disease, without genetic testing

What may raise clinical suspicion of HNF1B disease in patients with renal presentation?

1. Extrarenal findings
2. Family history

Extrarenal findings

1. No large cohort, and few data on natural history
2. Target organs

- Pancreas
- Liver :
  - fluctuating liver tests in 40-50% of adults – liver biopsy almost normal - long term prognosis unknown (severe worsening post kidney tranplant)
  - neonatal jaundice[1-2] with reduction of intrahepatic bile ducts
- Genital tract malformations (impaired fertility)
  - Males : epididimes cysts or bilateral absence of vas deferens
  - Females : bicornual uterus, hemiuterus, or uterus and upper vagina aplasia
- Brain : intellectual impairment with autistic traits[3]
  - Not well established in the spectrum of the disease
  - Only in patients with large deletion of the gene

[1]Roelandt, Hepatology 2012
[2]Beckers J Pediatr 2007
[3] Moreno-DE-Luca D, Am J Hum Genet, 2010

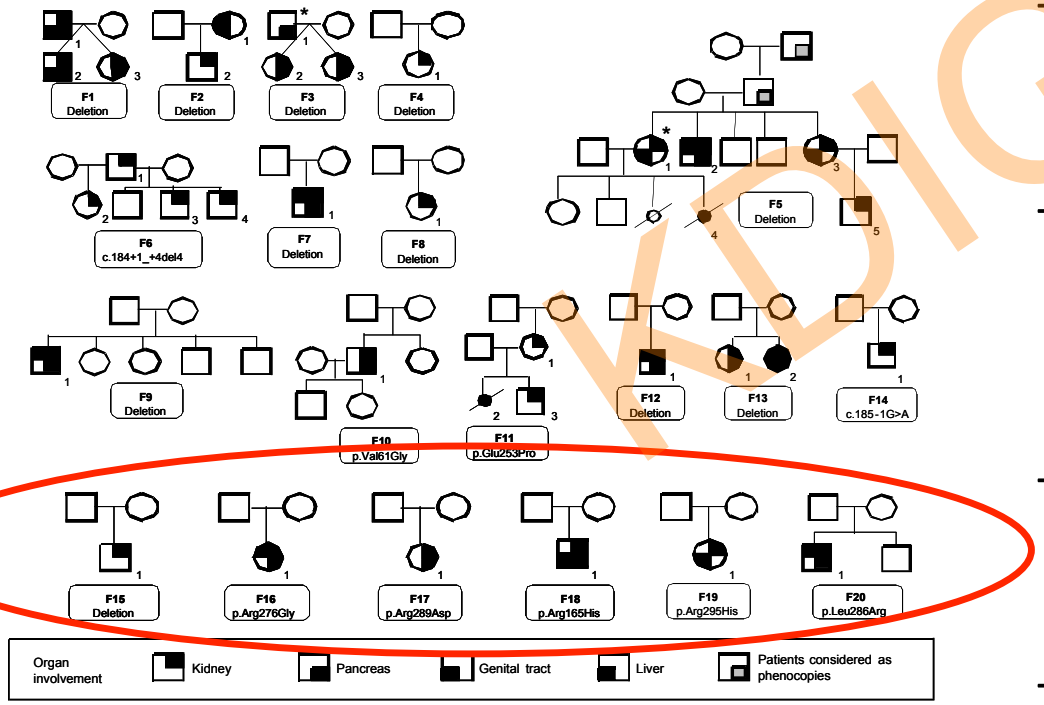
Extrarenal findings

- Pancreas
  - Diabetes mellitus (MODY5)
    - β-cell dysfunction and insulin resistance
    - Typically non-obese patients at a median age of 20-30 years, up to >70 years,
    - Clinically overt or detected by screening, or NODAT[1]
    - Course debated
      - exhibits a slowly progressive course with late requirement for insulin therapy[2]
      - or poor response to sulphonylurea[3]
    - (ketoacidosis may occur, in adult[4] or even in teenager[2])
  - Pancreas atrophy is detected in almost half the adult patients (CT) - pancreas exocrine failure should be routinely detected at diagnosis (low faecal elastase)

[1]Zuber, Nat Rev Nephrol
[2]Bellanné, Ann Intern Med 2004
[3] Pearson Diabetes Care 2004
[4] Faguer S, Kidney Int 2011

What may raise clinical suspicion of HNF1B disease in patients with renal presentation?

1. Extrarenal findings
2. Family history with AD



However

- In all series, 50-60% of cases are found to have *de novo* mutation
- In families with evidence for AD inheritance, wide phenotypic variability[1]
- Phenocopies can be detected by family screening
- Mosaicism[2] (rare)

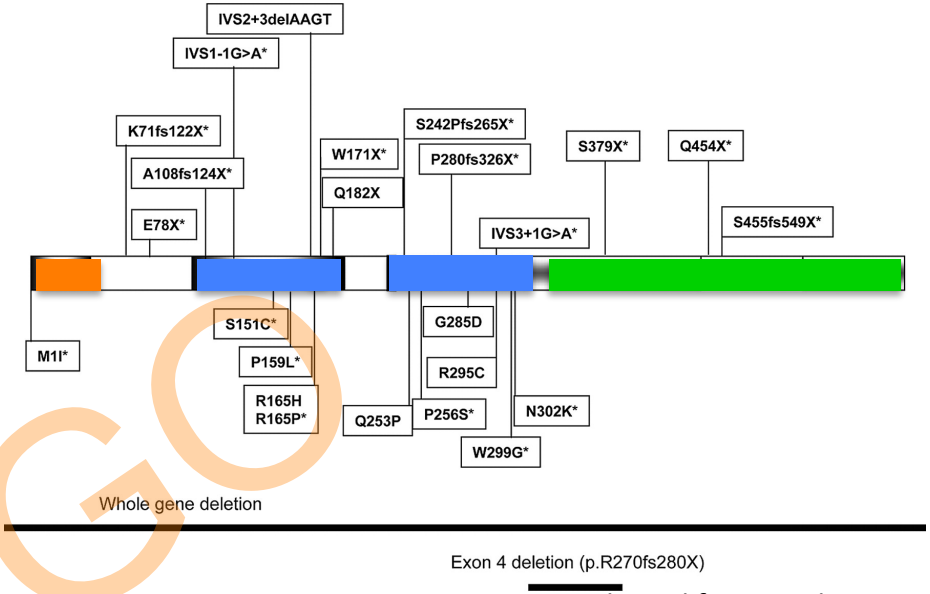
[1]review in Chauveau Nephrol Therap, 2012
[3]Yorifuji, J ClinEndocr Metab 2004

Thus, given
- the lack of pathognomonic characteristics
-and the wide overlap with other conditions,

a genetic test is mandatory to diagnose HNF1B disease

Mutations in *HNF1b*-related disease

- Gene located on 17q12



Adapted from Heidet L et al. CJASN 2010;5:1079-1090

- Genetic changes
  - 50% point mutations (> 50 reported), (missense, false-sense, splice-site mutation, or indel) are mostly private and located in the DNA-binding domain (clusters in exons 2 and 4)
  - 50% micro-chromosomal rearrangement

    mostly large recurrent deletion of 1.2–1.5Mb - rarely one single exon
  - very low risk of mosaicism
- No genotype-phenotype correlation
- Disease mechanism = haploinsufficiency

Genetic screening for *HNF1B* mutation
current approach

1)Large deletion?

2)If not, sequencing for point mutation

(Much easier than ADPKD or Alport)

Cost ≈ 380-780 euros in France

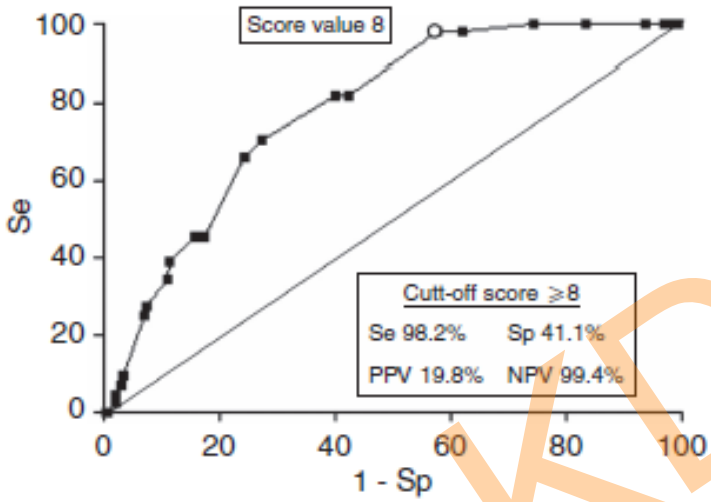
How to improve pre-genetic screening ? The HNF1B score

Characteristics	Item	Value
Family history		+2
Antenatal renal abnormalities	Uni/bilateral abnormality by renal echography	+2
Kidneys and urinary tract		
Left kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Right kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Electrolyte or uric acid disorders	Low serum Mg^{2+} (<0.7 mmol/l)	+2
	Low serum K^{+} (<3.5 mmol/l)	+1
	Early-onset gout (>30 years of age)	+2
Pathological findings	Oligomeganephronia or glomerular cysts	+1
Pancreas[a]	MODY or hypoplasia of tail and neck of the pancreas or pancreatic exocrine insufficiency	+4
Genital tract	Genital tract abnormality[b]	+4
Liver	Live test abnormalities of unknown origin[c]	+2

http://www.kidney-international.org clinical investigation

The *HNF1B* score is a simple tool to select patients for *HNF1B* gene analysis

Stanislas Faguer[1,2,3,4], Nicolas Chassaing[4,5], Flavio Bandin[2], Cathie Prouheze[2], Arnaud Garnier[6], Audrey Casemayou[2,3], Antoine Huart[1], Joost P. Schanstra[3,4], Patrick Calvas[4,5], Stéphane Decramer[2,3,4,6,7] and Dominique Chauveau[1,2,3,4,7]



Performance of the HNF1B score : ROC curve analysis
(433-individual cohort including 56 HNF1B cases)

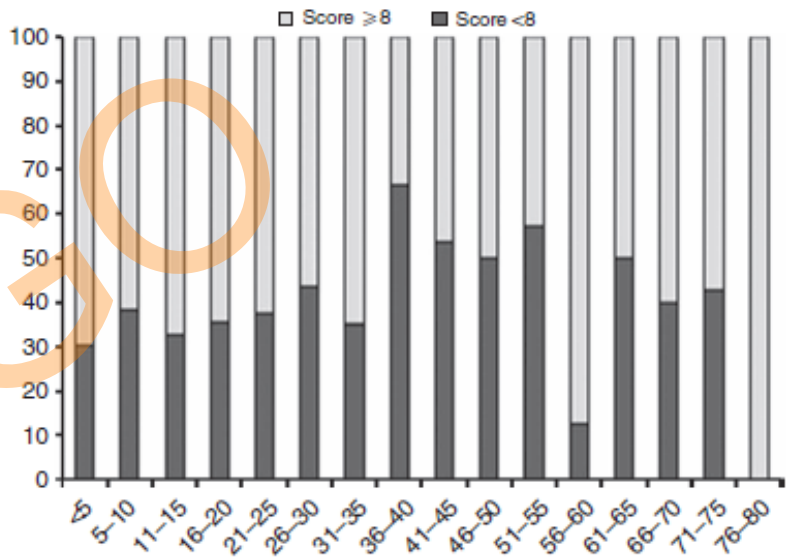


Figure 2| Distribution of patients (%) who would be proposed for *HNF1B* screening according to the *HNF1B* score (⩾8) and to age at genetic screening. *X* axis shows age ranges (years), and *y* axis shows percentage of patients with *HNF1B* score < or ⩾8.

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Table 2 | *HNF1B* score

Characteristics	Item	Value
Family history		+2
Antenatal renal abnormalities	Uni/bilateral abnormality by renal echography	+2
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Left kidney	Hyperechogenicity	+4
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	Early-onset gout (>30 years of age)	+2
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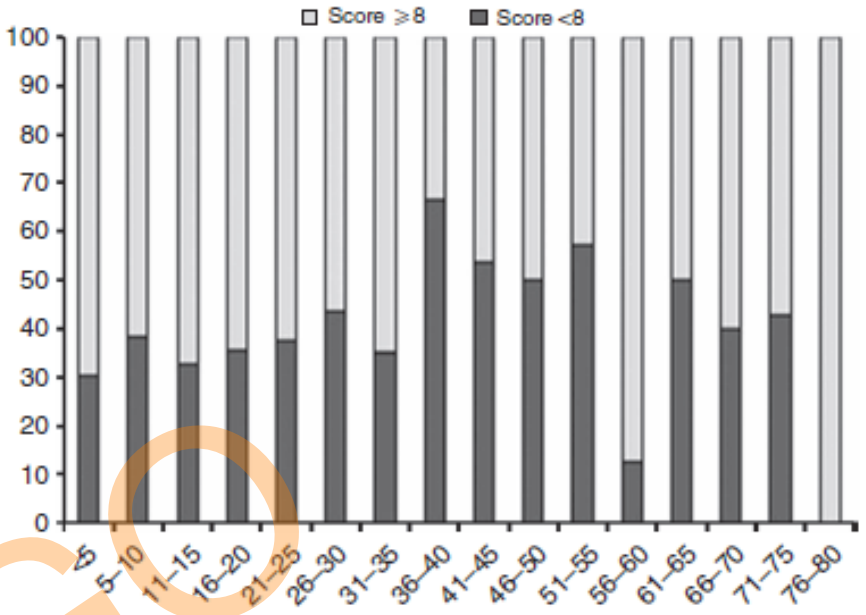

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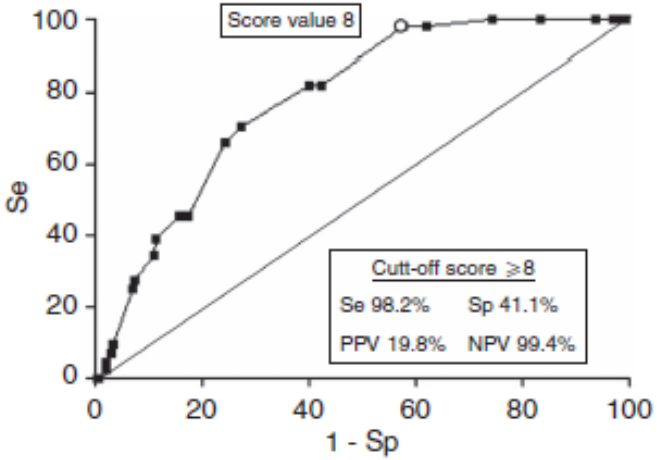
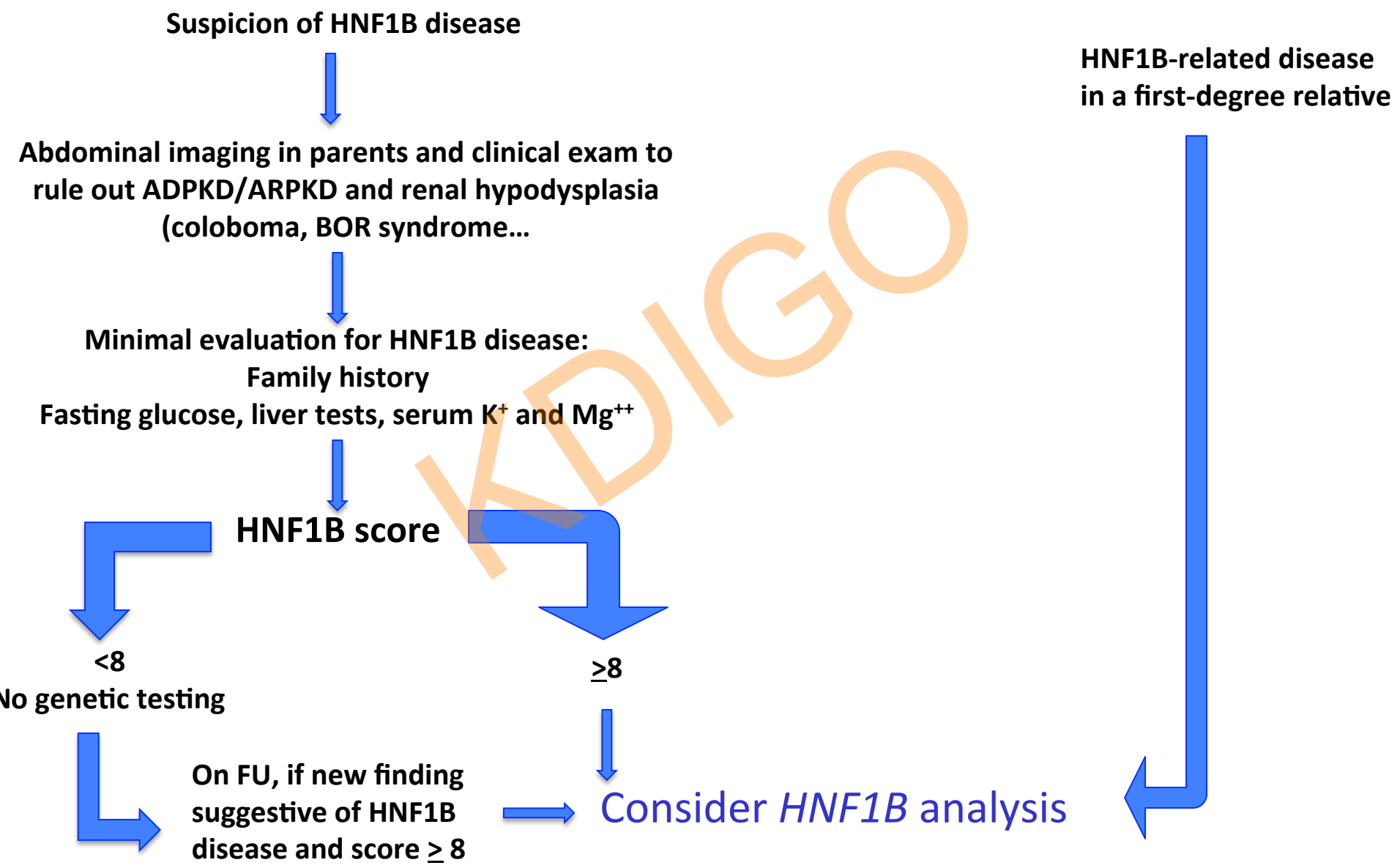


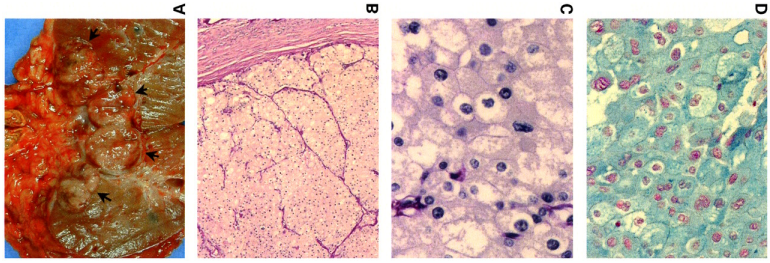
Figure 1 | Receiver operating characteristics (ROC) curve of the *HNF1B* score in a large cohort with *HNF1B* known status (*N* =433), showing the accuracy of the *HNF1B* score in

When to screen for HNF1B in patients with renal presentation?



Specific management in established HNF1B disease in adults

- Kidney
  - At presentation : Mg, K, S. creatinine & CT-scan (or MRI)
  - Yearly : Mg, K, S. creatinine - no imaging in the absence of clinical symptom
  - If hypoMg/hypoK: treat only if symptomatic
  - Avoid ACE and ARB
  - ?Screening for chromophobe renal cell carcinoma (2 case reports 37 and 54 years/ bi-allelic invalidation, in addition to germline mutation)
- Pancreas
  - At presentation : ?diabetes – fecal elastase
  - Yearly: diabetes FU – fecal elastase if symptom
- Liver
  - At presentation and yearly : liver blood tests
- Genital tract : only if symptomatic (?)
- Genetic counselling



Rebouissou S et al. Hum. Mol. Genet. 2005;14:603-614

Kidney and combined kidney-pancreas transplantation in HNF-1beta individuals

follow-up in 16 patients from 7 medical Centers

Faguer et al, submitted

- 16 patients (8F, 8M) – 7/16 (44%) large deletion
- Prior Tx :
  - DM in 6/16 (37%), 5 IDDM, mean age at diagnosis 21
  - Liver tests abnormalities in 7 (44%)
  - Exocrine pancreatic failure in 1

- At Tx
  - median age = 27 (5-53)
  - 14 SKT and 2KPT

- FU after 14 SKT
  - Median duration = 69±57 months (4-180)
  - Kidney :
    - Early acute oxalate nephritis n=1
    - Chronic rejection and Re-SKT n=3
  - Severe worsening or *de novo* abnormal liver tests : 7/14 (50%) – no cirrhosis
  - *de novo* post-transplant DM : 6/10 (60%), ≈ 3 months post-SKT

Borlak J, Niehof M. HNF4alpha and HNF1alpha dysfunction as a molecular rational for cyclosporine induced posttransplantation diabetes mellitus. *PLoS One* 2009

- Cytoplasmic calcineurin regulates NFAT (nuclear factor of activated T-cells)
- NFAT are a family of transcription factors expressed in renal, pancreas and liver epithelial cells during development

Hypothesis : could calcineurin inhibitors modify HNF1B expression in epithelial cells?

Lessons from SKT and KPT in HNF-1beta individuals : a plead for dedicated management

- CNI down-regulate HNF1-beta transcriptional activity : *HNF1B* patients are therefore close to bi-allelic inactivation

- Individualized management of ESRF
  - If IDDM or NIDM, consider KTP

    Poitou, Transplant Int 2012 and personal experience
  - In the absence of IDDM/NIDM
    - Test for exocrine pancreatic failure (fecal elastase), and add pancreas enzyme supplementation
    - Inform of the high risk for *de novo* PTDM
    - Minimize CNI exposure and consider prompt withdrawal of steroids

Contributors

- Toulouse

  Stanislas Faguer, Stéphane Decramer, Nicolas Chassaing, Patrick Calvas & Dominique Chauveau
- Limoges
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  JP Grünfeld, J Timsit, Christine Bellanne-Chantelot & Pierre Ronco

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