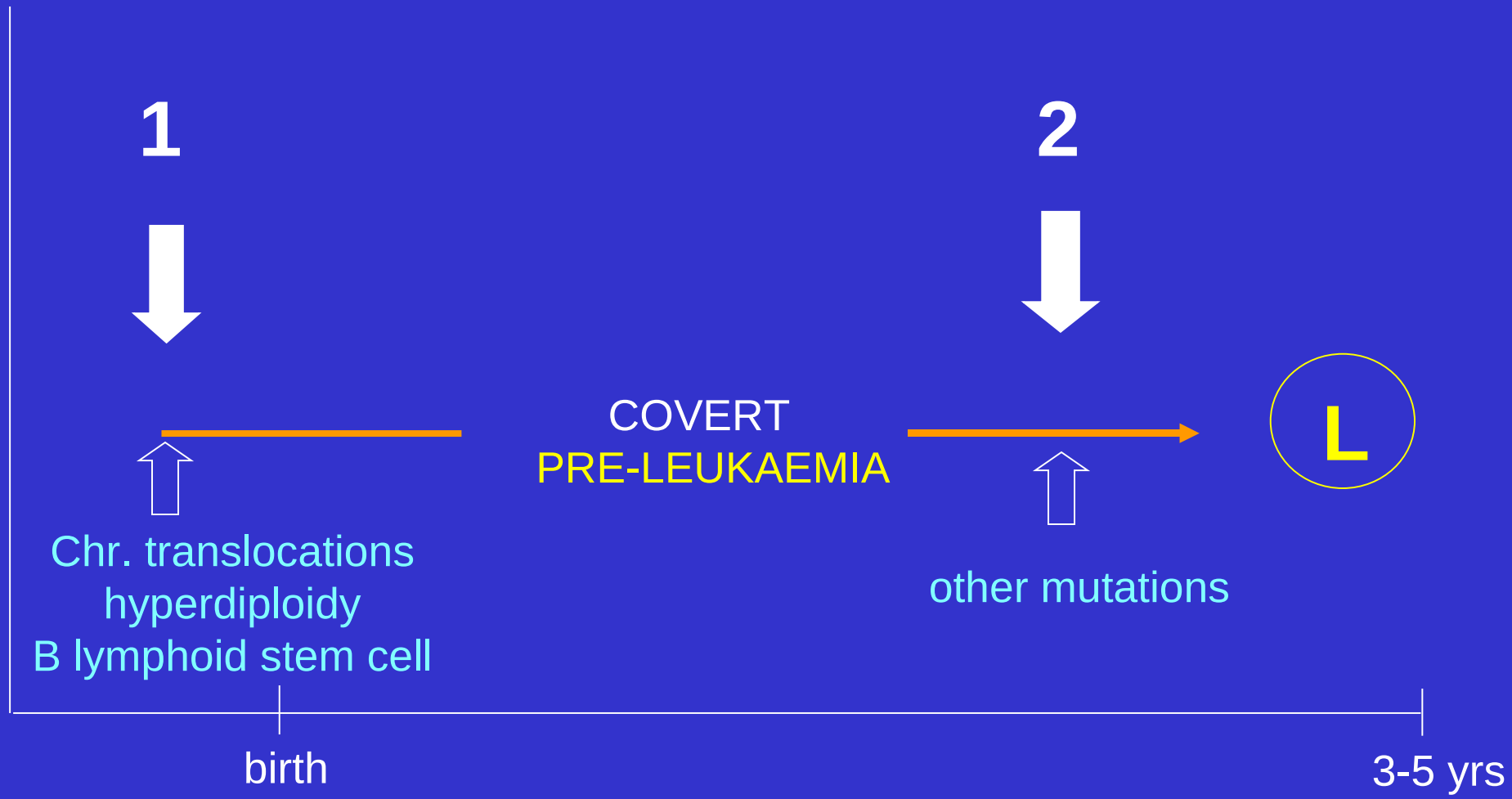
INFECTION, IMMUNE RESPONSES AND THE AETIOLOGY OF CHILDHOOD LEUKAEMIA

Mel Greaves

A MINIMAL 2 STEP MODEL FOR ACUTE LYMPHOBLASTIC LEUKAEMIA



PRE-NATAL ORIGINS OF PAEDIATRIC LEUKAEMIA

- Clonal relationships of concordant leukaemia in monozygotic twins
- Retrospective molecular scrutiny of archived neonatal blood spots of children with leukaemia
- Molecular screening of cord blood of new borns

EARLY OR INITIATING EVENTS IN LEUKAEMOGENESIS

- **Foetal haemopoiesis (liver / bone marrow?)**
- **Chromosome translocation / gene fusions**
  - ***MLL-AF4***
  - ***TEL-AML1***
  - ***AML1-ETO***
- **Chromosomal hyperdiploidy**
- **Chromosomal instability**
- **Mutations - *GATA1* in TMD / AML in Down's**

TEL-AML1 FUSION IS AN INITIATING EVENT BUT IS *INSUFFICIENT* FOR LEUKAEMOGENESIS

- Concordance rate in monozygotic twins is ~10%

  (Greaves et al, 2003, Blood, 102: 2321-2333)

- Mice transgenic for *TEL-AML1* are pre-leukaemic

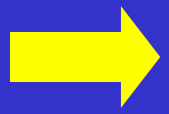
  (Tsuzuki et al, 2004, PNAS, 101: 8443-8448)

∴ secondary, post-natal events are critical

FREQUENCY AND RISK OF ACUTE LYMPHOBLASTIC LEUKAEMIA?

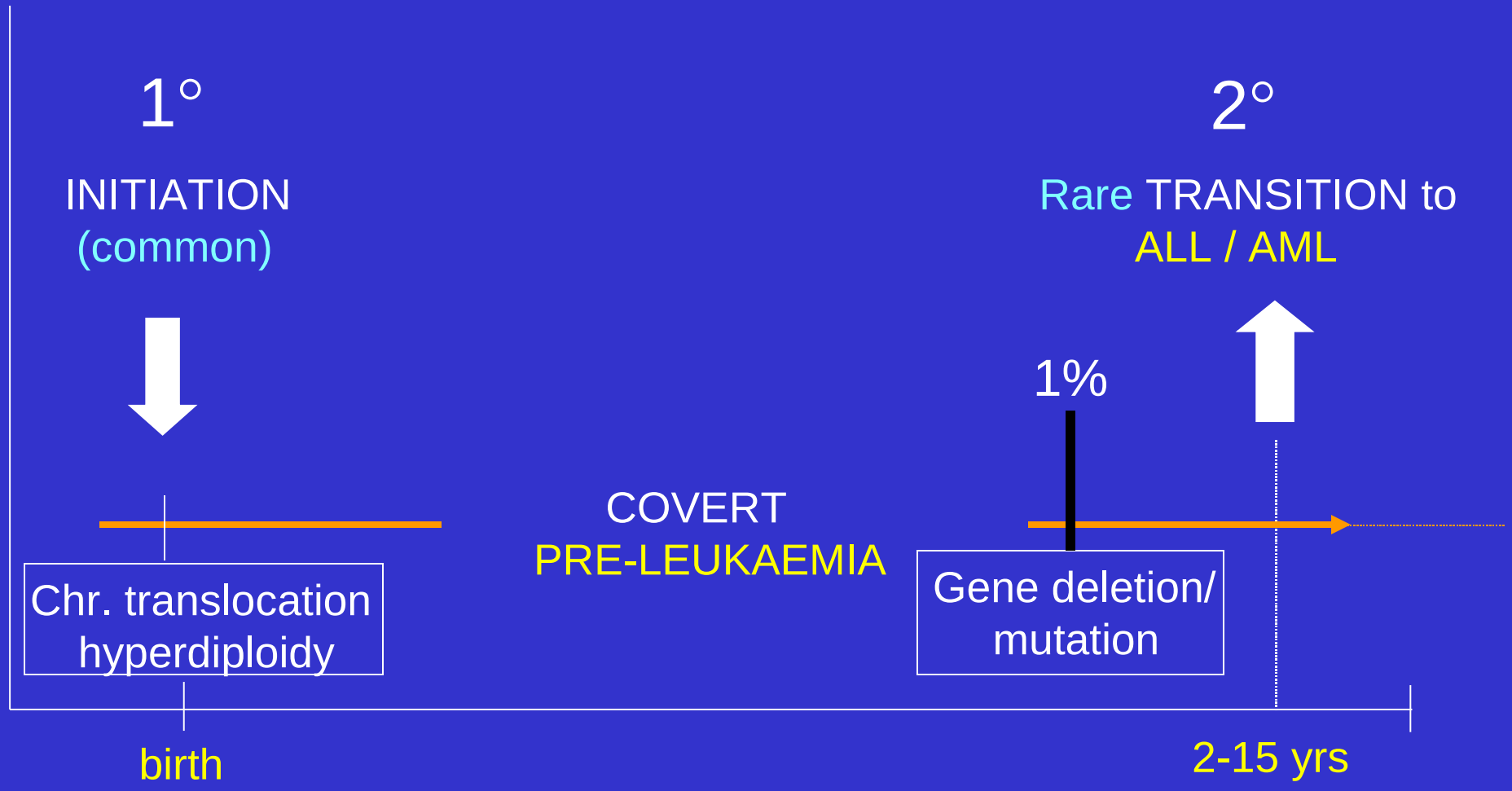
Risk of ALL	~ 1	in	2,000
Risk of ALL with *TEL-AML1*	~ 1	in	10,000
Risk of *TEL-AML1*$^{+}$ cord blood	~ 1	in	100

LEUKAEMIA IS INITIATED, PRE-NATALLY AT ~100 x THE DISEASE RATE



POST-NATAL SECONDARY EVENTS ARE THE BOTTLENECK FOR LEUKAEMIA AETIOLOGY

NATURAL HISTORY OF PAEDIATRIC ACUTE LEUKAEMIAS



MOLECULAR SCREENING FOR VIRAL SEQUENCES IN CHILDHOOD ALL

Virus Screened For	Screening Method
• Polyomaviruses JC and BK	Specific PCR*
• Parvovirus B19	Specific PCR
• Human herpesvirus family (HHV4, 5, 6, 7 and 8)	PCR using degenerate primers*
• Bovine leukaemia virus	Southern blotting
• TT virus	Specific PCR
• Exogenous microbial sequences	Representative difference analysis*

** MacKenzie J, Jarrett RF et al*

INFECTION-BASED HYPOTHESES FOR THE AETIOLOGY OF CHILDHOOD LEUKAEMIA

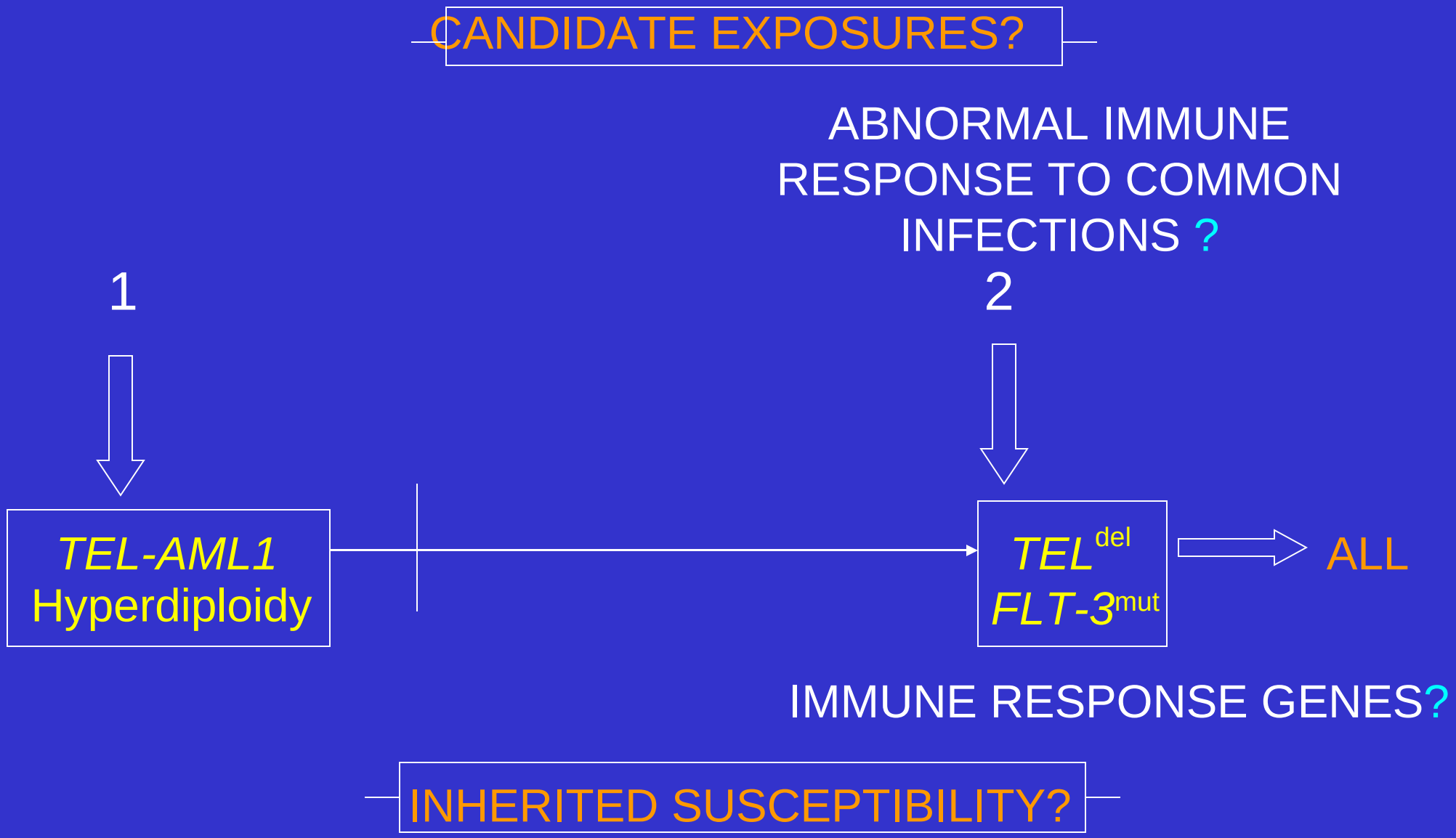
Greaves M (1988) *Leukemia*

The 'delayed infection' hypothesis

Model :

- Timing of common infections critical (- delay?)
  cf. hygiene hypothesis for allergies and type 1 diabetes
- Abnormal immune response facilitates expansion of pre-leukaemic clone
- Genetic susceptibility impacts on risk

A CAUSAL MECHANISM FOR CHILDHOOD LEUKAEMIA

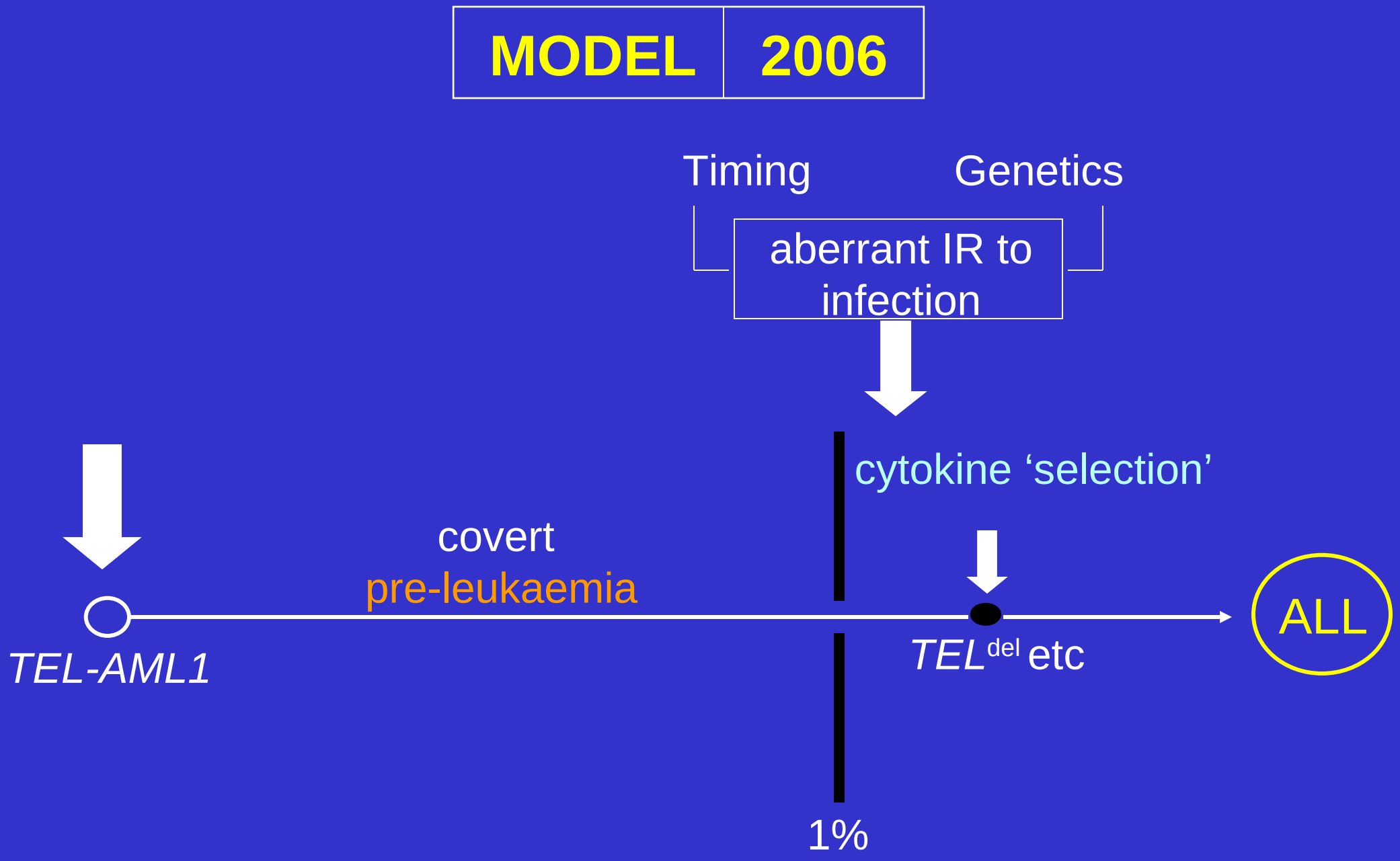


EPIDEMIOLOGICAL EVIDENCE SUPPORTING THE 'DELAYED INFECTION' HYPOTHESIS

- Increased common infections in *infancy* are *protective*

- Increased social contacts in *infancy* are *protective*
  - parity
  - attendance at playgroups

  (- proxies for infection)


MODEL 2006
Timing
Genetics
aberrant IR to infection
cytokine 'selection'
covert
pre-leukaemia
TEL-AML1
TEL del etc
ALL
1%