Genetic Susceptibility to Childhood Cancer

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There are two types of cancer gene

- Faulty genes that are present in egg or sperm and that are therefore present in every cell. **Cancer predisposition genes.**

- Faulty genes that are only present in the cancer itself not the rest of the body. **Somatically mutated cancer genes**
Cancer genes

• ~400 genes known to be involved in cancer (~1% human genes).

• 90% of known genes show somatic mutation, 20% germline and 10% both.
CANCER GENES

- gain of function
  - activated in tumours
    - Oncogenes

- loss of function
  - inactivated in tumours
    - Tumour suppressor genes
Genetic mutations

High / moderate / small increases cancer risk

- Clustering of cases ‘familial’
- Unusual phenotype ‘syndromic’
- Isolated cases ‘sporadic’
Genetic mutations

High / moderate / small increases cancer risk

Clustering of cases ‘familial’

Unusual phenotype ‘syndromic’

Isolated cases ‘sporadic’
Familial childhood cancer

• Familial forms of most cancers reported, but overall contribution to the cancer is very variable.
• Many causative genes identified by linkage analysis.
• Retinoblastoma (*RB1*), Wilms tumour (*WT1*), neuroblastoma (*ALK*), medulloblastoma (*SUFU*).
Retinoblastoma

- Embryonal tumour of the retina
- 1 in 20,000 ~40 in UK per year
- 30% bilateral
- 15% family history of retinoblastoma
- Due to \textit{RB1} mutations. Rb1 is a key regulator of cell cycle and of chromatin
- Paradigm for Knudson’s two-hit hypothesis
Retinoblastoma
Knudson’s two-hit hypothesis

Genetic

Non-genetic

Tumour
Retinoblastoma

- All familial cases are genetic – 50% risk recurrence and offspring risk
- Most bilateral, non-familial cases are genetic and due to *de novo* mutations – 50% offspring risk
- 15% unilateral RB due to *de novo* mutations -50% offspring risk
- Remainder have two somatic *RB1* mutations in the tumour, are not genetic, no risk to relatives
Genetic testing in retinoblastoma

• Blood test in all children with retinoblastoma
• If mutation found, can offer ‘cascade’ genetic testing to at-risk family members

Allows:
• Targeting / avoidance of surveillance
  • EUA from 2-3 weeks to 5yo (14 anaesthetics)
Genetic mutations

High / moderate / small increases cancer risk

Clustering of cases 'familial'

Unusual phenotype 'syndromic'

Isolated cases 'sporadic'
Childhood cancer syndromes

• Most childhood cancer syndromes are caused by mutations in tumour suppressor genes
  – Easier to inactivate rather than activate genes.
  – Better tolerated by an embryo.
• Mutation predisposes to cancer, it does not cause cancer alone, other events/mutations are required.
• Cancers due to germline mutations more likely to
  - occur at younger age
  - be bilateral/multifocal
  - be associated with other features
# Childhood cancer syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mechanisms</th>
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<tr>
<td>• Fanconi anaemia</td>
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<td>• Beckwith-Wiedemann</td>
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Wilms-Aniridia-Genitourinary-mental Retardation (WAGR) syndrome

100% aniridia

Genito-urinary abnormalities
Wilms tumour (30-50%)
Insidious renal disease
Fanconi Anaemia

- Rare, highly heterogeneous condition characterised by distinctive cellular phenotype, skeletal abnormalities, bone marrow suppression and risk of malignancy
Genetic mutations

High / moderate / small increases cancer risk

- Clustering of cases ‘familial’
- Unusual phenotype ‘syndromic’
- Isolated cases ‘sporadic’
Sporadic’ childhood cancer

- Sometimes due to syndromic genes but other features not present (e.g. *WT1*, *SUFU*).
- Sometimes due to ‘familial’ genes but reduced penetrance means relatives not affected (*DICER1*, *INI1*).
- Sometimes associated risks are only slightly increased (GWAS variants).
Association studies

SNP

..ACTGGGCTAGGAACATTAGAGCCCCGTTACACTTTCC..

..ACTGGGCTAGGAACATTATAGCCCCGTTACACTTTCC..

..ACTGGGCTAGGAACATTA\textcolor{red}{T}AGCCCCGTTACACTTTCC..

Analyse hundreds of thousands of common genetic variants in cases and controls in 1000s of samples.
SNP association studies

**CASES**

```
TAGGAACATTA
TAGGAACATTA
TAGGAACATTA
TAGGAACATTA
TAGGAACATTA
TAGGAACATTA
TAGGAACATTA
TAGGAACATTA
```

**CONTROLS**

```
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
TAGGAACATTAGAGCCCGTTC
```
Genome-wide association study

• Analogous to linkage study – mapping common variants and exploiting linkage disequilibrium.

• 100,000s SNPs analysed can capture all common variation.
• Successful in all cancers analysed (and many other diseases) to date, including childhood cancers such as neuroblastoma, Wilms tumour, leukemia.

• Risks conferred very small (RR1.1 – 1.7), which limits clinical utility.

• Variants often not in genes and cause of the association often not known.
Finding more genetic variants

• Various strands of evidence indicate that (many) other genetic variants that contribute to childhood cancer remain to be identified.

• Likely that genetic variants makes a contribution to every type of childhood cancer, but extent variable.

• New sequencing technologies are likely to yield new discoveries.
DNA sequencing and gene discovery

• Direct interrogation of genetic code can identify most classes of genetic variant.
• Until recent years very expensive and laborious and limited to ‘candidate’ genes.
• Successfully identified many cancer predisposition genes (TP53 in Li Fraumeni, BUB1B in MVA, Fanconi anemia genes).
Next-Generation Sequencing

- Extraordinary advances in sequencing technologies over last 5 years.
- Now possible to analyse thousands of genes or the whole genome quickly and (relatively!) cheaply.
- Revolutionising gene discovery.
Exome sequencing

- The ‘exome’ refers to all protein coding genes ~20,000
- Can analyse 200 exomes per month / sequencer @£250 each.
- Has already led to discovery of more syndromic childhood cancer genes.
- Familial childhood cancer, sporadic cancers……
FACT study

- Factors associated with childhood tumours study.
- Aims to identify and characterise genes predisposing to childhood cancer.
- National study. We recruit:
  - Any child with solid tumor
  - Familial childhood cancer clustering.
  - Childhood cancer cases with unusual phenotype.
Why research into genetic susceptibility?

• Direct clinical benefit.
• Insights into cancer causation.
• Insights into fundamental mechanisms and developmental processes.
• Much still to discover and understand.