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The Changing Face Of Rare Disease Diagnosis

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European Reference Network

for rare or low prevalence complex diseases

Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

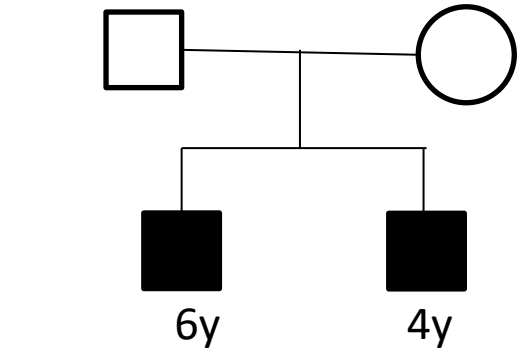
Remit

- How will the implementation of genomics change the role of clinicians?

- How will it change professionals' relationships with patients?

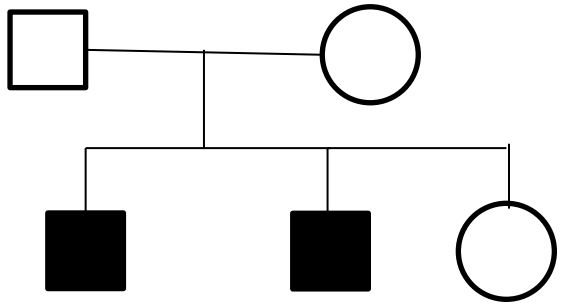
Family A, first seen in 1998

- Two brothers with intellectual disability
- Cause unknown
- Battery of tests by paediatrician including karyotype and FraX normal
- Parents wished for a further child but were worried



Family A, re-referred in 2006

- Now have a healthy daughter
- Microarray normal in both boys
- Some minor differences in facial features between siblings noted
- Entered into a research study
- No results returned

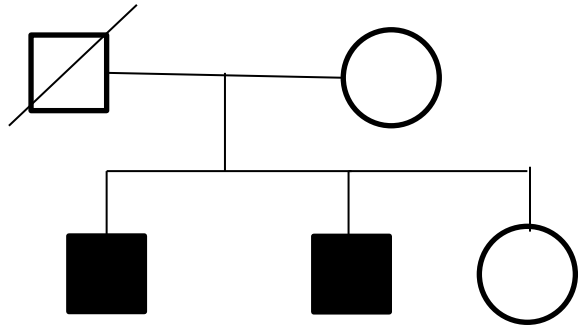


Intellectual disability
coarser facial features

intellectual disability
Seizures from 6m to 2y

Seen in 2016

- Daughter wondering about risks to her own offspring
- Father now deceased
- Siblings underwent whole exome sequencing through a research study

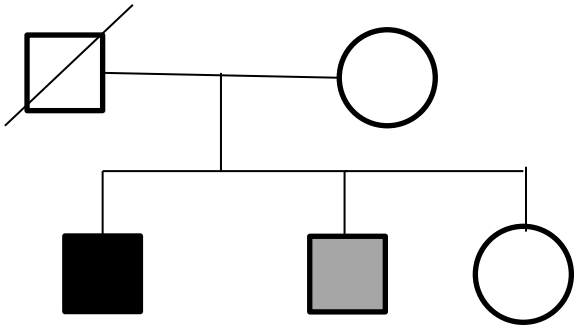


Intellectual disability
coarser facial features

intellectual disability
seizures 6m – 2yrs

Seen with results in 2018

- Sibling 1 has a variant in a well characterised gene. The same change has been described before. The condition is associated with congenital heart defects. Heart scan organised.
- Sibling 2 has a variant in a different gene. It has never been seen before. It's predicted to be pathogenic but reported as a variant of unknown significance (VUS) according to ACMG guidelines. It fits well with the phenotype.
- No father available for further testing, mum has neither variant
- Mum has looked up both conditions on internet and joined a Facebook group



How Has The Implementation Of Genomics Changed Things For Us As Clinicians?

- We are able to find answers for an larger number of families. It's satisfying.
- We don't rely on clinical skills for diagnosis so much. There are concerns we might "de-skill"
- We are having to learn different skills: how to interpret genomic variants, how to communicate more complex information to families. We have adjusted training programmes to take this into account
- We have to be much more comprehensive in the way we consent patients for testing
- We are attending a lot more multidisciplinary meetings to discuss results
- We are giving many results which are not "black and white" and are worrying about whether a variant reported as a VUS today will end up being classified as pathogenic in the future. How can we make sure the family will get an update?
- We are able to give more accurate recurrence risks in some but not all cases and provide more families with opportunities for prenatal/preimplantation testing
- We are identifying conditions that we have never come across before and have to do a lot of reading to learn about these
- We as geneticists are answering a lot of queries from mainstream clinicians about results and what they mean. We need to skill others up to deal with some of these queries themselves
- We are doing more teaching to everyone, from schoolchildren to our mainstream consultant colleagues
- We are learning a lot from patients, in some cases more than they learn from us!

How Might Implementation Of Large Scale Genomic Testing Change Our Relationships With Patients?

- We have more to offer patients, with a greater chance of finding a diagnosis but don't build up the same relationships with them through seeing them through their "Diagnostic Odyssey"
- Going through the formalities of the complex consenting process is daunting for patients and some may become more anxious or suspicious – "If it takes an information sheet that long and a consent form so complex to explain this test it must be quite serious or experimental"
- Many patients who have been unhappy with negative results over the years are delighted to have an answer and our relationships with them improve significantly
- Receiving results that are of uncertain significance is difficult and patients might be quite dissatisfied with us giving these
- Following diagnosis, patients often quickly find out more than we can about their condition and we need to acknowledge this and work in partnership to understand natural history
- Patients can quite legitimately be frustrated when we give them a diagnosis of a newly described condition and then say that we don't know anything about the disorder.
- We will most likely work more closely with patient support groups on initiatives like rare disease registers, management guidelines, specialist clinics and development of clinical trials. We will need resources for both patients and professionals to do this.

GenIDA
https://genida.unistra.fr

Development

Physical development

Most children have some mild delay in their physical development. However most would be expected to walk and gain other physical skills albeit slightly behind their peers.

Learning

Almost all children will have mild learning problems. Some may have more significant problems with learning. It is possible that some may have none at all. Some may have very specific areas requiring learning support.

Behaviour

Some children have been reported to have challenging behaviours. These include self-injuring behaviours such as biting and head banging. Temper tantrums and outburst have also been described. Immature behaviour compared to peers is also seen. However some children do not have any behavioural concerns.

Speech

Speech is normally mildly delayed but most children are expected to learn to speak, albeit at a slower rate than their peers.

Growth

Most children and adults will be shorter than average. For some this may be still within the normal range but for others this may be significantly below it. The same is true for head size which can vary from average to well below the lowest average values.

Management recommendations

At diagnosis

- Genetic testing and counselling about the implications of PUF60 related syndrome
- ECG (measurement of heart's electrical activity) and echocardiogram (ultrasound scan of heart) if not already done
- Eye and hearing checks
- Spine X-ray including neck
- Kidney scan if not previously done

After diagnosis

- Long term follow up by a paediatrician (for children)
- Further eye checks may be recommended
- Follow up may be required by heart or kidney doctors if abnormalities are detected
- Brain scan (MRI or MRA) if indicated by neurological symptoms or seizures

Families say ...

" 'The photograph on the front page is of our son having fun and being himself with his friends! Our son is a happy, cheeky boy with a fun sense of humour. He enjoys life to the full. He is a special boy who has the support and help of his amazing sisters, supportive family and friends on a daily basis. We all actively encourage him to be the best he can be and believe in himself - you can do it! "

Inform Network Support

Rare Chromosome Disorder Support Group,
The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
Tel: +44(0)1883 723356
email: info@rarechromo.org
www.rarechromo.org

Join Unique for family links, information and support

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

This booklet was compiled by Dr Karen Low, Clinical Genetics StR, and reviewed by Dr Dr Sarah Smithson Clinical Geneticist, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust.

Version 1 (AP)

Rare Chromosome Disorder Support Group: Charity Number 1110661
Registered in England and Wales: Company Number 5460413

Understanding chromosome disorders Unique

PUF60 related syndrome

Summary

- Large scale genomic testing is having significant benefits for patients , though it won't solve every case and we'll need to take care not to lose clinical skills

- Moving to whole genome testing requires acquisition of some new skills, especially for those who haven't ordered genomic tests before. However, the principles of testing and of communicating results are essentially the same, just scaled up

- For the next few years we are all on a steep learning curve and we'll need adequate resources, both time and financial for genomic education, rare disease registers and natural history studies

- Multidisciplinary working, including working with patients will be key to deriving the most benefit from genomic testing

The End Of The Story

- Sibling 1 has had a normal heart scan
- Evidence for pathogenicity of the variant in sibling 2 is accumulating. Database searches identified a de novo likely pathogenic variant involving the same DNA codon. **Reporting variants is a dynamic process.**
- The daughter does not carry either variant and feels reassured
- Mum has found the diagnosis helpful when filling in forms for her two sons. Though neither condition can be cured, she is relieved that neither condition is associated with significant shortening of lifespan or late onset health problems. This had always been worrying her.