PTEN-related disorders

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Rare diseases: facts and figures

The UK defines a ‘rare disease’ as one that affects 1 in 2,000 or less of the population...

...so, collectively, rare disease will affect 1 in 17 of the population at some point in their life.

In total, that's about 3 million people currently in the UK who will be affected by a rare disease.

- Small numbers
- Collecting evidence
- Level of proof
- ? Needs patient power

There are between 5,000 and 8,000 different rare diseases...

...and 80% of them have a known genetic origin.
One gene, many names

And what is a syndrome?
Bannayan -Riley -Ruvalcaba syndrome
- 1989 (Gorlin)

- Macrocephaly (Big head size)
- Lipomas
- Penile freckling
- Developmental delay
- Gut hamartomas
- Motor delay and hypotonia
- Thyroid disease
Cowden Disease 1963

- Named after Rachel Cowden
- Breast – fibrocystic disease and cancer
- Thyroid adenomas
- Mucocutaneous lesions of the face and mouth
- Intellectual disability

- Autosomal Dominant Inherited Cancer Syndrome
- Incidence~1 in 200,000

- Later reports predominantly by dermatologists
PTEN and the syndromes

Bannayan-Riley-Ruvalcaba syndrome

Cowden syndrome

Lhermitte-Duclos

PTEN
10q23
Nelen - 1996
Liaw - 1997
Marsh - 1997
Arch - 1997

Proteus syndrome

Autism

VATER – hydrocephalus

Benign familial macrocephaly

PTEN and the syndromes

Bannayan-Riley-Ruvalcaba syndrome

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Autosomal Dominant Inheritance

What we know
- 50:50 = 1 in 2 chance of passing on gene change
- Men or women can be affected

What we don’t understand
- Different severity in different family members

YouTube Video: https://youtu.be/dw-raR6E9zU?list=PLpMgTX_sXoj6kA9i-04a126NP7zGSY-hA
Autosomal Dominant Inheritance

Parents

Gametes

At conception

Affected

Affected

Unaffected

Unaffected
And

- PTEN gene changes are not always inherited from a parent
- If you have a PTEN gene change, there is a 50:50 = 1 in 2 chance of passing this on to children
- We can’t predict severity
- We can offer prenatal diagnosis
- Pre-implantation genetic diagnosis is another possible option
- Genetic Counsellors can talk through options in detail
Making the diagnosis in children

Table 3. Pediatric Clinical Criteria for PTEN Testing

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Percent Prevalence in CC Data Set of Pediatric Probands with PTEN Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Macrocephaly (≥ 2 SD)</td>
<td>100%</td>
</tr>
<tr>
<td>2. At least one of the following four additional criteria should be present:</td>
<td></td>
</tr>
<tr>
<td>- Autism or developmental delay</td>
<td>82%</td>
</tr>
<tr>
<td>- Dermatologic features, including lipomas, trichilemmomas, oral papillomas, penile freckling</td>
<td>60%</td>
</tr>
<tr>
<td>- Vascular features, such as arteriovenous malformations or hemangiomas</td>
<td>29%</td>
</tr>
<tr>
<td>- Gastrointestinal polyps</td>
<td>14%</td>
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</tbody>
</table>

*In addition, pediatric-onset thyroid cancer and germ cell tumors (testicular cancer and dysgerminoma) are recognized associations of Cowden syndrome and should provoke consideration of PTEN testing.
Head Circumference

Males

<table>
<thead>
<tr>
<th>Years</th>
<th>Age</th>
<th>cm</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

Females

<table>
<thead>
<tr>
<th>Years</th>
<th>Age</th>
<th>cm</th>
<th>%</th>
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**KEY**
- Proband: X
- Relative: X

Measure the greatest circumference as illustrated with the tape touching the occipital prominence at the rear of the head and passing around the forehead as the midpoint between the eyebrows and the hairline. Measure to the nearest completed millimetre. The recommended Lasso tape is designed to measure both children and adults.
PTEN, learning difficulties and autism

- Between 10 and 20% of children with autism and a big head have a PTEN gene alteration
- Some inherited gene change from a parent
- Some have a new gene change. Genetic but not inherited
- 10 – 20 % of people with a PTEN gene change have some learning difficulty

http://consultqd.clevelandclinic.org/2015/02/pten-mutations-and-autism-the-search-for-individualized-treatments-gets-underway/
Making the diagnosis in adults

<table>
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<tr>
<th>Organ</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>Lhermitte-Duclos/Brain</td>
</tr>
<tr>
<td>Breast</td>
<td>Kidney</td>
</tr>
<tr>
<td>Bowel</td>
<td>Endometrium</td>
</tr>
<tr>
<td>Skin</td>
<td>Big Head (macrocephaly)</td>
</tr>
</tbody>
</table>

- Thyroid
- Lhermitte-Duclos/Brain
- Kidney
- Endometrium
- Big Head (macrocephaly)
What else do we know?

- Cancer risks – medical language refers to “benign” and “malignant” tumours
- Benign – an unusual growth of part of the body, can be skin or organs inside the body
  Cause problems because they are unsightly, a nuisance, uncomfortable, sometimes painful or because of where they are.
- Malignant – a growth that is a cancer.
  Can grow slowly to start with
  Can be difficult to know if benign or malignant
  In time can spread out of control without appropriate treatment
  Treatment when small/quite new may improve outcomes
What are the risks of cancer?

Can we detect it early with screening?

Is there good quality evidence?

Will screening help? What age should it start?

Are there other options?

What are the pitfalls?
Screening

Thyroid

Breast

Bowel

Skin

Lhermitte-Duclos/Brain

Kidney

Endometrium
Thyroid = a gland in the throat

- Produces a hormone called thyroxine that regulates metabolism

Benign problems are common (75%)
- multinodular goitre
- nodules
- adenomas

Malignancy
- Previously reported as 3-10% lifetime risk
- Recent literature epithelial thyroid cancer is approximately 35% [Tan et al 2012]. Median age of onset was 37 years; seven years was the youngest age at diagnosis [Ngeow et al 2011]
Breast cancer risk

• Most common associated malignancy
  • 25 – 50 %
  • Young onset 38 – 50 years

• More recent reports
  • 81% systematic review Riegert-Johnson DL et al Hered Cancer Clin Pract. 2010
  • 85% C Eng Group Tan MH et al Eng C Group Clin Cancer Res. 2012
Endometrium

- Consistent finding across reports
  - 14.1% of females with PTEN alteration (Pilarski)
  - 7.6% of female with PTEN alteration (Tan 2011)
  - 17% clinically affected females (Pilarski)
  - Tan 2012 Lifetime risk estimate 19 to 28% by 70 years
- American and French groups recommend screening with USS/endometrial biopsy
- Evidence that this is useful is poor
- In UK recommend discussion of hysterectomy

What is endometrium?

It’s the lining of the womb
Renal cell carcinoma = kidney

- 5% of 107 clinically tested adults (pilarski)
- 3% to 6.7% of adults who had research testing (Tan 2011)
- 2% (Bubien)

- Tan et al (2012) 34% lifetime risk
- Median age 49, mean 45.4 2:1 male to female ratio
- As a result screening added to NCCN screening guidance from 40
- French guidance from 30 years
Colonoscopy was performed in 107 patients at mean age 37.4.

Ninety-nine (92.5%) had polyps

64% of patients were estimated to have 50 or more polyps

Majority benign

Colorectal cancer was found in 12 patients (11.2% of total cohort, 12.8% of patients with pathology reviewed) with mean age 46.7 (range 35-62) years

Lifetime risk for colorectal cancer is estimated at 9%, with the starting age at risk in the late 30s (Tan et al 2012)
Key points

• **Cancer risks are very low in childhood**

• **Screening tests can be good**
  
  *But e.g.*
  
  *Stress/anxiety/tolerate*
  
  *Time off work*
  
  *Is it effective? False positive*
  
  *How often should it be done?*
  
  *Need more evidence/proof*
Screening

**Thyroid**
As a minimum screen from 16 by USS and TFT. Younger as guided by family history or after informed discussion with family.

**Breast**
Annual MRI from age 30, mammography from 40. Consider risk reducing surgery.

**Bowel**
Colonoscopy at age 35 & 55. Polyp f/u as required.

**Lhermitte-Duclos/Brain**
Brain MRI only if symptomatic.

**Kidney**
Annual renal USS/MRI from 40.

**Endometrium**
Consider risk-reducing hysterectomy.

**Skin**
Baseline dermatological review & appropriate f/u.

Agreed by UK Cancer Genetics Group May 2017.
• Patients were included in the audit if they had a PTEN mutation or likely pathogenic variant or were at 50% risk, were 16 years or older at time last advice given, with most recent advice given between August 1st 2010 and August 1st 2015.

• A total of 175 patients were included in the survey.

• Anonymous – Can’t identify patients from the data
What if I’ve not seen a geneticist for ages?

• How do I access screening?
• Ask your GP to refer you back to the closest Clinical Genetics service for a review appointment
• Some Genetic Centres may allow you to request a review appointment if you have been seen previously.
• http://www.bsgm.org.uk/information-education/genetics-centres/
Questions?
• Ni Y, Zbuk KM, Sadler T, et al. Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. Am J Hum Genet 2008;83:261–268. - SDH testing should be considered for germline PTEN mutation-negative CS/CS-like individuals, especially in the setting of breast, thyroid, and/or renal cancers.


• Germline alterations in RASAL1 in Cowden syndrome patients presenting with follicular thyroid cancer and in individuals with apparently sporadic epithelial thyroid cancer.

• Ngeow J¹, Ni Y, Tohme R, Song Chen F, Bebek G, Eng C.


Chromosomes, DNA, and Genes

Adapted from Understanding Gene Testing, NIH, 1995
Chromosomes

- Chromosomes are made of DNA.
- Each contains genes in a linear order.
- Human body cells contain 46 chromosomes in 23 pairs – one of each pair inherited from each parent.
- Chromosome pairs 1 – 22 are called autosomes.
- The 23rd pair are called sex chromosomes: XX is female, XY is male.

Gene for cystic fibrosis (chromosome 7)

Gene for sickle cell disease (chromosome 11)
**Figure 2.** PTEN functional motifs and germline mutation spectra. PTEN has a core promoter region followed by nine exons which encode phosphatase, C2, PDZ, and two PEST domains. Mutations have been identified in the promoter and every exon. For point mutations, length of line correlates with number of probands with specific mutation reported. For large rearrangements, number of lines corresponds to number of probands with reported deletion/duplication. Blue = missense mutation; red = nonsense/frameshift (truncating) mutations; orange = splice alterations; yellow = large deletions; green = large duplications.
Genes code for proteins = Genes give an instruction
Figure 1. PTEN’s signaling pathway, depicting genes with their corresponding syndromes.
What causes genetic conditions?

- Functional protein
- Nonfunctional or missing protein
**Dominant**

These individuals are called Heterozygotes with one copy of the altered gene they are affected.

**Recessive**

Homozygotes must have two copies of the altered gene to be affected.

**X-linked recessive**

Males with an altered gene on the X-chromosome are always affected.
Autosomal dominant inheritance

Parents

At conception

Affected

Affected

Unaffected
NCCN Diagnostic criteria for Cowden Syndrome 2015

**Major criteria**

Breast cancer  
Endometrial cancer  
Follicular Thyroid cancer  
Multiple GI hamartomas or ganglioneuromas  
Macrocephaly >97\textsuperscript{th} centile (58cm in women, 60cm in men)  
Macular pigmentation of glans penis  
Mucocutaneous lesions  
• One biopsy proven trichilemmoma  
• Multiple palmoplantar keratoses  
• Multifocal or extensive oral mucosal papillomatosis  
• Multiple cutaneous facial papules (often verrucous)  

NCCN Diagnostic criteria for Cowden Syndrome 2014

**Major Criteria**
- Breast cancer
- Endometrial cancer
- Follicular Thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly >97th centile (58cm in women, 60cm in men)
- Macular pigmentation of glans penis
- Mucocutaneous lesions

**Minor criteria**
- One biopsy proven trichilemmoma
- Multiple palmoplantar keratoses
- Multifocal or extensive oral mucosal papillomatosis
- Multiple cutaneous facial papules (often verrucous)
- Macular pigmentation of glans penis

- Autistic Spectrum disorder
- Colonic cancer
- Lipoma
- Glycogenic acanthosis of the oesophagus
- Papillary or follicular variant of follicular thyroid cancer
- Thyroid structural lesions e.g. adenoma, goitre, nodule(s)
- Intellectual disability (IQ< 75)
- Single hamartomatous GI polyp
- Renal cell carcinoma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

PTEN Testing Criteria

- Individual from a family with a known PTEN mutation
- Individual meeting diagnostic criteria for CS/PHTS
- Individual with a personal history of BRRS
- Adult Lhermitte-Duclos syndrome
- Autistic Spectrum disorder and macrocephaly
- Two or more biopsy proven trichilemmomomas
- Two or more major criteria inc. macrocephaly
- Three major criteria, without macrocephaly
- One major and at least three minor criteria
- Four minor criteria
- At risk individual with a relative with a clinical diagnosis of CS/PHTS for whom testing has not been performed. The at risk individual must have any one major criterion or two minor criteria