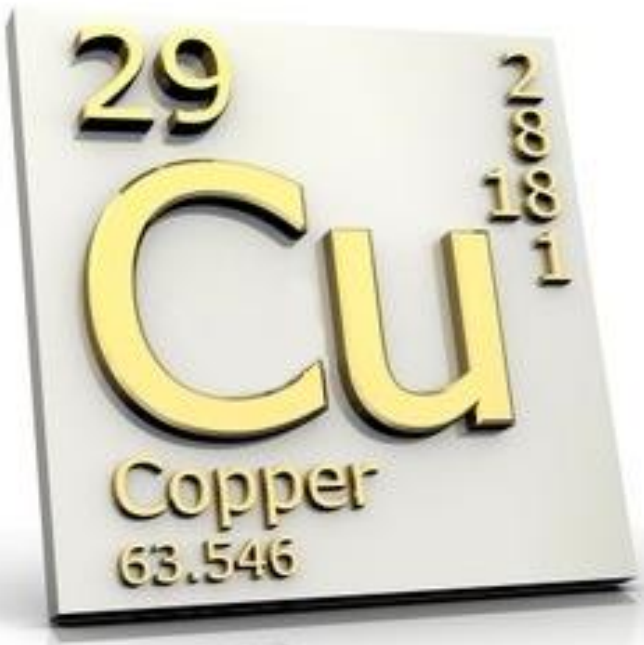
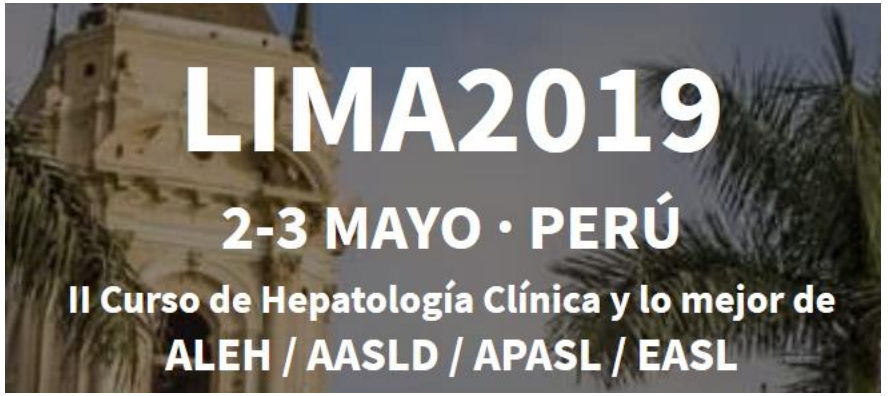
Wilson Disease

Successes, challenges, controversial aspects, unmet needs





http://fpaa.es/
http://enfermeaddewilson.org

Background

Monogenic autosomal-recessive disorder of hepato-cellular copper deposition

Pathogenic variants in the copper-transporting gene, ATP7B

↓

Disrupted copper homeostasis

Copper transporter deficit	> 700 mutations

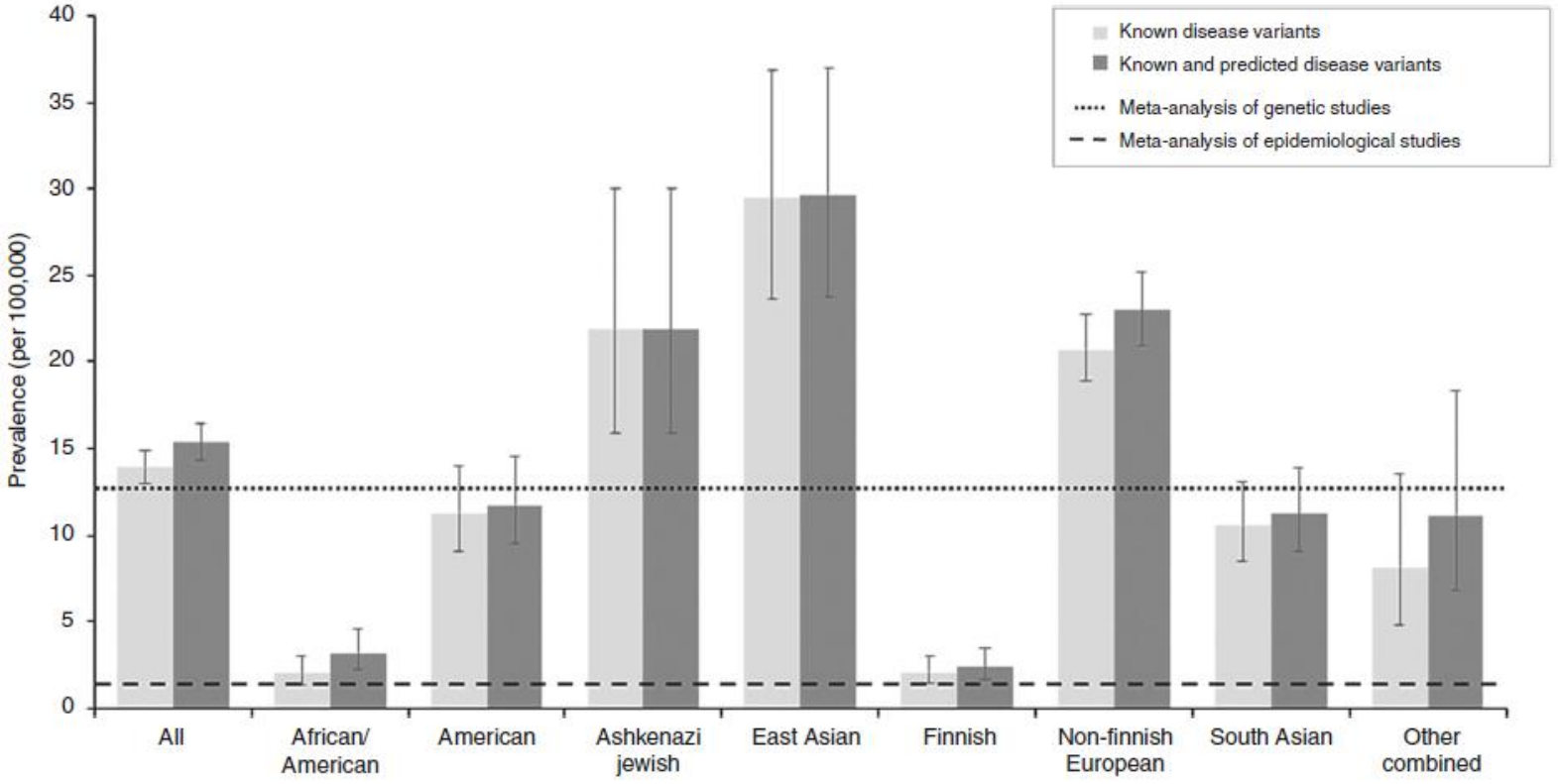
↓

Accumulation of unbound copper: Multisystemic disorder

Liver	CNS	Cornea	Kidneys

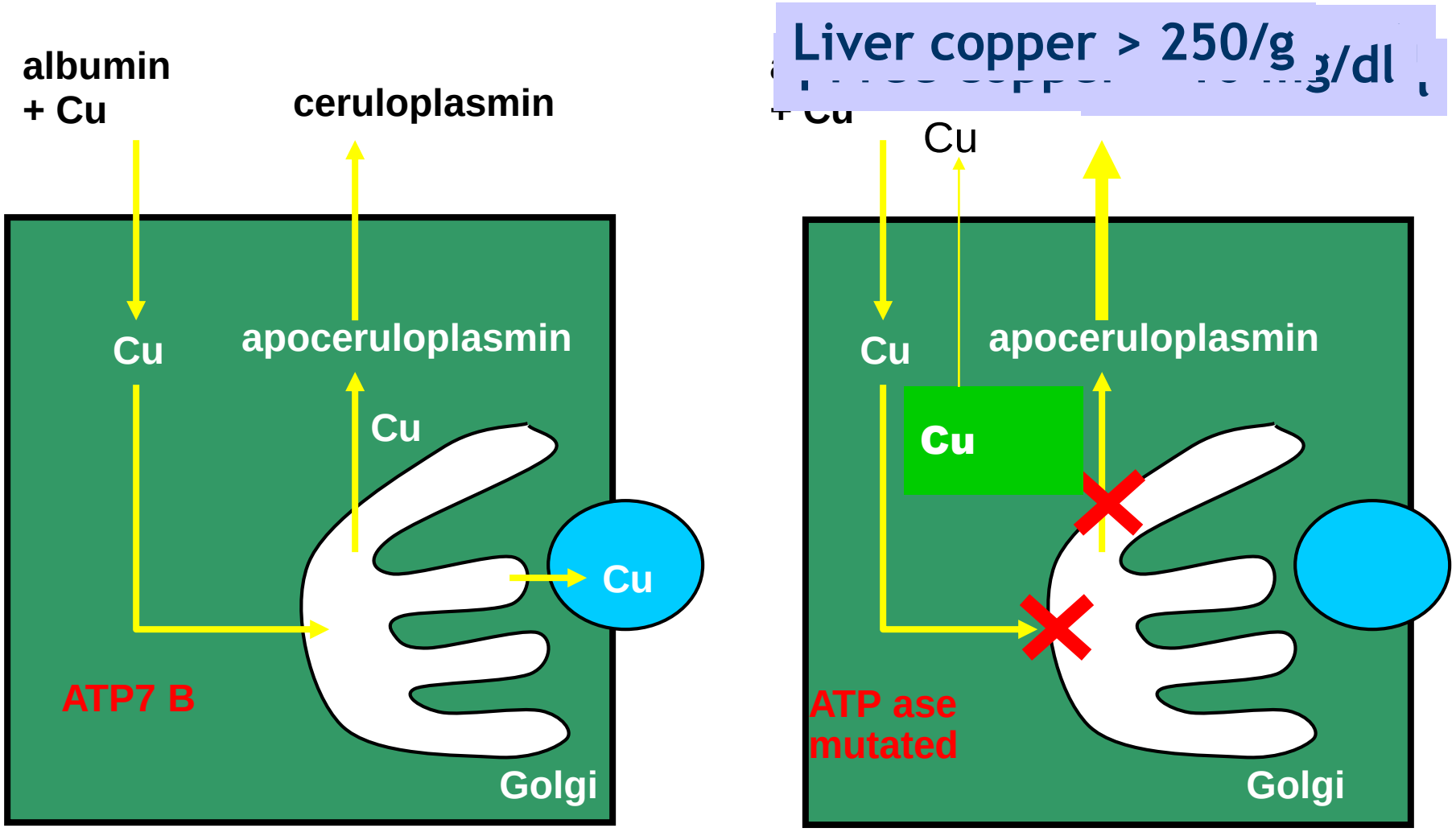
Epidemiology

1:30.000 persons
1:1000 with liver disease (1:6-10 after excluding frequent causes)



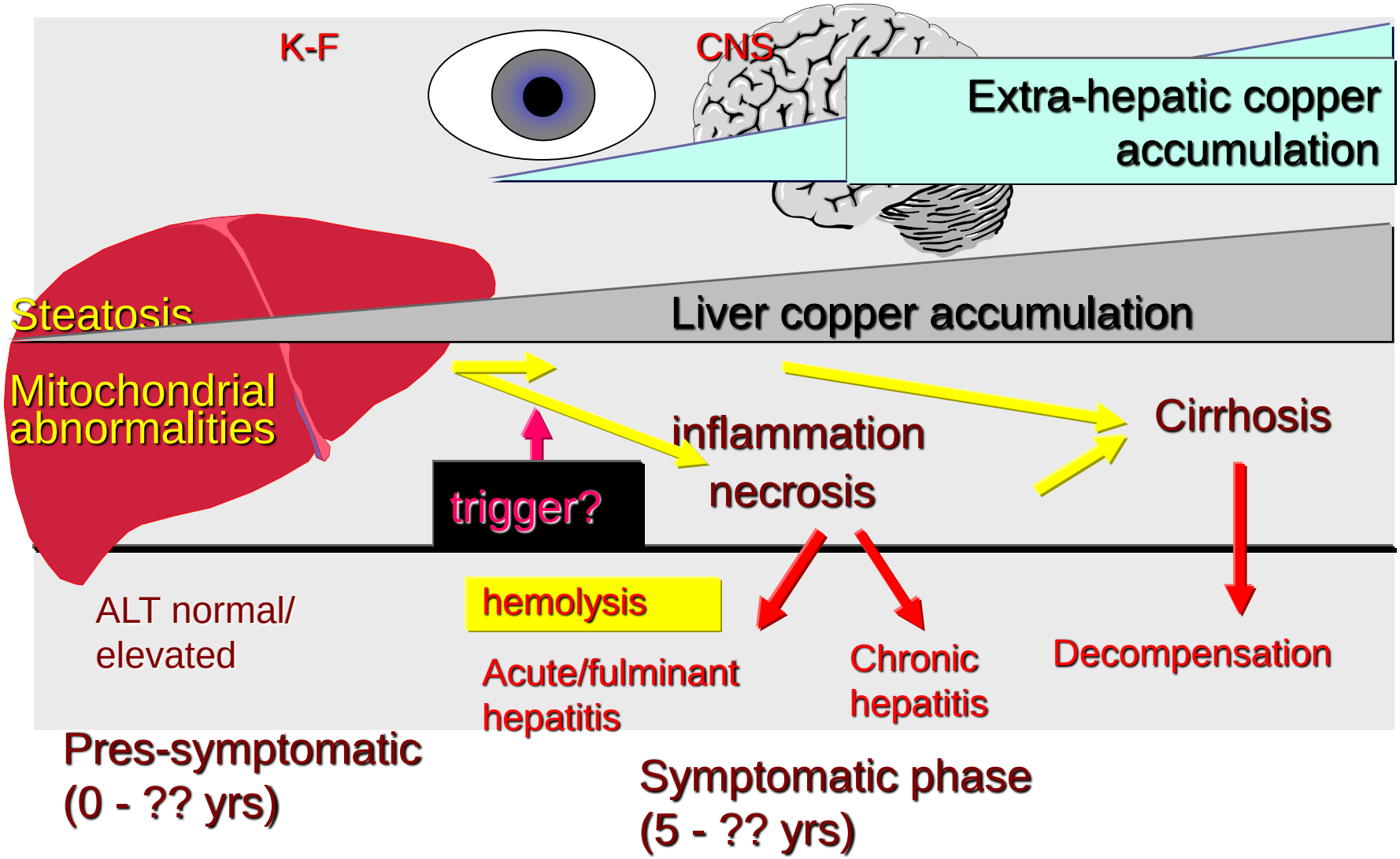
Genetics in Medicine (2018) https://doi.org/10.1038/s41436-018-0309-9

Copper metabolism



Diapositiva cedida amablemente por el Dr M Bruguera

Natural course of the disease



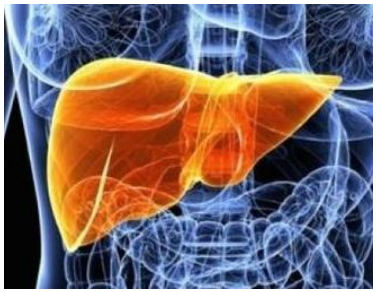
First CHALLENGE / Unmet NEED

Think about this disease

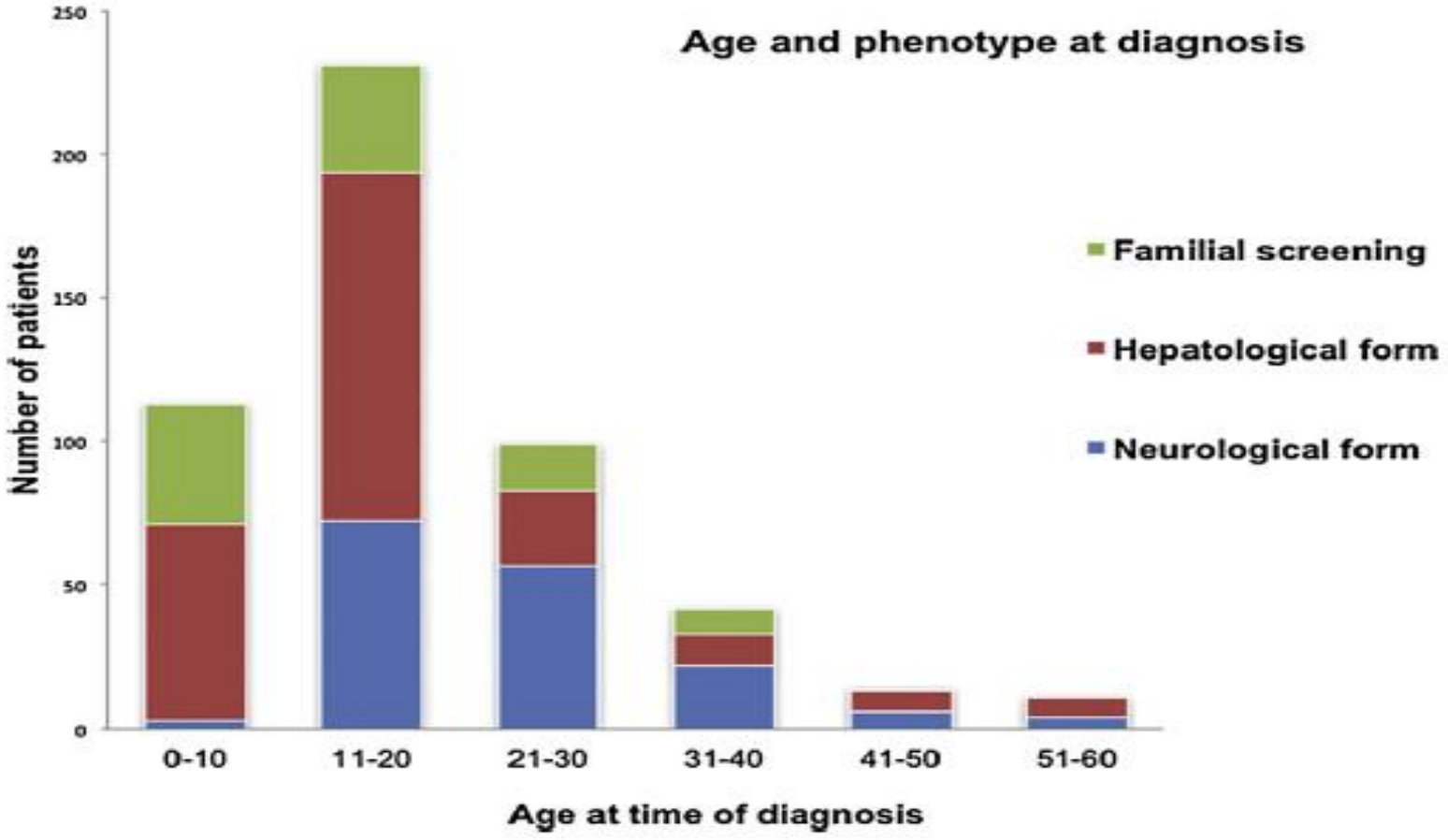
WD as a Differential Diagnosis in many syndromes

Clinical presentation

How	• Variable between patients (despite same genetic variant) • Asymptomatic-Florid
Symptoms	• Variable • Depends on type & severity organ(s) affected
When	• Any age • Generally: young age to adulthood (5-35 yrs)

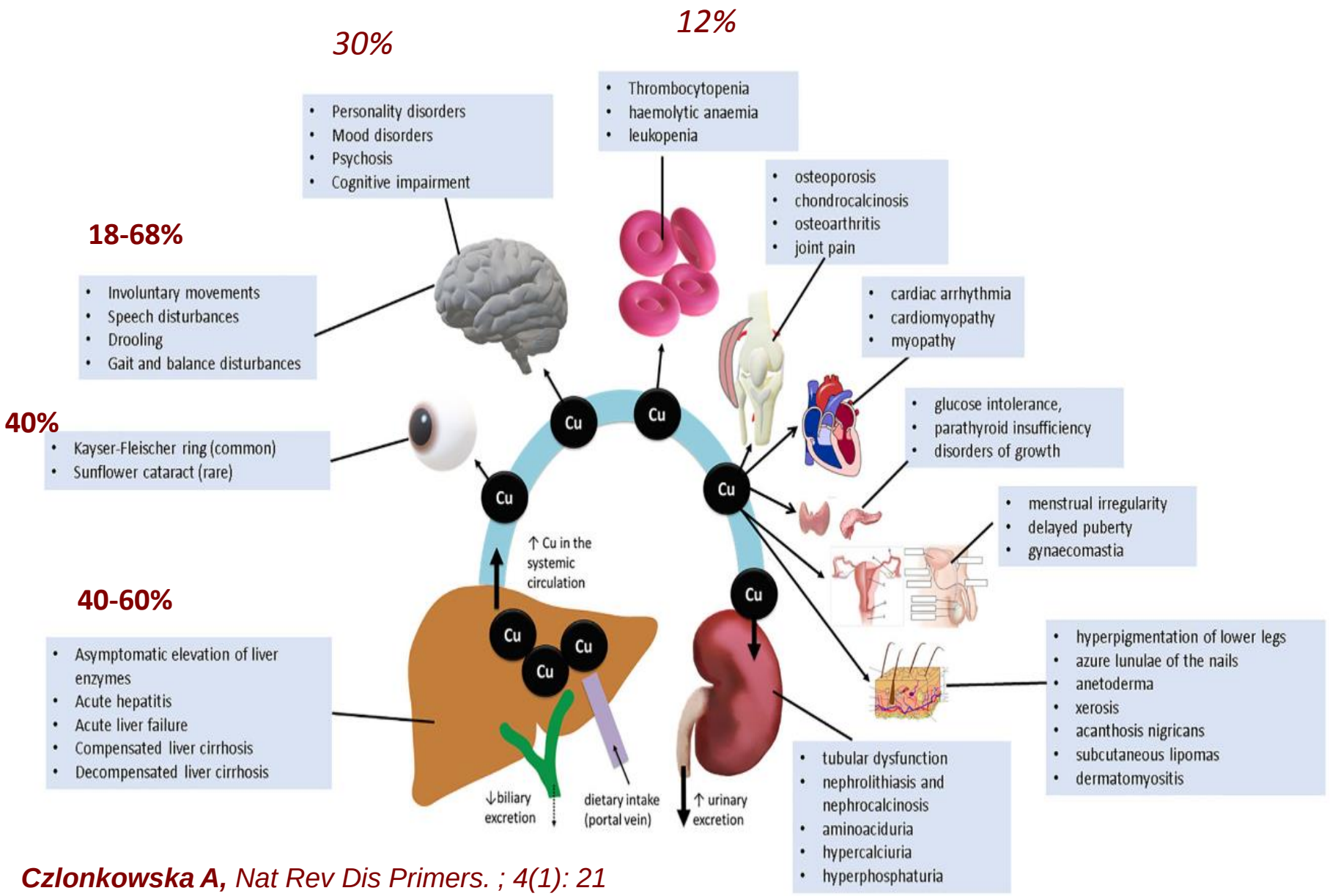


Age and phenotype at diagnosis from the French Wilson's disease registry (n=604)



Litwin T et al; J Neurol Sci 2012;312(1—2):31—5

Wilson Disease as a multisystemic disorder



Czlonkowska A, *Nat Rev Dis Primers. ; 4(1): 21*

Psychiatric symptoms

- 30-63% at diagnosis
- Prevalence > general population
- Median time to diagnosis: 2.4 yrs (> than in neurologic forms 1.5 yrs- or liver-0.5 yrs)
- 20% have visited a psychiatrist before diagnosis
- Varied symptomatology
- More frequent symptoms:
  - ✓ Depression (30%)
  - ✓ Inadequate behaviour with personality changes (30%)
  - ✓ Cognitive changes, attentional disorders (28%) ("problemas cole")
  - ✓ Irritability (22%)

Treatment:

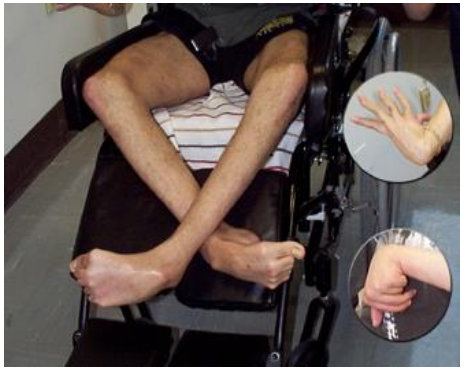
- Psychotropic medication (Lithium, neuroleptics, Tricyclic antidepressive, BZD …)
- Psicotherapy

Zimbrean et al. Gen Hosp Psychiatry, 2014

Atypical neurologic manifestations

- Greater age at presentation
  - More than 20%: > 30 yrs
  - Case of a 74 woman diagnosed because of KF ring (Czlonkowska, 2008)

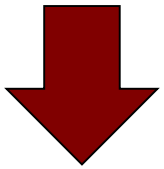
- Less classical phenotypes:
  - **Orthostatic tremor**
  - **Epilepsy** (5%, cortical lesions, resistant to anti-epileptic drugs)
  - Mioclonias
  - Atypical oculomotor movts
  - Autonomic dysfunction (26-38%)
  - Sleep disorders (hypersomnia, -REM-…)



1. Sd. Rígido-acinético (Parkinson síndrome)
2. Pseudoesclerosis con predominio de temblor
3. Ataxia
4. Sd.Distónico.

Second CHALLENGE/Unmet Need

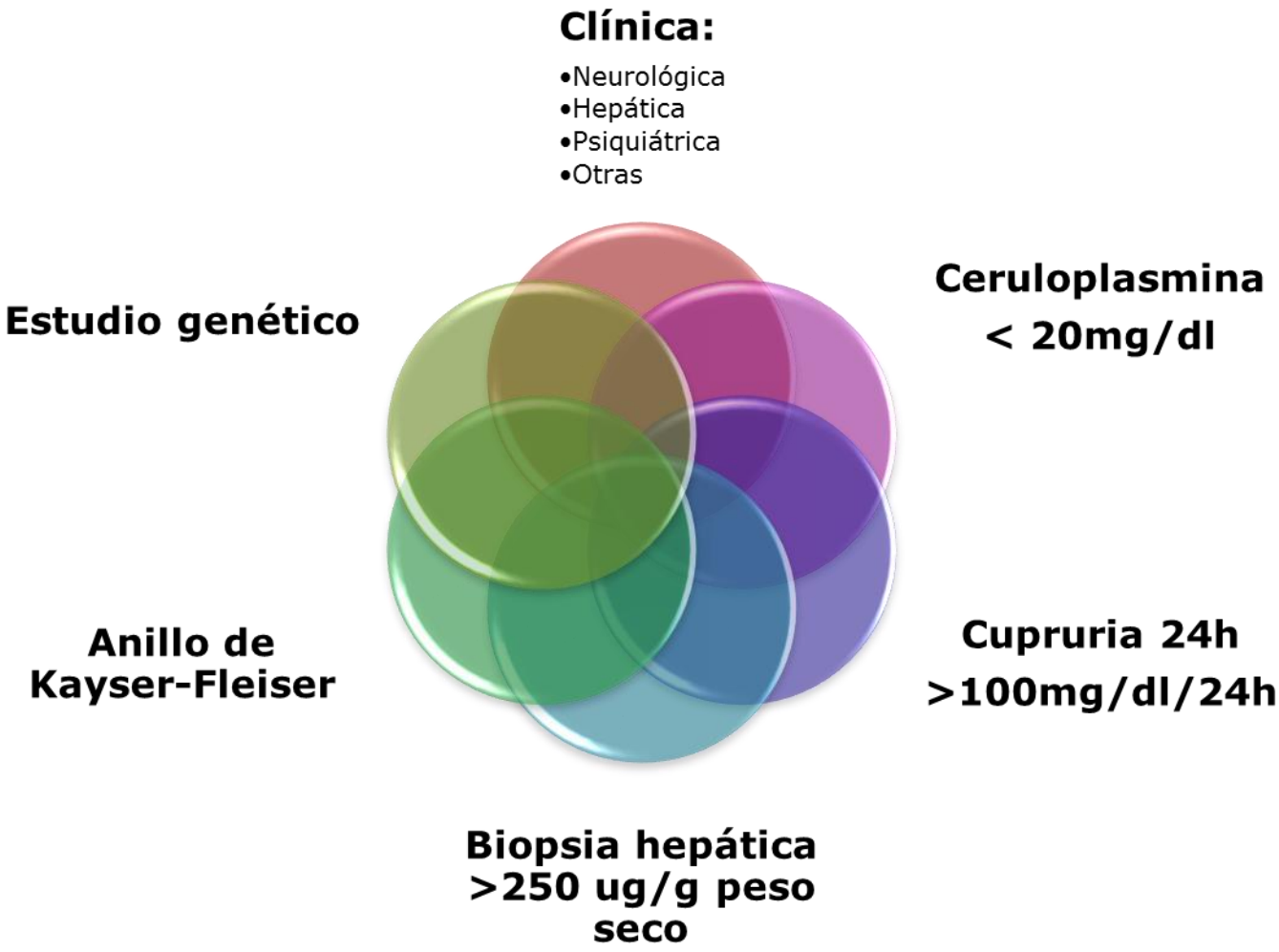
Absence of a specific and sensible diagnostic test



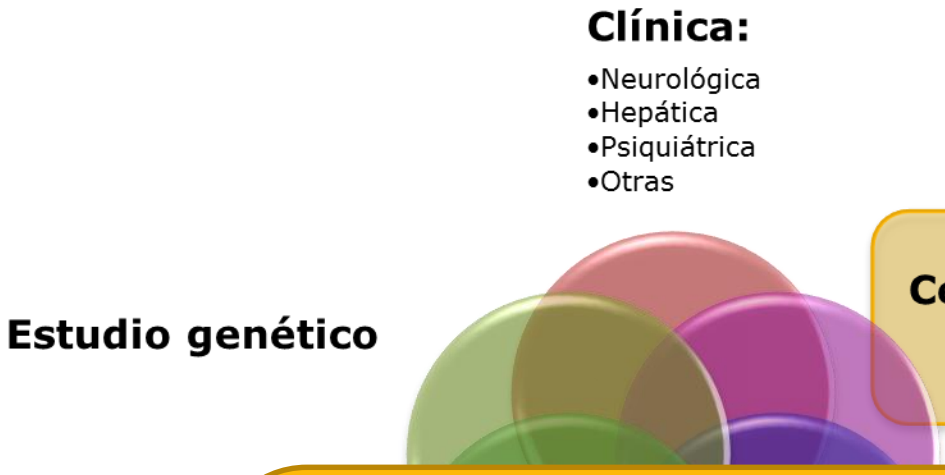
Genetic testing:

- Need to incorporate genetic testing into current algorithms
- Population studies

Absence of a specific and sensible diagnostic test



Absence of a specific sensible diagnostic marker



Ceruloplasmina (CPL)
< 20mg/dl

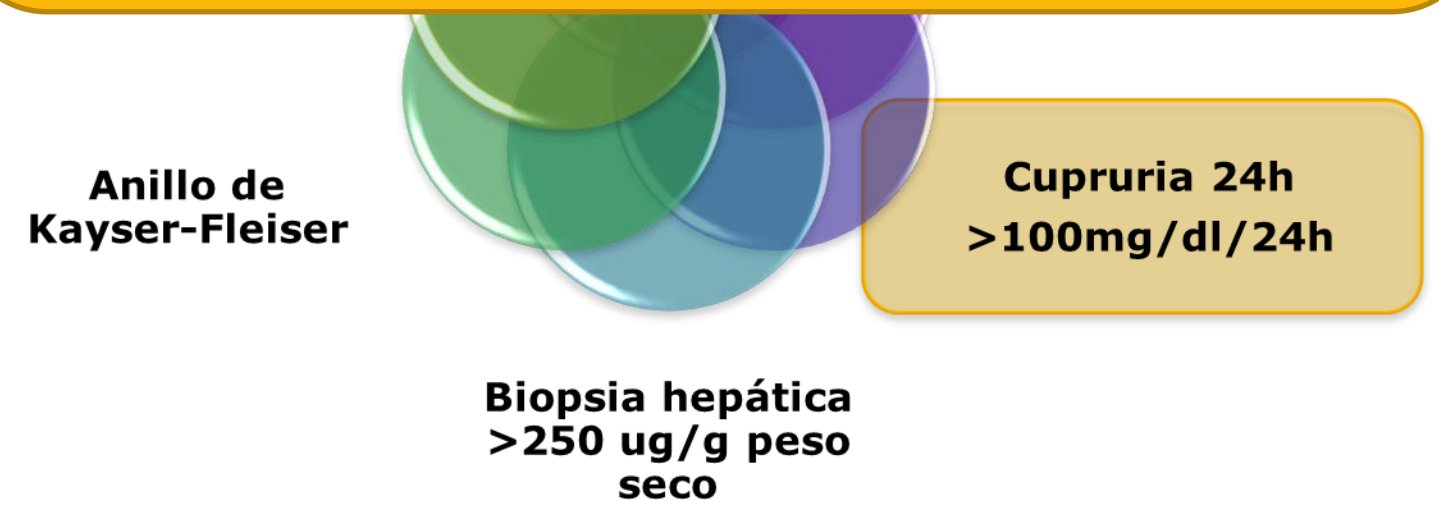
Main serum copper transporter (measurement: enzymatic method >immunoprecipitation)

- **Wilson D**: < 70-85% of cases (technical problems)
- **False positive**: AIH, severe liver insufficiency, aceruloplasminemia, celiac disease / malnutrition, heterogygotes
- **False negative**: liver inflammation, treatment with estrogens, pregnancy, children.

< 10 mg/dl: EW

Absence of a specific sensible diagnostic marker

- Increased in WD (> 100 ug/24h, 40 ug in children)
- Normal in 16-23% of patients (mostly children & asymptomatic)
- Pediatric population: Cupruria post D-Penicilamine (> 1690 ug/24h).
- Increased in AIH, chronic cholestatic liver diseases.
- Used for diagnosis and treatment monitoring.



Absence of a specific sensible diagnostic marker

Novelty : direct measurement copper through fluorescence X (*Kaščáková S. J Pathol Clin Res. 2016)*

Clínica:

- Neurológica
- Hepática
- Psiquiátrica
- Otras

plasmina

mg/dl

ria 24h

g/dl/24h

Liver copper increased (> 250 ug/g dry weight):

(fresh or paraffin-embeded tissue, > 1cm):

- Inconvenient: copper distribution is NOT homogeneous, impact of extensive fibrosis
- Increased in cholestatic liver diseases.
- Decreased if significant fibrosis

Biopsia hepática >250 ug/g peso seco

NO BIOPSY:
- If already dx
- If treated

* < 50 ug: highly unlikely
* 50-250 ug: probable

Absence of a specific and sensible diagnostic test: discrepancias (n=126)

Discordant results in 58% cases:

- Decreased ceruloplasmin (CP): 88%
- 24hr cupruria >100 mcg/24h: 43%.

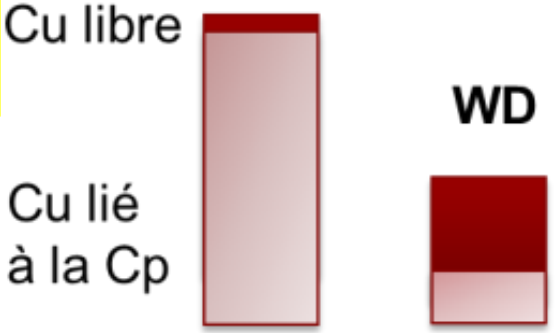
In 79% of these cases, diagnosis was confirmed through intrahepatic copper quantification.

Genetic testing in 83% of those tested (only 50% of the study population)

Relative low reliability of classical copper studies

- CP: < 0.10 g/L
- 24 h urine copper: > 1.6 µmol/24h (100 ug/24h

BUT, in WD, these tests
- Normal in 3% of patients
- Abnormal in **16% of heterozygous carriers**



Development of a new test to quantify free copper not linked to CP, independently of CP quantification:
= exchangeable copper (CuEXC) and the ratio REC (CuEXC/total copper)

El Bakhli et al. Clin Chim Acta, 2011
J.-M. Trocello et al. Mov. Disord., 2014

Exchangeable copper (CuEXC): free serum copper

=> **REC** (ratio CuEXC/total copper) useful for:

- **Diagnosis**
- **Family screening**

if **REC > 18,5%** (Sp y Se = 100%)

El Bakhli et al. Clin Chim Acta, 2011
J.-M. Trocello et al. Mov. Disord., 2014

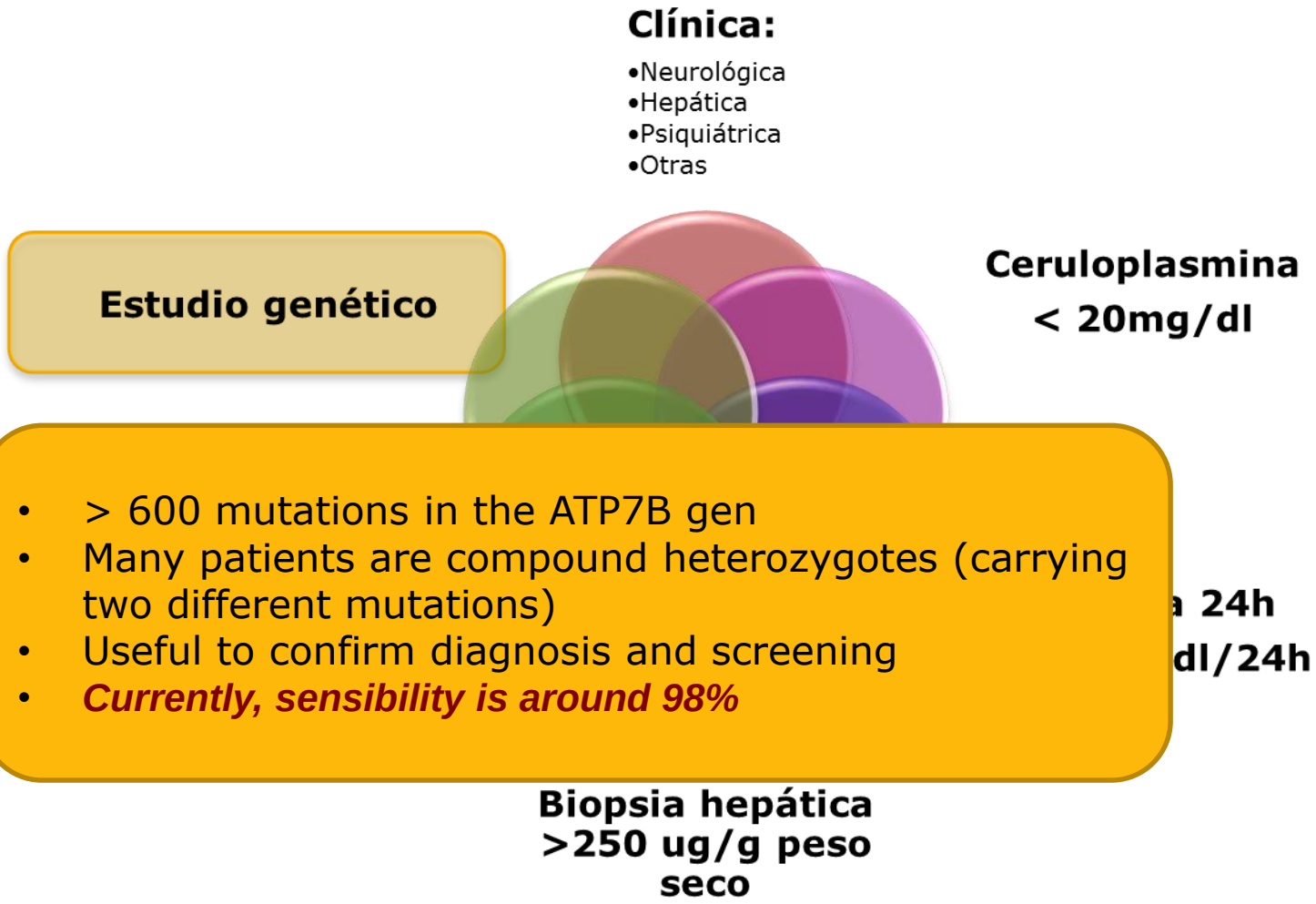
⇒ **CuEXC high** (> 2.08 μmol/l) associated with extrahepatic manifestations (Se: 85.7%; Sp: 94.1%).

=> **CuEXC is an indirect marker of the severity of extrahepatic involvement**:

- Correlates with KF (p=0.01)
- Correlates with neurologic score UWDRS (p=0.01)
- Correlates with brain MRI changes (p=0.04)
- Does not correlate with liver disease severity

Poujois et al. J Orphan Rare dis 2019

GENETIC TESTING



- > 600 mutations in the ATP7B gen
- Many patients are compound heterozygotes (carrying two different mutations)
- Useful to confirm diagnosis and screening
- ***Currently, sensibility is around 98%***

La mutación más frecuente en Europa es la H1069Q.
www.wilsondisease.med.ualberta.ca/database.asp

Liver presentation

Leipzig diagnostic algorithm score

Typical clinical symptoms and signs	
KF rings	
Present	2
Absent	0
Neurologic symptoms**	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>0.2 g/L)	0
0.1-0.2 g/L	1
<0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

Other tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>4 µmol/g)	2
0.8-4 µmol/g	1
Normal (<0.8 µmol/g)	-1
Rhodanine-positive granules*	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0

TOTAL SCORE	Evaluation:
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol 2012

Age and Sex but Not ATP7B Genotype Effectively Influence the Clinical Phenotype of Wilson Disease.

Ferenci P[1], Stremmel W[2], Członkowska A[3], Szalay F[4], Viveiros A[5], Stättermayer AF[1], Bruha R[6], Houwen R[7], Pop TL[8], Stauber R[9], Gschwantler M[10], Pfeiffenberger J[2], Yurdaydin C[11], Aigner E[12], Steindl-Munda P[1], Dienes HP[13], Zoller H[5], Weiss KH[2].

1,357: hepatic (n = 711) or neurologic disease (n = 461)

Most frequent mutations:
H1069Q (c.3207C>A; allele frequency: 46.9%),
P767P-fs (c.2304dupC; 2.85%),
P1134P-fs (c.3402delC; 2.8%),
R969Q (c.2755C>T; 2.18%).

NO correlation between mutations and individual clinical manifestation

Hepatology. 2019 Apr;69(4):1464-1476

Third CHALLENGE/ Unmet need

Research with new compounds

Impact on QOL / Impact on family

Long term follow up

Transition from childhood to adulthood

Multidisciplinary Units

Treatment


Zinc
Trientina
Tetratiomolibdato
D-Penicilamina
Arsenal terapéutico de la Enfermedad de Wilson
Dimercaprol

“start low and go slow”

WTX-101 Phase 2 study

N=28

- 9 naïve, 9 treated <28 days, 10 treated beween 28 days-2 yrs

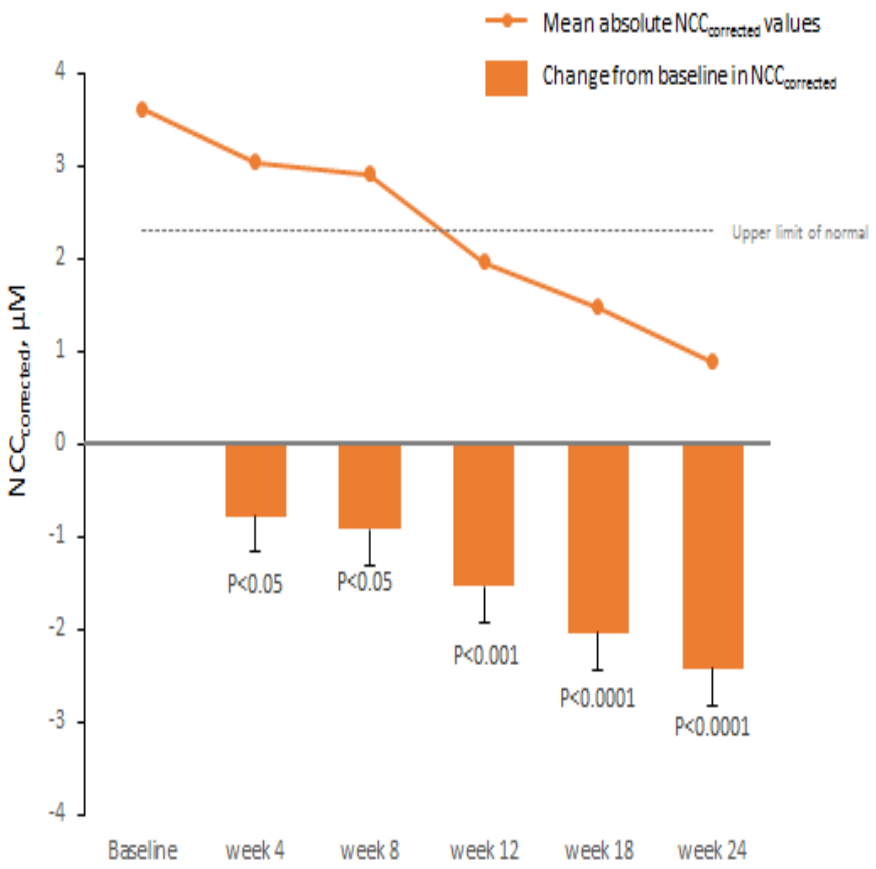
Most neurologic forms

~50% cirrhosis

22 completed 24 weeks therapy

- 3D/C WTX101 due to transaminitis
- 3 D/C WTX101 due to difficulties monitoring (severe neuropsychiatric symptoms)

71% with CR at week 24



Weiss et al, Lancet Gastroenterology

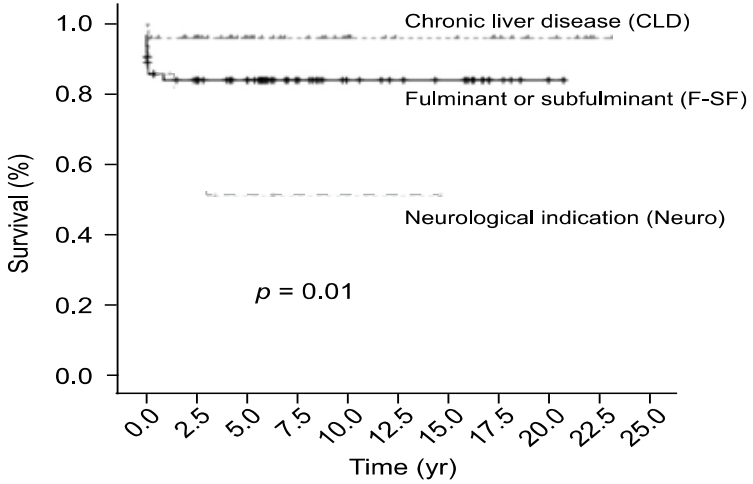
Special circumstances

LIVER TRANSPLANTATION

1- Results: excelent (90% at 5 yrs. In fulminant: 75%)

2- ¿Life donor? No if homozygous donor, yes if heterozygous

3- **No in chronic neurologic impairment / Yes in recent abrupt neurologic deterioration following chelator therapy or treatment D/C (adolescent) -20 cases**



Patients at risk

F-SF WD	64	46	39	25	18	15	13	5	1	0
CLD	50	41	31	24	16	13	13	9	6	1
Neuro	7	4	2	1	1	1	0	0	0	0

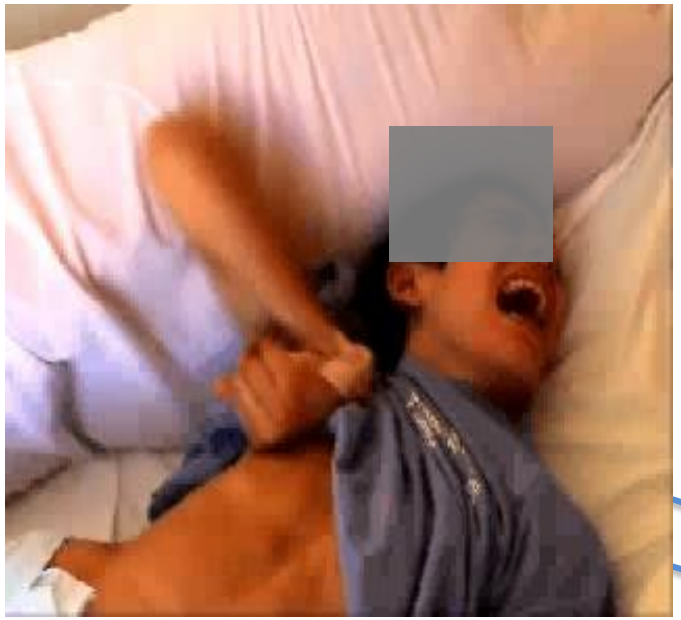
Case

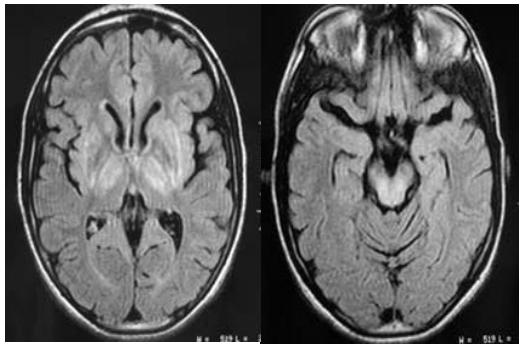
Patient

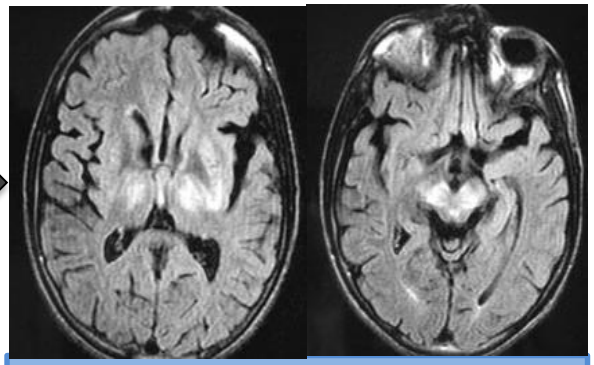
WD diagnosis at 13 yrs
Mild dystonia
Trientine (DP: adverse events)
Changes in brain MRI
=> Clinical response

15 yrs: treatment D/C ….

Fulminant neurologic impairment
That persisted and progressed despite Trientine and Zinc





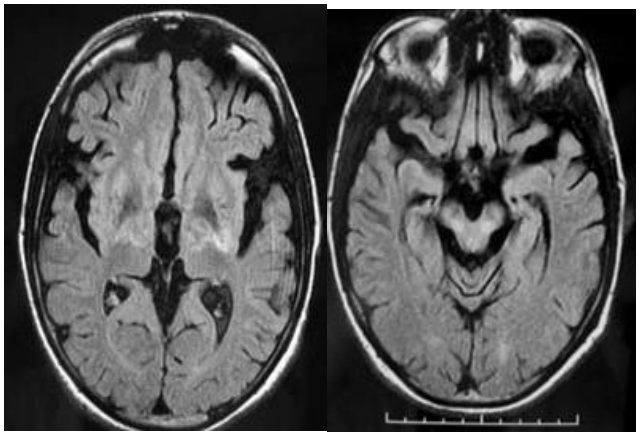


5 months later:
Liver transplantation

Case report: follow-up

6 months post LT

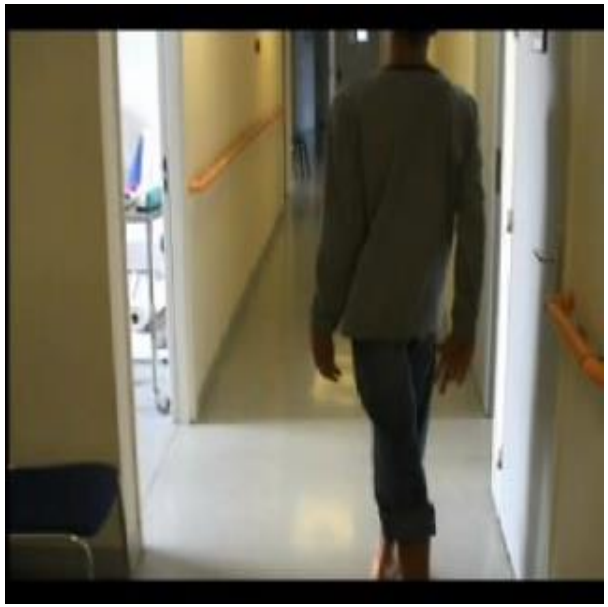
Stands up, some steps



Improvement of brain MRI: decrease of signals in basal ganglia

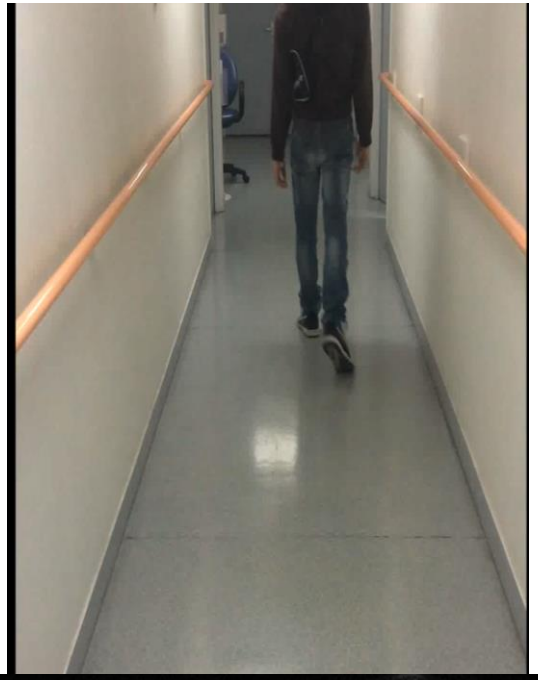
1 year post LT

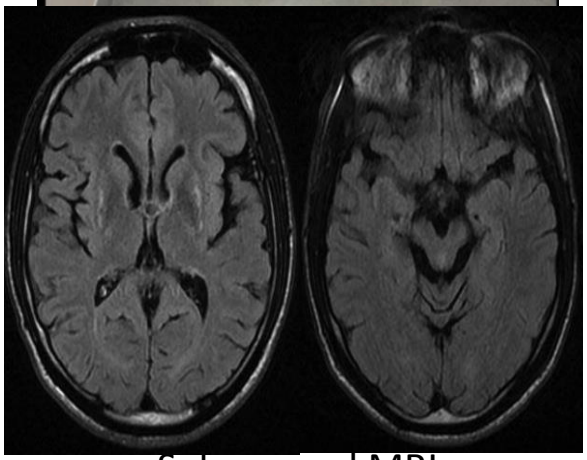
Walks, autonomous for daily activities



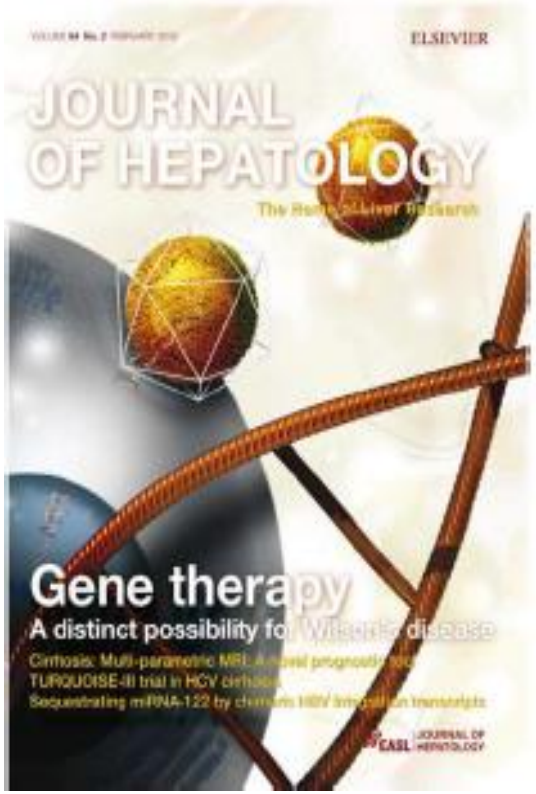
12 years post LT

Completely autonomous
Married, children





Sub-normal MRI



WD gene therapy using an ATP7B minigene

6-week old WD mice	Untreated	miniATP7B-AAV $5x10^{12}$ vg/kg IV
Liver transduction	-	20%
Fecal ^{64}Cu excretion	↓	✓
Urinary Cu excretion	↑	✓
Hepatic Cu	↑	✓
Histology	Hepatitis/fibrosis	✓
Survival	↓	✓
Serum ceruloplasmin	↓	✓
Serum liver biochemistry	Chronic hepatitis	✓
Hematology	Anemia	✓

Similar results were obtained in male and female mice and in 6 and 12 week old animals In the absence of toxicity in WT animals

summary:

EDITORIAL

Unidades multidisciplinarias en hospitales de referencia para mejorar la atención de los pacientes con enfermedad de Wilson

Multidisciplinary units in tertiary referral hospitals to improve management of Wilson disease

- The cause lies in **copper metabolism** due to mutations in the ATP7B copper transporter gen (monogenic autosomal recessive disorder)
- Can present at **any age** with variable symptomatology (neuropsychiatric, liver, ..)---THINK ABOUT IT!!!
- Relatively easy **diagnosis** in many patients, but available tools (ceruloplasmine, cupruria, liver copper) not always inequivocal……DELAYED TIME!!!!
- **Genetic testing** (mutations in the 2 alleles of the ATP7B gene), is a highly sensible alternative, but lack (or 1) mutations does not exclude the possibility of WD
- There is an **efficacious treatment** which underlines the relevance of early diagnosis when injury is reversible.
- For the first time in years, **future perspectives**
- Importance of **Multidisciplinary Units**

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