Genetics of Acromegaly, or Doc, what's caused my tumour & are my kids at risk?

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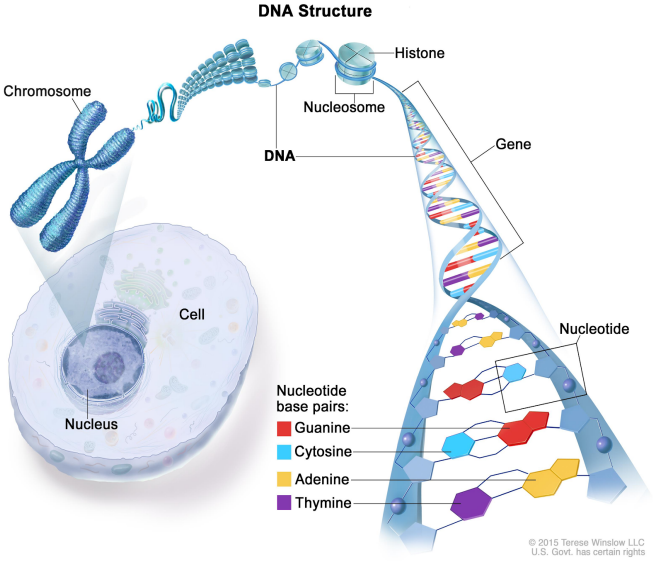
Almost 50% of the childhood-onset acromegaly have an identifiable genetic background AIP (Aryl hydrocarbon receptor Interacting Protein) mutations are the most common familial cause of isolated acromegaly and gigantism

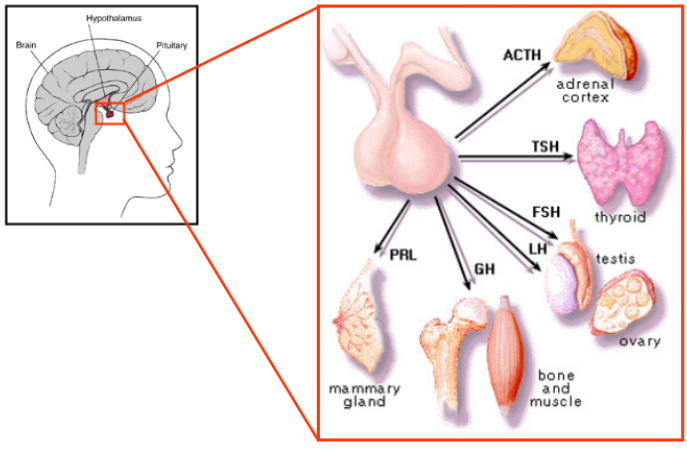
We were very privileged to have Dr Marianne Elston with us, an endocrinologist at Waikato Hospital. I found over 40 research items under her name, including the survey on acromegaly many members participated in a few years back. Her research has seen her awarded a PhD from Australia's prestigious Kolling Institute of Medical Research in Sydney for research into the molecular basis of pituitary tumours. She won the emerging young researcher at the Kudos awards in Hamilton in 2010 for her work concerning the identification of genes involved in the development of pituitary tumours.

We started off with a brief overview of pituitary tumours and acromegaly. Pituitary is commonly known as the master gland or as described by Sir Walter Langdon-Brown "leader of the endocrine orchestra" since it affects almost every organ in the human body. The anterior lobe makes up approximately 80% of the gland.



Pituitary tumours are very common, in autopsy studies 14.4% of people had a pituitary tumour, 22.5% in radiological studies (*Ezzat et al. 2004*). Clinically significant tumours occur in approximately 1 in 1000 people (*Daly et al. 2006*).

Pituitary tumours can cause problems by mass effects & hormonal dysfunction. As the pituitary tumour grows it can push onto the optic nerves and affect vision resulting in gradual reduction of visual fields. The tumour can also push the normal pituitary gland causing a loss of normal pituitary hormones. In acromegaly, the pituitary tumour makes too much growth hormone.



Hypopituitarism is a term to describe the loss of one or more pituitary hormones. Some pituitary

hormones are more important than others. For example ACTH controls cortisol which is essential for life. Growth hormone even though it is not essential for life, is important for muscle, bone & general well being in adults.

Other very rare non-pituitary cause of acromegaly include neuroendocrine tumours elsewhere in the body producing too much growth factor.

The cause of pituitary tumours remain largely unknown, with familial syndromes (result directly from gene defects inherited from a parent) accounting for less than 5% of those with acromegaly. Most pituitary tumours are sporadic (meaning random, spontaneously occurring) with no known inherited genetic basis. Over the past decade there have been many advances in the field of genetics.

www.23andme.com/en-int/gen101/genes/

Tumours may develop from two common mechanisms. Firstly from the loss of a tumour suppressing gene (genes that help prevent tumours forming), or secondly due to overactivity of a proto-oncogene (genes that help cause cancer).

We moved onto the most important question “Doc, could my kids get this?” There are around 6 genes that we know of involved in Familial pituitary tumours. We will go through these below.

MEN1 - mutations in the tumour suppressor gene *MEN1* causes multiple endocrine neoplasia type 1 (MEN1). This is rare occurring in 1/10,000 to 1/100,000 people, or around 1.2% of those with acromegaly. Think about MEN1 if someone has a pituitary tumour and another feature such as high calcium. It is commonly known as the 3 “P”s disease:

- Parathyroid disease - almost all by approx age 50. Results in high calcium, which can presents with kidney stones, bone aches, fatigue, depression etc.
- Pituitary tumours in approx 30-40%
- Pancreas - neuroendocrine tumours approx 30-75%

MEN4 presents with similar features to MEN1 but is due to a different gene mutation - *CDKN1B*. It is extremely rare with only 9 patients with pituitary tumours & *CDKN1B* reported worldwide, of these 5 had acromegaly. If someone presents with MEN1 features but no *MEN1* gene mutation is found, then consider testing for a *CDKN1B* mutation.

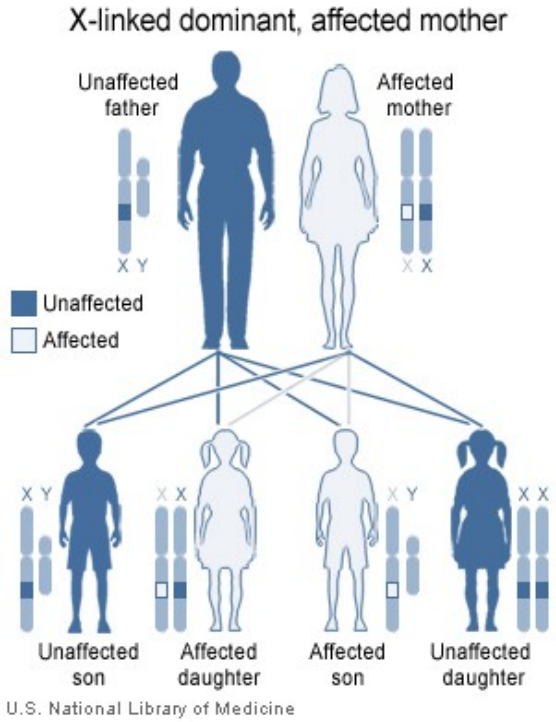
AIP mutations were first described in 2006 and stands for Aryl hydrocarbon receptor Interacting Protein. This is the most common familial cause of acromegaly and gigantism. People with *AIP* mutations often present at a young age e.g. <30yrs and with large tumours. *AIP* mutations are found in up to 33% of those presenting younger than 18 yrs old, 13% in those <30 yrs, and just

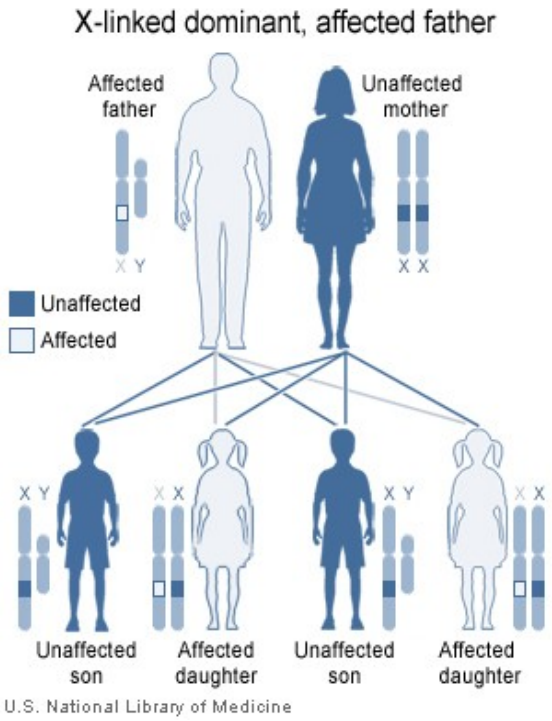
3% when assessing patients of all ages with acromegaly. Luckily not everyone who carries this mutation develops pituitary disease.

The famous Irish giants have been found to have the *AIP* mutation. One of the most well known was Charles Byrne (1761-1783) and he was over 2.3m tall, and he became a celebrity in England. Unfortunately he died age just 22 probably due to complications from the then undiscovered acromegaly. Byrne was living in London contemporaneous with the pre-eminent surgeon and anatomist of the time John Hunter. Hunter had a reputation for collecting unusual specimens for his private museum, and as Byrne's health deteriorated he feared that Hunter wanted his body for dissection (a fate reserved at that time for executed criminals) and probable display. Byrne had made express arrangements with friends that when he died his body would be sealed in a lead coffin and buried at sea. But his burial wishes were thwarted and his worst fears realised when John Hunter arranged for Byrne's cadaver to be snatched on its way to sea. Hunter then reduced Byrne's corpse to its skeleton and four years later put Byrne's skeleton on display in his Hunterian Museum, where it still resides and now located in the Royal College of Surgeons, London. (*http://surgicat.rcseng.ac.uk/Details/collect/4123*)

Carney Complex is an autosomal dominant condition most commonly caused by mutation in the *PRKAR1A* gene, which may be a tumour suppressing gene. People with this condition gets spotty skin pigmentation, heart issues and endocrine hyperactivity. They develop acromegaly due to pituitary hyperplasia and overactivity rather than pituitary tumours. There are about 500 cases reported worldwide.

SDHx (Succinate dehydrogenase) mutations are associated with phaeochromocytomas and paragangliomas, which are adrenaline & noradrenaline-secreting tumours. In very rare cases pituitary tumours may occur including acromegaly.





GPR101 gene duplications have been linked to X-linked acrogigantism (XLAG). A form of infant-onset gigantism, some cases were sporadic and some were inherited. There have been only 31 patients reported worldwide, causing very early onset gigantism age <5yrs, and usually starts at age 1.

McCune-Albright syndrome are caused by mutation in *GNAS* gene. Features include cafe-au-lait spots, bone and endocrine issues (including acromeglay, cushings, overactive thyroid).

Neurofibromatosis type 1 have been rarely associated with acromegaly, it is unclear if this is just coincidence or an increased risk.

Bearing in mind 95% of acromegaly occurs sporadically and are not inherited, almost 50% of the childhood-onset cases have an identifiable genetic background. Dr Elston went on to discuss the current guidelines at Waikato Hospital for genetic testing. She suggests patients who fulfill the following criteria be offered tested (criteria & funding varies depending on DHB):

- All patients with gigantism - underlying genetic cause can be identified in up to 50%
- Acromegaly if onset age <30 years old, especially if macroadenomas
- Family history of acromegaly - given the rarity of acromegaly this suggests possible inherited genetic cause
- If clinical features suggestive of possible syndrome e.g. high calcium caused by hyperparathyroidism, and an associated neuroendocrine tumour

Genetic testing is a new field and many patients may find this daunting, therefore testing has to be discussed on a case by case. Advantages of testing includes knowing to look for other associated conditions, earlier disease pick up in family members, and reassurance for family who don't carry the mutation. There are also disadvantages such as anxiety for the patient & family member if a mutation is found; testing may identify mutations that we are still uncertain if they are disease causing. Also there may be insurance implications in the future so discussion with your Endocrinologist and referral to genetics service is recommended if considering testing.

For more info go to "The genetics background of acromegaly" by M. Gaelha et al. Published in journal Pituitary Feb 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5334425/