

Wilson's disease from a COMP perspective

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Diagnostics

- MRI (brain)
- PET (dopamine)
- PET (copper)

Patient care

- WD team
- Patient support group
- Long term treatment with Trientine

Genetics

- WD gene mutations
(Manifold sequencing)

Psychiatrics

- Mapping psychopathology
and neurophysiology

*Progressive lenticular degeneration
a familial nervous disease associated with
cirrhosis of the liver*

SAK Wilson

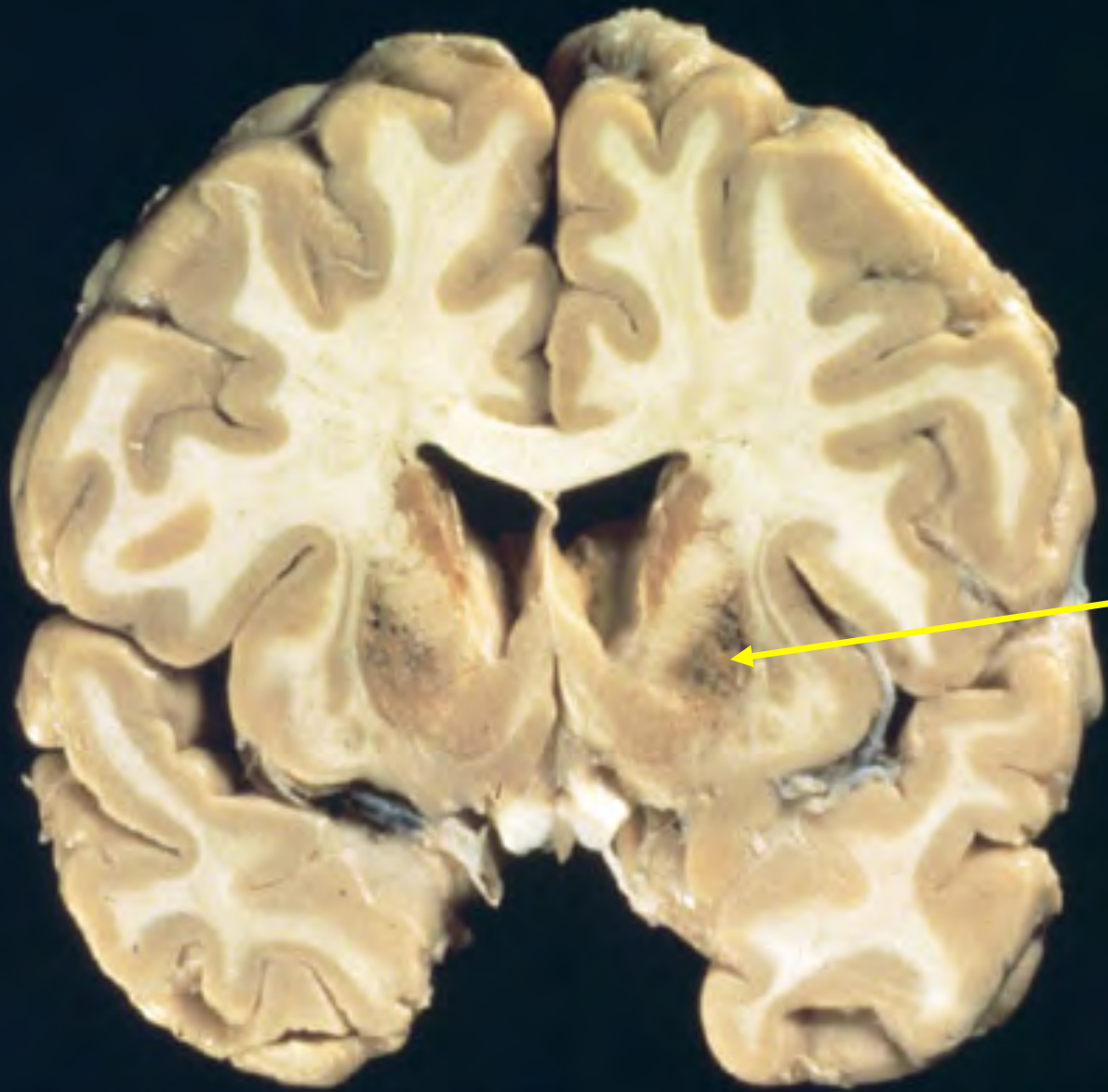
Thesis, Univ. of Edinburgh, 1911



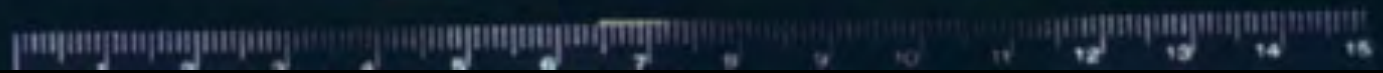
Spasticity

Tremor

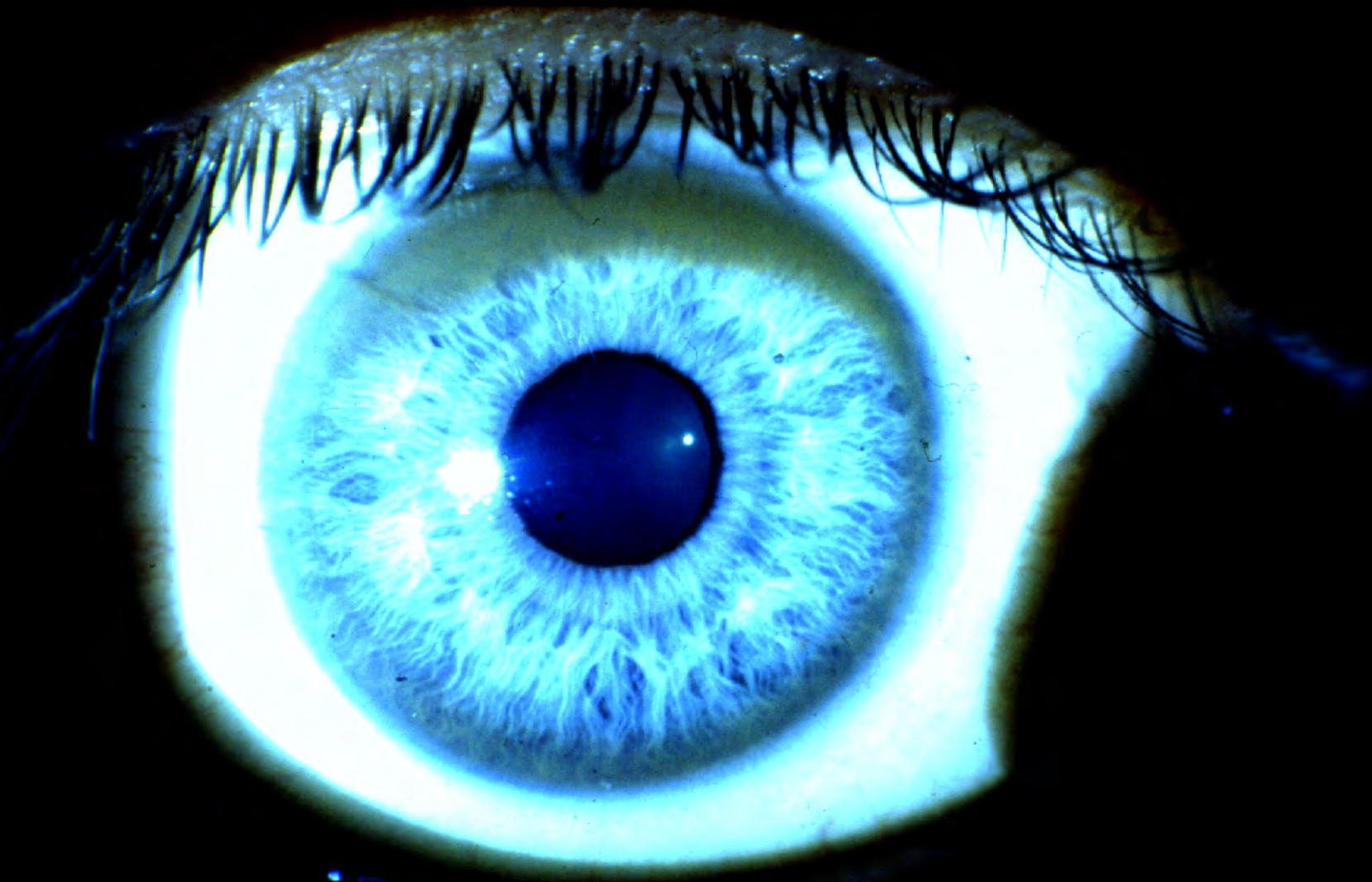
Contractures



Basal
ganglia



Kayser-Fleischer ring







”As the doctor says of a wasting disease, to start with it is easy to cure but difficult to diagnose; after a time, unless it has been diagnosed and treated at the outset, it becomes easy to diagnose but difficult to cure .”

Niccolo Machiavelli, *The Prince*, 1514
(transl. George Bull)

The Penicillamine Story
(From: J M Walshe, *Movement Disorders*,
Vol. 18, No. 8, 2003)

Early 1950s Univ. College Hosp. London :

JM Walshe, using paper chromatography, observed a new compound in the urine of a patient treated with penicilline - penicillamine.

Penicillamine reacted with ferric chloride: blue colour, presence of an SH-group

Chelating properties?

Boston City Hosp., 1955: JM Walshe

- Denny-Brown/Uzman working on patients with WD
- Treatment with British antilewisite (BAL) i.m. – painful, toxic, tachyphylaxis
- Patient Joe G failing on BAL treatment
- JM Walshe – Penicillamine – copper removing?
- 2 g from prof. Sheehan working on chemical synthesis of penicillin at MIT

Penicillamine "toxicity testing"

- No published data on toxicity in man/little in animals
- JMW observation: Anyone treated with penicilline (including JMW) excreted penicillamine in the urine – apparently without ill effect
- 1st study in man: JMW took 1 g of penicillamine - a crystalline powder smelling sulphur
 - JMW being well and alive next morning...

”Clinical Trial” – no ECs, No FDA...

...gave the 2nd g to patient Joe G

Result: Satisfactory copper excretion

- Conclusion: Further studies with penicillamine justified
- More penicillamine needed – MSD provided several grams - but MSD penicillamine failed to induce cupriuresis...
- JMW test: No blue colour with ferric chloride (tap water) - long storage – autooxidisation – no SH-radical - no copper chelation

Penicillamine production story

- Mann's Fine Chemicals, New York produced 50 g of penicillamine
- JMW brought this to his father, Sir Francis Walshe, prof. in Neurology in London
3 patients with WD were treated:
All responded well - No 1 and 2 were put back on BAL

Penicillamine story, cont.

Patient No 3, Shirley

- severely parkinsonian, failed to improve on BAL - prime case for a trial of a new therapy (no ECs, No drug safety committees)
- JMW prepared penicillamine, packed into capsules, gave to Shirley - 450 mg/d.



Shirley improved but not until after 1
year of treatment (low dose)

- Married
- Three children
- 47 years of penicillamine treatment –
1.5 kg in all



*Walshe JM, Penicillamine,
a new oral therapy for
Wilson's disease.
Am J Med 1956;21:487-95*

Penicillamine Story, cont.

Production problems

Solution:

The Distillers Company Biochemicals –

main manufacturers of penicilline by
fermentation - produced penicillamine

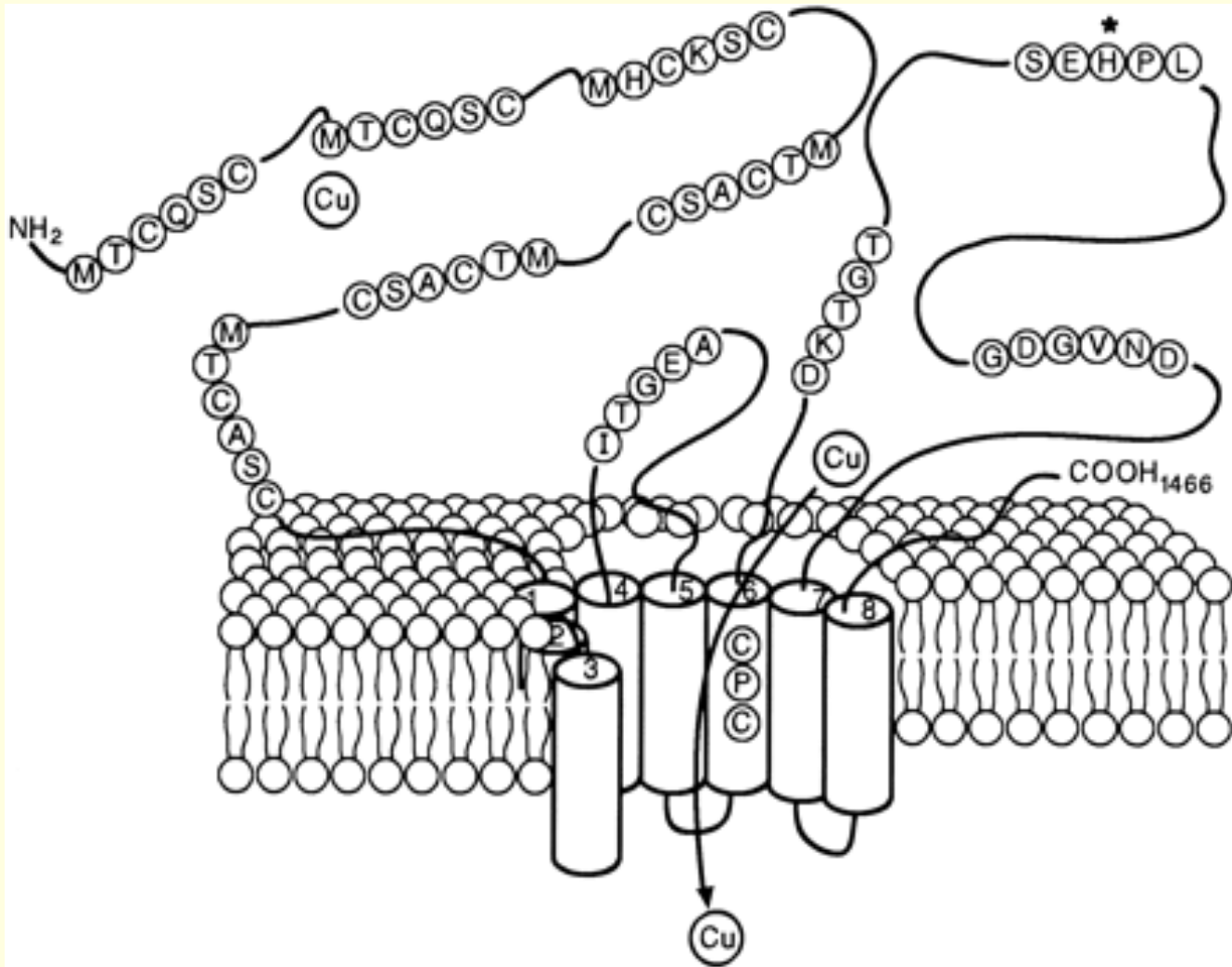


Wilson *disease* history

1993

WD gene cloned by three independent groups:
Bull et al, Tanzi et al and Yamaguchi et al

The Wilson's disease gene encodes a copper transporting ATPase which is expressed in hepatocytes - maintains copper homeostasis – excretion of excess copper into the bile



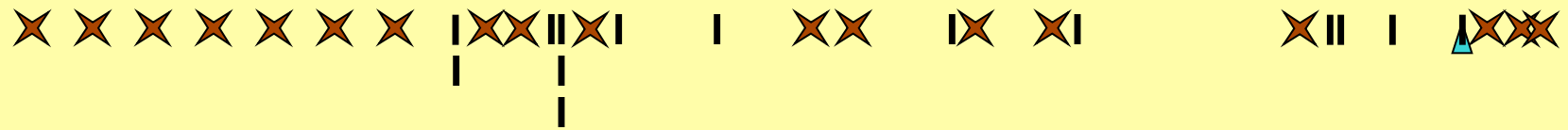
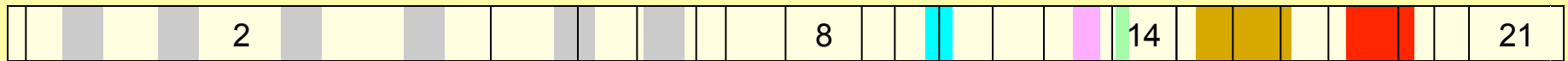
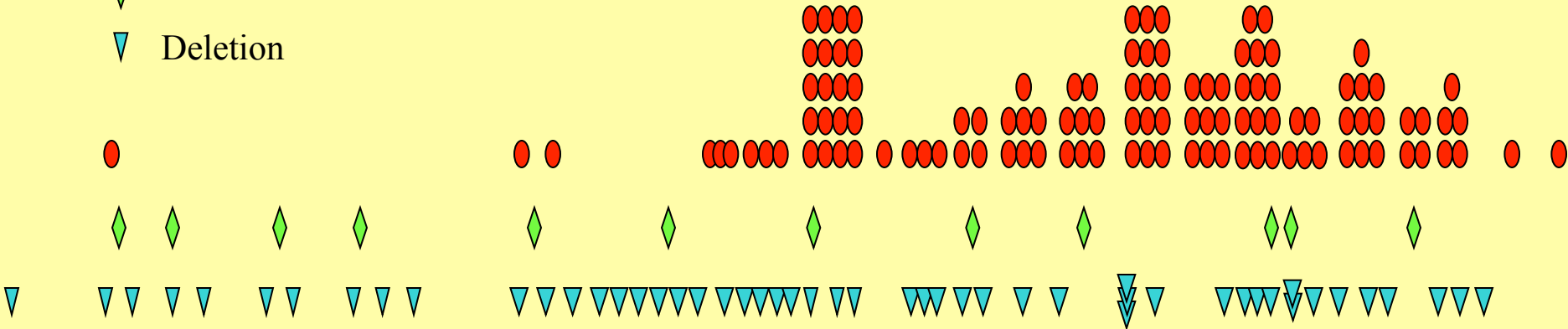
Semin Liver Dis 2000;20:353-64

All registered mutations in *ATP7B* 14/02/02

● Missense-mutation

◇ Insertion

▽ Deletion



✕ Nonsense-mutation

| Splice-site-mutation

▲ Deletion in splice-site

Copper-binding domain

Trans-duction domain

Putative channel region

Phosphorylating domain

ATP-hinge

The COMP perspective

*All treatments presently used have
been developed in academic
institutions*

1954 Peters, Oxford (BAL)

1956 Walshe, Boston (penicillamine)

1961 Schouwink, Arnhem (zinc sulphate)

1969 Walshe, Cambridge (triethylene tetramine -
Trientine),

1984 Walshe, Cambridge, (tetrathiomolybdate)

1983 Brewer, Ann Arbor, (zinc acetate)

Conclusions – Drugs for Wilson's disease:

- thanks to academic scientists
- thanks to serendipity
 - and lately
- thanks to the Orphan Drug legislation, EU Directive 2001/04
- treatment for Wilson's disease has become generally available to patients within the EU

Conclusions

Present and Future treatments:

In the future: Gene therapy, cell therapy...based on current molecular knowledge

At present: Liver transplantation in liver failure

At present: Zinc acetate authorised in the US (Galzin) and EU (Wilzin – *Orphan Drug*)

Trientine in the US and in the UK/EU (*Orphan Drug Designation*)

Tetrathiomolybdate used experimentally in the US and EU

Penicillamine – still the main drug
for Wilson's disease –
after 50 years on the market!



John M. Walshe