



HNF1B and the brain



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HNF1B

Genetics already discussed

Aspects that are established:

renal cysts

diabetes

involvement of pancreas, liver, genital system

gout, or elevated blood level of key component, urate

These aspects discussed in other talks

Less researched: HNF1B and the brain

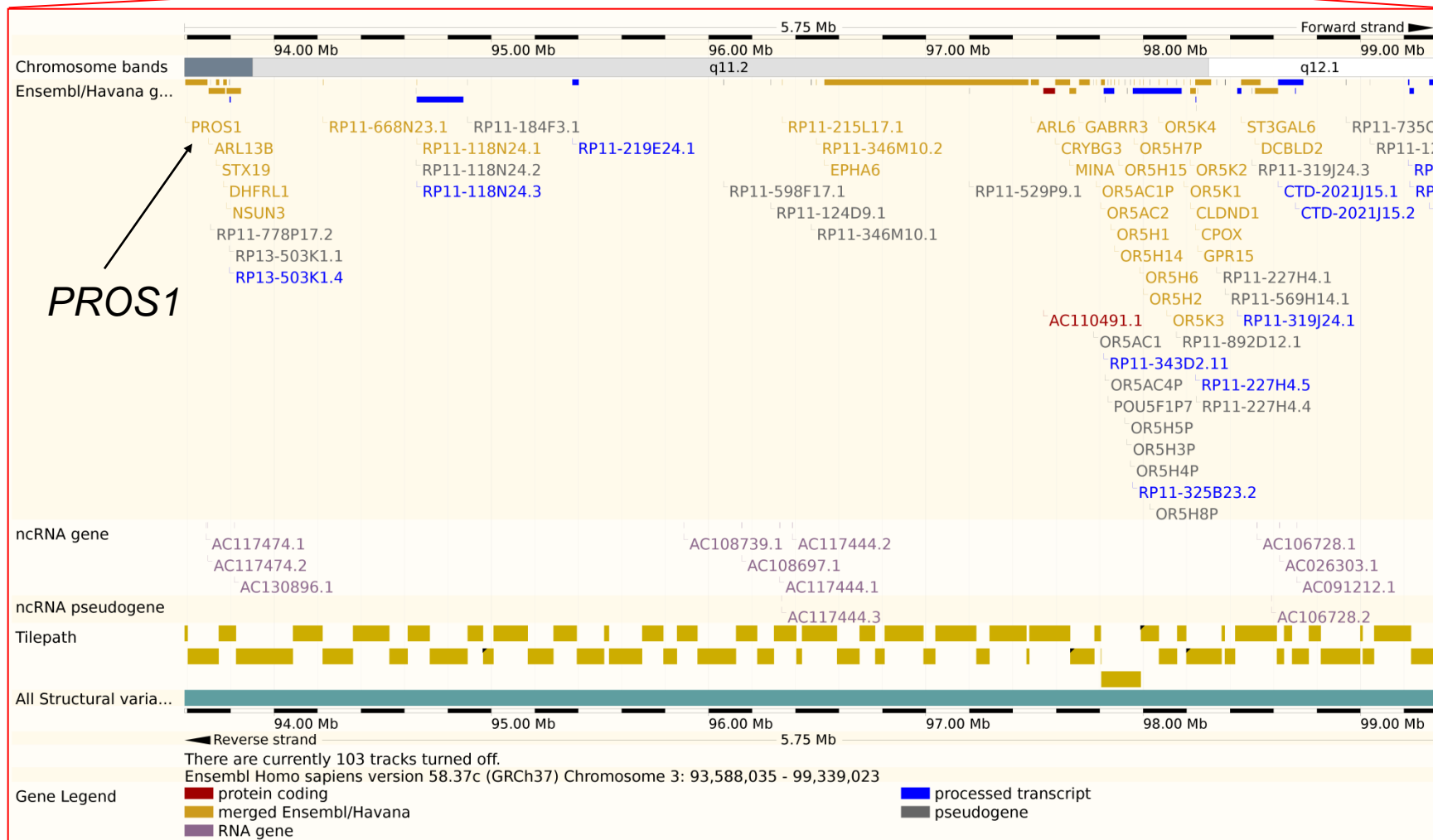
HNF1B and the brain

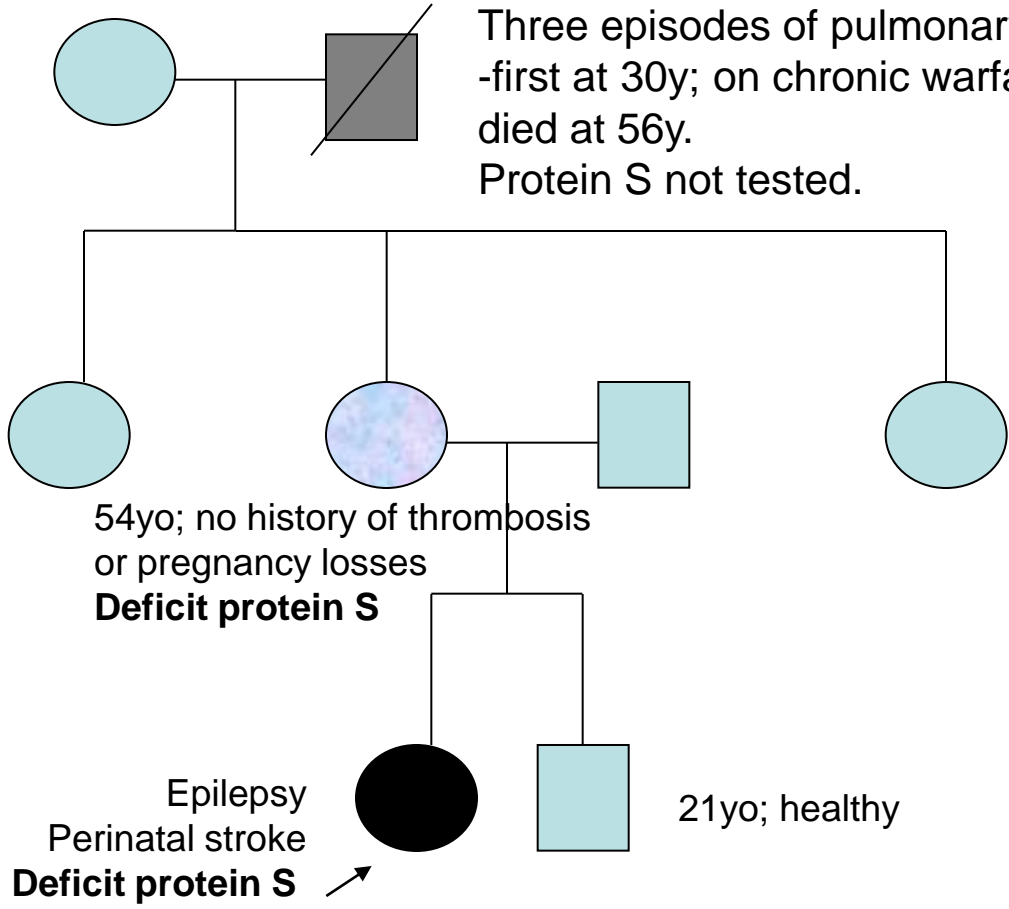
Why look at this?

- A number of perspectives
- There are already reports of brain involvement
- Understanding the full range of consequences can help overall in managing the problems that may arise
- Problems can be anticipated, with forward planning or increased awareness that they might occur
- May prevent unnecessary tests
- Helps us understand what is going on
- In the long-term, may be important for treatment options

- 25 year old female
- Fits from 6 months – 3 years
- Early left hand preference
- Brain scan: ‘stroke around the time of birth’
- Fits again from 9 years, drugs not working
- Seizures thought to come from area around the stroke

Heterozygous deletion 3q11.2





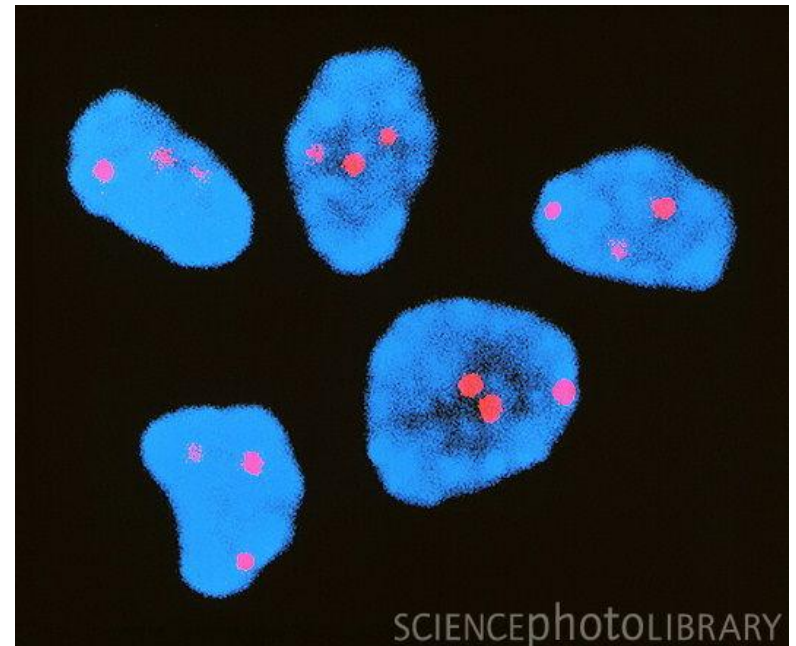
HNF1B

HNF1B

Genetics: type of genetic change important for various aspects
Point mutation versus deletion or duplication of the gene

Number of copies of a gene may be important – a balance,
need the right number of copies

Familiar example:
Down Syndrome



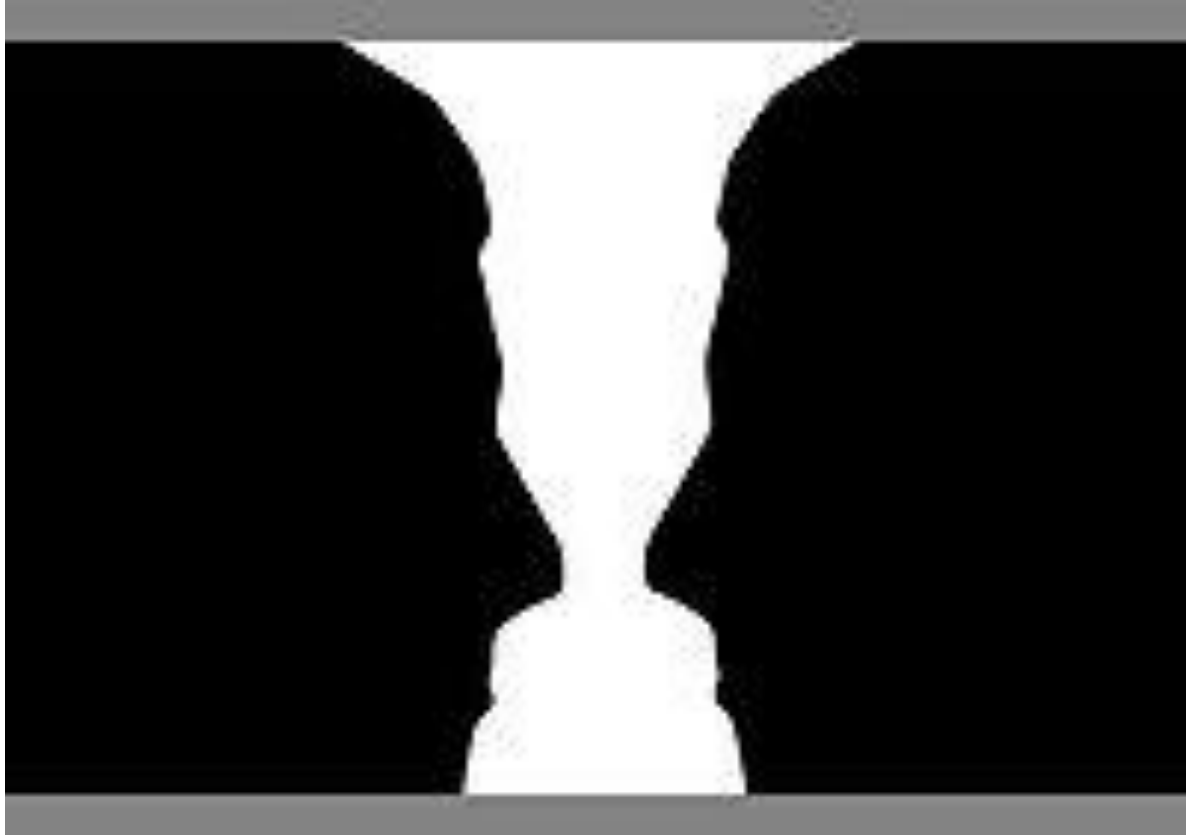
HNF1B and the brain

Early reports did not feature any suggestion brain might be involved

Deletion or duplication of the gene typically associated with deletion or duplication of several (e.g.15-19) adjacent genes

Deletion was thought to be one of the few examples of a genetic change of this size that did not have an effect on the brain

HNF1B and the brain



HNF1B and the brain



HNF1B and the brain

But most of our genes are active in our brains

The brain is an amazingly complicated thing

Many genes are involved in its construction and its working

The genes may be active at one time, and not at another,
they may be active in one part of the brain and not in another

You only see what you are looking for

Doctors can be blinkered!

Most early reports came from kidney or diabetes specialists

HNF1B and the brain

What sort of effect can gene changes (such as deletions) have on the brain?

Common results can include:

epilepsy

intellectual difficulties

autism / autistic spectrum disorder

difficulties with limb movements

behavioural problems

These conditions are important to identify and manage

HNF1B

Working out whether a gene has an effect on the brain can be difficult – not easy to study the brain.

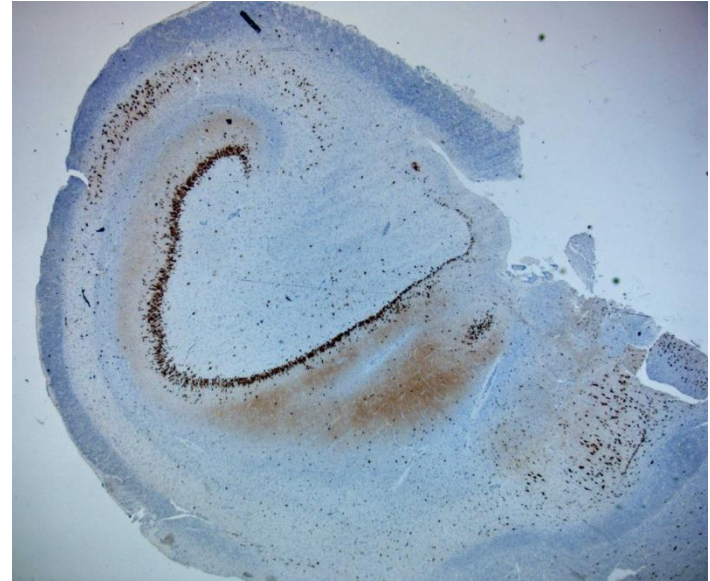
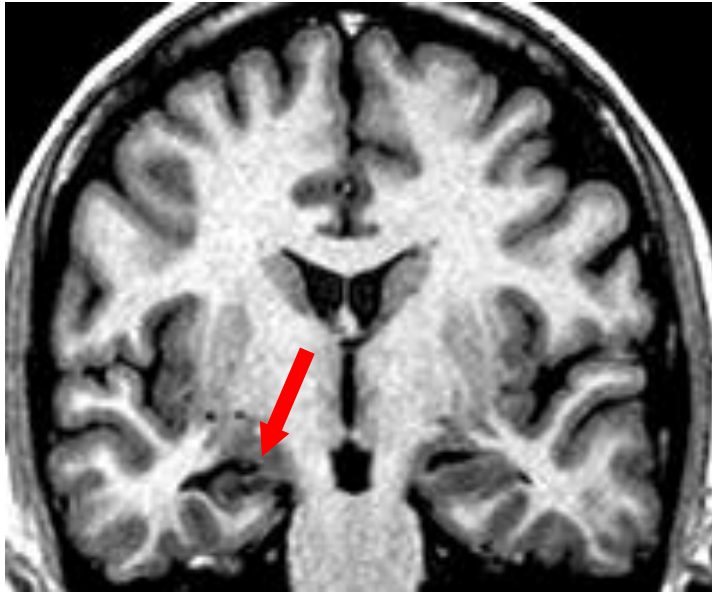
Blood tests may not help

Cannot usually take a part (biopsy) of the brain

MRI scans, cognitive tests and other tests may help

Sometimes, access to brain tissue is possible

Looking at it the other way round



A revelation to a brain doctor



17q12 rearrangements



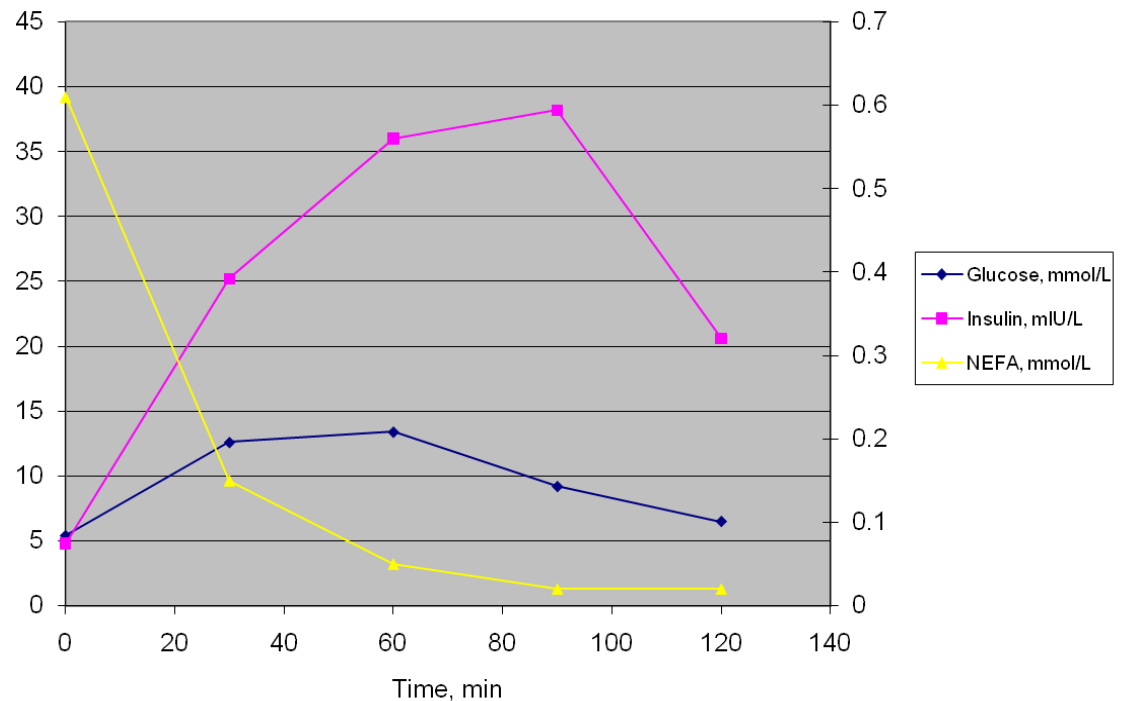
Bernardini et al, 2009. MRKH syndrome

_syndrome_2patients

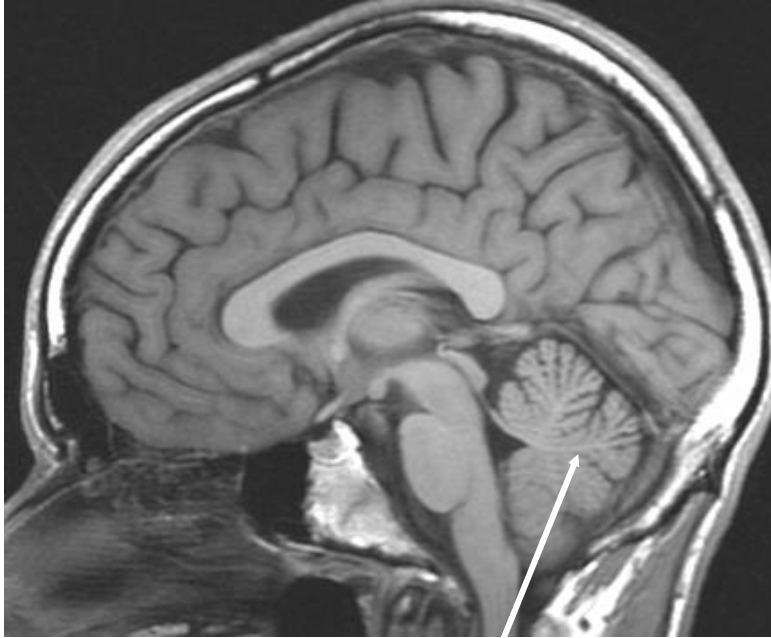


DECIPHER

DECIPHER



Important consequences



Acetyl-CoA

NEFA

Acetoacetyl-CoA

3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA)

Mevalonate

Mevalonate-P

Mg++ low

Mevalonate-PP

glucose high

Isopentenyl-PP

Protein Isoprenylation

Geranyl-PP

4OH-Benzoate

Decaprenyl-PP

Farnesyl-PP

Geranylgeranyl-PP

Squalene Synthetase

Decaprenyl-4OH-benzoate

Squalene

Polyprenyl-PP

DIRECT IMPACT ON CARE

CoQ₁₀

Cholesterol

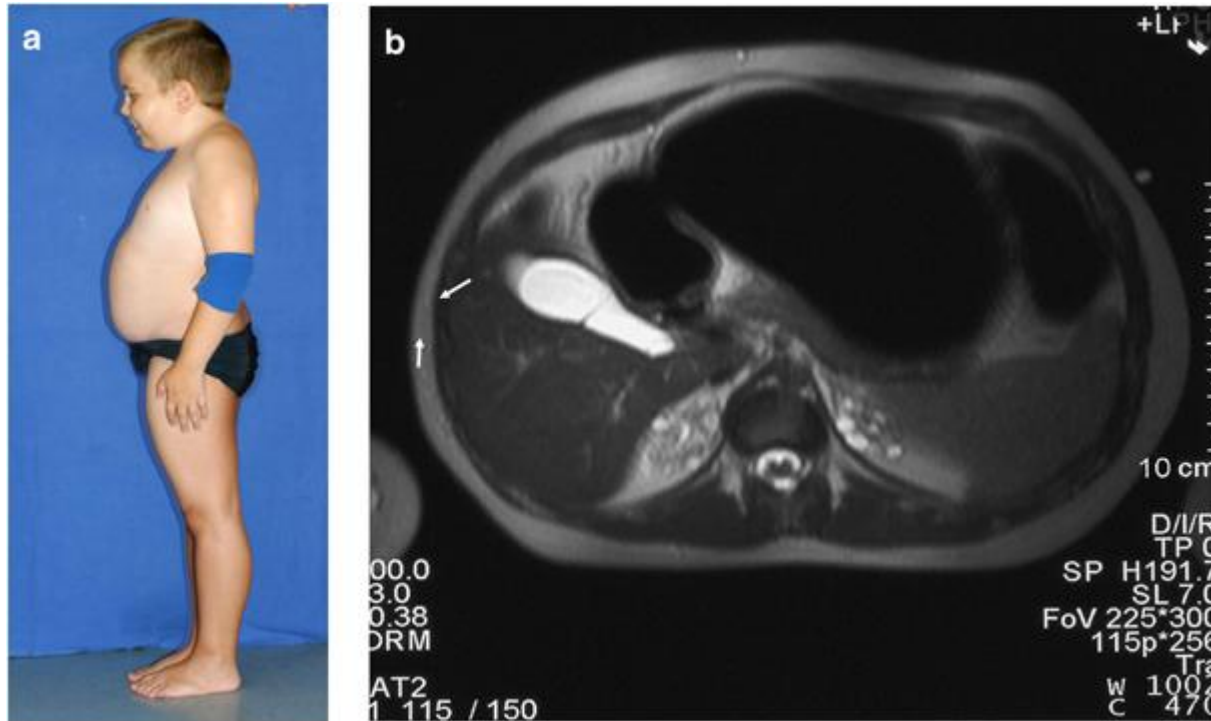
Dolichol

Dolichol-PP

HNF1B and the brain

How common are these things?

HNF1B and the brain

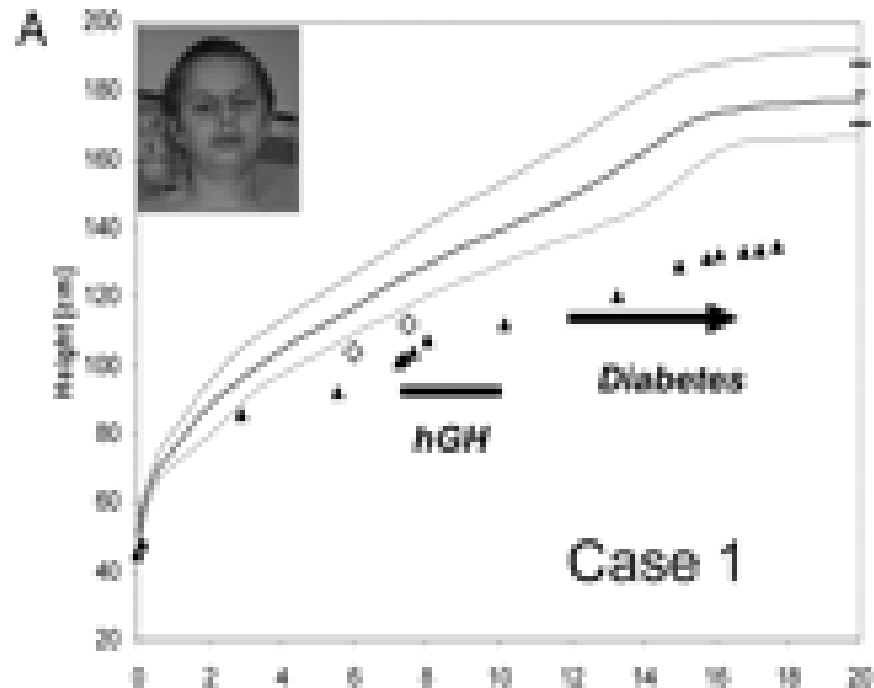


Muller, Klopocki et al. 2006

DELETION

Movement, speech and behavioural problems ('resembling autism')

HNF1B and the brain



Raile, Klopocki et al. 2009
One more person

5 DELETIONS

Movement, speech and social problems

HNF1B and the brain

Loirat et al. 2010

3/53 DELETIONS

Three children with kidney disease and autism

Greater than expected number in 53 children

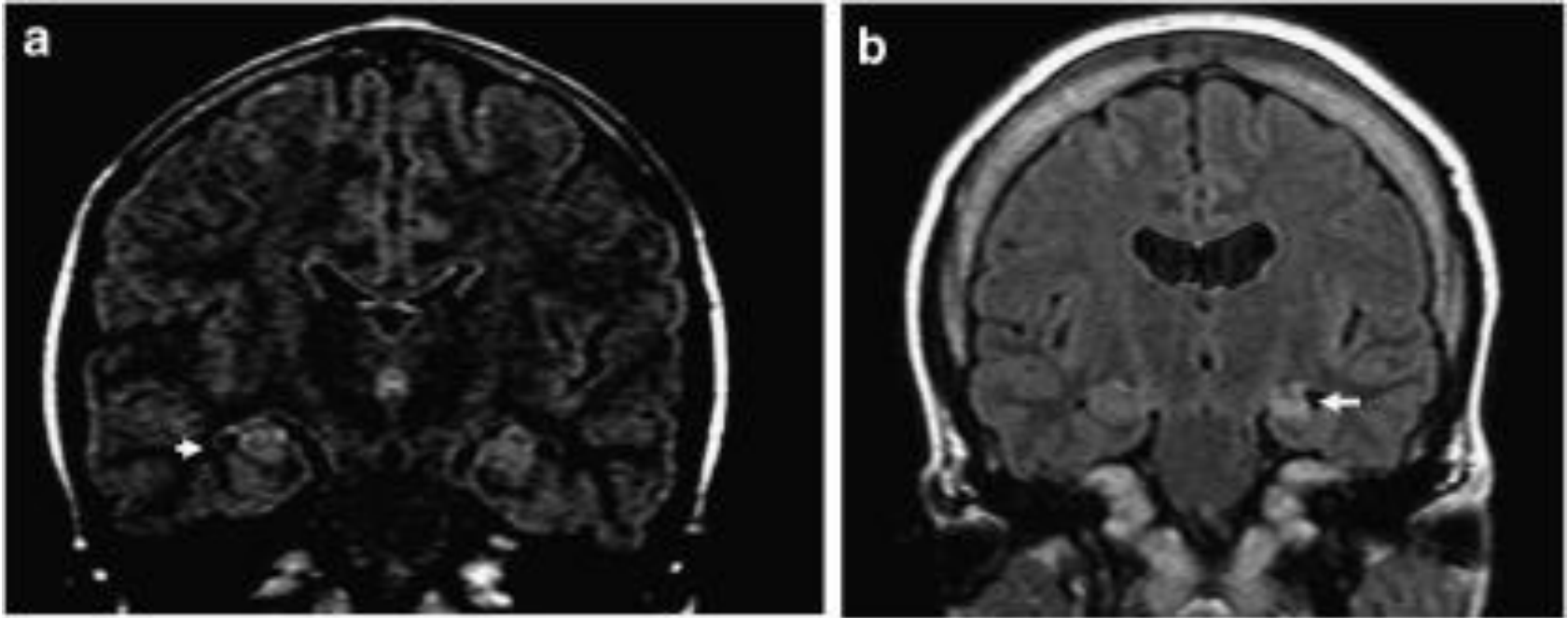
Movement, speech and social problems

Authors noted:

“These neurological phenotypes could be underestimated since these patients are generally followed up by nephrologists and/or diabetologists for adult cases who may not be aware of the variable expression of autism. ”

Need a more systematic approach

HNF1B and the brain



Nagamani et al. 2010

4 DELETIONS / 5 DUPLICATIONS

Three people with deletions and 4/5 with duplications had brain involvement

Speech problems, epilepsy; intellectual, behaviour difficulties

HNF1B and the brain

Looking at it the other way, systematically – the study that needed to be done

Moreno-De-Luca et al. 2010 18 DELETIONS in a study of 15749 people
15 people studied in detail

Speech and intellectual problems; autism/ASD in all six males with deletion
Confirmed findings in another group of people with the condition

HNF1B and the brain

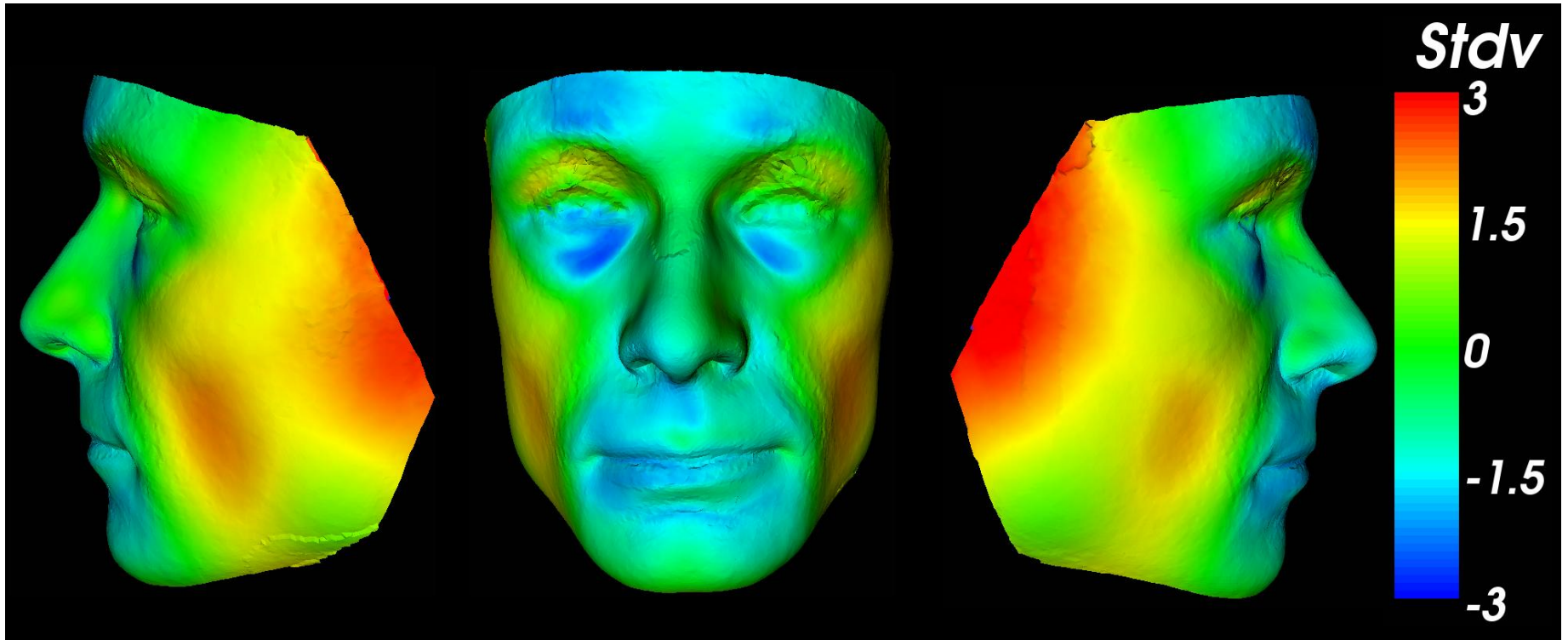
First suggestion of a common facial appearance?



**** All these findings seem to be when there is a deletion or duplication,
not a point mutation****

HNF1B and the brain

First suggestion of a common facial appearance?



**** All these findings seem to be when there is a deletion or duplication, not a point mutation****

HNF1B and the brain

Findings are variable

7 year old girl with deletion: normal intellect

Brother, aged 2.5: slowed motor development

Father: intellectual difficulties, cannot read or write – NO
DELETION

Mother: mild intellectual difficulties - has the deletion

George et al. 2011

HNF1B and the brain

Less researched: HNF1B and the brain

There does seem to be some effect

The effect is variable

Difficult to be precise because of several complicating issues

how people are picked up

who sees people who are affected

what they look for, when they look for it

numbers

variable effects of the deletion/duplication itself

'penetrance' 'expressivity'

HNF1B and the brain

Less researched: HNF1B and the brain

There does seem to be some effect

Autism, autistic spectrum disorder:

characterised by problems with social interaction, communication, repetitive patterns of interest and behaviour, usually starting early in life

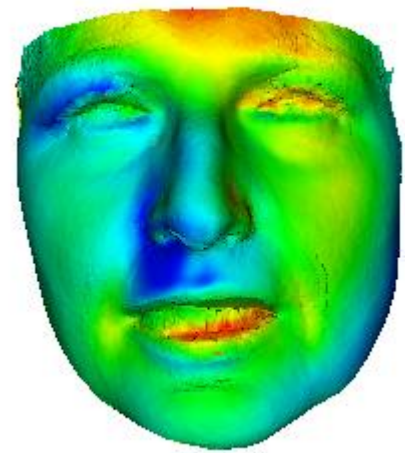
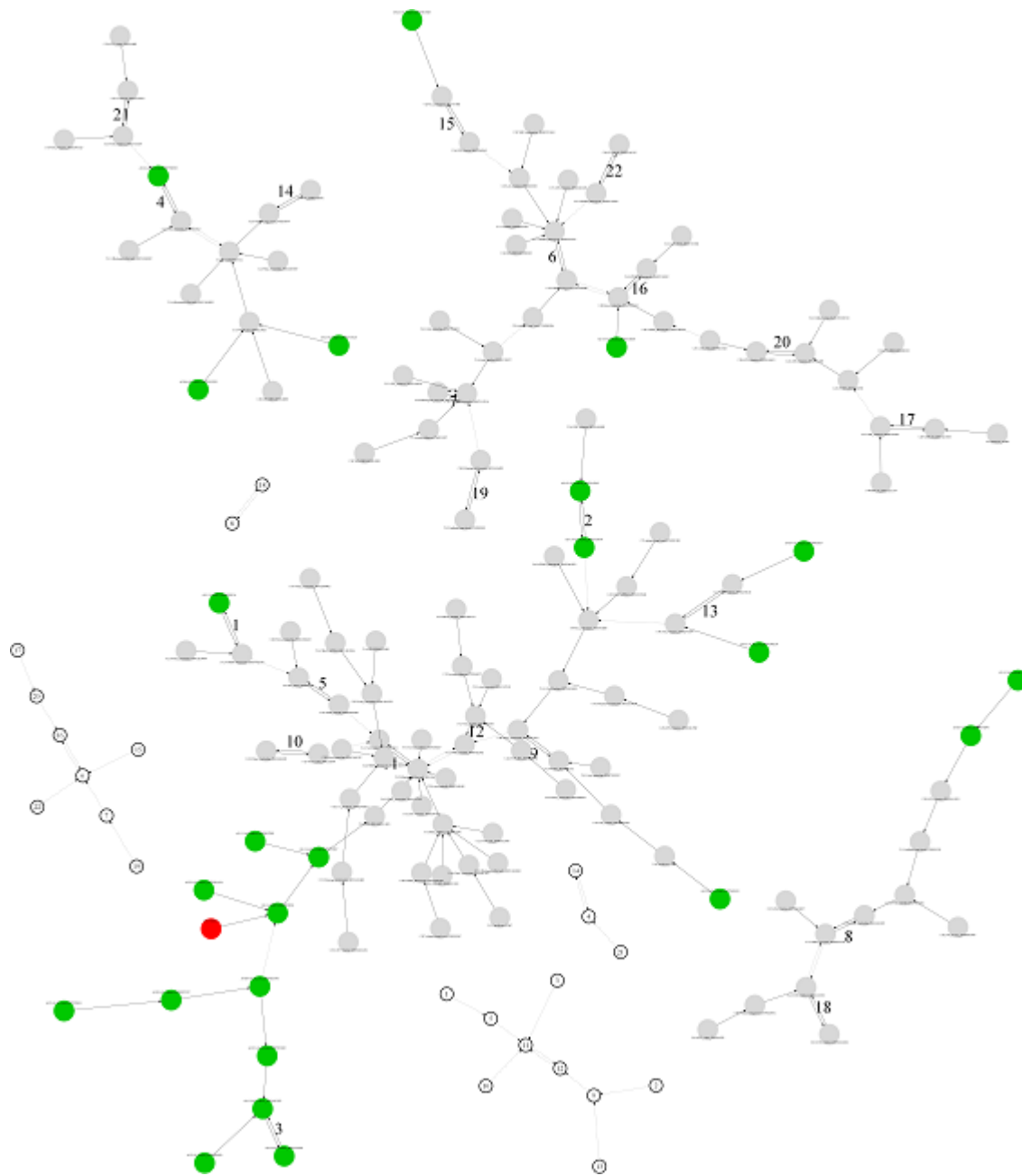
HNF1B and the brain

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Research going on

Our research along a number of lines

Photography



ANGELMAN

