

Aetiology of Childhood Leukaemia

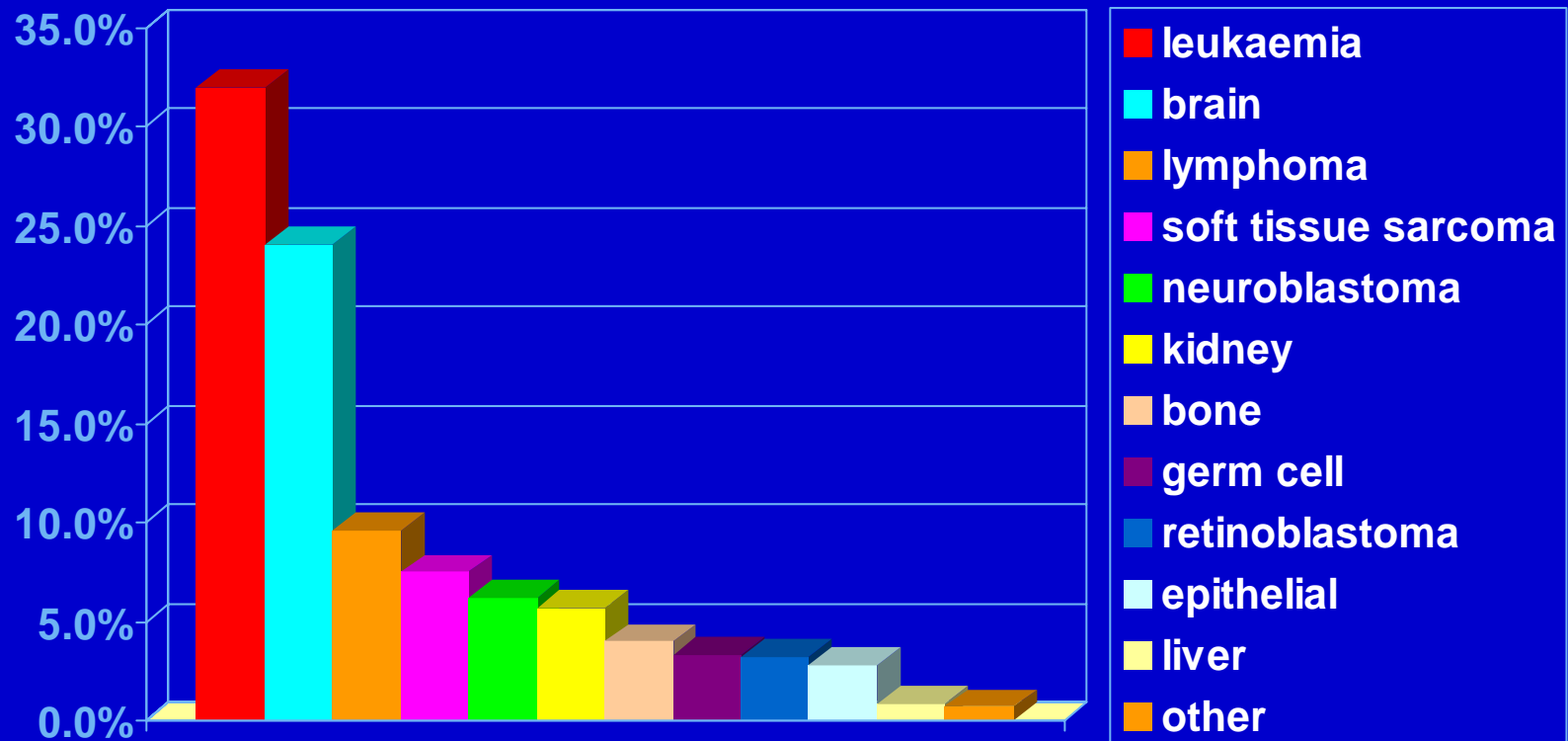
Tracy Lightfoot

Epidemiology & Genetics Unit

THE UNIVERSITY *of York*



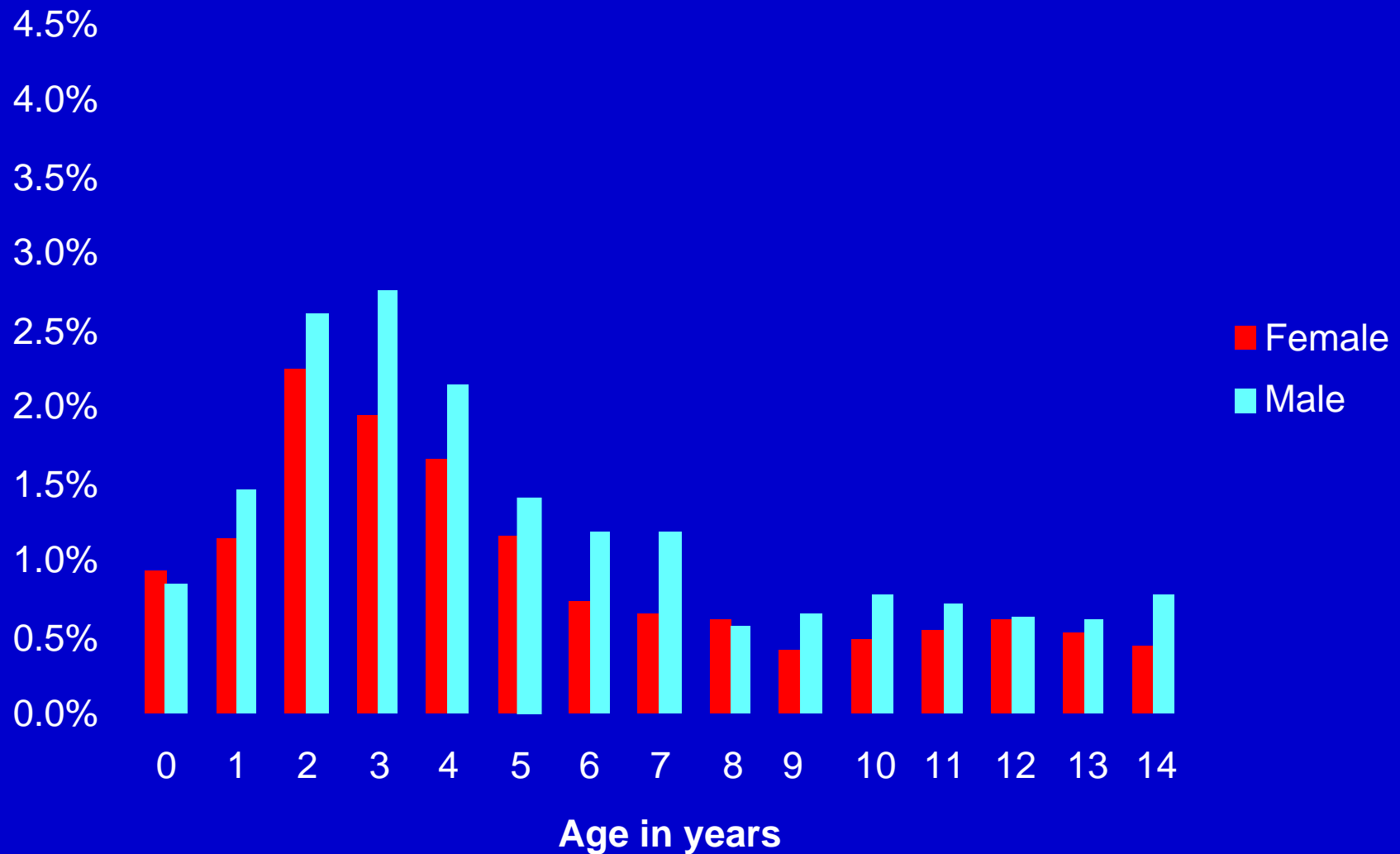
Childhood Cancer



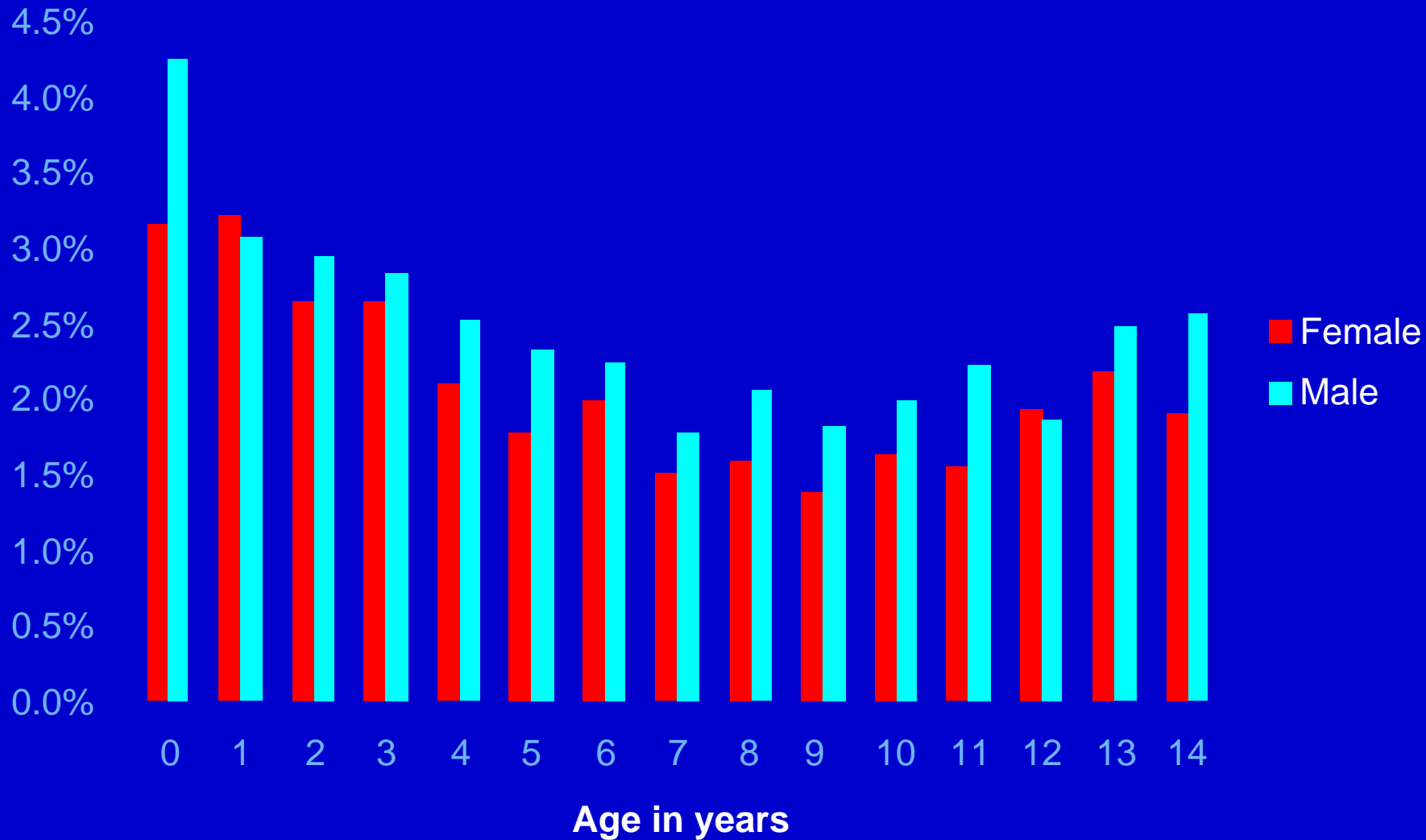
What is Leukaemia ?

- Leukaemia is a clonal disease originating in a single cell
- It evolves by the accrual of mutations within a clone resulting in genetic diversification
- Dominant mutant subclones are then naturally selected
- The nature of the clone and how far it has evolved determines the clinical outcome
- Delay in diagnosing increases the likelihood that the clone will have progressed to the point that additional mutations will have been acquired

Age distribution of childhood leukaemia



Childhood cancers other than leukaemia



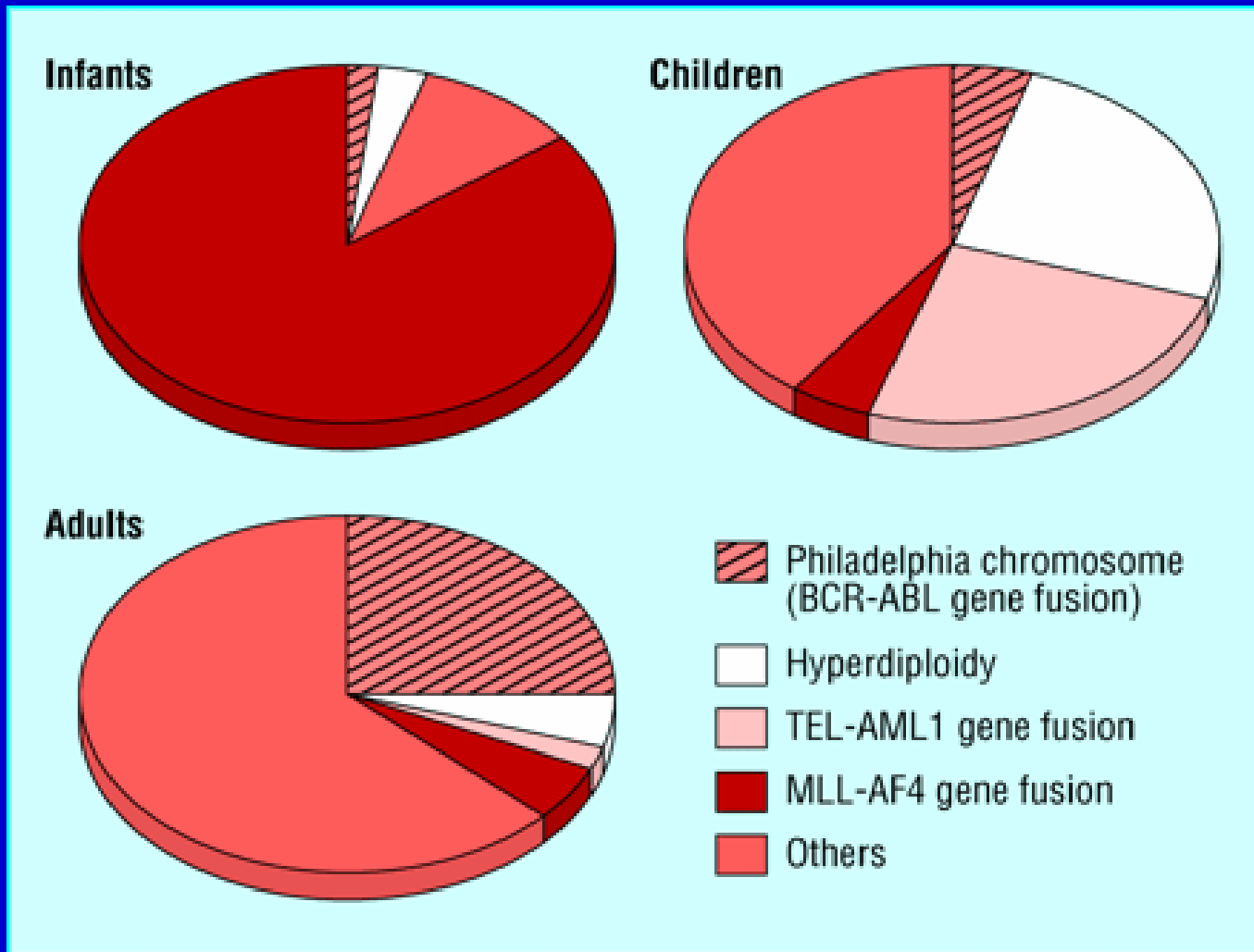
Childhood Leukaemia

- Biological heterogeneity is well documented
- Two major morphological subtypes:
 - Acute lymphoblastic leukaemia (ALL)
 - Acute myeloblastic leukaemia (AML)
- Characterised by molecular alterations, over 200 of which have been identified
- Chromosomal translocations are common along with simple gains/losses of chromosomes
- In more advanced disease, gene deletions and mutations are also relatively common

Subtypes of childhood ALL

Cell type involved	Chromosome abnormality	Molecular Lesion
B-cell (infants)	11q23 translocations	<i>MLL-AF4</i> , <i>MLL-ENL</i> , and other fusions
B-cell precursor	hyperdiploidy	Increased gene dosage
	t(12;21)(p13;q22)	<i>TEL-AML1</i> fusion
	t(1;19)(q23;p13)	<i>E2A-PBX1</i> fusion
	t(9;22)(q34;q11)	<i>BCR-ABL</i> fusion
T-cell precursor	1q deletion; t(1;14)(p32;q11)	<i>SIL-SCL</i> fusion

Molecular subsets of ALL in infants, children and adults



Taken from Greaves, BMJ 2002

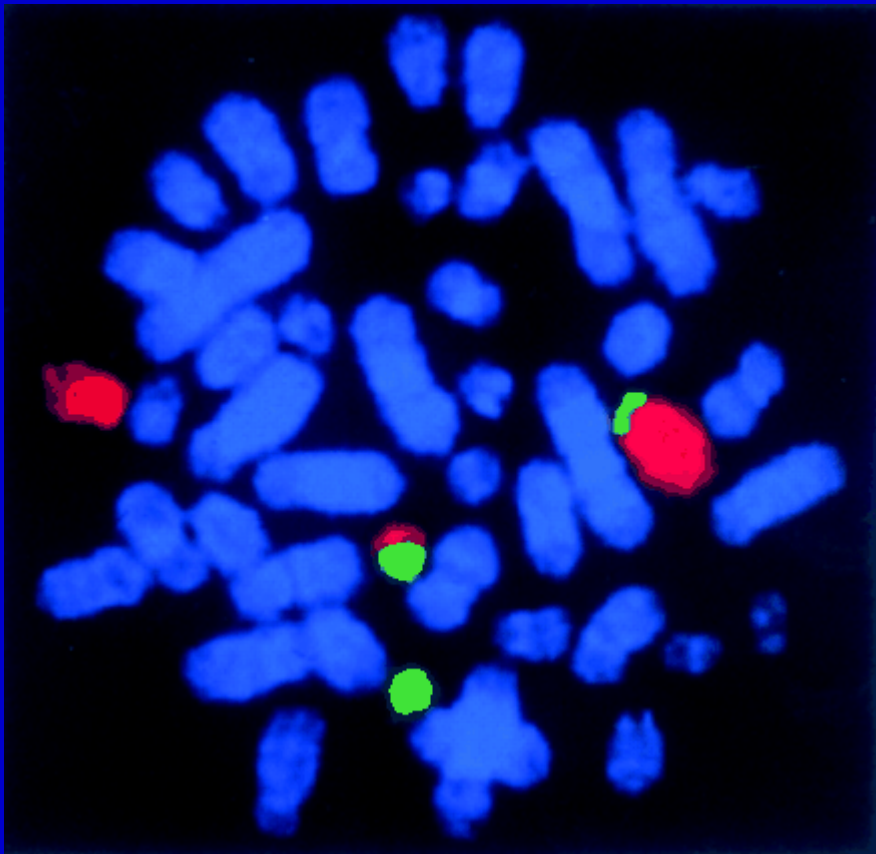
Subtypes of childhood AML

Cell type involved	Chromosome abnormality	Molecular Lesion
In infants	11q23 translocations	<i>MLL-AF6, -AF9, -AF10</i> or other fusions
	t(8;21)(q22;q22)	<i>AML-ETO</i> fusion

Genes of interest

- *MLL*
 - found in infant ALL and secondary t-AML
 - over 50 partner genes
 - regulates homeotic gene expression and chromatin stability
- *AML1*
 - frequently involved in leukaemogenesis
 - combines with *TEL* → *TEL-AML1*
 - activated tyrosine kinase or novel protein
- Knockout studies have demonstrated that *AML1/TEL/MLL* are all essential for haemopoiesis

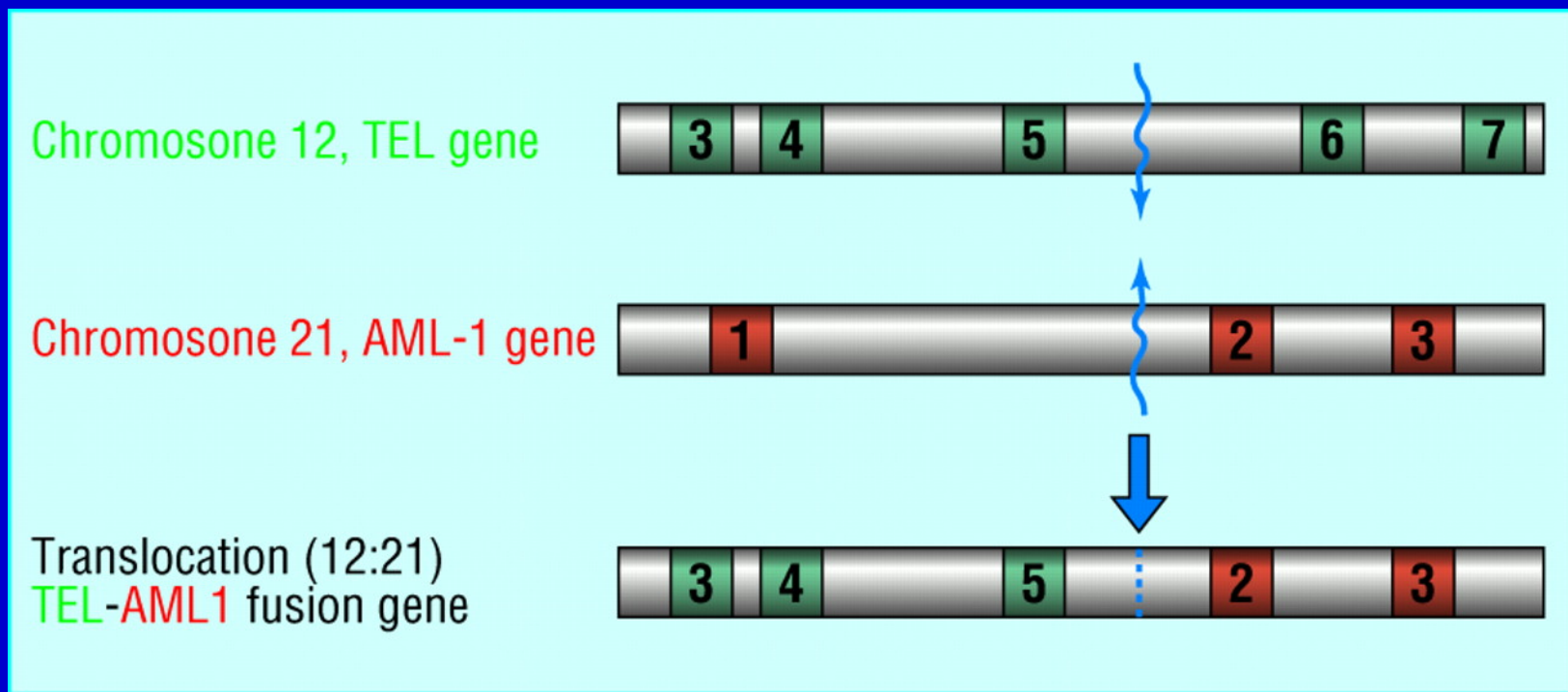
Chromosomal translocation to form the TEL-AML1 fusion gene



Chromosome 12 – red

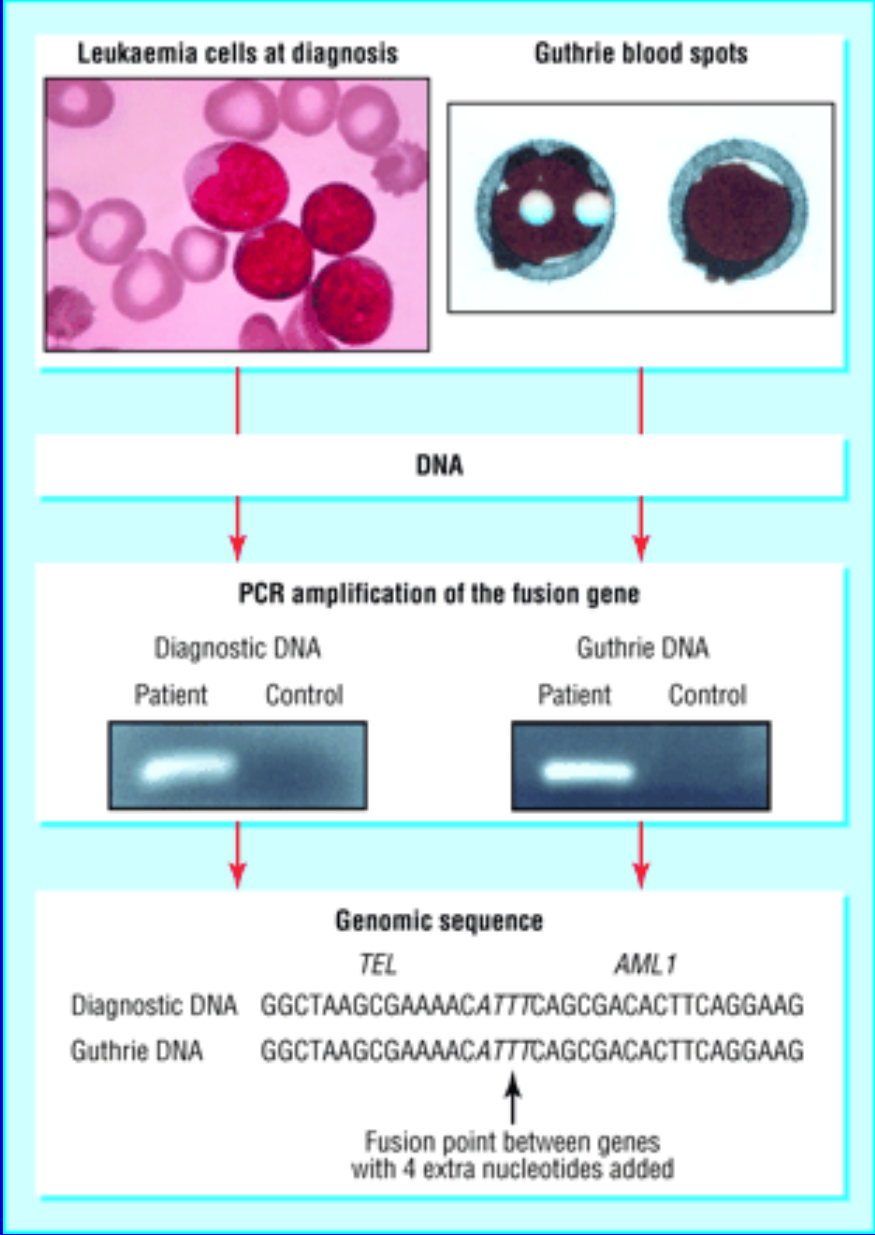
Chromosome 21 – green

TEL-AML1 gene fusion

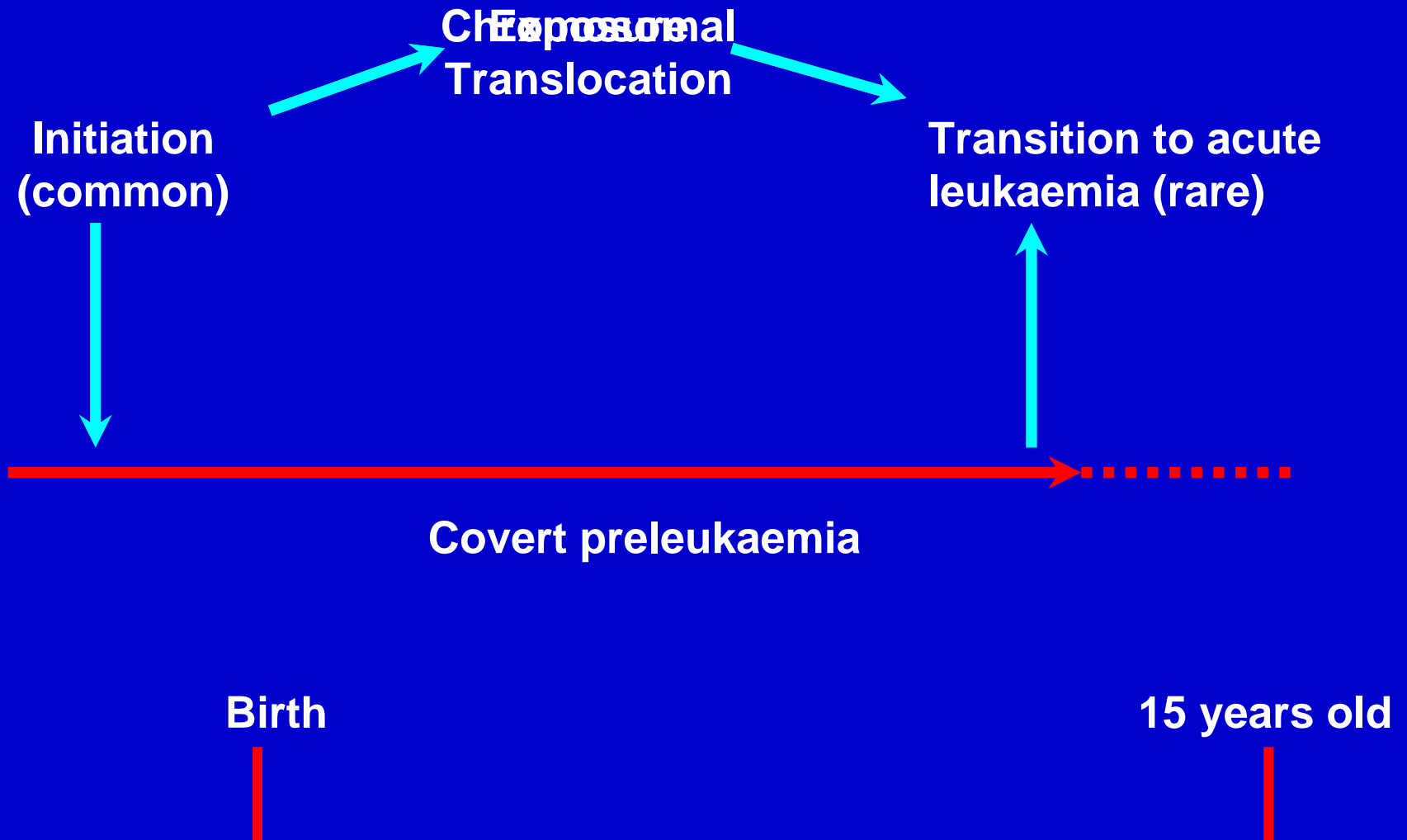


Origin of childhood leukaemia

- Neonatal blood spots and cord bloods from newborns support the hypothesis that chromosomal translocations can initiate leukaemia *in utero*
- Wiemels *et al* demonstrated *TEL-AML1* mutations in 6 out of 9 patients using Guthrie cards
- Animal modelling studies and twin concordance rates support the theory that initiation can occur *in utero*



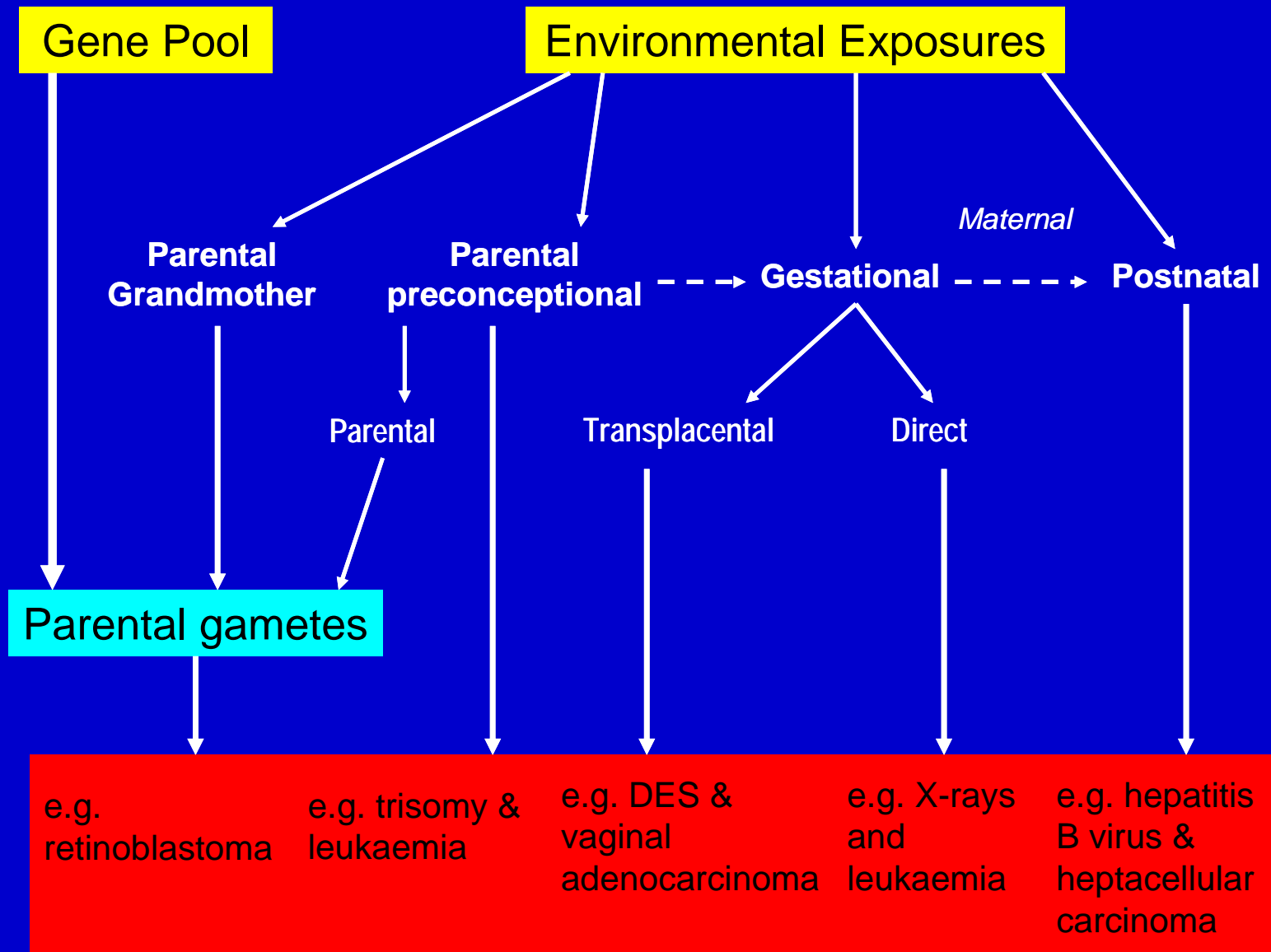
“Two hit” model for childhood leukaemia



- What is the second hit?
- Is there a single cause for all types of childhood leukaemia?
- Is there a role for a gene-exposure interaction?

Mechanisms of exposure

- Prenatal and early life exposures are believed to be important determinants of leukaemia
- Several possible mechanisms by which exogenous agents may be involved in the aetiology of childhood leukaemia
 - Early maternal contact
 - Paternal
 - *In utero*
 - Postnatally



Candidate exposures

- In adults and children, there is epidemiological evidence to suggest that certain exposures may play a role in the development of some subtypes of leukaemia and lymphoma
 - Ionising radiation
 - Chemical (e.g. benzene)
 - Viruses
 - bacteria
- However, whether any of these exposures have a major role in childhood cancer is unclear

In utero exposures

- DNA topoisomerase II inhibitors
- Folate
- Viruses
- Chemicals
- Infections

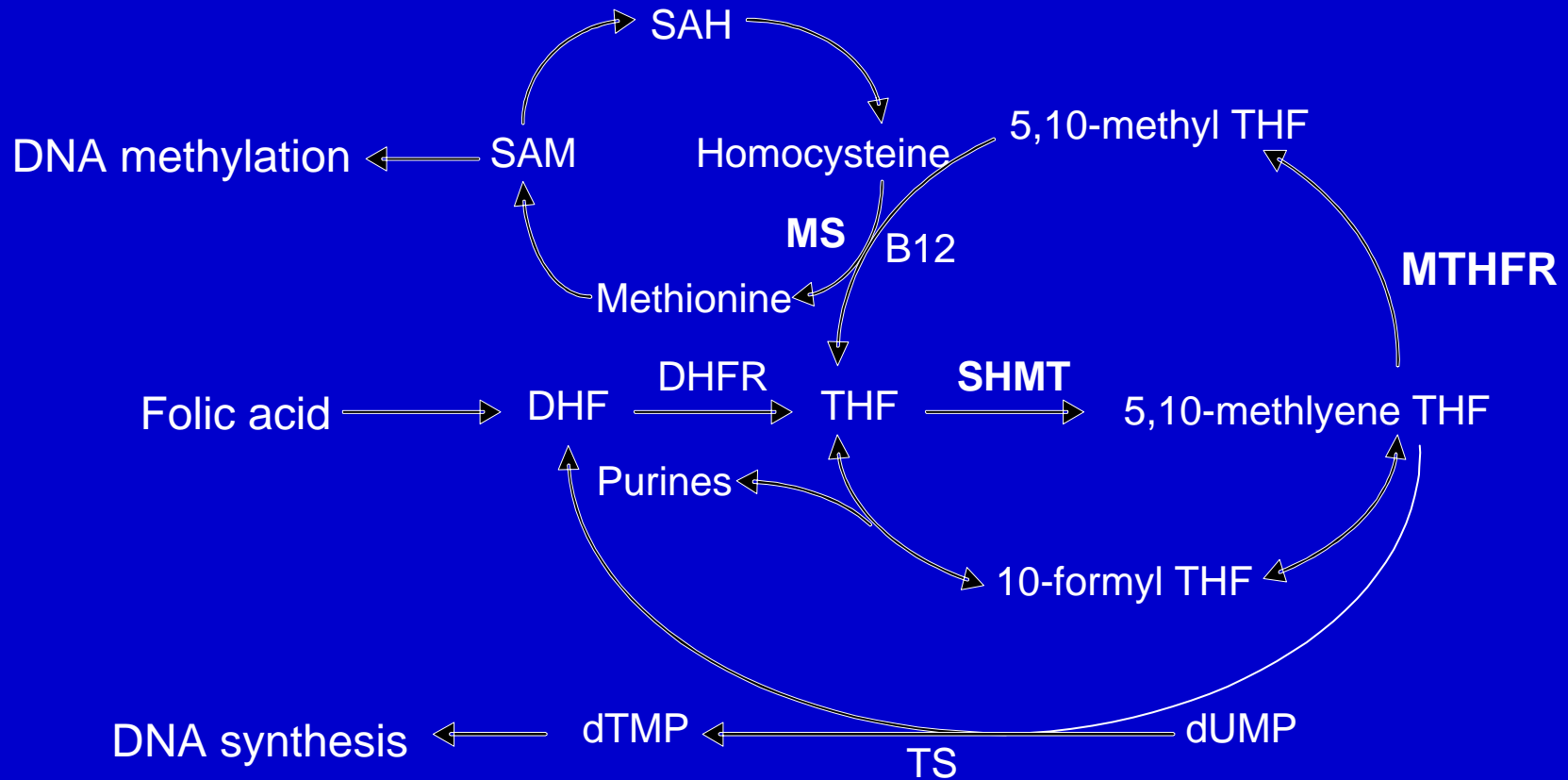
DNA topoisomerase II inhibitors

- *MLL* rearrangements seen in adult cases of leukaemia after chemotherapy using DNA topoisomerase II inhibitors
- Greaves suggested that *in utero* exposure may be important in infant leukaemia risk
- Extensive list of inhibitors
 - Benzene metabolites, bioflavonoids, herbal medicines, anthraquinone laxatives, pesticides
 - Present in tea, coffee, wine, fruits
- Some studies have identified increase risk of ALL following exposure
- Not clear whether due to inhibition of DNA topoisomerase II or affects on other pathways
- Single case where mother of child with leukaemia had been exposed to premethrin with evidence of *MLL* gene fusions

Folate

- Folate deficiency influences DNA methylation, impairs DNA synthesis and repair
- Major enzyme studied to date is *MTHFR*
- Polymorphisms have been reported at positions 677 and 1298
- Studies have reported that these polymorphisms are associated with reduced risk of ALL

Folate Pathway



Other areas of interest

- Breast feeding
- Reproductive technologies
- Infections
 - Two hypotheses that abnormal response to infections may play a role in the development of ALL in children
 - “delayed infection”
 - “hygiene hypothesis”

Summary

- Genetic and environmental factors have been implicated in the aetiology of many human diseases including childhood cancer
- There is increasing genetic evidence to suggest that gene arrangements can originate *in utero*
- However, whilst many environmental agents have been suggested as risk factors for childhood leukaemia the data are conflicting and often contradictory and the search for the candidate exposure – assuming they exist-continues
- Predominantly research has focused on the index child but we may be able to gain further insight by examining other family members