

Intrachromosomal amplification of chromosome 21 (iAMP21) and apparent precursor der(15;21)

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Overview

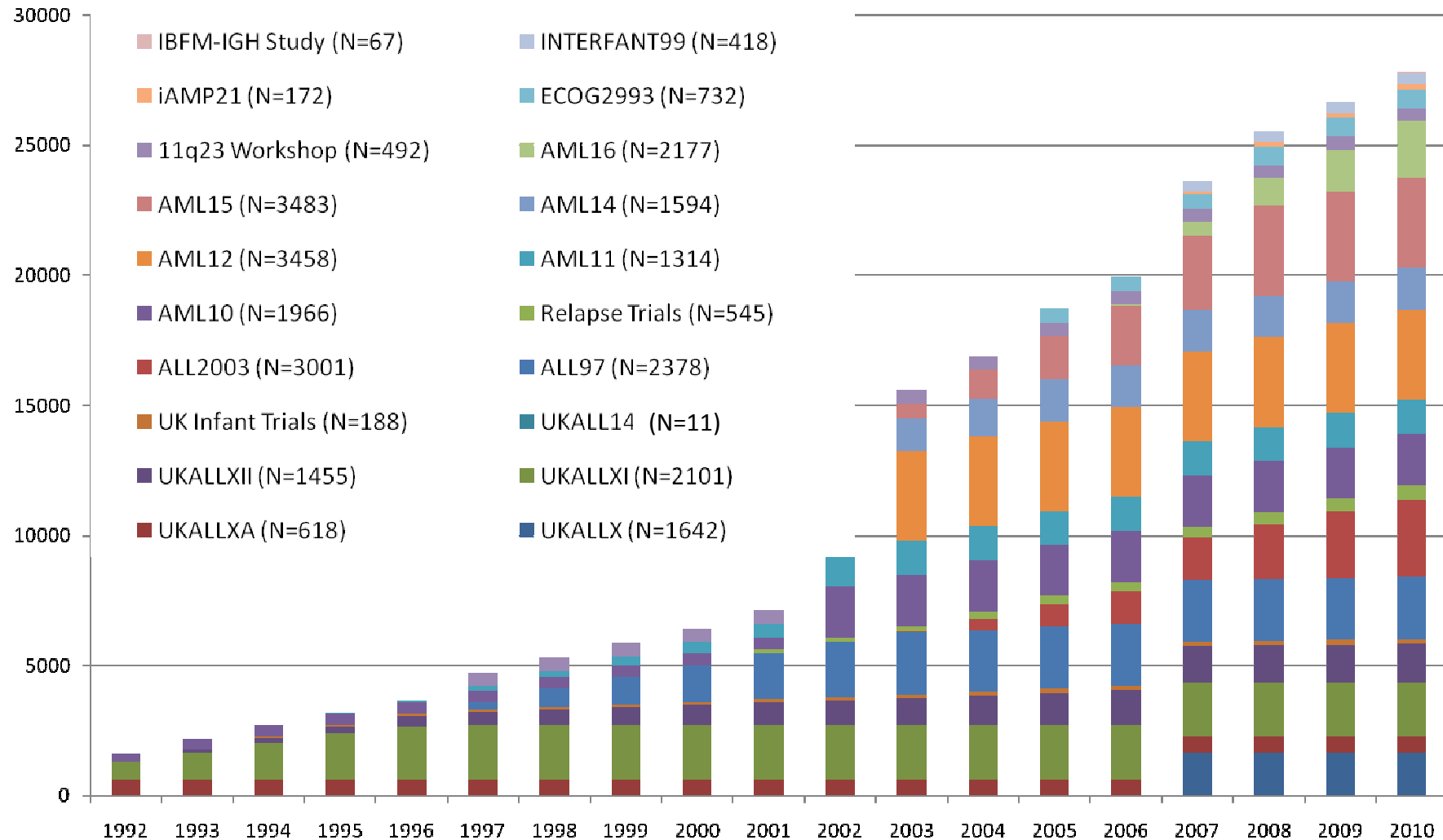
- An introduction to LRCG
- iAMP21 – a success story
- Ongoing studies
- A possible link to constitutional abnormality

Leukaemia Research Cytogenetics Group

- Established in 1992 with funding from LLR
- Collect cytogenetic data for UK treatment trials of acute leukaemia
- Discover and characterise new genetic abnormalities in acute leukaemia using cytogenetic and molecular approaches
- Investigate the epidemiology and prognostic relevance of new and existing genetic abnormalities

Annual accrual of cases to the LRCG Database

Total Cases = ~28,000 [31st December 2010]

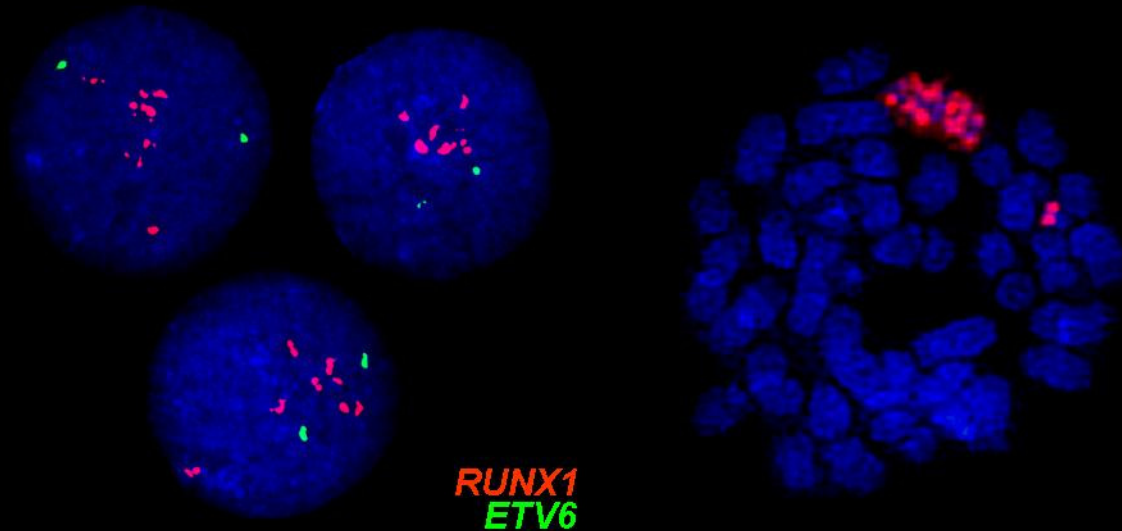
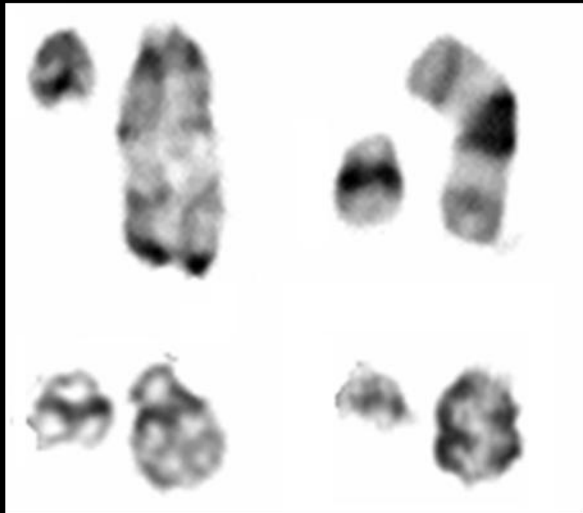


The origins of iAMP21.....

Detected during routine screening for *ETV6-RUNX1* fusions by FISH

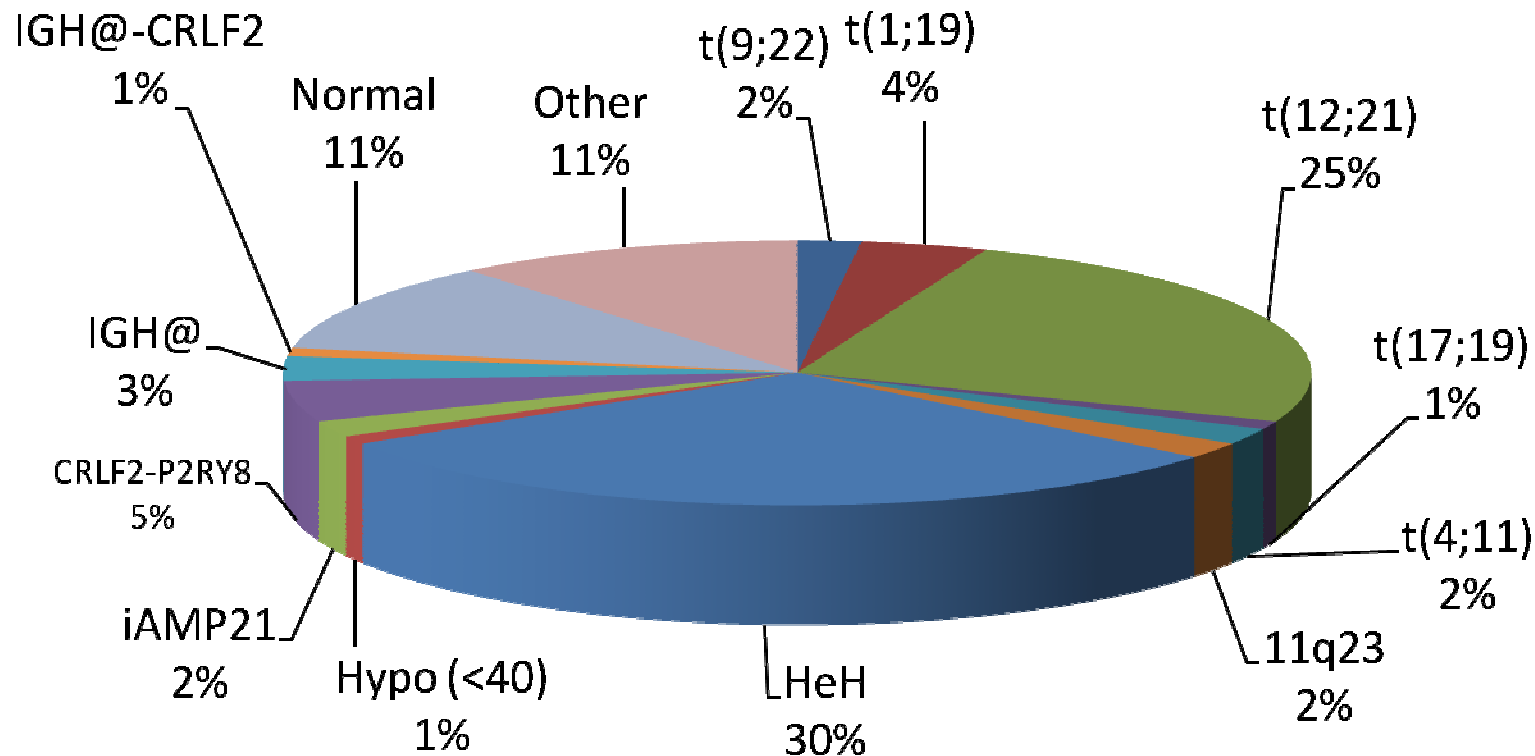


Multiple copies of *RUNX1* along the length of abnormal 21



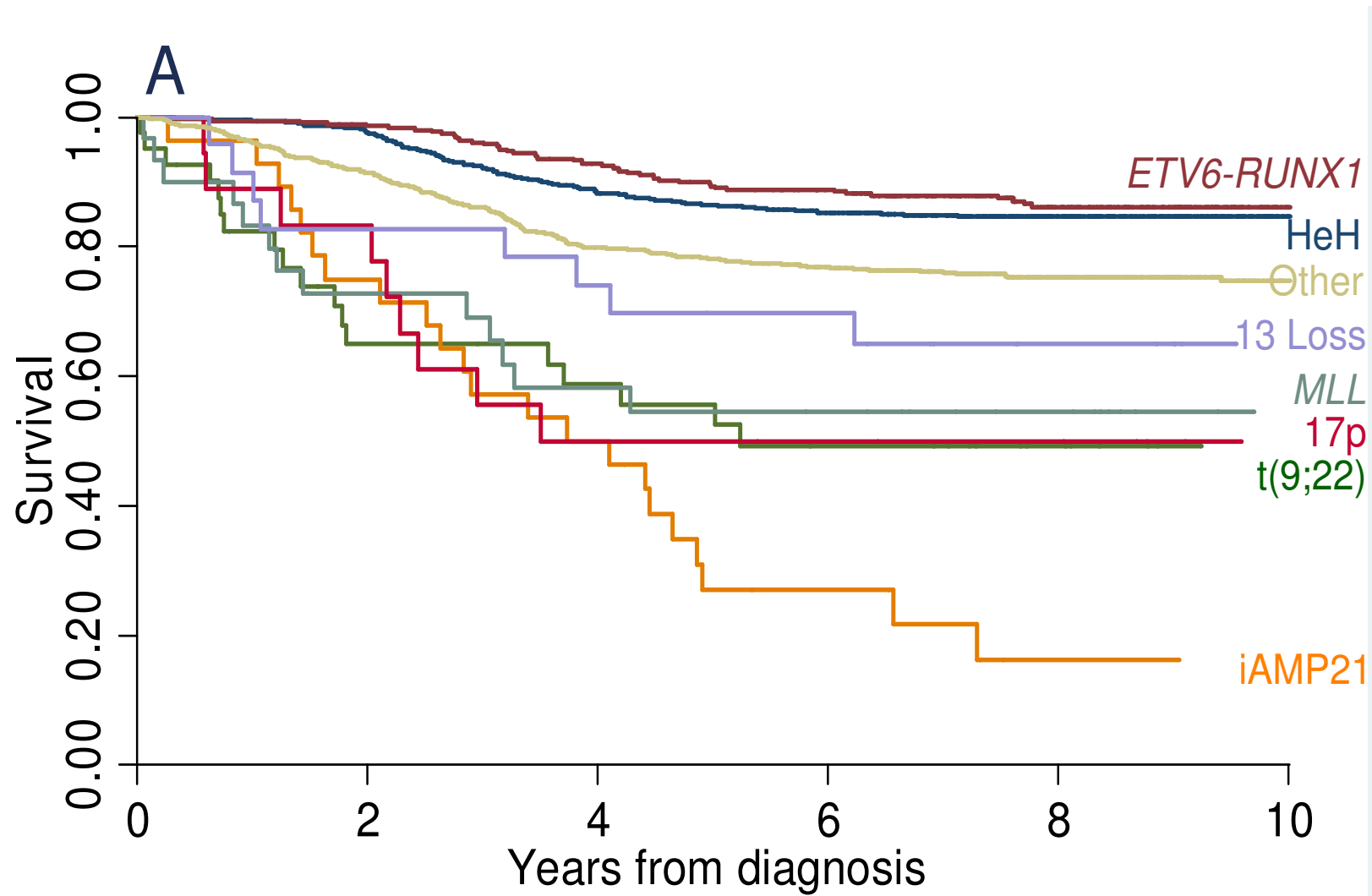
iAMP21 as a specific BCP-ALL subgroup

- Represents 2% of all childhood BCP-ALL

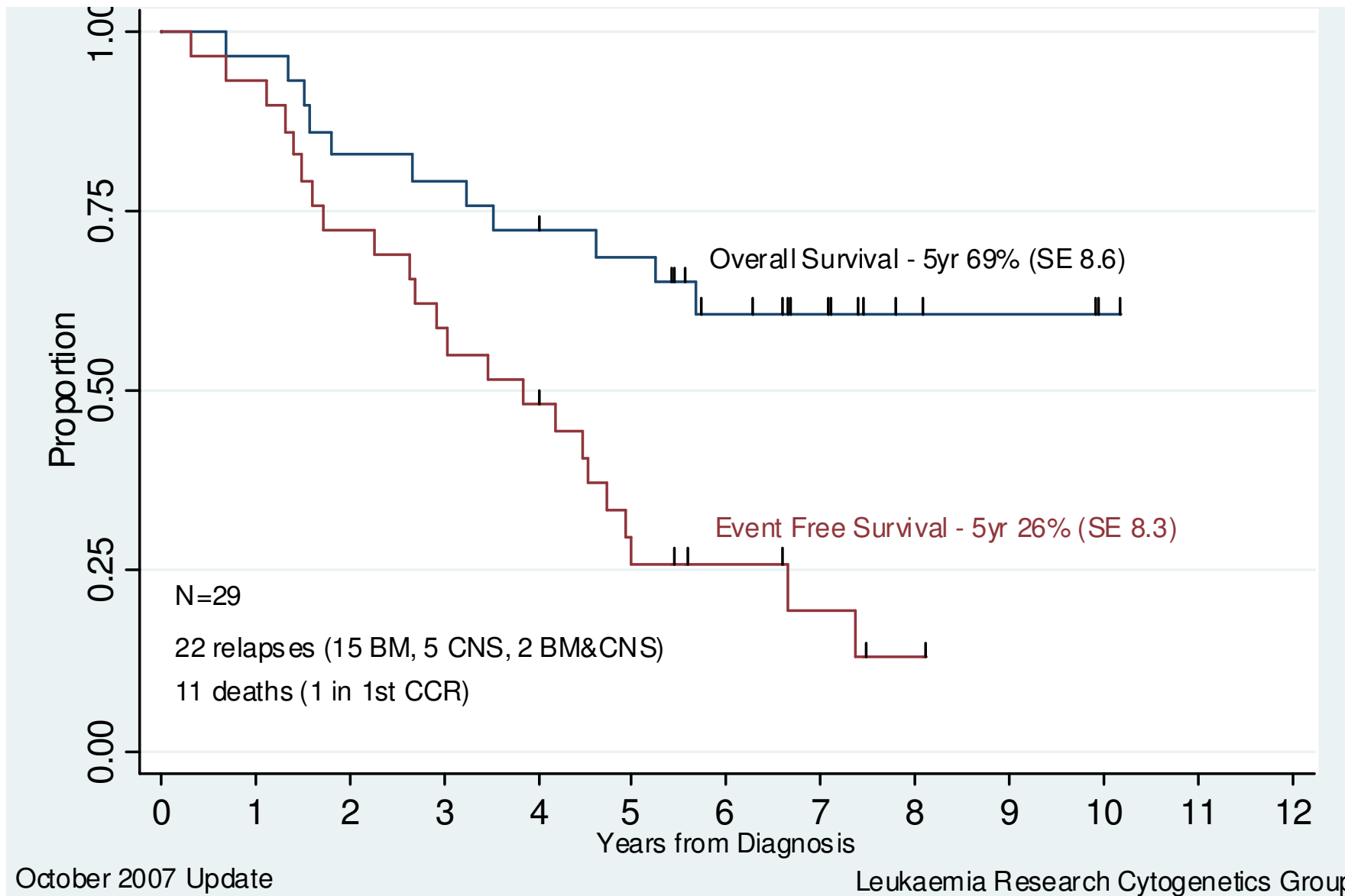


- Tends to arise in older children (9-10 years)
- Associated with low WBC

ALL97: Risk of relapse for iAMP21



Outcome of iAMP21 patients on ALL97



Ongoing studies

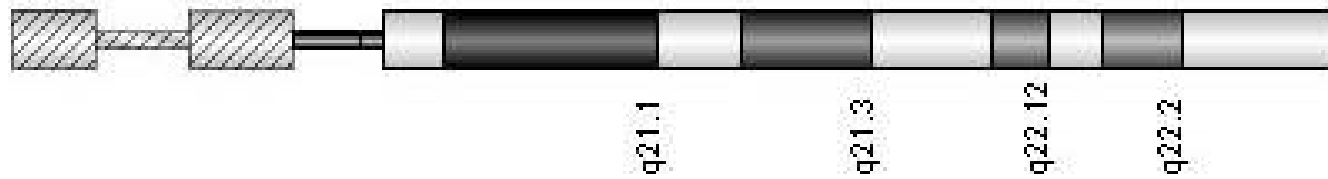
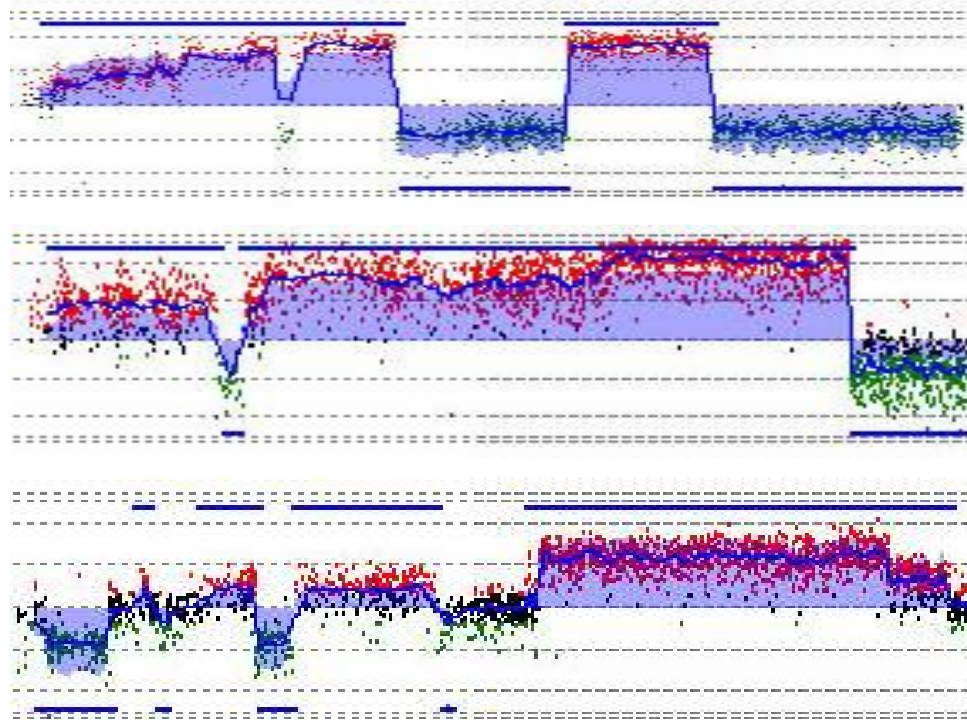
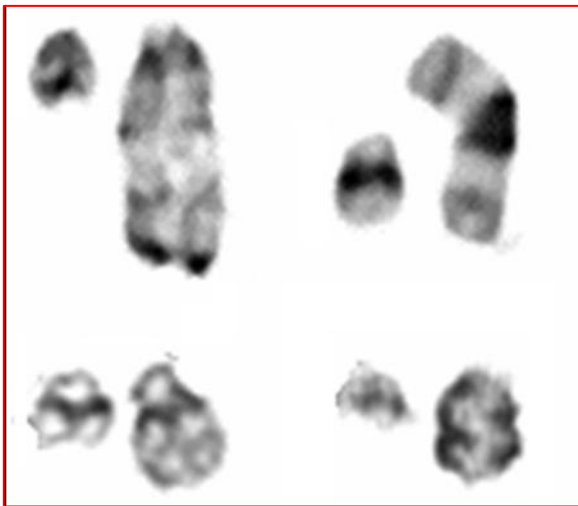
- genomic studies to characterise abnormality using aCGH (n=17) and FISH/MLPA (n=94)
 - identify initiating mechanism
 - co-operating lesions
- collecting new data from UK and international trials (n=307)
 - demographics
 - cytogenetic and FISH data

Key points from our iAMP21 genomic study:

- Complexity of chromosome 21

Complexity of chromosome 21

Each case shows a different pattern of gains and loss

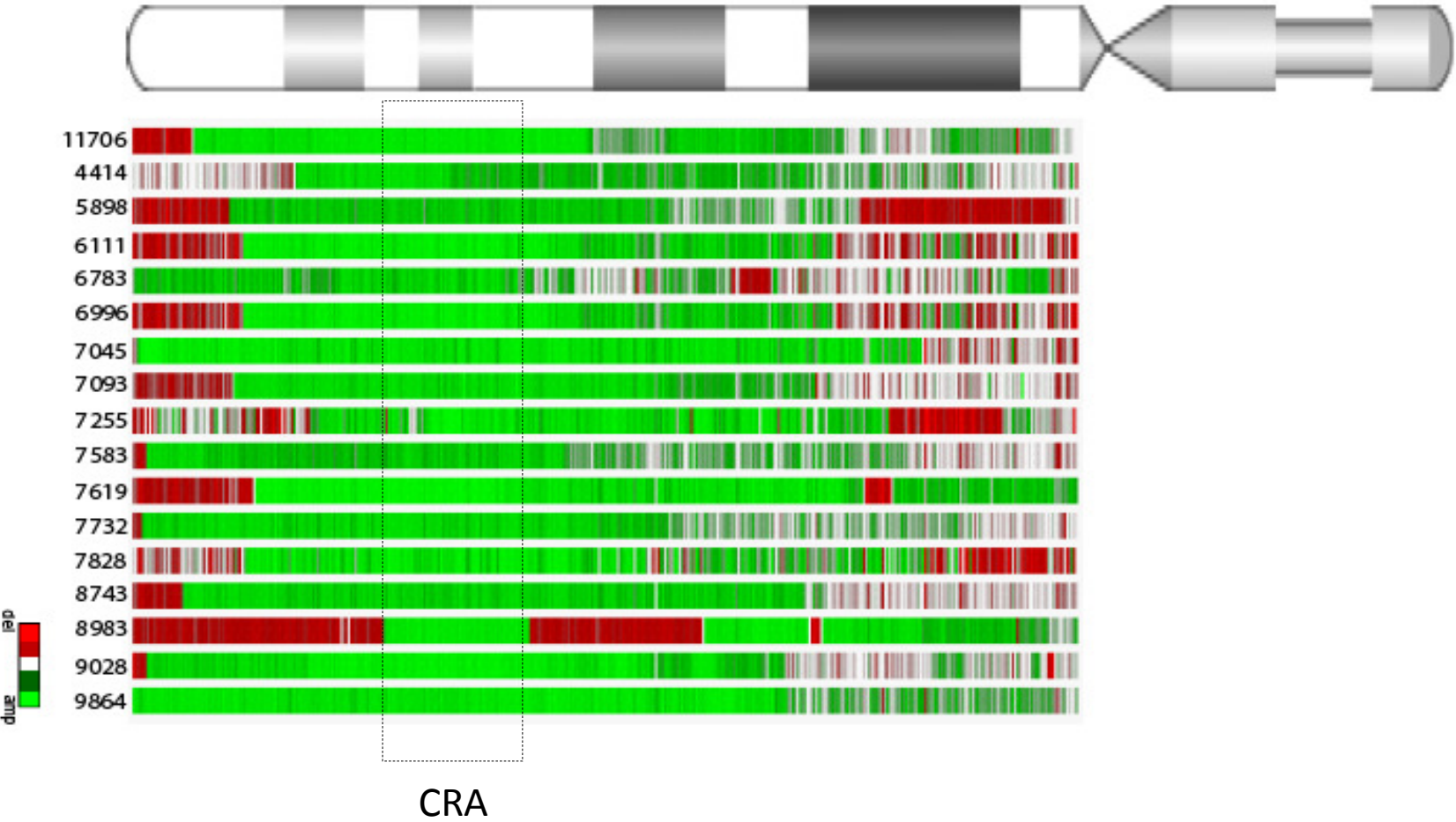


Key points from our iAMP21 genomic study:

- Complexity of chromosome 21
- Common regions of amplification and deletion

Copy number abnormalities of chromosome 21

1. Common region of amplification (CRA): 32,813,553-37,941,484 bp = 5.1Mb



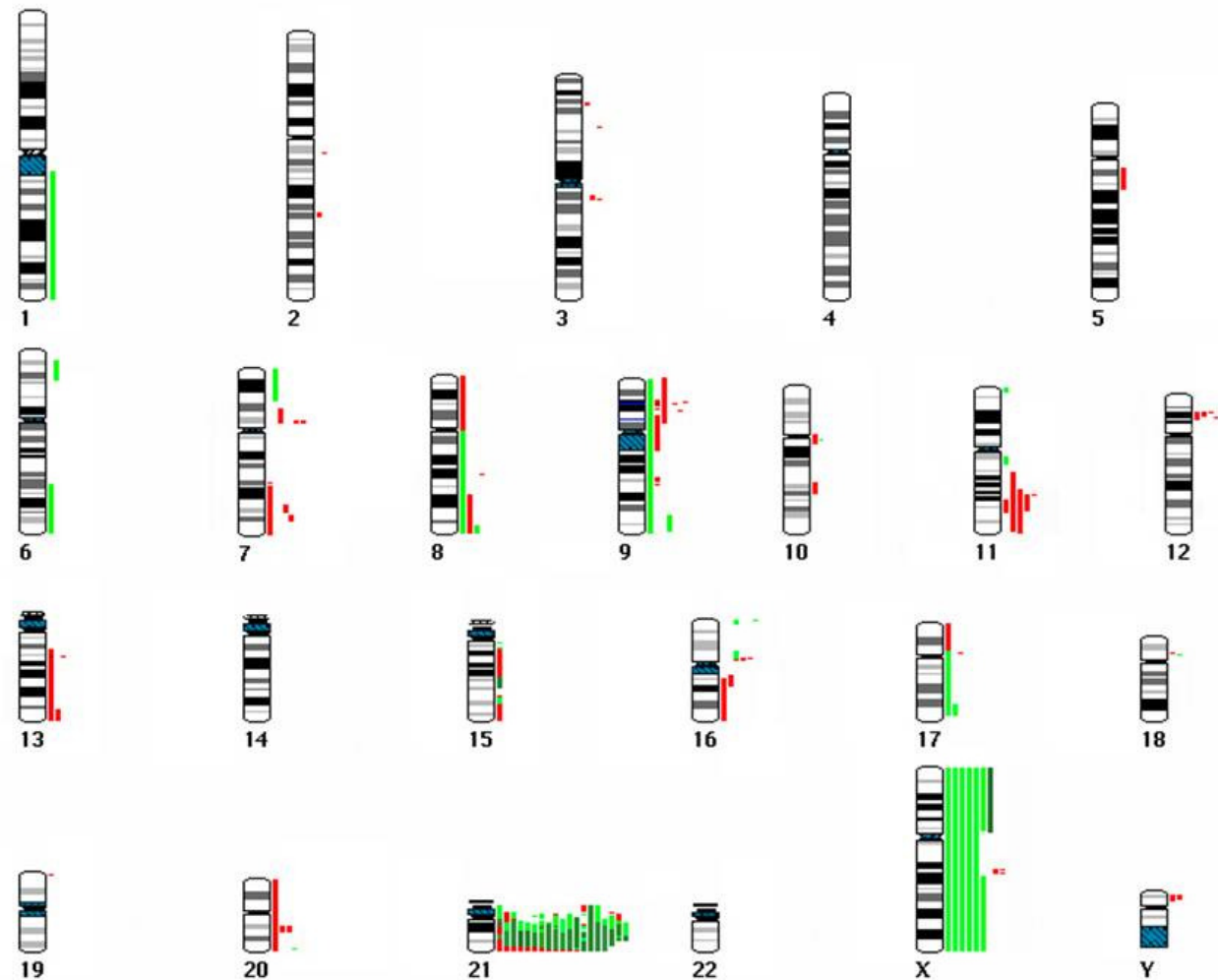
2. Telomeric deletion in most iAMP21 cases

Key points from our iAMP21 genomic study:

- Complexity of chromosome 21
- Common regions of amplification and deletion
- Chromosome instability is restricted to 21

Genome outside chromosome 21

- Relatively quiet genome
- Chromosome instability of 21 only
- Gain of X



Key points from our iAMP21 genomic study:

- Complexity of chromosome 21
- Common regions of amplification and deletion
- Chromosome instability is restricted to 21

Points arising from our data collection:

- 3 cases involving chromosome 15

der(15;21)

- Rare constitutional abnormality
- The frequency of Robertsonian Translocations in an unbiased series of newborns is ~0.1% (Jacobs et al 1992 J Med Gen 29 103-108).
- der(15;21) accounts for 0.5% of all Robertsonian translocations (Gardner & Sutherland)
- Frequency of about 1/100,000

Summary

- We have a huge excess of der(15;21) in our iAMP21 cohort
- Predisposing constitutional abnormality or just coincidence?

Future Studies

- Awaiting SNP6.0 results on all 3 cases
- Material available for whole genome sequencing in collaboration with the Sanger
- Scour the world for more cases
 - One case from Belgium

WATCH THIS SPACE!



Acknowledgements

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All members of the LRCG past and present :

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