PHTS research

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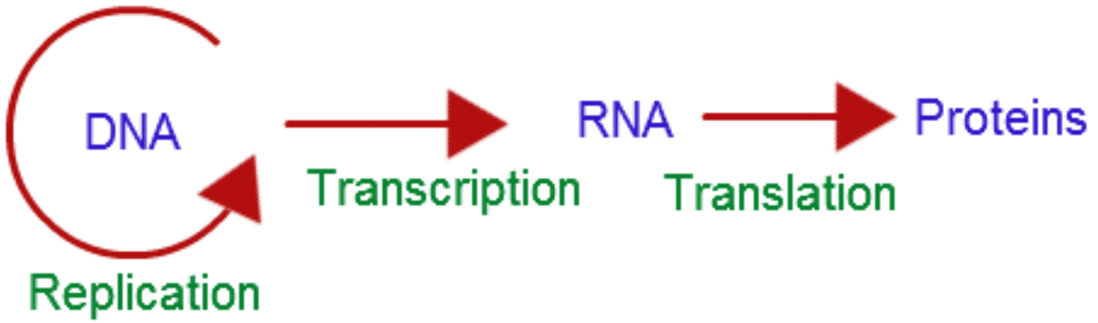
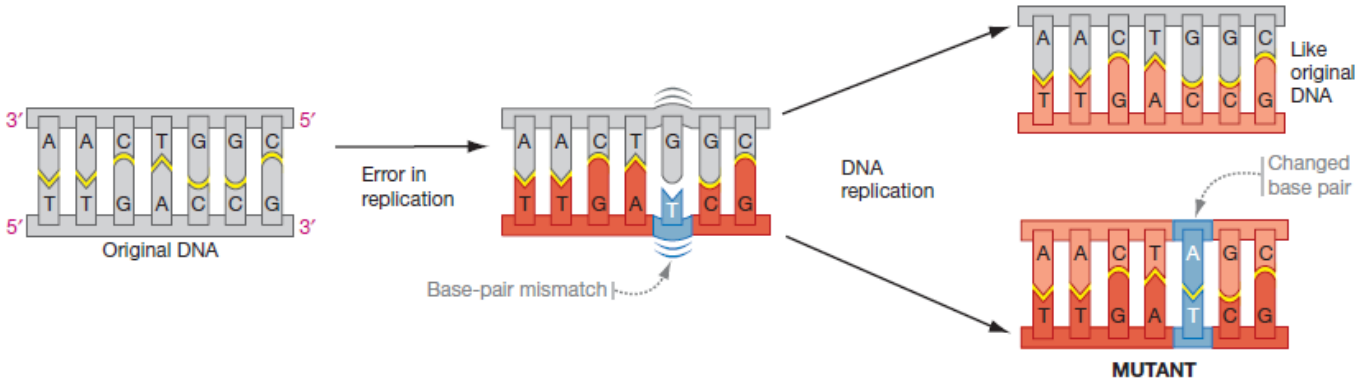
Overview

1. Some basic concepts of inherited/germline mutations
2. Introduction to PTEN
3. PTEN and PHTS research so far
4. Current efforts in PHTS research
5. Challenges

Genetic disorders arise from DNA mutations

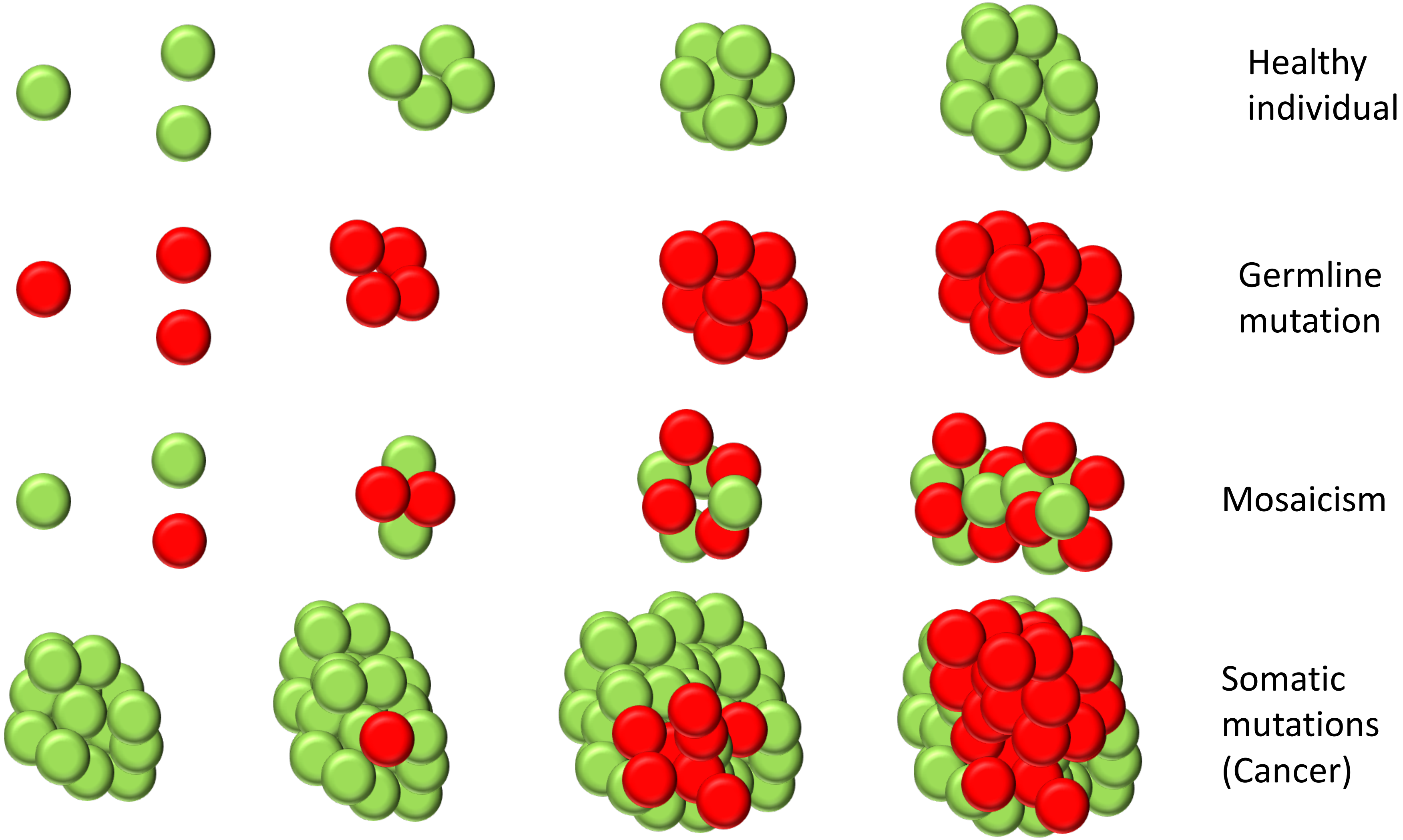


Proteins form the workforce of a cell



DNA mutations result from errors in DNA replication

How are mutations inherited/ acquired



Introduction to PTEN

- Discovered in 1997 as a gene commonly mutated in human cancers
- It has 403 amino acids
- It is a protein which chews up PIP3, a signalling molecule, which controls cell division, metabolism and survival.
- A defect in this ability of PTEN can lead to uncontrolled cell division leading to benign tumours and cancer
- Somatic mutations in PTEN are commonly associated with human cancers
- Germline mutation in PTEN causes PHTS

Tissue	*PTEN* alteration in human cancer	Neoplasms and tumours in PHTS
Breast	Mutation <5%, LOH 40%, promoter methylation 50% and loss of expression ~40%	25–50% lifetime risk for women
Endometrium	Mutation 35–50%	Yes
Thyroid	Homozygous deletion <10%, promoter methylation >50%, and rearrangement in most papillary thyroid carcinomas	Yes
Prostate	Frequent LOH and miR-22 and miR-106b–25 cluster overexpression	NR
Leukaemia or lymphoma	Deletion 10% of T-ALL and 27% mutation in T-ALL	NR
Glioma	LOH >70%, mutation 44% (coincident with LOH) and miR-26a amplification	Dysplastic gangliocytoma of the cerebellum in LD
Melanoma	LOH 30–60%, mutation 10–20% (metastases) and >50% frequent promoter methylation in patients with XP	NR

Tissue	*PTEN* alteration in human cancer	Neoplasms and tumours in PHTS
Lung cancer	Mutation infrequent, promoter methylation frequent, miR-21 upregulation 74% and loss of PTEN 74%	Occasional
Liver	Mutation <5%, PTEN expression lost in 12% and PTEN expression lost in HepC HCC	NR
Bladder	LOH 23%, homozygous deletion 6%, mutation 23% (late stage) and decreased or absent PTEN expression 53%	NR
Kidney	LOH 25%	NR
Pancreas	Altered localization common	NR
Adrenal pheochromocytoma	LOH more common in malignant than in benign tumours	NR
Colon and intestine	Up to 18% mutated and up to 19% LOH depending on tumour type	Yes and benign polyps in >90%

Hollander et al., 2011

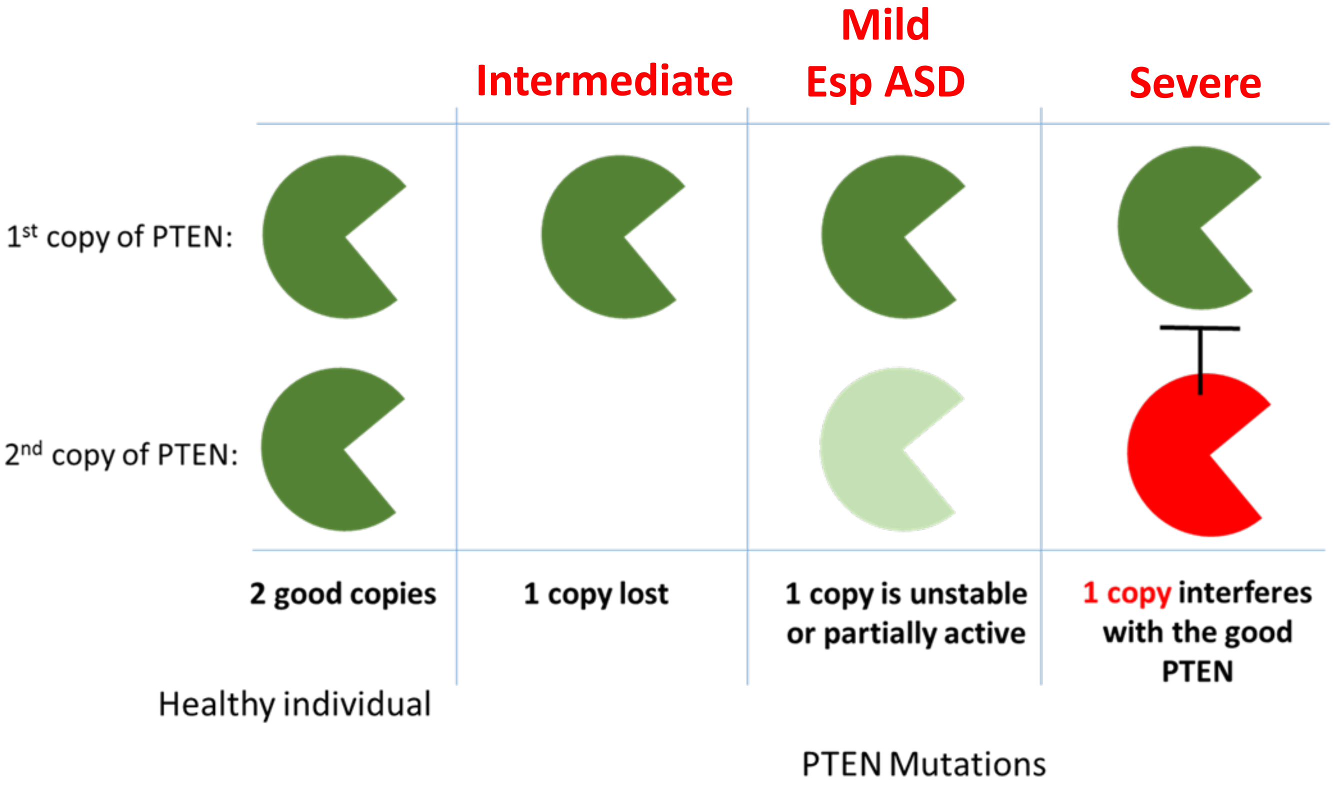
PTEN and PHTS research so far

- In 1998 it was discovered that PTEN is required to metabolise PIP3 and thus is a tumour suppressor
- The first PTEN mouse models was made between 1998-2000 and it was shown that loss of one copy of PTEN led to tumours of the GI tract, thyroid, breast, endometrium and prostate. This is consistent with tumours found in PHTS patients
- Various studies since then has uncovered how PTEN works and mechanisms that regulate the amount of PTEN in cells
- Various mouse models have been generated to study the role of PTEN in tumour suppression
- Information from patients (both PHTS and cancer) has enabled us to correlate our findings in mouse models with what is seen in the clinic
- Studies on mouse models allows us to conduct pre-clinical drug trials for cancer treatment

Current efforts in PHTS research

Q1. Is there a correlation between type of PTEN mutation and outcome of the disease ?

- 242 mutations have been identified in PHTS patients
- Only a small subset of these mutations have been studied for effects on PTEN function



Nick Leslie
Heriot Watt University
Edinburgh

Current efforts in PHTS research

Q1. Is there a correlation between type of PTEN mutation and outcome of the disease ?

- 242 mutations have been identified in PHTS patients
- Only a small subset of these mutations have been studied for effects on PTEN function

This classification is based on a very small number of PTEN mutations and a very small number of patients

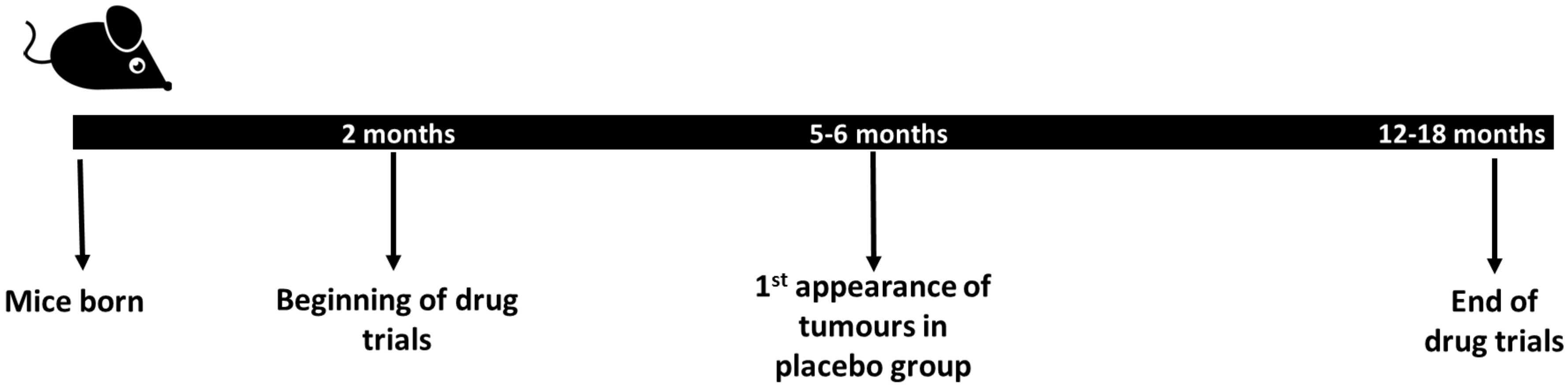
Currently, Nick Leslie and his team are studying more mutations. We hope that this information along with patient data will allow us to see if there is a correlation.

Hopefully, this will allow us to predict the prognosis of PHTS

Current efforts in PHTS research

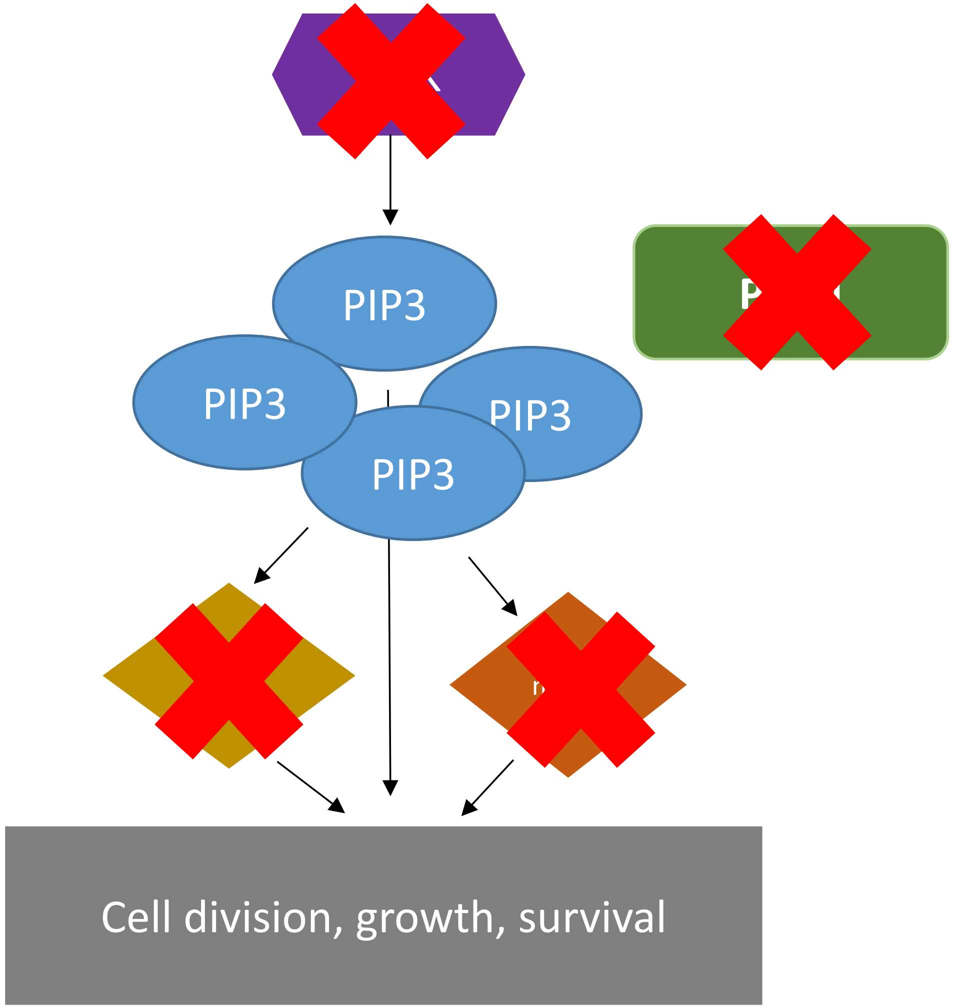
Q2. Can we prevent/delay cancer in PHTS patients ?

We have developed mouse models for PHTS



Real mouse age	1 mth	2 mths	4 mths	6 mths	8 mths	10 mths	1 yrs	2 yrs	3 yrs
Human age (yrs)	14	20	26	34	42	50	58	70	100

What drugs can be used for PHTS ?



Current efforts in PHTS research

Q3. Can we address ASD in our mouse models?

- We also study ASD in our mouse model
  - We can look at brain size and morphology
  - Studying the brain cells (neurons) gives us a better idea of how different PTEN mutations affect the neurobiology of these mice
  - We can do behavioural studies in these mice models to understand which functions are compromised
  - We would like to do pre-clinical drug trials to see if we can alleviate ASD

Challenges in PHTS research

- Very little patient information which makes it difficult to establish patterns
- Mouse models are not genetically diverse as humans. We keep our mice in a controlled environment. It makes it difficult to understand what extrinsic factors contribute to diversity of phenotype seen in the clinic
- We would like to understand why only a subset of tissues get cancer in PHTS patients and if this information can be used to develop new therapies for PHTS

Thank You