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
Three episodes of pulmonary emboli:
- first at 30y; on chronic warfarin therapy;
died at 56y.
Protein S not tested.

54yo; no history of thrombosis or pregnancy losses
Deficit protein S

Epilepsy
Perinatal stroke
Deficit protein S

21yo; healthy
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
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Early reports did not feature any suggestion the 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.
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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,
you 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
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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
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
Important consequences

Acetyl-CoA

Acetoacetyl-CoA

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

Mevalonate

Mevalonate-P

Mevalonate-PP

Isopentenyl-PP

Geranyl-PP

4OH-Benzoyl

Decaprenyl-PP

Squalene Synthetase

Decaprenyl-4OH-Benzoyl

Squalene

Polyprenyl-PP

Squalene Synthetase

CoQ_{10}

Cholesterol

Dolichol

Dolichol-PP

NEFA

Mg^{++} low

glucose high

Protein Isoprenylation

DIRECT IMPACT ON CARE
HNF1B and the brain

How common are these things?
HNF1B and the brain

Muller, Klopacki et al. 2006

Movement, speech and behavioural problems (‘resembling autism’)
HNF1B and the brain

Raile, Klopocki et al. 2009

One more person

Movement, speech and social problems
HNF1B and the brain

Loirat et al. 2010

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
Nagamani et al. 2010

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

Speech problems, epilepsy; intellectual, behaviour difficulties
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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
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First suggestion of a common facial appearance?

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

Our research along a number of lines

Photography