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PTEN-related disorders

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Rare diseases: facts and figures

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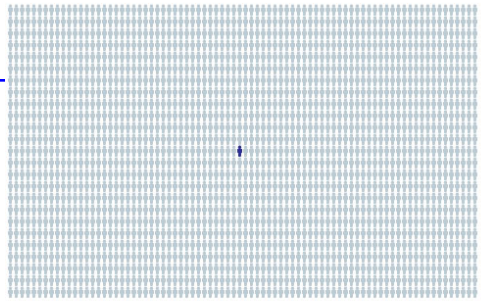
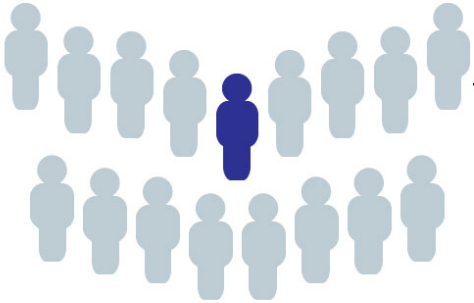
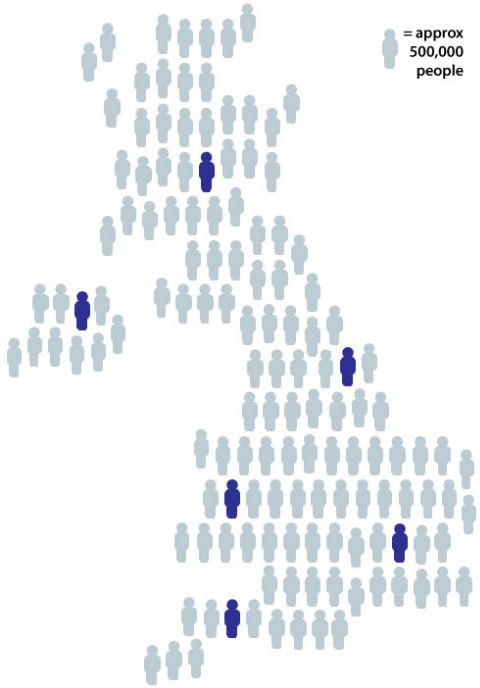
The UK defines a 'rare disease' as one that affects **1 in 2,000** or less of the population…



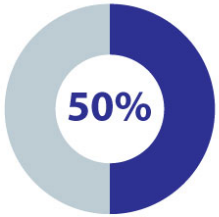
… so, collectively, rare disease will affect **1 in 17** of the population at some point in their life



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



50% of newly diagnosed cases of rare diseases are in children



There are between **5,000** and

8,000

different rare diseases...

… and **80%** of them have a known **genetic origin**

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

One gene, many names

And what is a syndrome?

Bannayan -Riley -Ruvalcaba syndrome - 1989 (Gorlin)

Macrocephaly
(Big head size)

Lipomas

Developmental delay

Penile freckling

Gut hamartomas

Motor delay and hypotonia

Thyroid disease

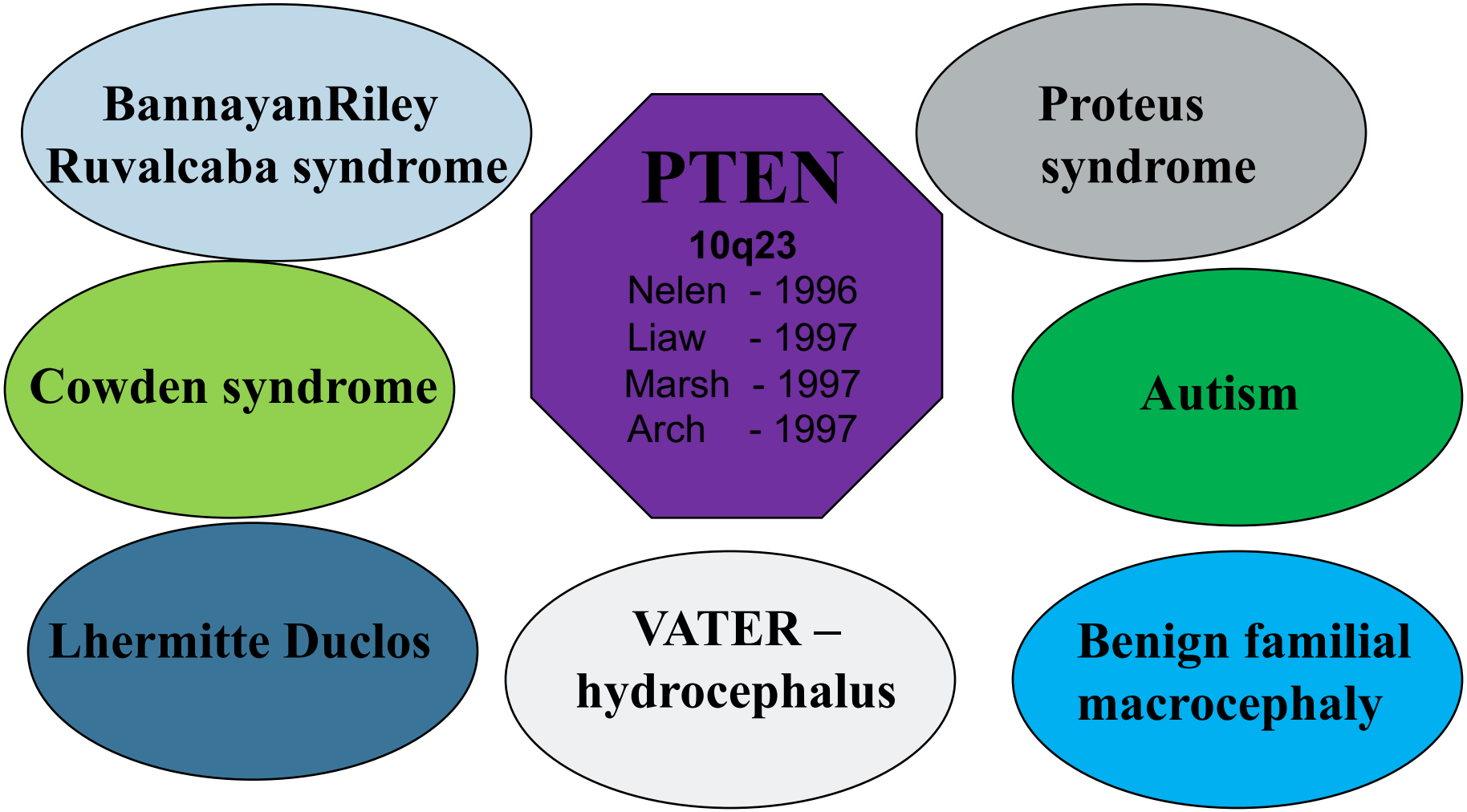
Cowden Disease 1963

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

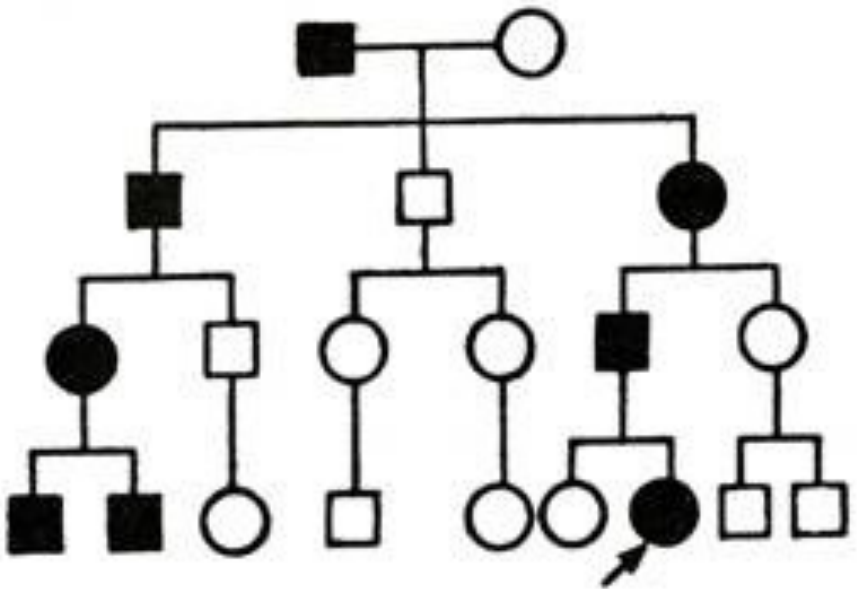
- **Autosomal Dominant Inherited Cancer Syndrome**
- **Incidence~1 in 200,000**

- Later reports predominantly by dermatologists

PTEN and the syndromes



Autosomal Dominant Inheritance



What we know

•50:50 = 1 in 2 chance of passing on gene change

•Men or women can be affected

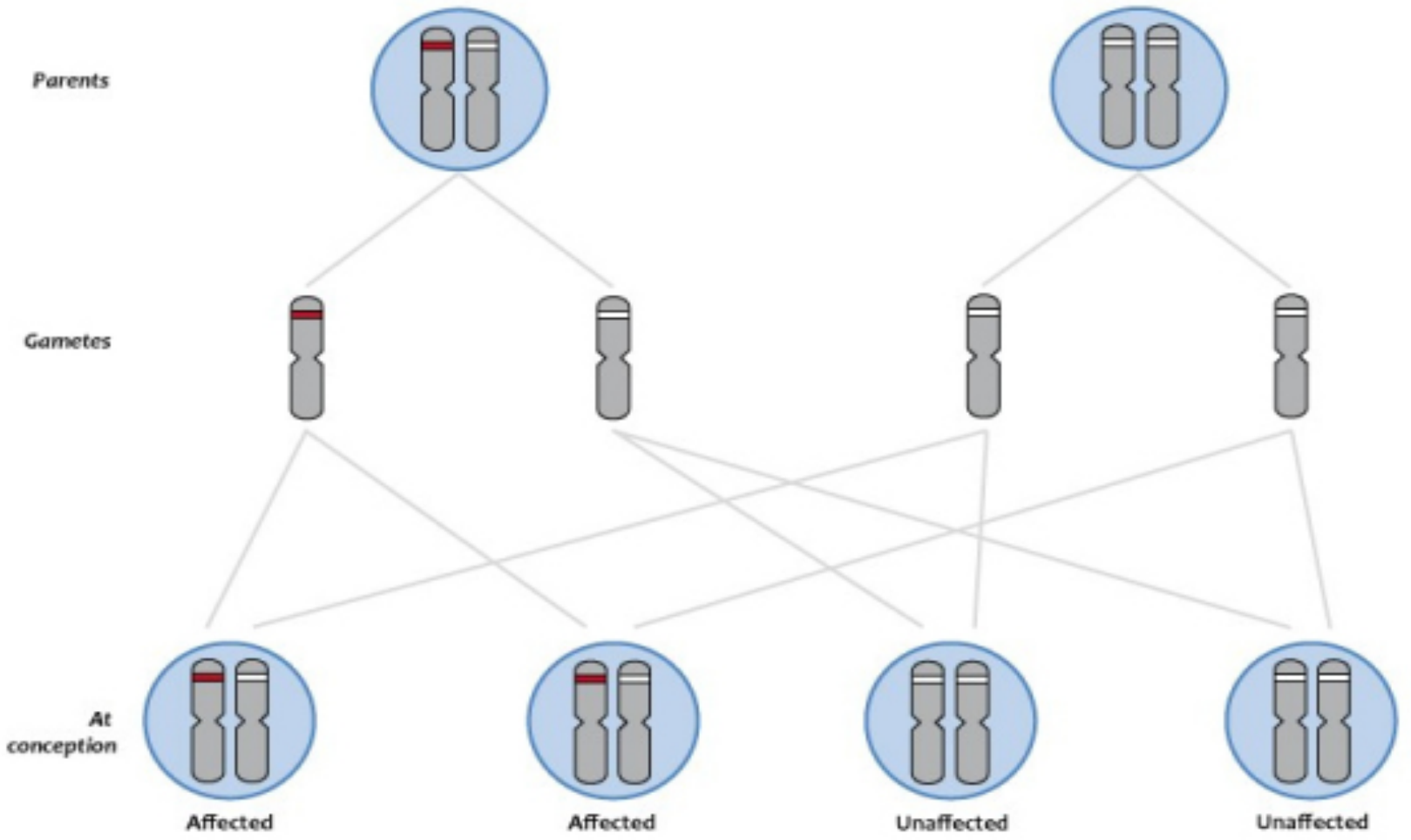
What we don't understand

•Different severity in different family members

- https://youtu.be/dw-raR6E9zU?list=PLpMgTX_sXoj6kA9i-04a126NP7zGSY-hA

Genomics Education Programme

Autosomal Dominant Inheritance



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[a]

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

[a] 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.

A Clinical Scoring System for Selection of Patients for PTEN Mutation Testing Is Proposed on the Basis of a Prospective Study of 3042 Probands

Min-Han Tan,[1,2] Jessica Mester,[1,2,5] Charissa Peterson,[1,2] Yiran Yang,[1,2] Jin-Lian Chen,[1,2] Lisa A. Rybicki,[2,3,4] Kresimira Milas,[5] Hollv Pederson.[6] Berna Remzi.[7] Mohammed S. Orloff.[1,2,3] and Charis Eng[1,2,3,5,8,9,*]

The American Journal of Human Genetics *88*, 42–56, January 7, 2011

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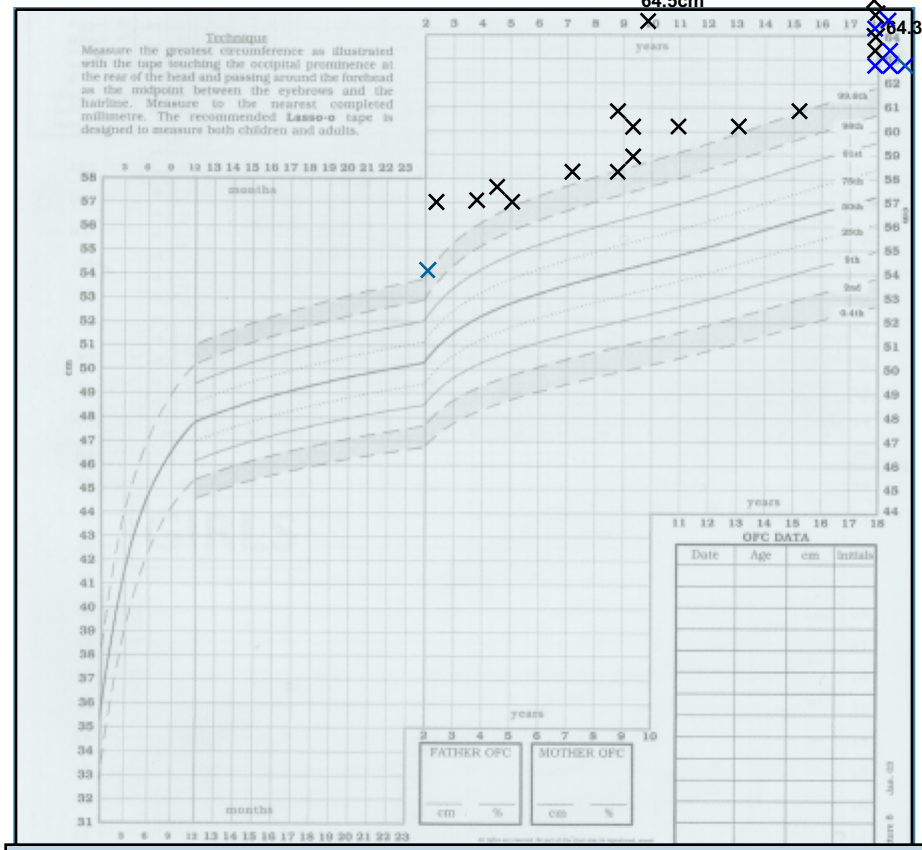
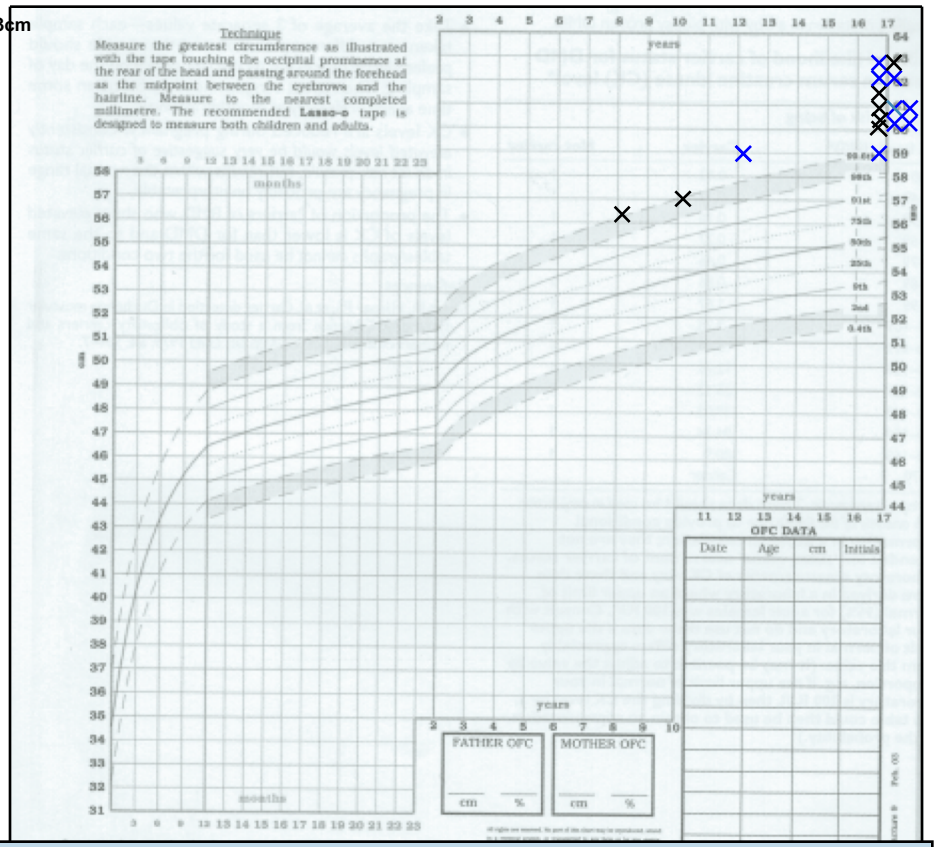
Head Circumference

Males



Females



KEY

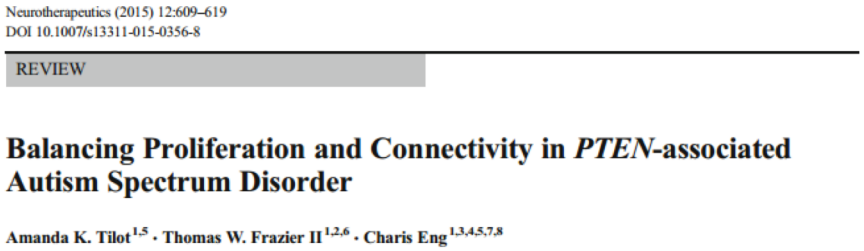
Proband ×

Relative ×

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/


Neurotherapeutics (2015) 12:609–619
DOI 10.1007/s13311-015-0356-8

REVIEW

Balancing Proliferation and Connectivity in *PTEN*-associated Autism Spectrum Disorder

Amanda K. Tilot[1,5] · Thomas W. Frazier II[1,2,6] · Charis Eng[1,3,4,5,7,8]


Molecular Psychiatry

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nature.com > Journal home > Table of Contents

Original Article

Molecular Psychiatry **20**, 1132-1138 (September 2015) | doi:10.1038/mp.2014.125

Molecular and phenotypic abnormalities in individuals with germline heterozygous PTEN mutations and autism

T W Frazier, R Embacher, A K Tilot, K Koenig, J Mester and C Eng

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SEARCH PUBMED FOR
T W Frazier
R Embacher

PTEN is a tumor suppressor associated with an inherited cancer syndrome and an important regulator of ongoing neural connectivity and plasticity. The present study examined molecular and phenotypic characteristics of individuals with germline

Making the diagnosis in adults

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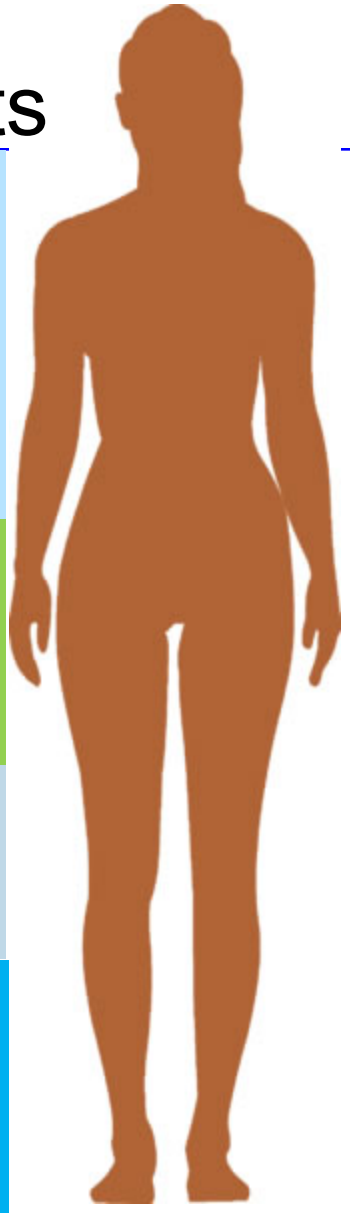
Thyroid

Breast

Bowel

Skin



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

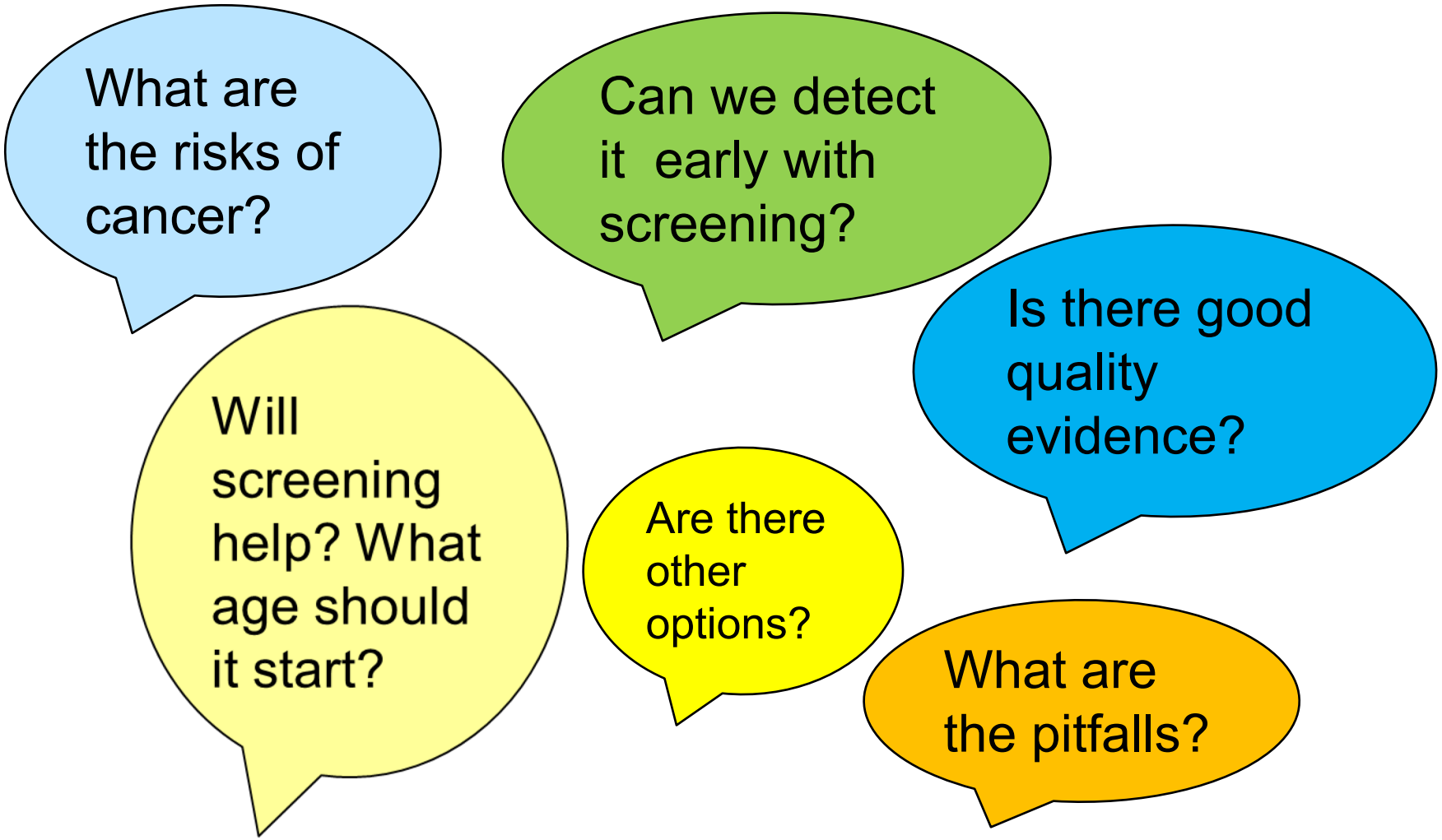
  Cause problems because they are unsightly, a nuisance, uncomfortable, sometimes painful or because of where they are.
- Malignant – a growth that is a cancer.

  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

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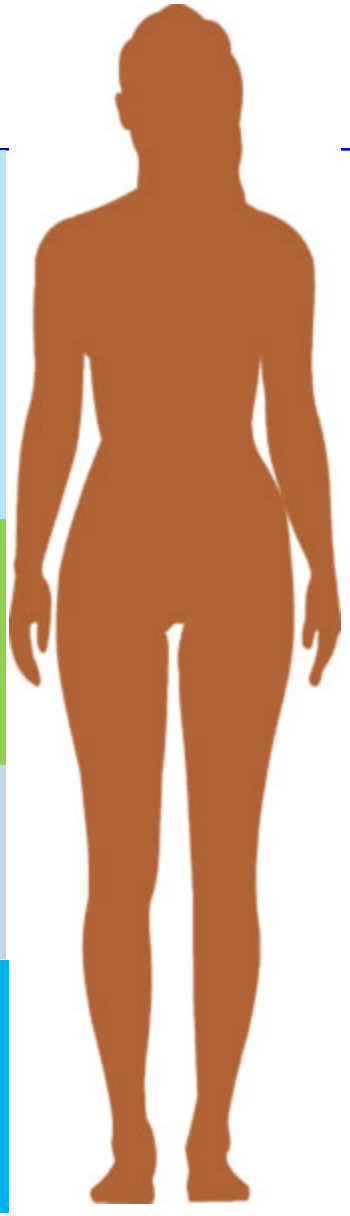
Thyroid

Breast

Bowel

Skin



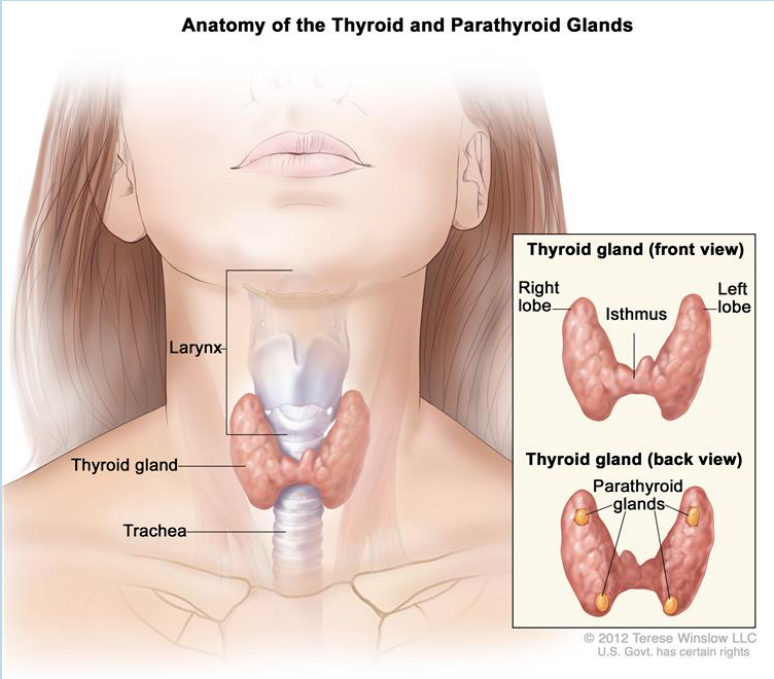
Lhermitte-Duclos/Brain

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

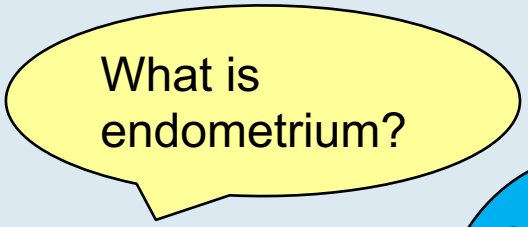
- Previously reported as 3-10% lifetime risk
- Recent literature epithelial thyroid cancer is approximately 35% [Tan et al 2012]. Median age of onset was 37 years; seven years was the youngest age at diagnosis [Ngeow et al 2011]

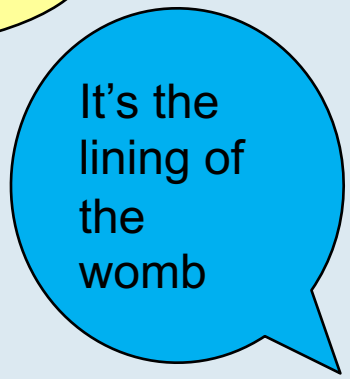
Breast cancer risk

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

- More recent reports
  - 77% French group Bubien V et al. J Med Genet. 2013
  - 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

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

Good review Stanich et et WGJ 2014

- 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)

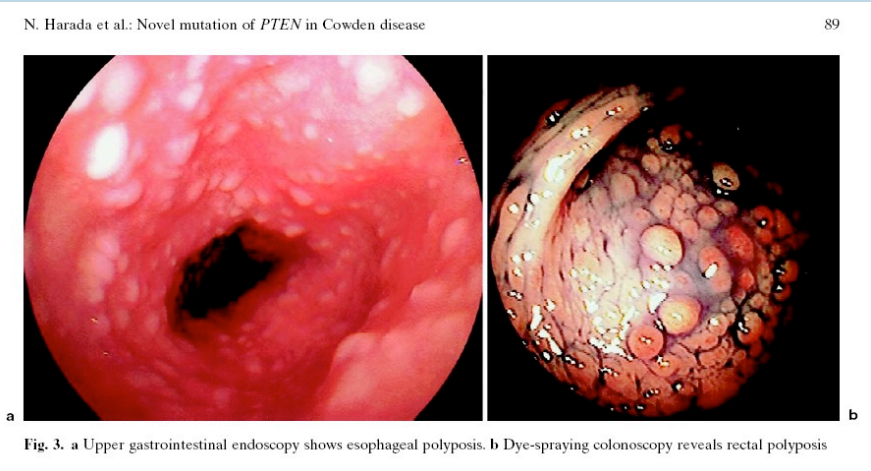


Fig. 3. **a** Upper gastrointestinal endoscopy shows esophageal polyposis. **b** Dye-spraying colonoscopy reveals rectal polyposis

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

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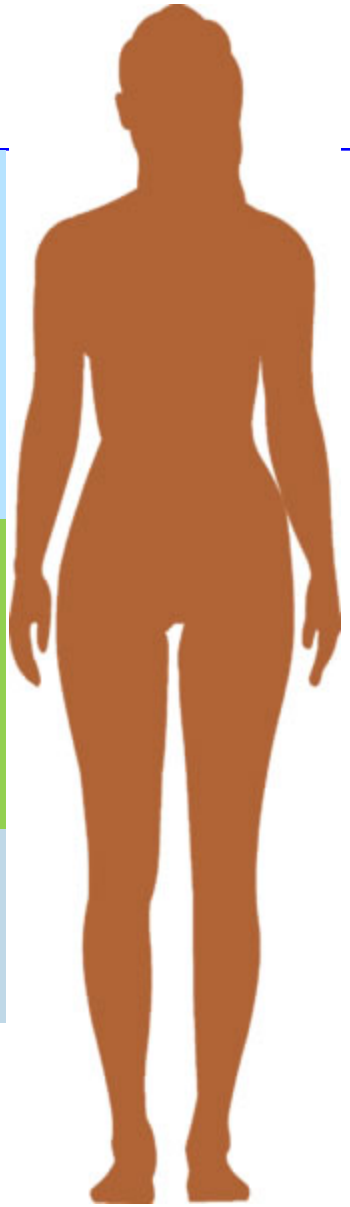
Screening

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?

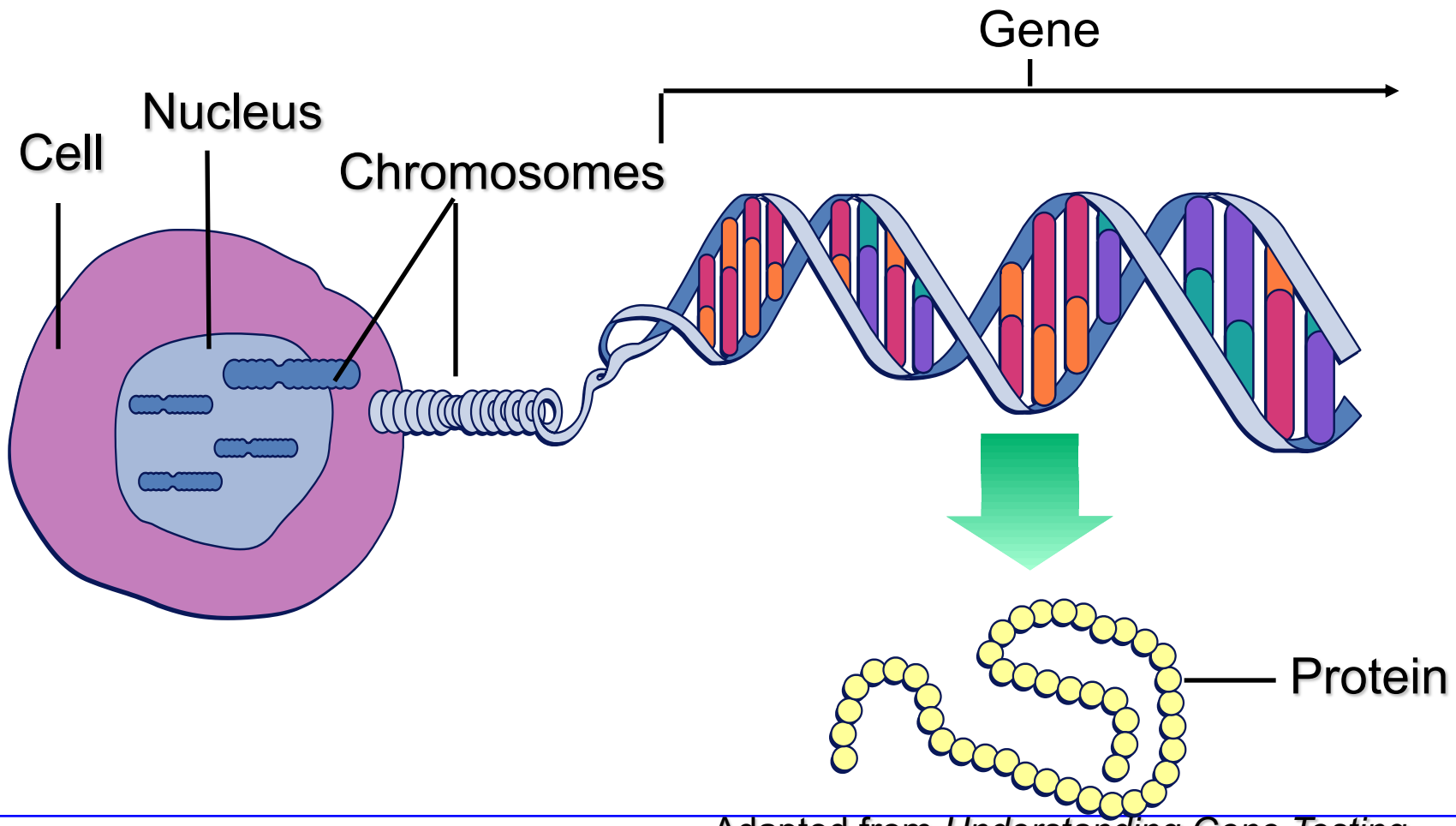
- How do I access screening?
- Ask your GP to refer you back to the closest Clinical Genetics service for a review appointment
- Some Genetic Centres may allow you to request a review appointment if you have been seen previously.
- http://www.bsgm.org.uk/information-education/genetics-centres/

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.
- J Clin Endocrinol Metab. 2014 Jul;99(7):E1316-21. doi: 10.1210/jc.2014-1225. Epub 2014 Apr 8.
- **Germline alterations in RASAL1 in Cowden syndrome patients presenting with follicular thyroid cancer and in individuals with apparently sporadic epithelial thyroid cancer.**
- Ngeow J[1], Ni Y, Tohme R, Song Chen F, Bebek G, Eng C.
- Ni Y, He X, Chen J, et al. Germline SDHx variants modify breast and thyroid cancer risks in Cowden and Cowden-like syndrome via FAD/NAD-dependant destabilization of p53. Hum Mol Genet 2012;21:300–310.
- Orloff MS, He X, Peterson C, et al. Germline PIK3CA and AKT1

  Mutations in Cowden and Cowden-like Syndromes. Am J Hum Genet 2013;92:76–80.
- Bennett KL, Mester J, Eng C: Germline epigenetic regulation of KILLIN in Cowden and Cowden-like syndrome. JAMA 2010;304:2724–2731.

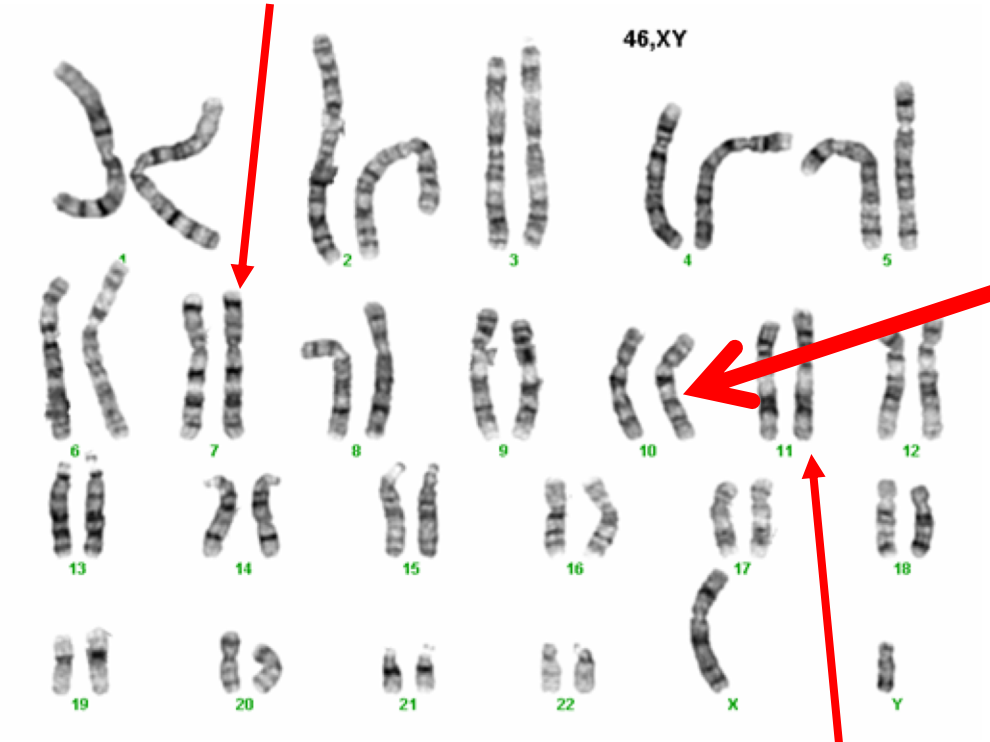
Chromosomes, DNA, and Genes



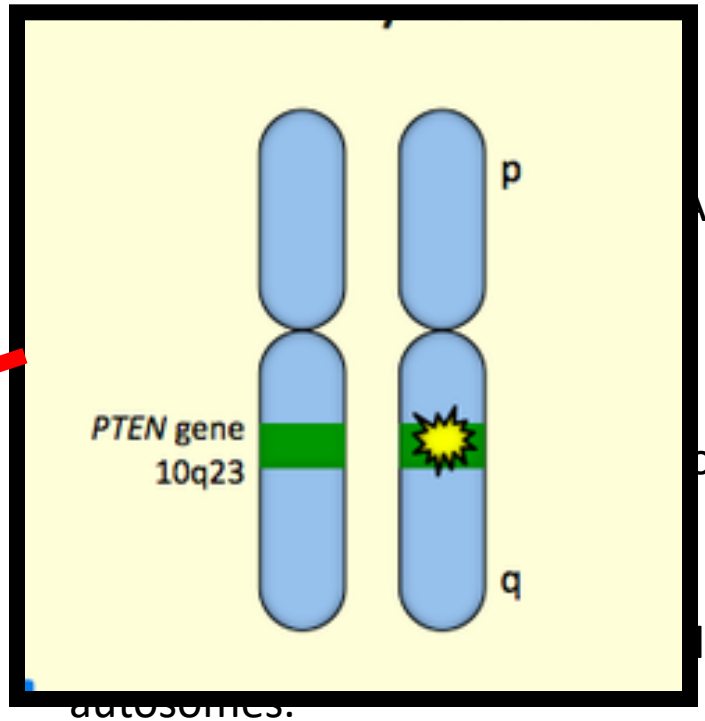
Adapted from *Understanding Gene Testing*, NIH, 1995

Chromosomes

Gene for cystic fibrosis (chromosome 7)



Gene for sickle cell disease (chromosome 11)



- The 23rd pair are called sex chromosomes:
  XX is female, XY is male.

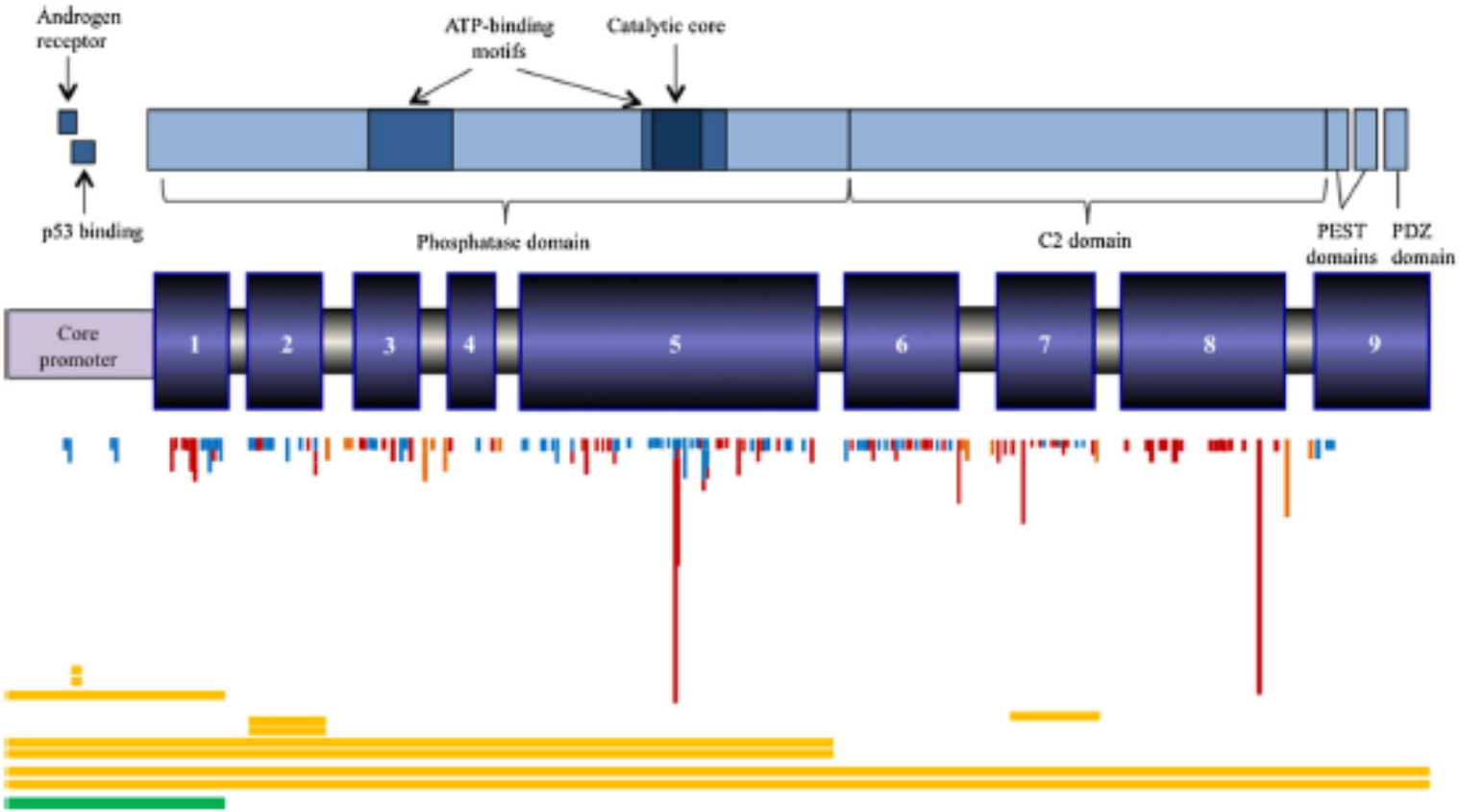
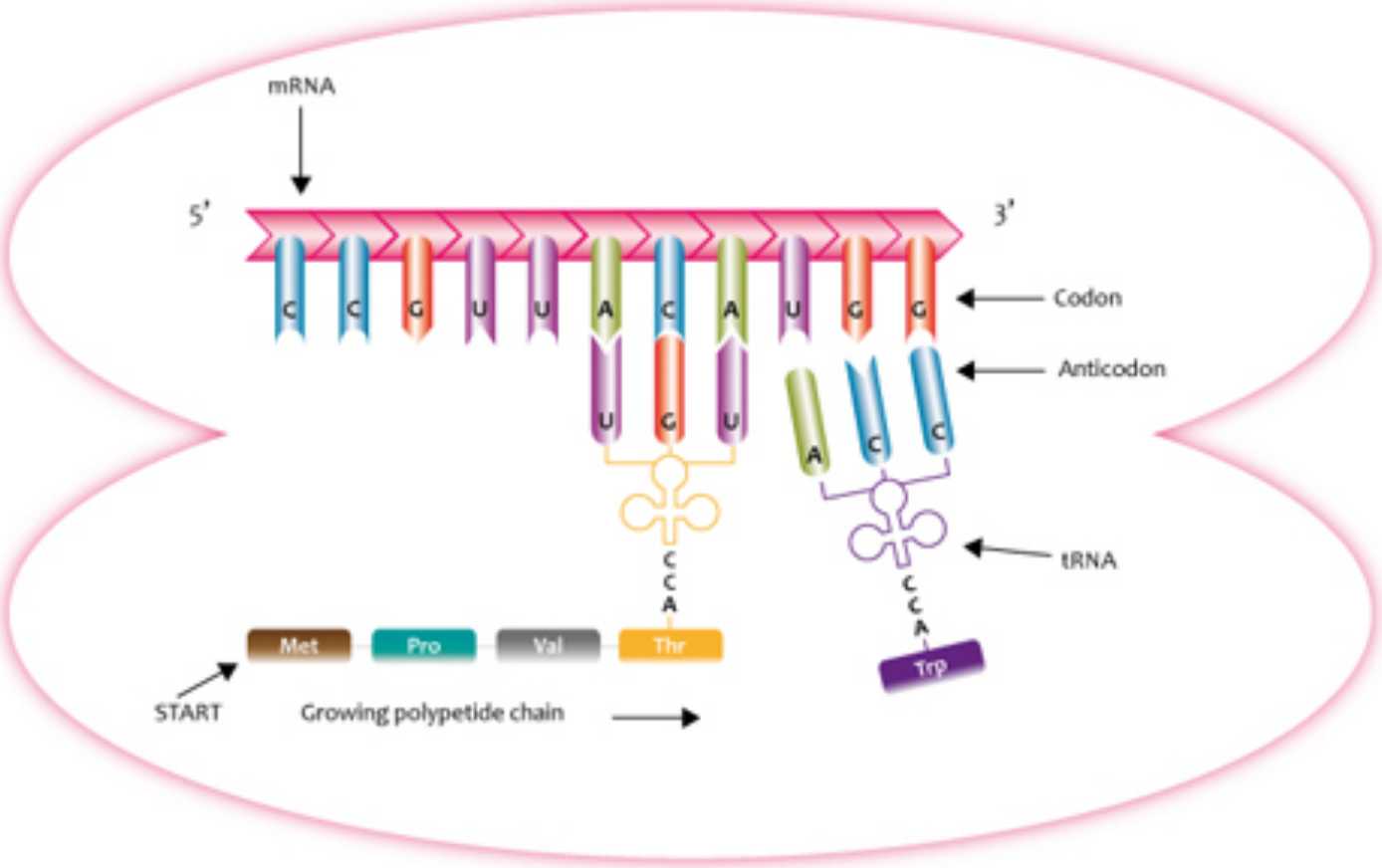


Figure 2. *PTEN* functional motifs and germline mutation spectra. *PTEN* has a core promoter region followed by nine exons which encode phosphatase, C2, PDZ, and two PEST domains. Mutations have been identified in the promoter and every exon. For point mutations, length of line correlates with number 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.

Mester J, Eng C. 2013. When overgrowth bumps into cancer: The PTEN-opathies. Am J Med Genet Part C Semin Med Genet 163C:114–121.

Genes code for proteins = Genes give an instruction



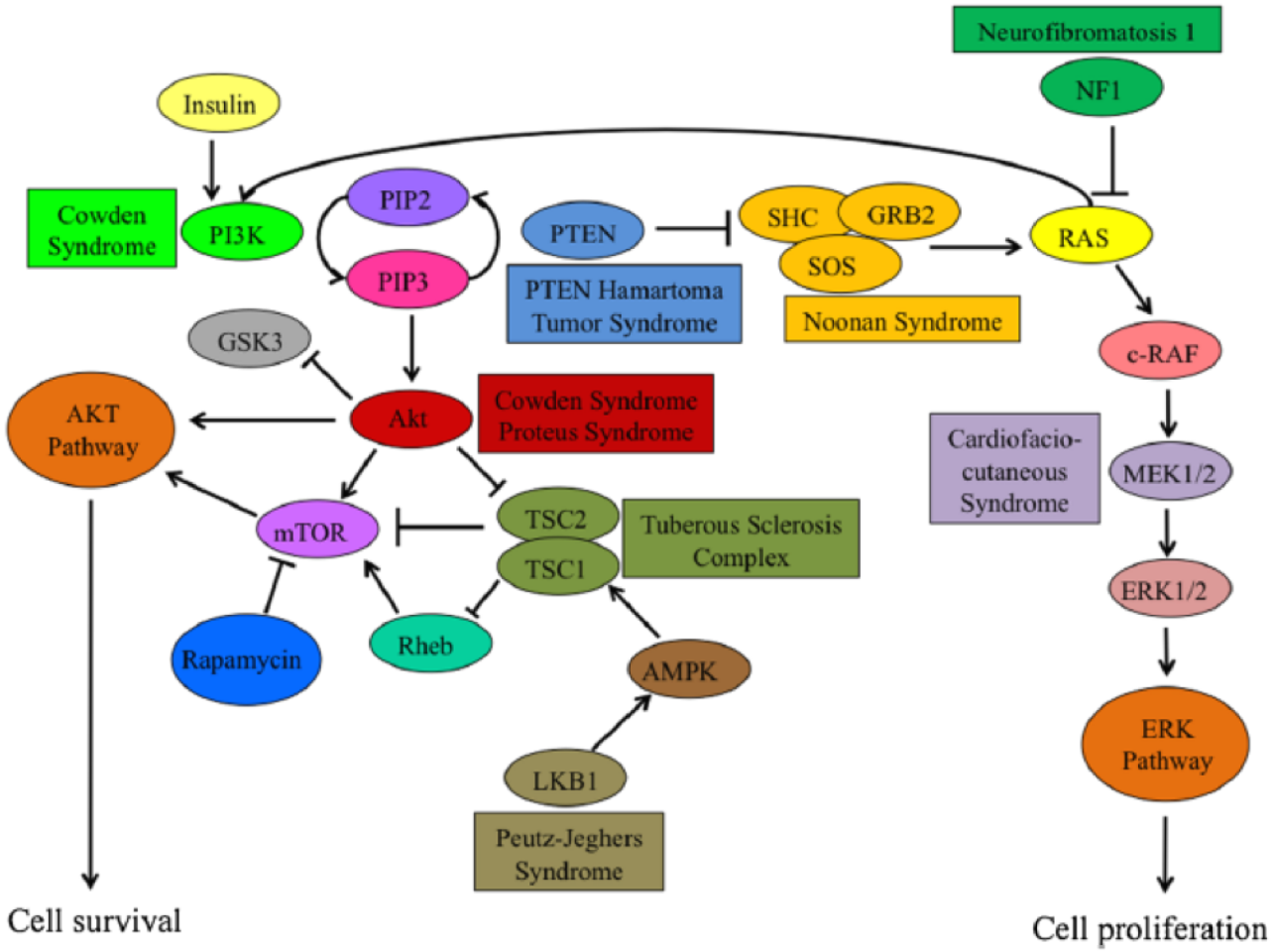
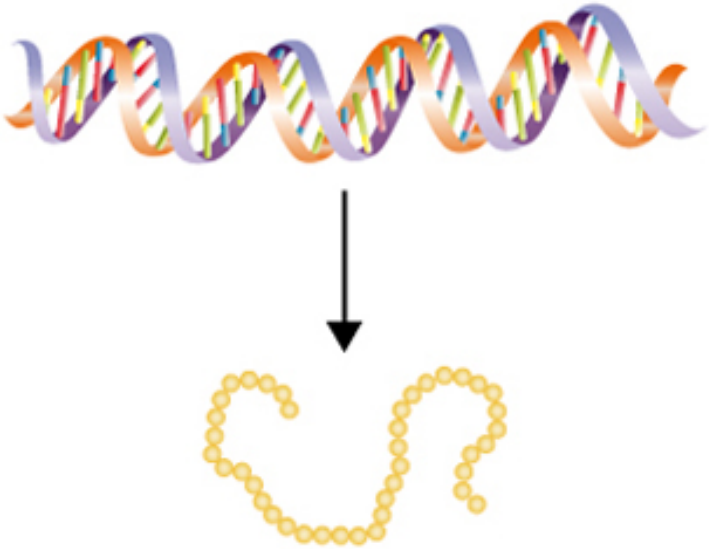


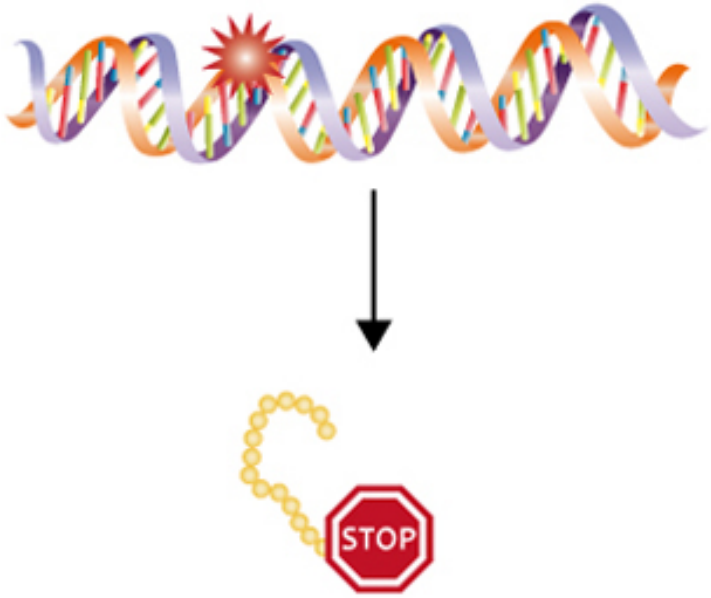
Figure 1. PTEN's signaling pathway, depicting genes with their corresponding syndromes.

Mester J, Eng C. 2013. When overgrowth bumps into cancer: The PTEN-opathies. Am J Med Genet Part C Semin Med Genet 163C:114–121.

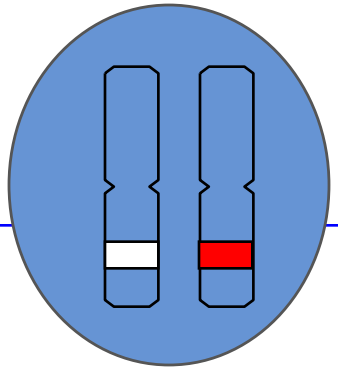
What causes genetic conditions?



Functional protein

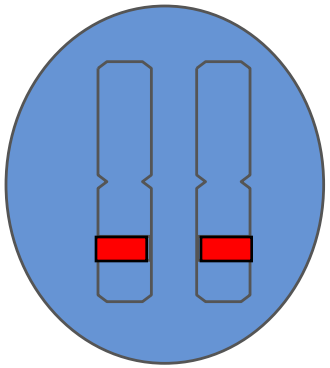


Nonfunctional or missing protein



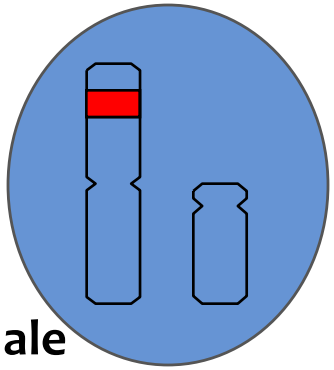
Dominant

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



Male

X-linked recessive

Males with an altered gene on the X-chromosome are always affected

Autosomal dominant inheritance

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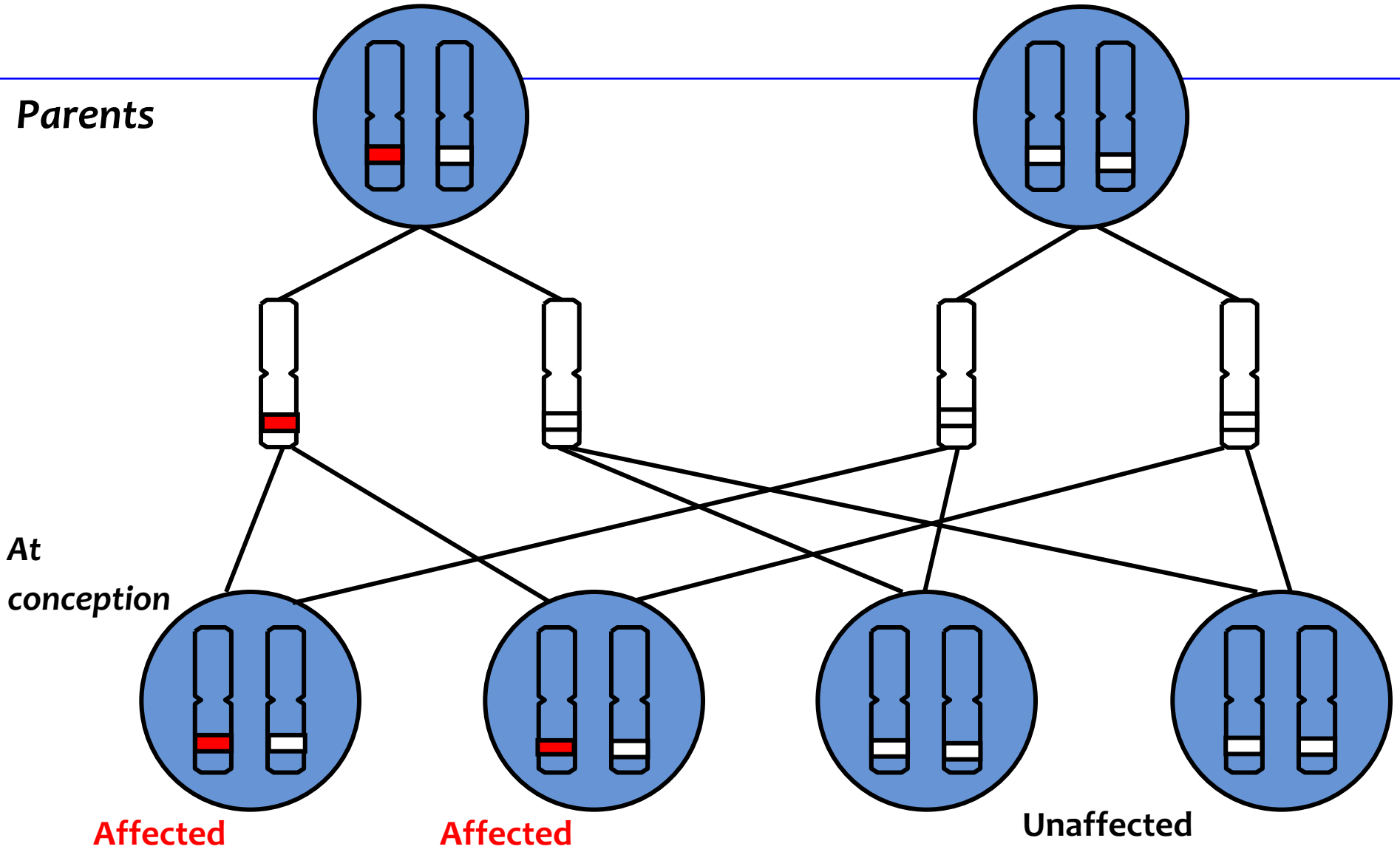

NCCNDiagnostic criteria for Cowden Syndrome 2015

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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
•One biopsy proven trichilemmoma
•Multiple palmoplantar keratoses
•Multifocal or extenisve oral mucosal papillomatosis
•Multiple cutaneous facial papules (often verrucous)

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

NCCN Diagnostic criteria for Cowden Syndrome 2014

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Multiple palmoplantar keratoses
Multifocal or extenisve oral mucosal papillomatosis
Multiple cutaneous facial papules (often verrucous)
Macular pigmentation of glans penis

Minor criteria
- 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)

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

PTEN Testing Criteria

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- **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 trichilemmomas**
- **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**