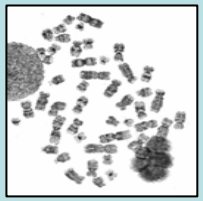
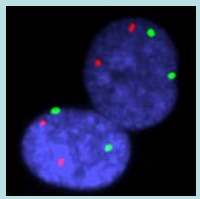
Genetics of Adolescent/Young Adult ALL (Cytogenetics)

Christine J Harrison
Professor of Childhood Cancer Cytogenetics

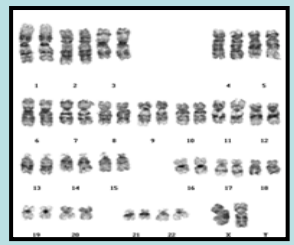
Leukaemia Research Cytogenetics Group

Cytogenetics Group



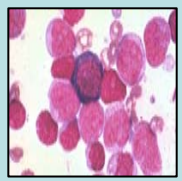


UK Cancer Cytogenetics Group

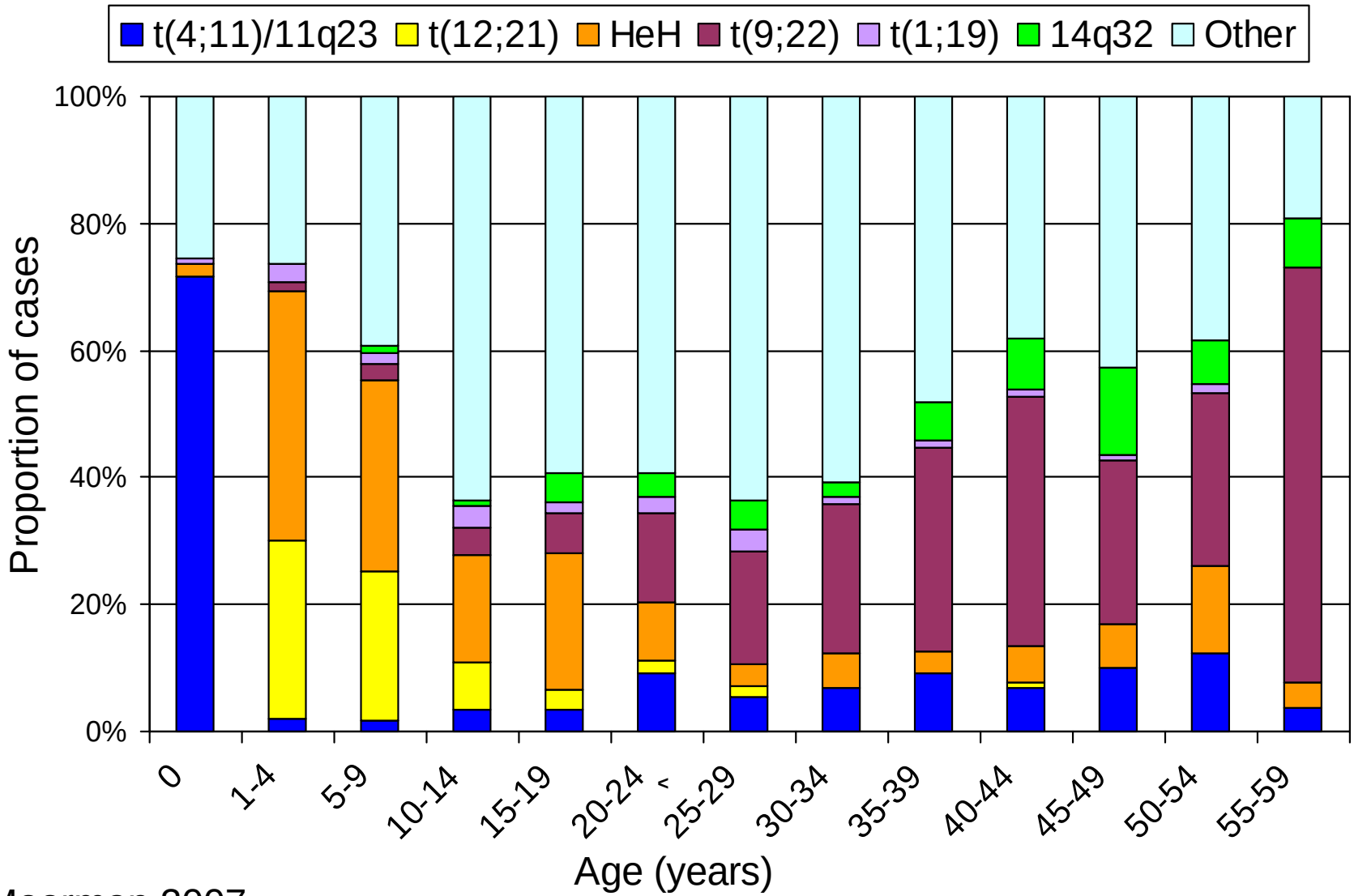


Clinical Trial Service Unit

Clinical Trial Coordinators

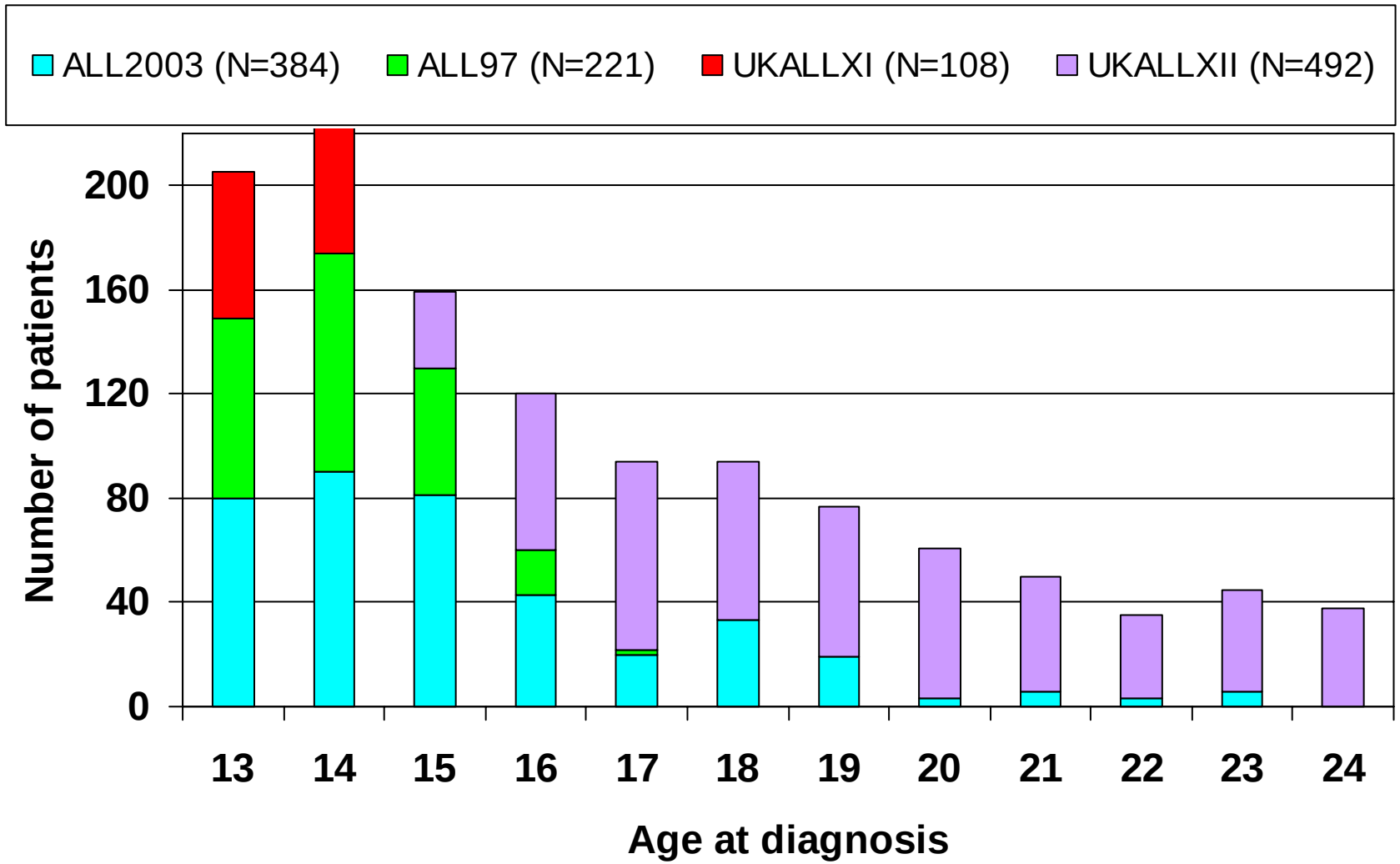


Cytogenetic subgroup by age



Moorman 2007

AYA by Age at Diagnosis and Treatment Trial 1990-present (n=1,205)



Pediatr Blood Cancer 2007;48:254–261

Adolescents With Acute Lymphoblastic Leukaemia: Outcome on UK National Paediatric (ALL97) and Adult (UKALLXII/E2993) Trials

Ramya Ramanujachar, MRCPCH,[1] Sue Richards, PhD,[2] Ian Hann, MD,[1,3] Anthony Goldstone, MD,[4] Christopher Mitchell, PhD,[5] Ajay Vora, MD,[6] Jacob Rowe, MD,[7] and David Webb, MD[3]*

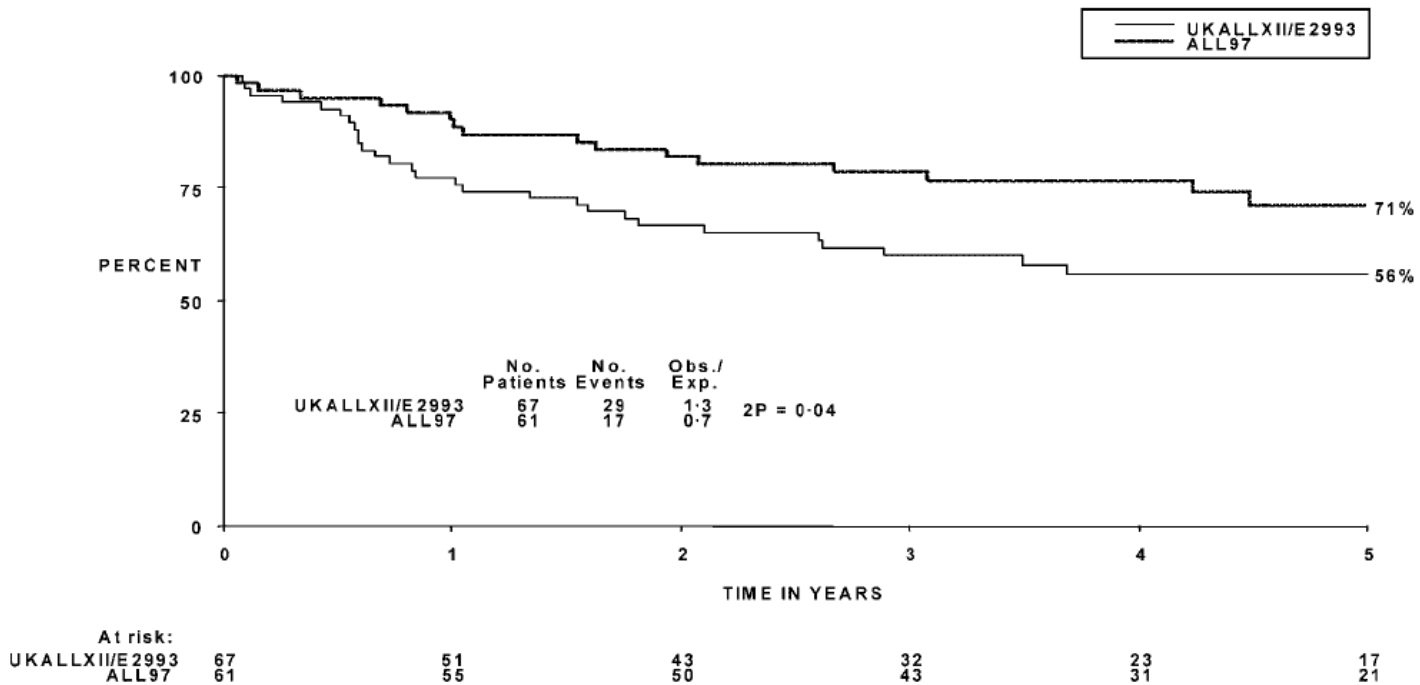


Fig. 1. Overall survival of patients aged 15, 16 and 17 years in the UKALL trials; Abbreviations used: Obs, observed, Exp, expected.

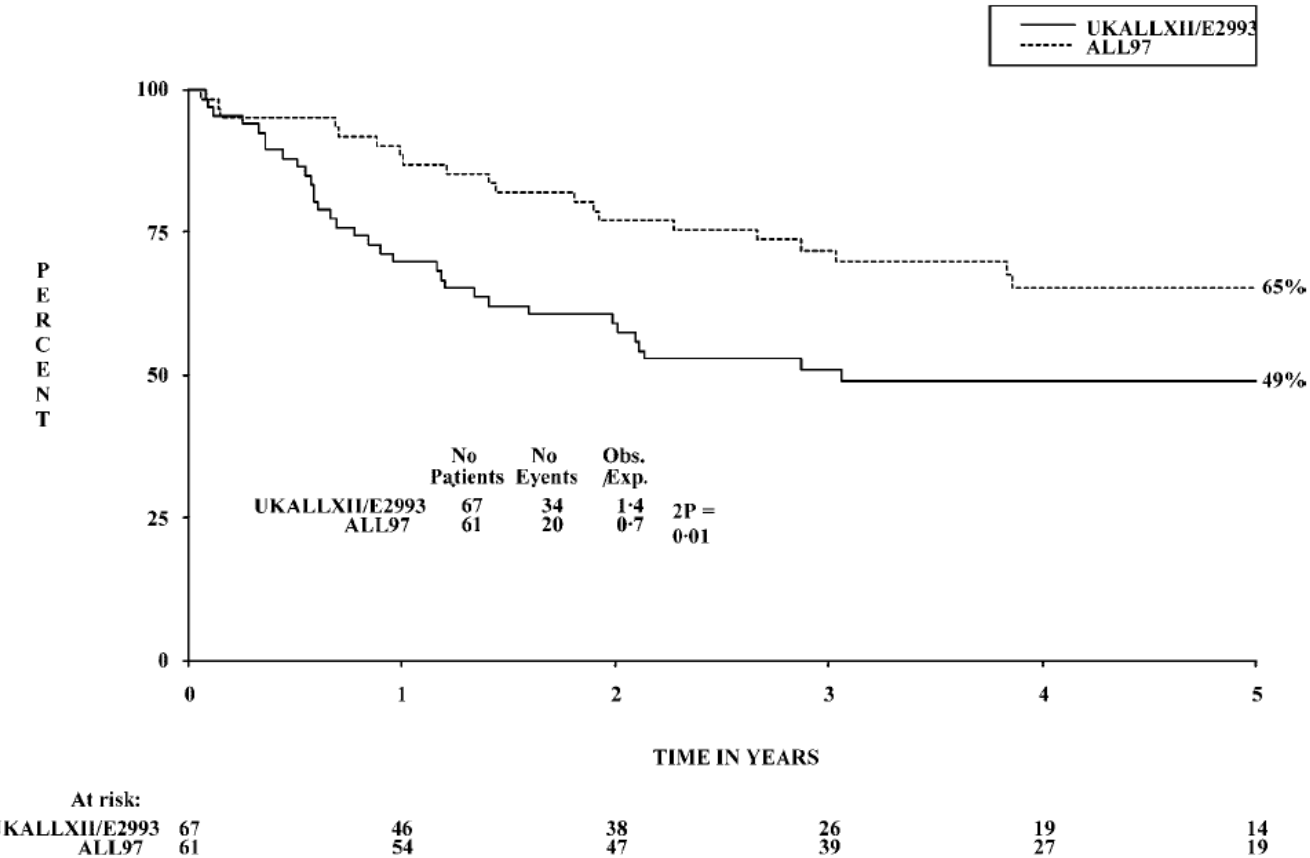
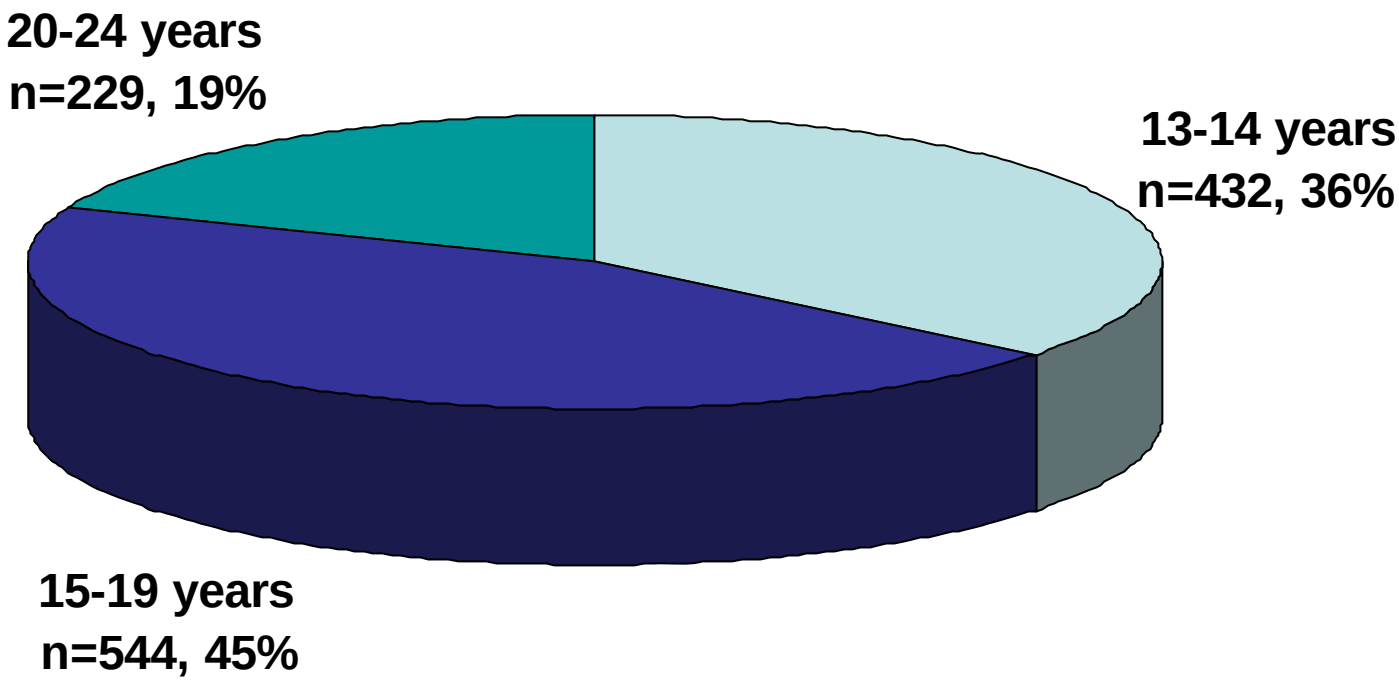
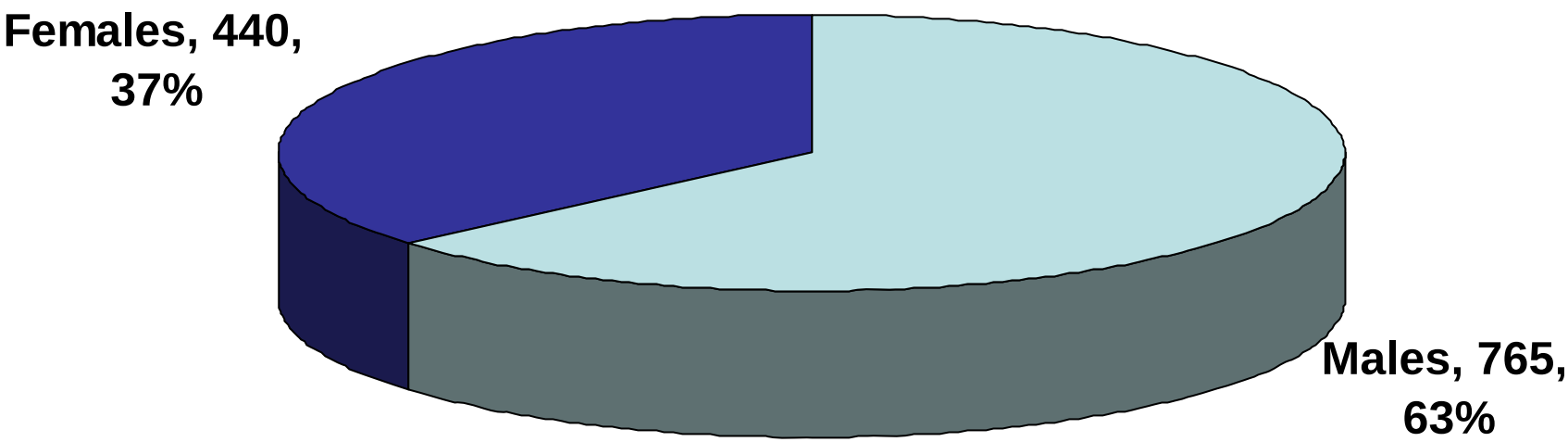


Fig. 2. Event free survival of patients aged 15, 16 and 17 years in the UKALL trials; Abbreviations used: Obs, observed; Exp, expected.

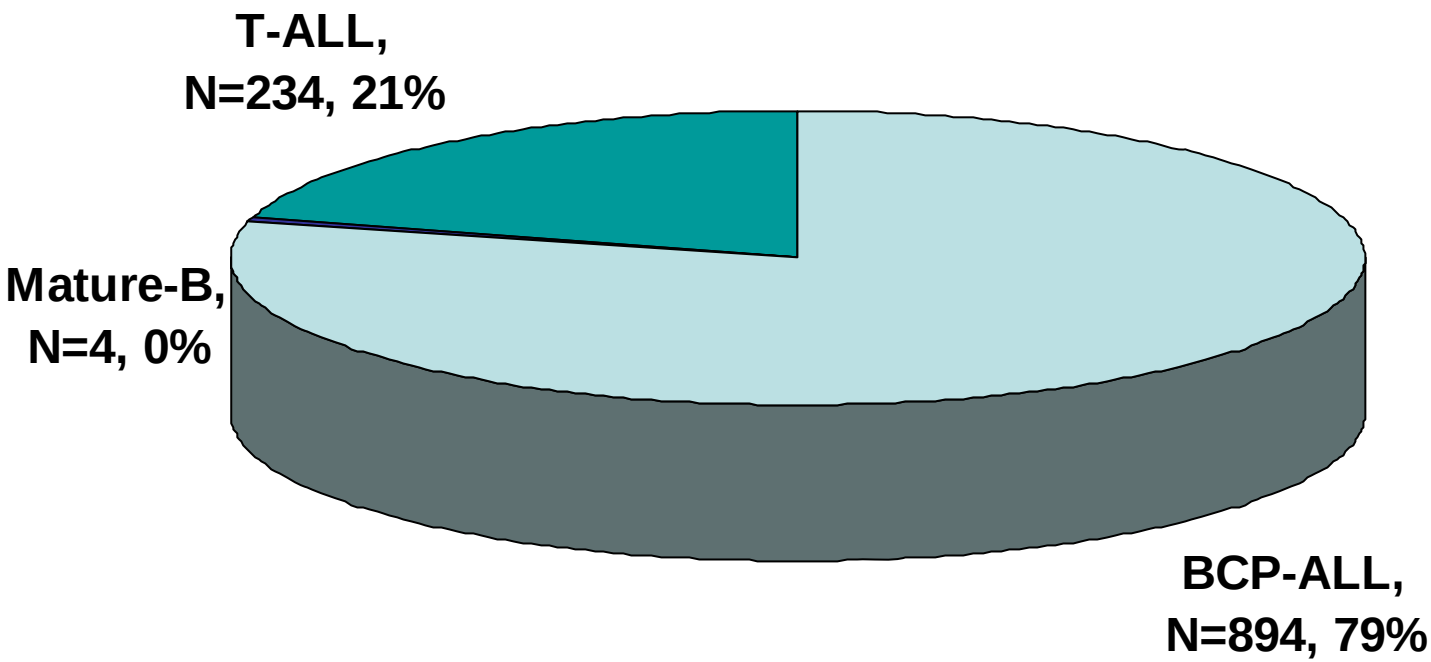
Age groups (n=1,205)



Sex Ratio (1.74M:1F)

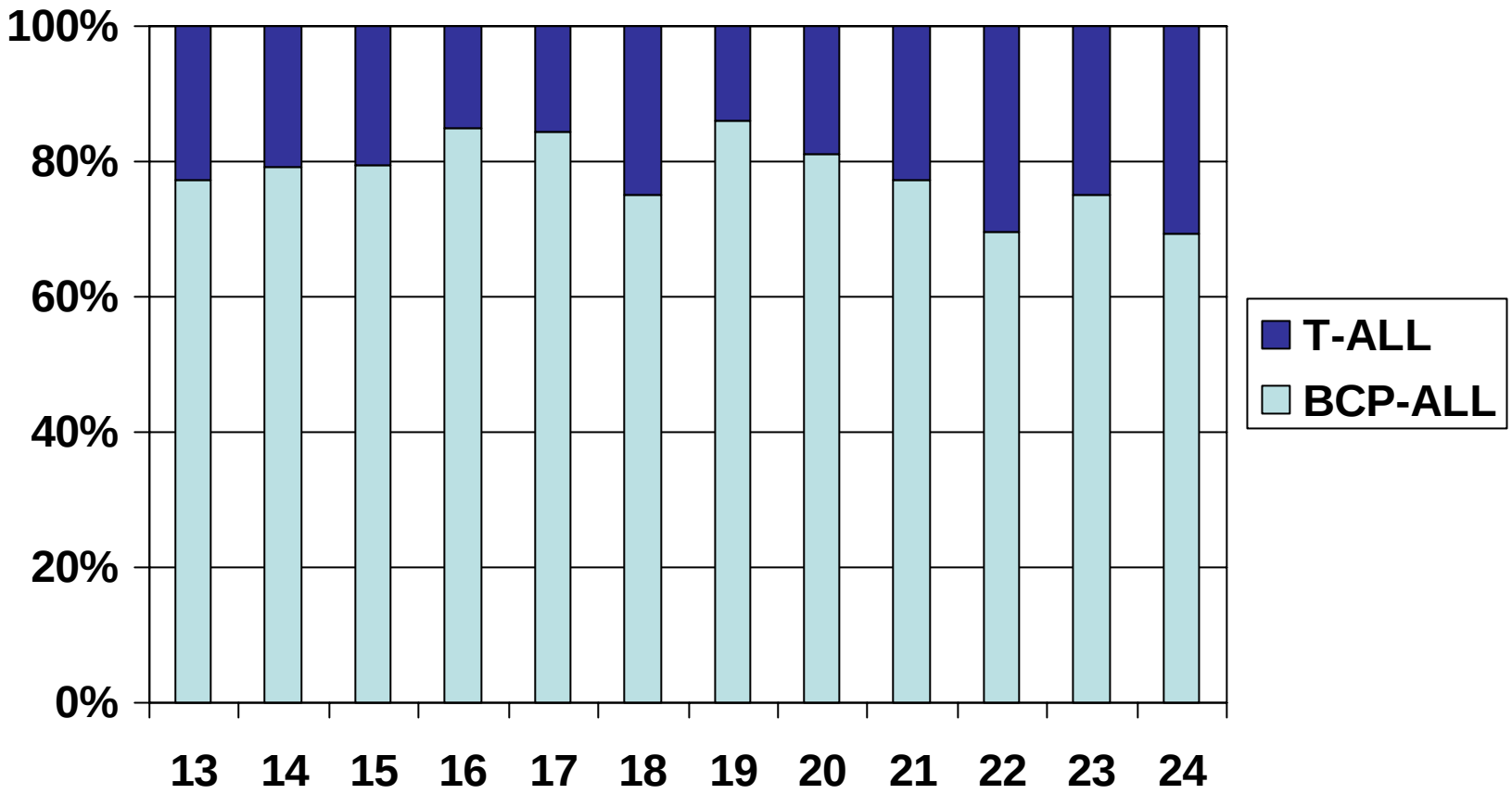


Immunophenotype (n=1,132)



Immunophenotype not known in 73 (6%) cases

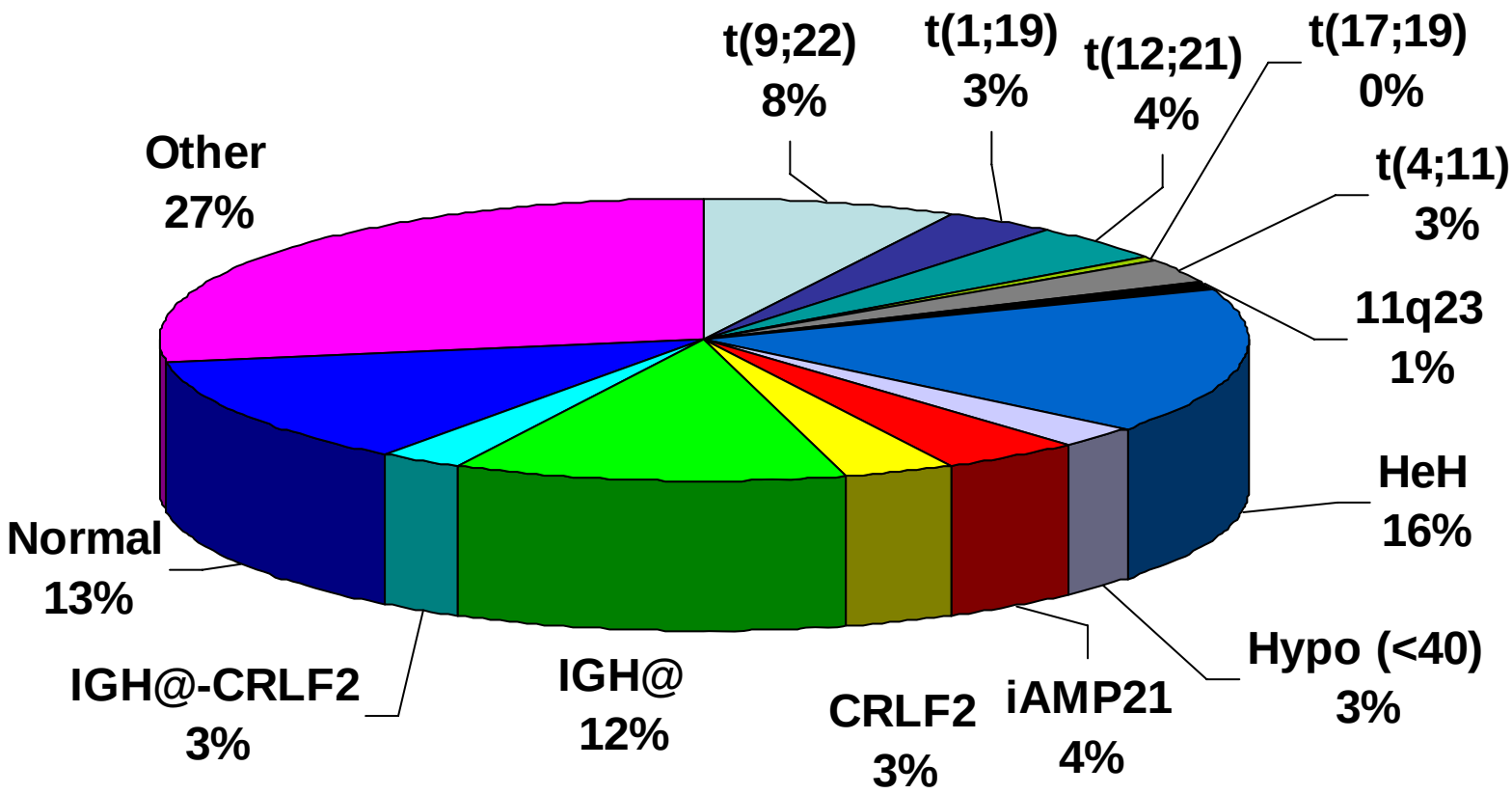
Age-specific incidence of T-ALL



Estimates of the incidence of T-ALL specific abnormalities

Abnormality	**Incidence**		
	Children	**AYA**	**Adults**
SIL-TAL1/t(1;14)	22%	16%	9%
t(11;14)(p13;q11)/*LMO2*	12%	2%	0%
t(10;14)/*TLX1* (*HOX11*)	2%	4%	24%
t(5;14)/*TLX3* (*HOX11L2*)	17%	11%	6%
CALM-AF10	2%	8%	0%
CDKN2A/B	51%	46%	44%
MLL	4%	5%	0%
NUP214-ABL1	2%	3%	3%

Cytogenetics of BCP-ALL in 13-24 year olds (n=837)



Estimates of the incidence of BCP-ALL specific abnormalities

Abnormality	No. Positive	No. Tested	Incidence	<13 years	>24 years
t(9;22)	68	781	9%	2%	20%
t(1;19)	27	696	4%	3-5%	3-5%
t(12;21)	25	531	5%	25%	<1%
t(17;19)	4	696	<1%	<1%	<1%
t(4;11)	27	780	4%	2%	5-10%
11q23	6	780	1%	2%	2%
HeH	149	754	20%	35%	10%
Hypo (<40)	23	754	3%	1%	5%
iAMP21	26	531	5%	<2%	<2%
IGH@	31	216	14%	3%	15%
IGH@-CRLF2	8	284	3%	<1%	~5%
CRLF2	5	115	4%	~5%	?
Normal	102	696	15%		
Other	227	696	33%		

4 cases had iAMP21 plus CRLF2 and 2 cases had iAMP21 plus an IGH translocation

“Others”

Total n=227

- Abnormal 9p ~50%
- +21 ~4%
- +8 ~4%
- +5 ~4%

Cancer Genetics and Cytogenetics 148 (2004) 159–162

Short communication

Is trisomy 5 a distinct cytogenetic subgroup in acute lymphoblastic leukemia?

Rachel L. Harris, Christine J. Harrison, Mary Martineau, Kerry E. Taylor, Anthony V. Moorman*

Table 1
Clinical, survival, cytogenetic and FISH data for seven patients with ALL and trisomy 5

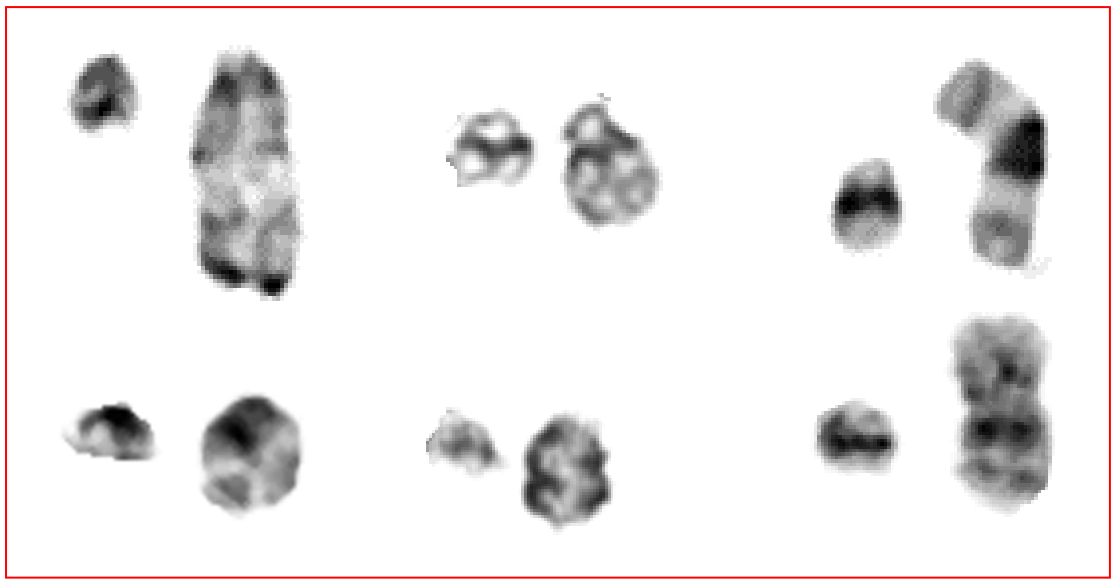
Case no.	Age (yr)/ Sex	Diagnosis	WBC ($\times 10^9$/L)	Time from diagnosis to 1st Rel (mo)	Time from diagnosis to 2nd Rel (mo)	Overall survival (mo)	Karyotype	Interphase FISH *TEL-AML1*	Interphase FISH *BCR-ABL*	Interphase FISH *MLL*
3112	7/M	Com/pre-B ALL	88.0	43	—	55+	47,XY,+5[9]/46,XY[1].ish +5(wcp5+)	Neg	Neg	Neg
1642	9/M	Com ALL	13.3	—	—	82+	47,XY,+5[5]/46,XY[3].ish +5(wcp5+)	—	—	—
2955	10/M	Com/pre-B ALL	5.3	33	—	33+	47,XY,+5[20]	Neg	Neg	Neg
1323	14/M	Com ALL	19.0	38	50	52	47,XY,+5[6]/46,XY[4]	—	—	—
3209	14/M	Com/pre-B ALL	1.4	—	—	53+	46,X,−Y,+5[6]/46,XY[8]	Neg	Neg	Neg
4765	27/M	Pre-B ALL	17.6	—	—	14+	47,XY,+5[6]/46,XY[7]	—	Neg	—
2478	31/F	Com ALL	7.4	37	41	43	47,XX,+5[3]/47,XX,+8[4]/ 46,XX[2]	—	—	—

The common/pre-B immunophenotype was $CD10^+$, $CD19^+$; cytoplasmic μ-chain was not tested.
Abbreviations: Com, common; Neg, negative; Rel, relapse; WBC, white blood cell count.

Duplication of chromosome 21
involving amplification of *RUNX1*

Intrachromosomal amplification of chromosome 21

iAMP21



Leukemia (2003) 17, 547–553

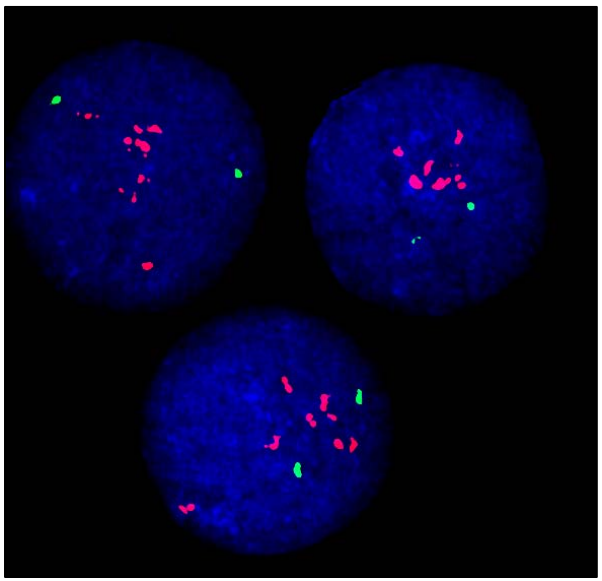
www.nature.com/leu

Amplification of *AML1* on a duplicated chromosome 21 in acute lymphoblastic leukemia: a study of 20 cases

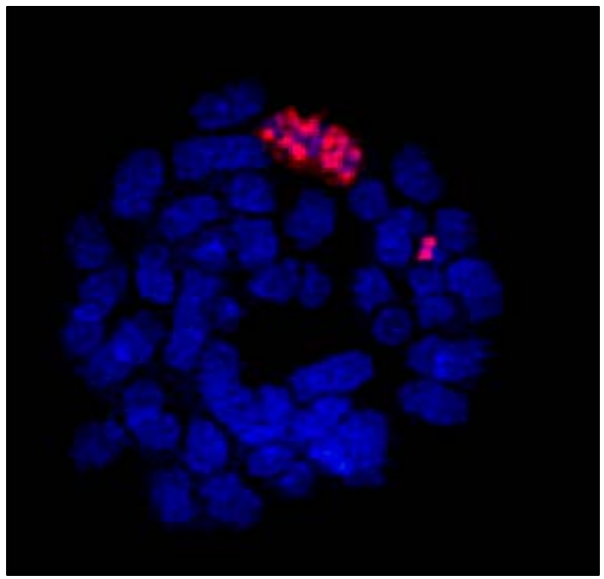
L Harewood[1,4], H Robinson[1], R Harris[1], M Jabbar Al-Obaidi[1], GR Jalali[1], M Martineau[1], AV Moorman[1], N Sumption[1], S Richards[2], C Mitchell[3] and CJ Harrison[1] on behalf of the Medical Research Council Childhood and Adult Leukaemia Working Parties

[1]*Leukaemia Research Fund Cytogenetics Group, Cancer Sciences Division, University of Southampton, Southampton, UK;* [2]*Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK; and* [3]*Paediatric Oncology, John Radcliffe Hospital, Oxford, UK*

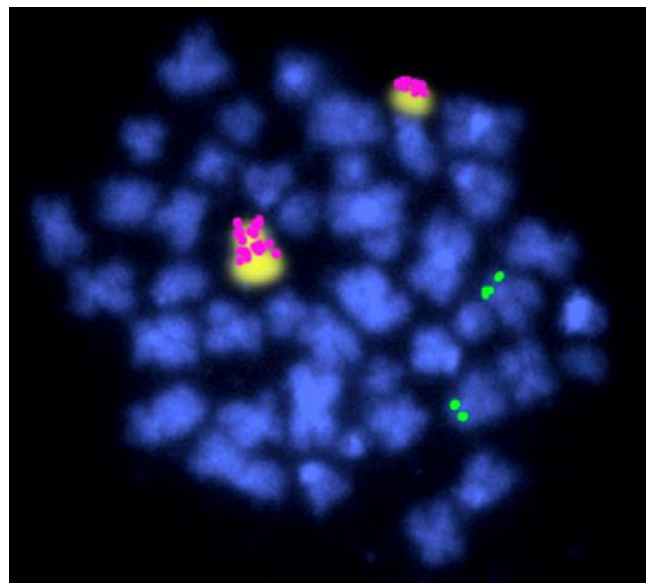
Interphase FISH



Metaphase FISH



Metaphase FISH



Amplification of band q22 of chromosome 21, including *AML1*, in older children with acute lymphoblastic leukemia: an emerging molecular cytogenetic subgroup

Leukemia (2003) 17, 1679–1682. doi:10.1038/sj.leu.2403000

TO THE EDITOR

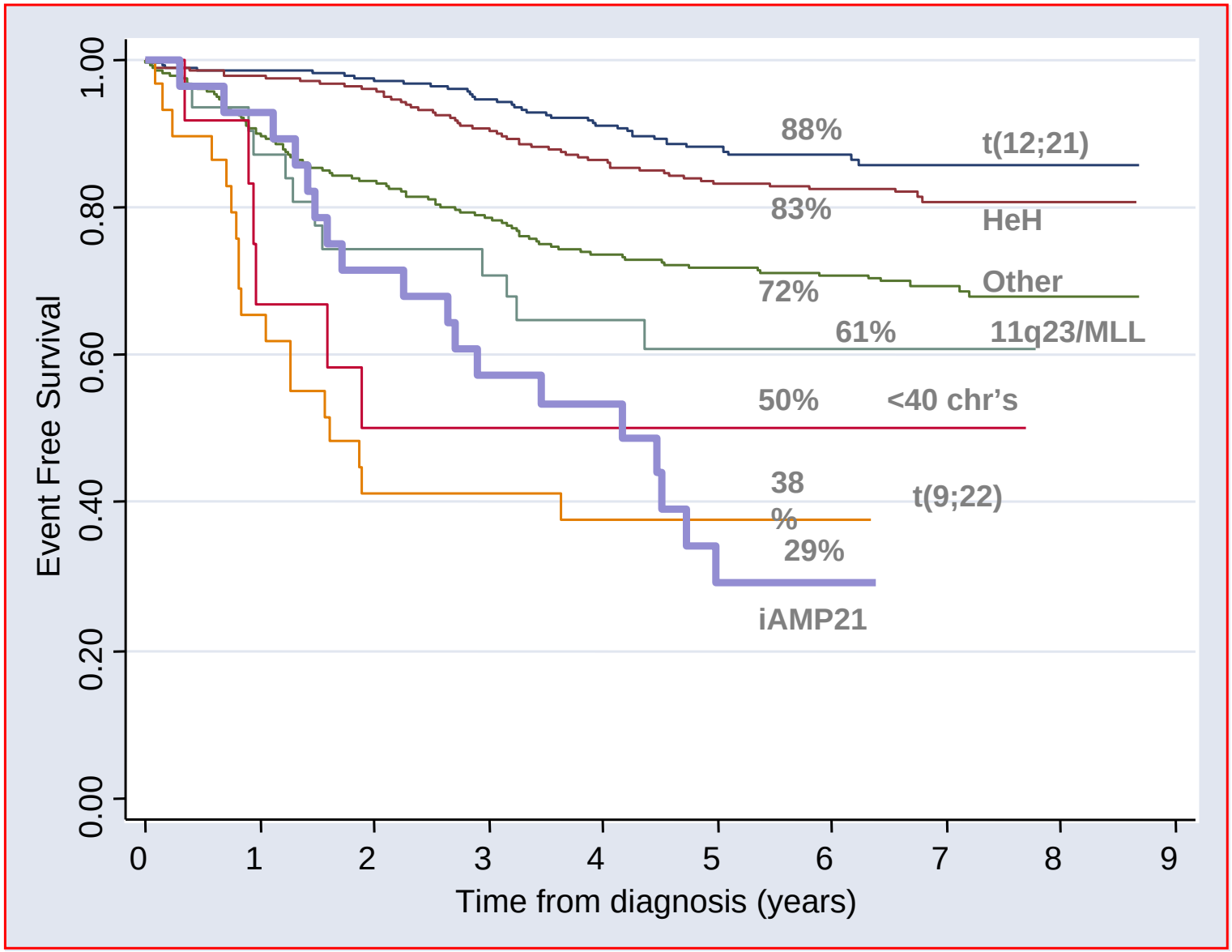
J Soulier[1]
L Trakhtenbrot[2]
V Najfeld[3]
JM Lipton[3]
S Mathew[4]
H Avet-Loiseau[5]
M De Braekeleer[6]
S Salem[7]
A Baruchel[1]
SC Raimondi[8]
SD Raynaud[7]

[1]*Centre Hospitalier Universitaire (CHU) Saint Louis, AP-HP, Paris, France;*
[2]*The Chaim Sheba Medical Center, Tel-Hashomer, Israel;*
[3]*The Mount Sinai Medical Center, New York, NY, USA;*
[4]*New York Presbyterian Hospital-Cornell Campus Cornell University Weill Medical College, New York, NY, USA;*
[5]*CHU Nantes, France;*
[6]*CHU Brest, France;*
[7]*CHU Nice, France;*
[8]*Jude Children's Research Hospital, Memphis, TN, USA*

Demographic Profile of iAMP21 patients

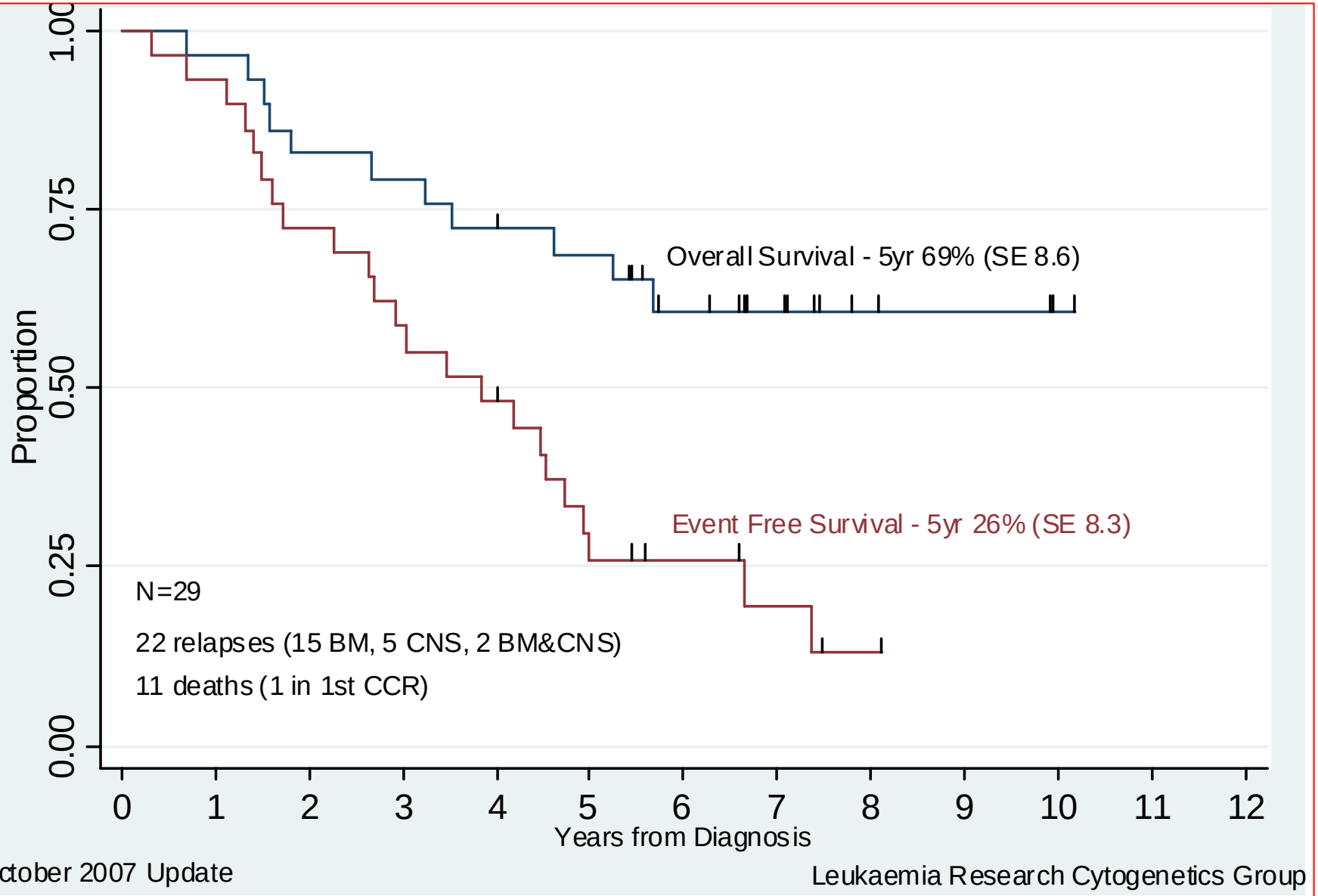
- Older children/Adolescents
  - Median age 10 years
- Common/Pre-B immunophenotype
- Low WBC

EFS of 28 iAMP21 patients on MRC ALL97



Moorman et al (2007) Blood 109:2327

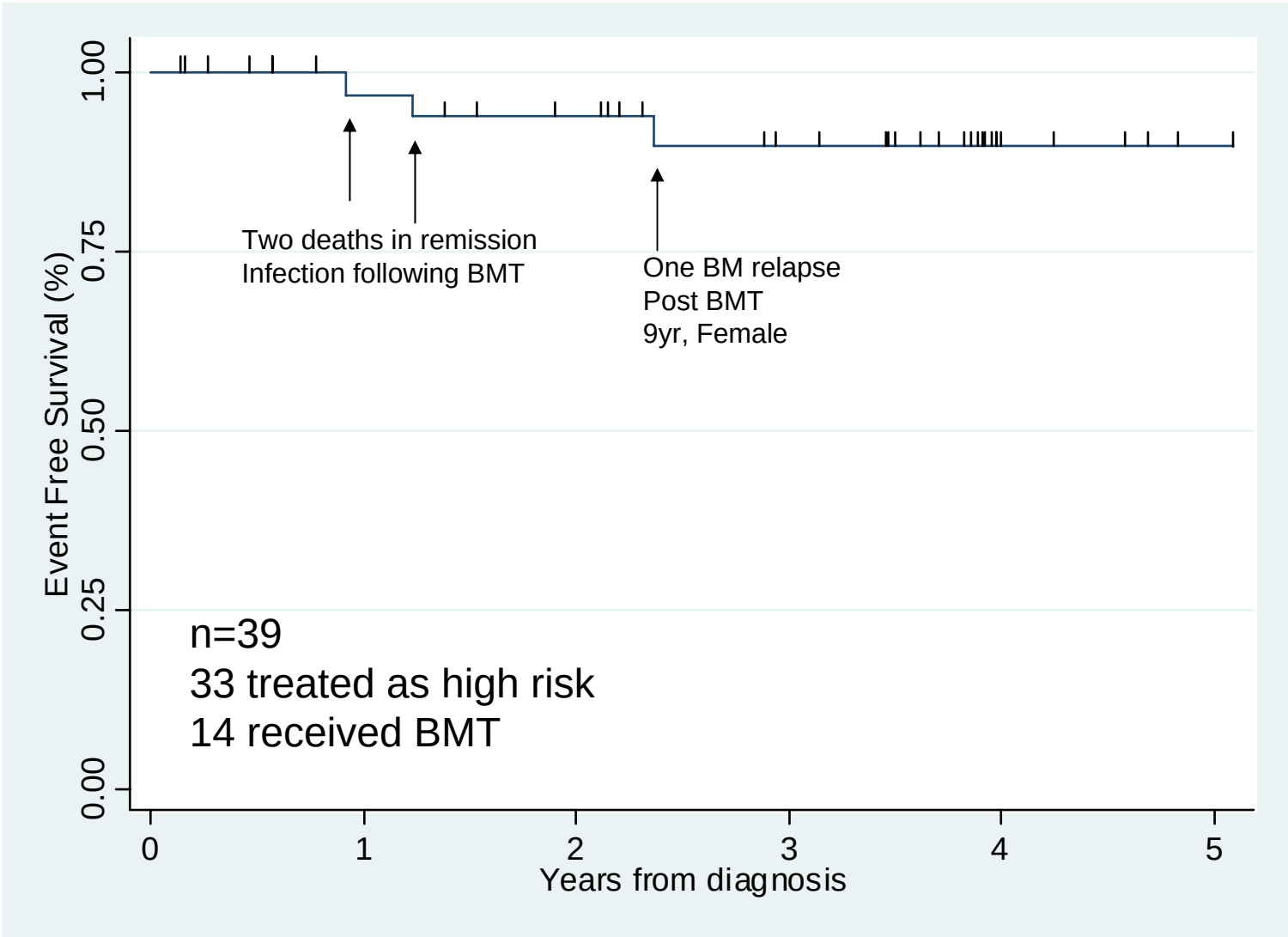
Outcome of iAMP21 patients on MRC ALL97



Decision

To treat iAMP21 patients as high-risk
in the current childhood trial: ALL2003

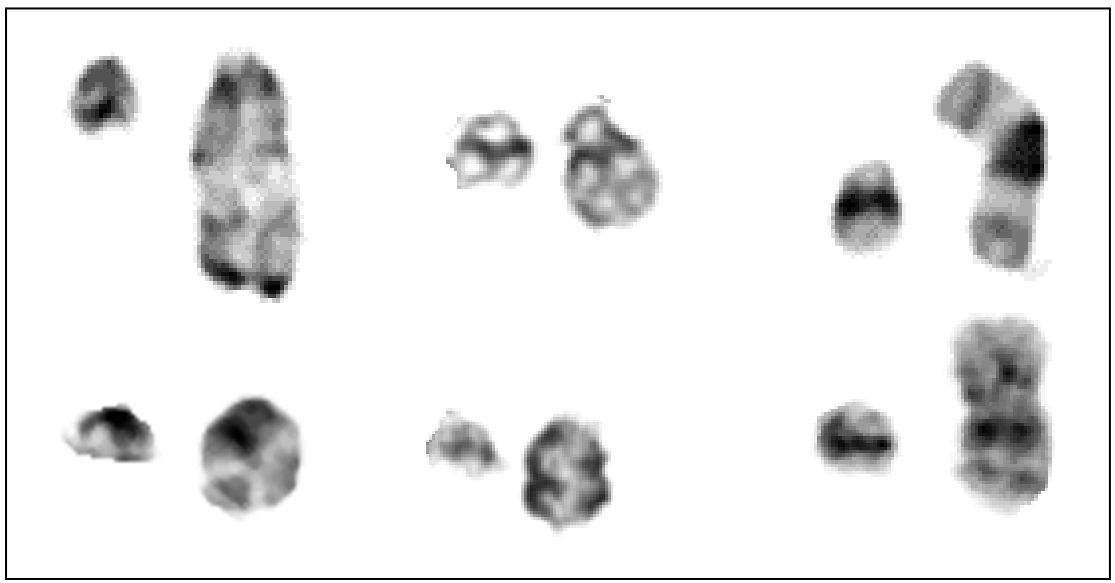
iAMP21: outcome in ALL2003



iAMP21

Duplication of chromosome 21 involving amplification of *RUNX1*

Every abnormal chromosome 21 has a different morphology

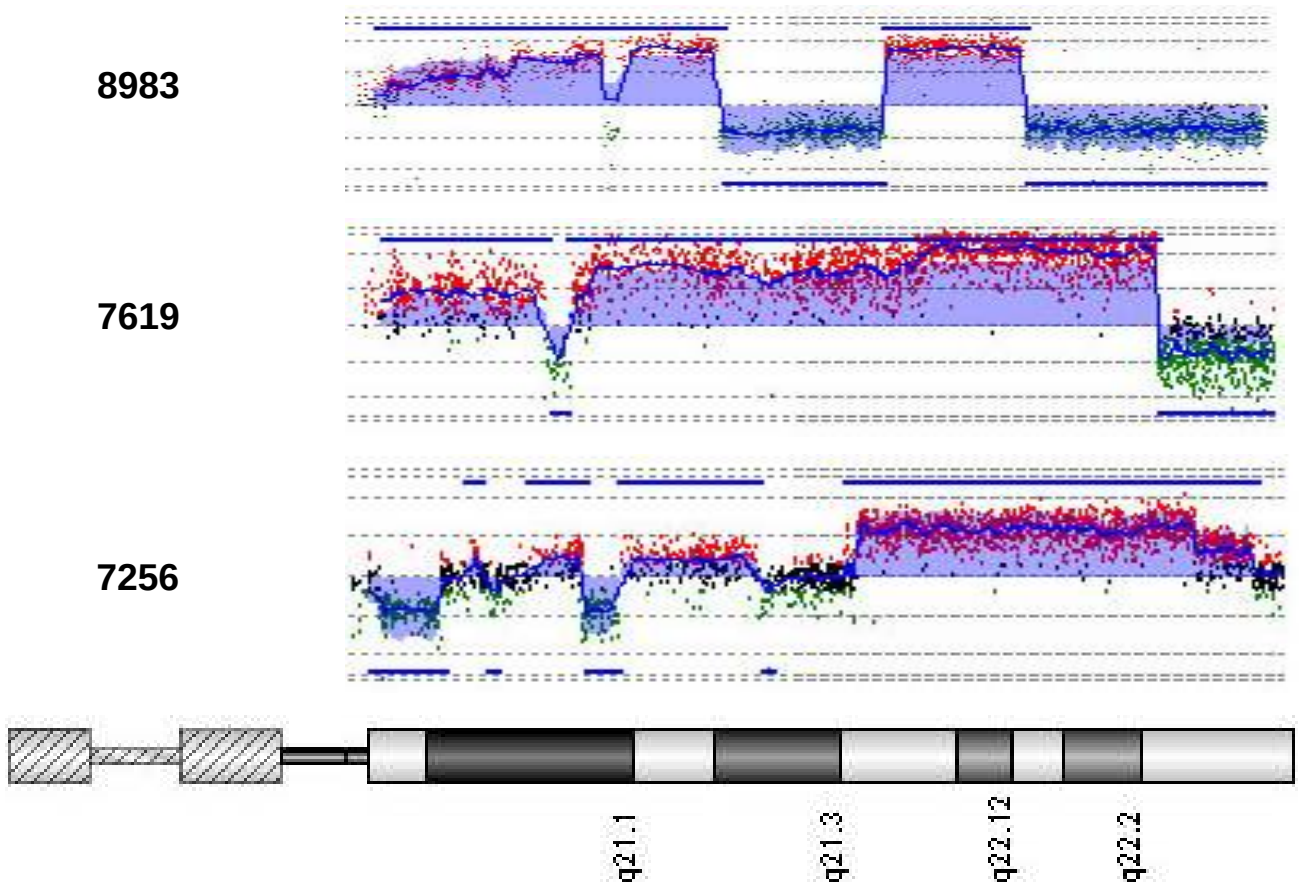


PNAS

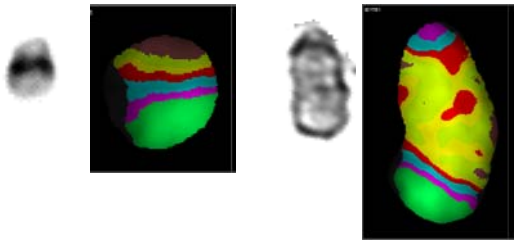
Complex genomic alterations and gene expression in acute lymphoblastic leukemia with intrachromosomal amplification of chromosome 21

Jon C. Strefford*†¶, Frederik W. van Delft†¶, Hazel M. Robinson*, Helen Worley*, Olga Yiannikouris‖¶, Rebecca Selzer‖, Todd Richmond‖, Ian Hann**, Tony Bellotti††, Manoj Raghavan¶, Bryan D. Young¶, Vaskar Saha†¶, and Christine J. Harrison*†

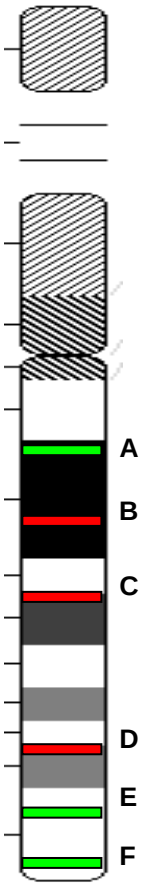
*Leukaemia Research Cytogenetics Group, Cancer Sciences Division, University of Southampton, Southampton SO16 6YD, United Kingdom; †Cancer Research UK Children's Cancer Group and ¶Medical Oncology Unit, Institute of Cancer, Queen Mary University of London, London ET 4NS, United Kingdom; ‖NimbleGen Systems, Inc., Madison, WI 53711; **Department of Haematology, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, United Kingdom; and ††Computer Learning Research Centre, Royal Holloway, University of London, Egham, Surrey TW20 0EX, United Kingdom



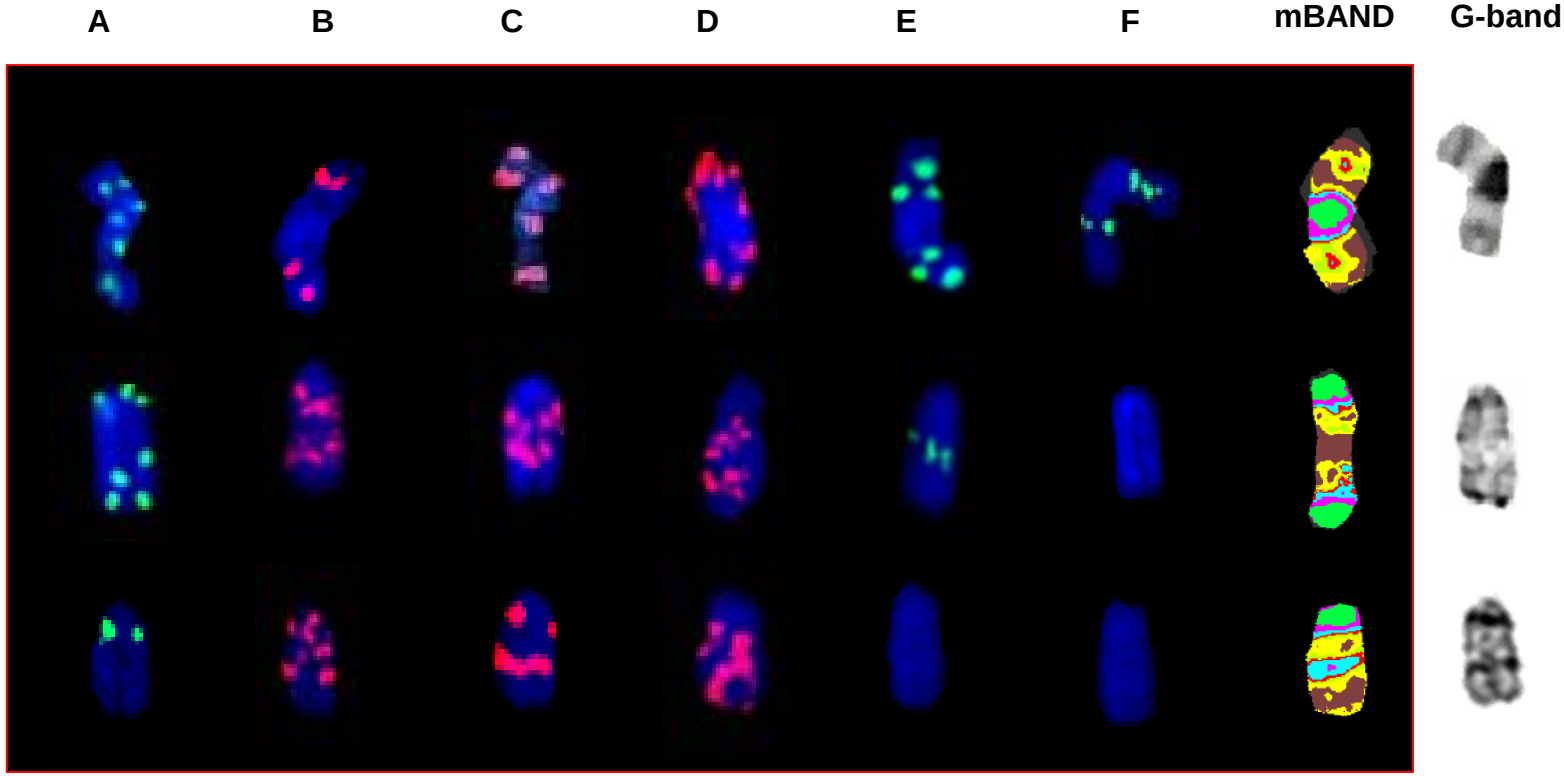
G banding



mBANDING

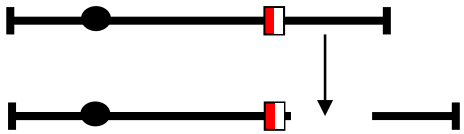


BAC Probes



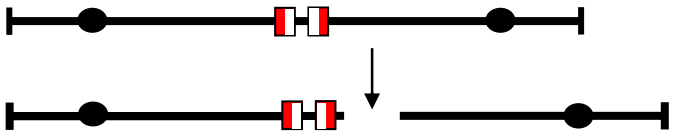
Robinson *et al* (2007) Genes Chromosomes Cancer **46**:318-26

The Breakage-Fusion-Bridge cycle

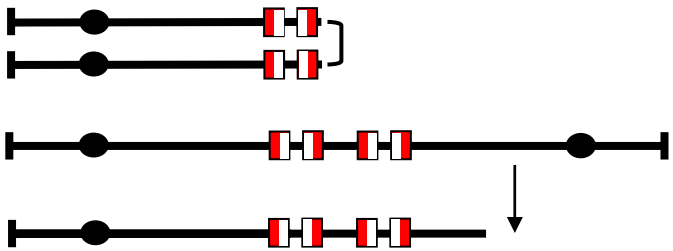


A double-strand DNA break results in loss of a telomere and the formation of an unstable chromosome

Following replication the two sister chromatids fuse to form a dicentric chromosome



During anaphase this dicentric pulls apart resulting in breakage of the fusion bridge and production of an unstable chromosome with an inverted repeat



This process is repeated until the chromosome becomes stabilised by gaining a telomere. In this way it is possible to generate a chromosome with ladder like amplification.

KEY

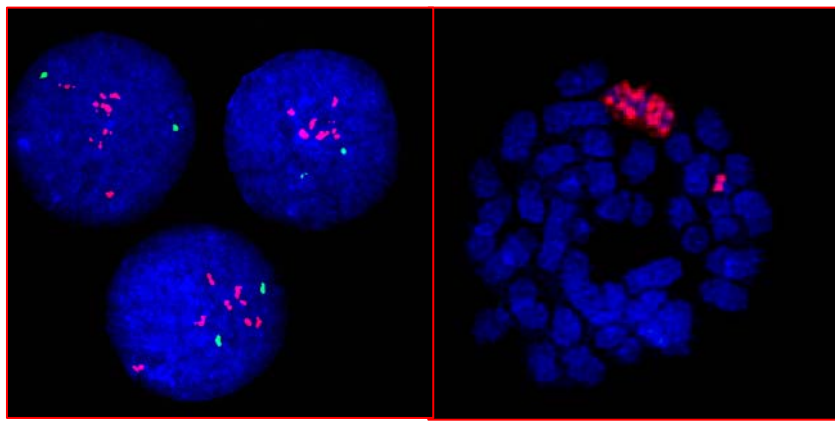
Telomere

Centromere

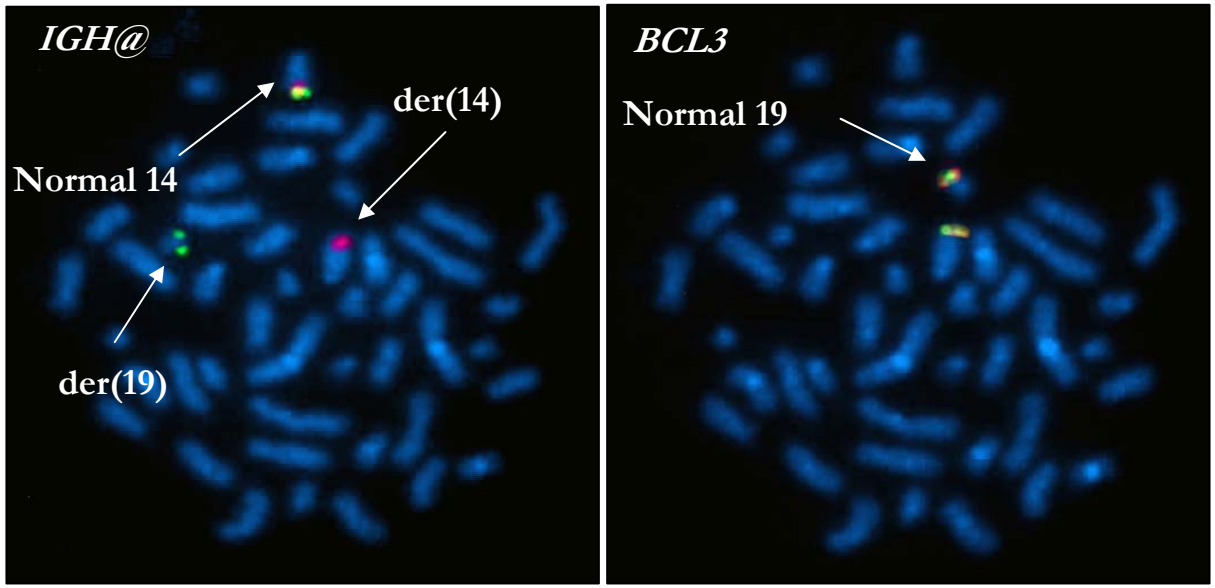
RUNX1

iAMP21

- iAMP21 defines a distinct patient subgroup of older children/young adults with a poor prognosis
- Chromosomal instability gives rise to complex intrachromosomal rearrangements of chromosome 21
- Genome wide they show the same abnormalities of B-cell differentiation genes
- No obvious differentially expressed genes
- Studies are in progress to determine the initiating mechanism
- Currently FISH with probes directed to *RUNX1* is the only reliable diagnostic method



IGH@ translocations in BCP-ALL



GENES, CHROMOSOMES & CANCER 39:88–92 (2004)

BRIEF COMMUNICATION

t(14;19)(q32;q13): A Recurrent Translocation in B-Cell Precursor Acute Lymphoblastic Leukemia

Hazel M. Robinson, Kerry E. Taylor, G. Reza Jalali, Kan Luk Cheung, Christine J. Harrison, and Anthony V. Moorman*

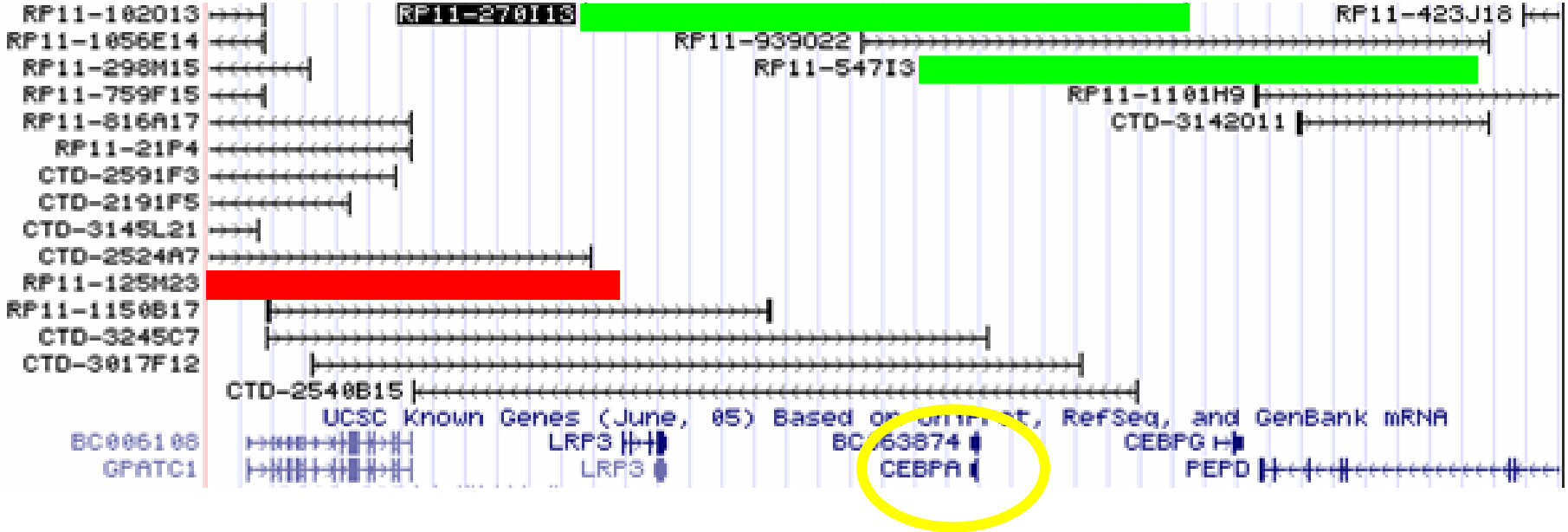
Leukaemia Research Fund Cytogenetics Group, Cancer Sciences Division, University of Southampton, Southampton, UK

blood

2006 108: 3560-3563
Prepublished online Jul 27, 2006;
doi:10.1182/blood-2006-03-010835

Overexpression of CEBPA resulting from the translocation t(14;19)(q32;q13) of human precursor B acute lymphoblastic leukemia

Elise Chapiro, Lisa Russell, Isabelle Radford-Weiss, Christian Bastard, Michel Lessard, Stephanie Struski, Helene Cave, Sandra Fert-Ferrer, Carole Barin, Odile Maarek, Veronique Della-Valle, Jonathan C. Strefford, Roland Berger, Christine J. Harrison, Olivier A. Bernard, Florence Nguyen-Khac and the Groupe Francophone de Cytogénétique Hématologique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RP11-298M15
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CTD-3245C7
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RP11-939022
RP11-547I3
RP11-1101H9
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UCSC Known Genes (June, 05) Based on Unigene, RefSeq, and GenBank mRNA
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LRP3
LRP3
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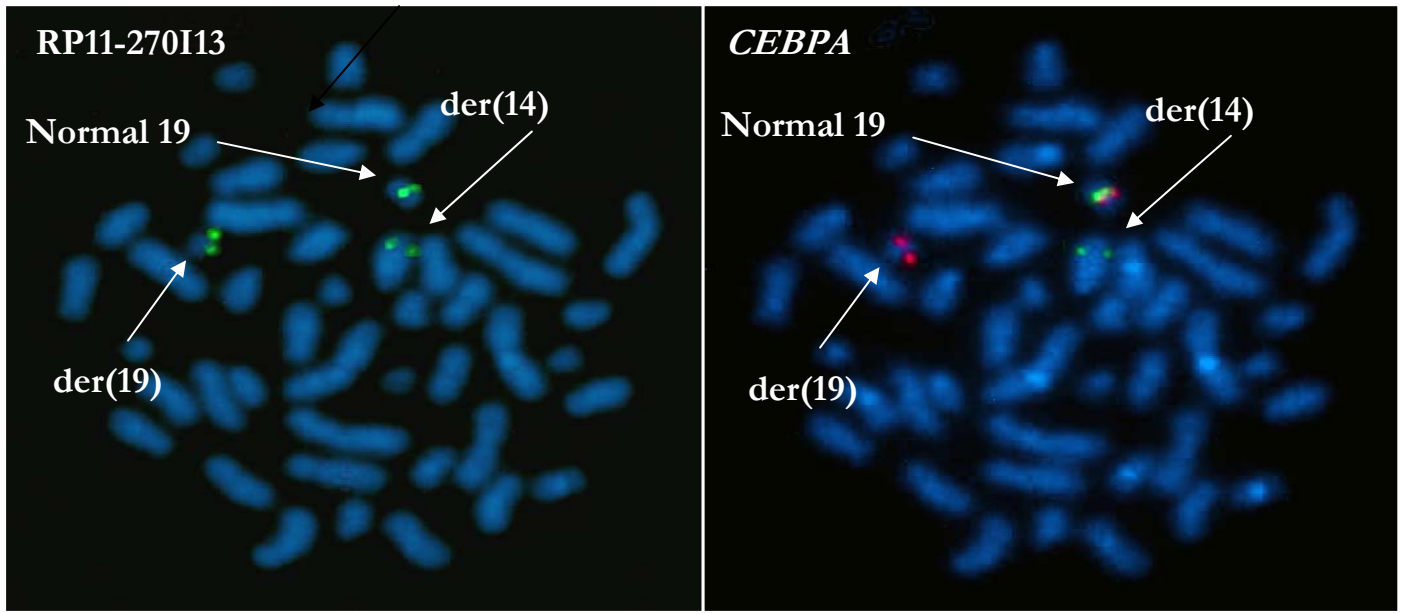
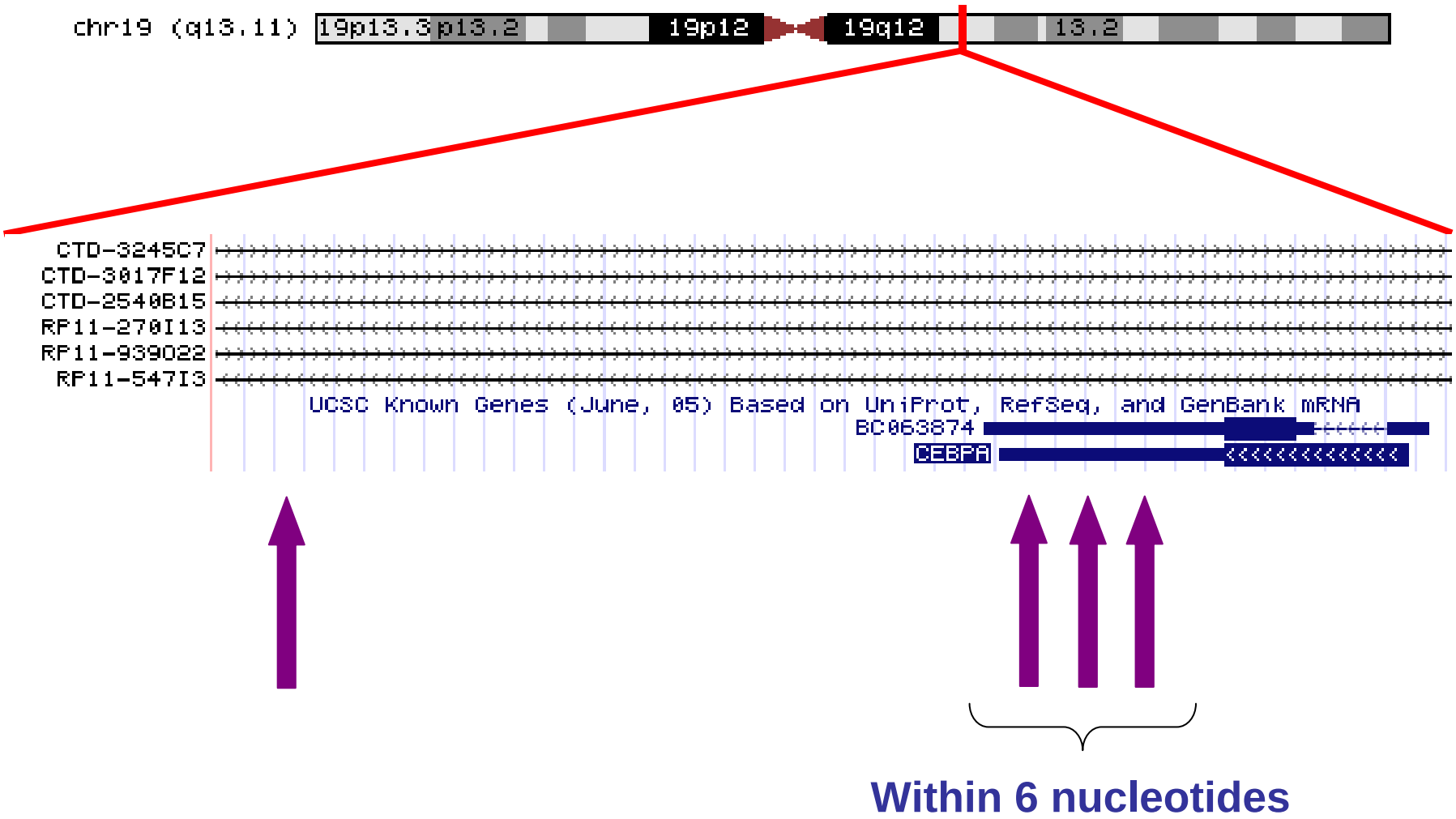
CEBPA
CEBPG
PEPD


RP11-270I13
Normal 19
der(14)
der(19)
CEBPA
Normal 19
der(14)
der(19)

IGH@-CEBP family



Within 6 nucleotides

blood

2007 109: 3451-3461
Prepublished online Dec 14, 2006;
doi:10.1182/blood-2006-08-041012

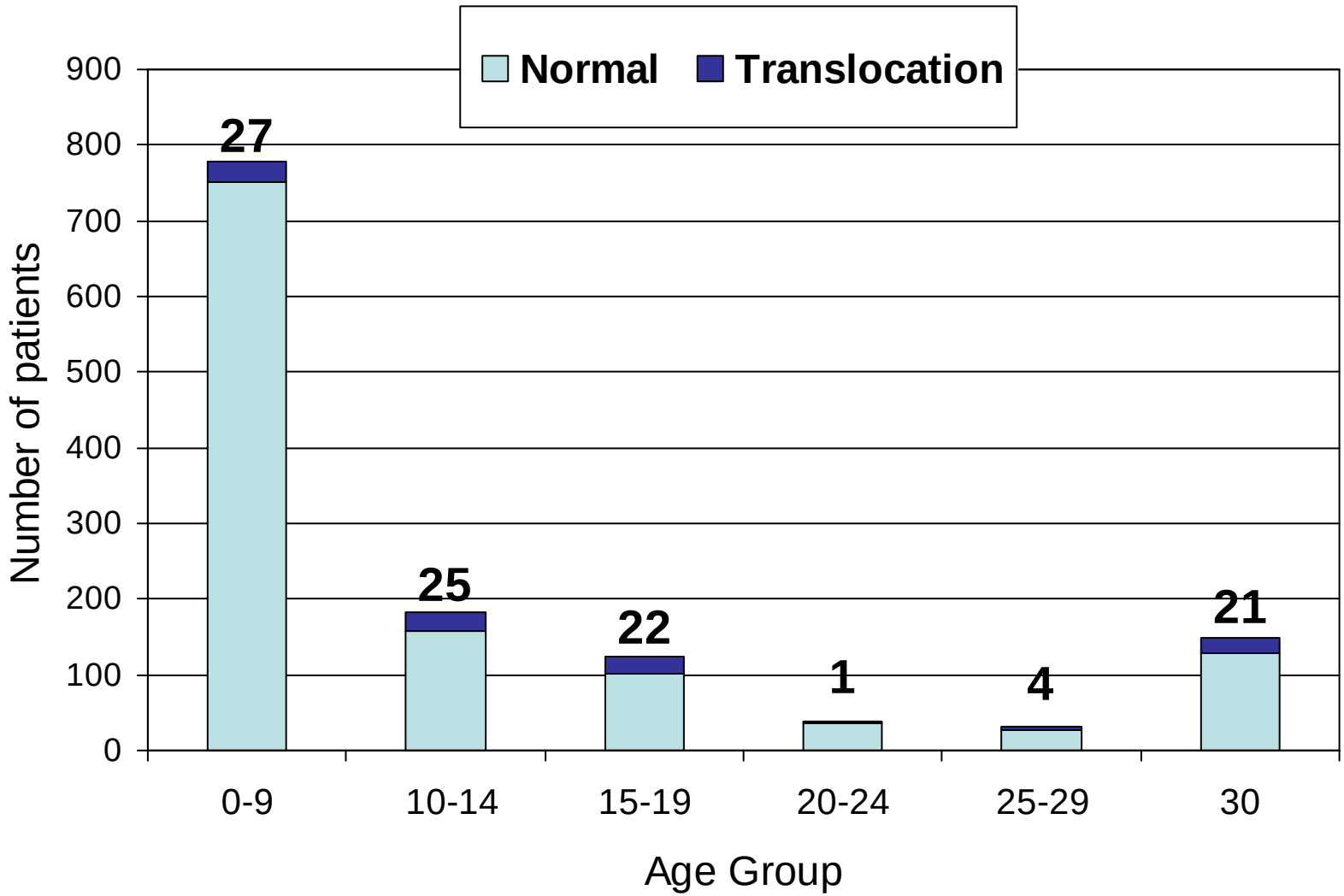
Five members of the CEBP transcription factor family are targeted by recurrent IGH translocations in B-cell precursor acute lymphoblastic leukemia (BCP-ALL)

Takashi Akasaka, Theodore Balasas, Lisa J. Russell, Kei-ji Sugimoto, Aneela Majid, Renata Walewska, E. Loraine Karran, David G. Brown, Kelvin Cain, Lana Harder, Stefan Gesk, Jose Ignacio Martin-Subero, Mark G. Atherton, Monika Brüggemann, Maria José Calasanz, Teresa Davies, Oskar A. Haas, Anne Hagemeijer, Helena Kempski, Michel Lessard, Debra M. Lillington, Sarah Moore, Florence Nguyen-Khac, Isabelle Radford-Weiss, Claudia Schoch, Stéphanie Struski, Polly Talley, Melanie J. Welham, Helen Worley, Jon C. Strefford, Christine J. Harrison, Reiner Siebert and Martin J. S. Dyer

IGH Testing in ALL by Age (n=1,304)

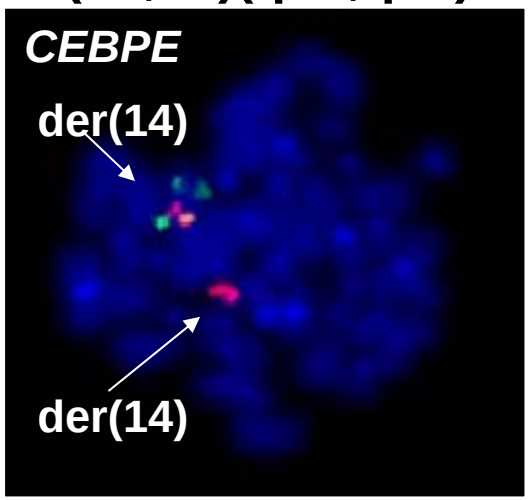
3% <10 yrs, 14% >10 years

NB Selected screening

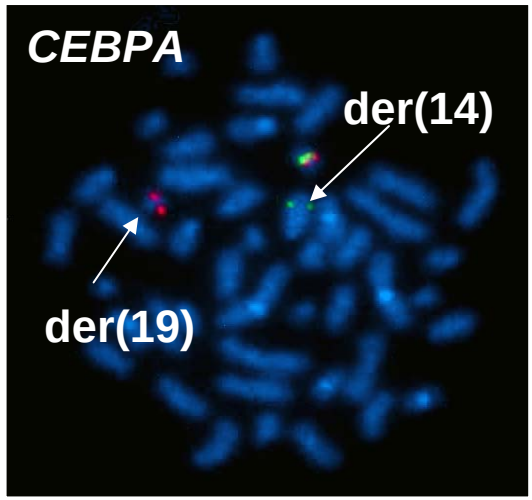


IGH@-CEBP family

t(14;14)(q11;q32)

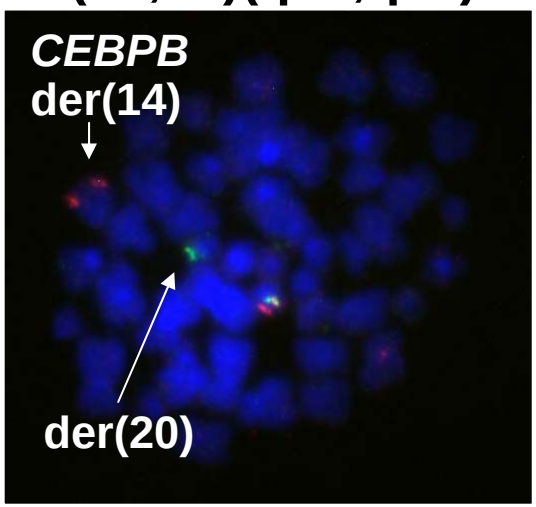


t(14;19)(q32;q13)

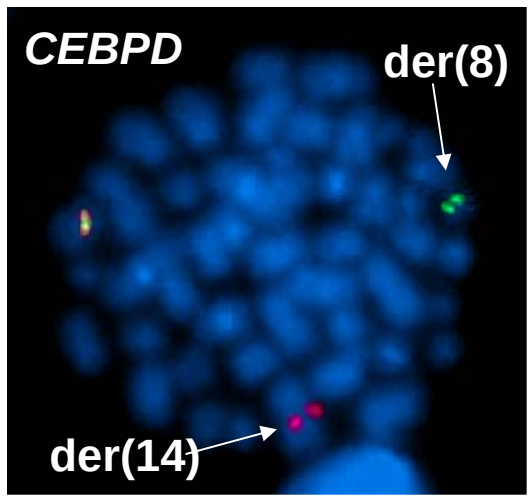


***IGH@* translocations**

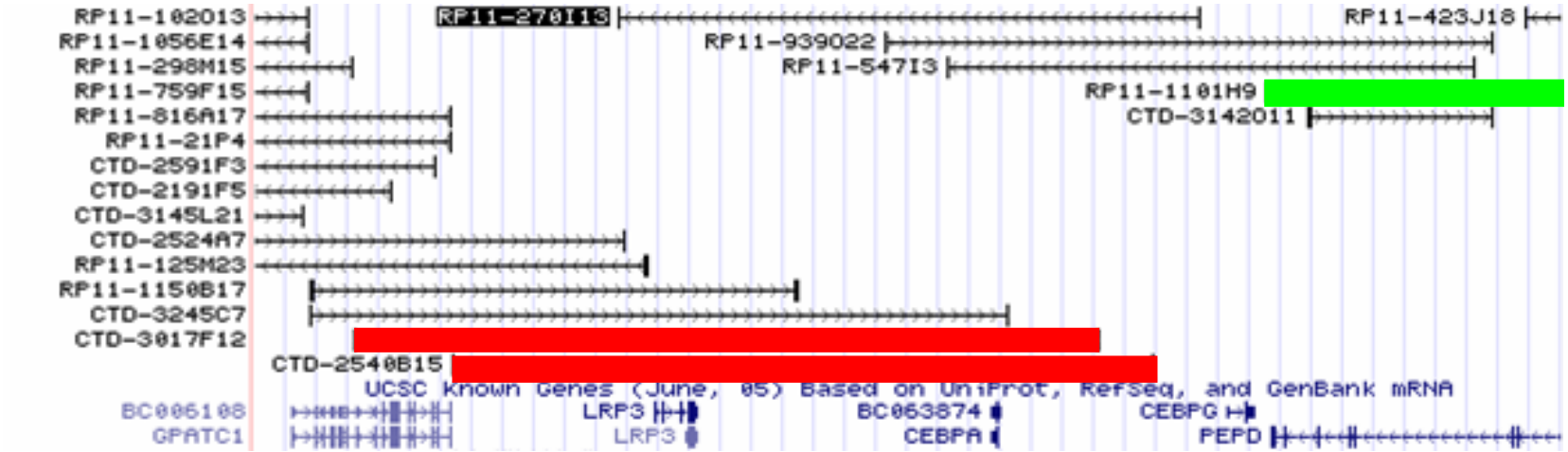
t(14;20)(q32;q13)

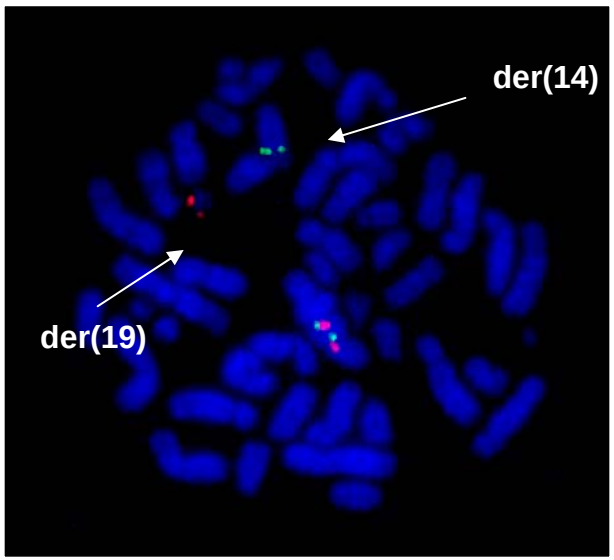


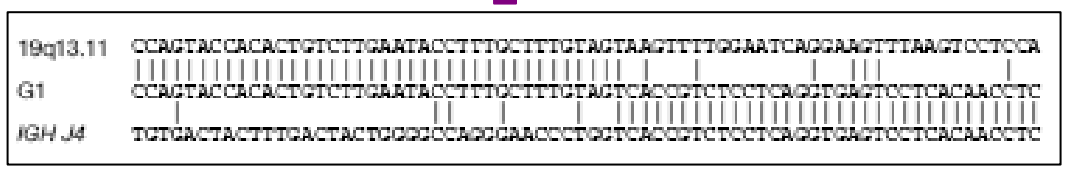
t(8;14)(q11;q32)



IGH@-CEBPG

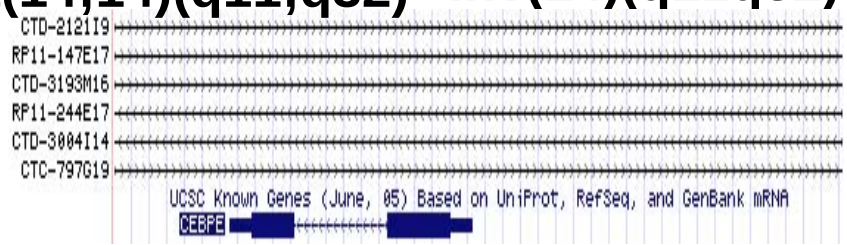

RP11-102O13
RP11-1056E14
RP11-298M15
RP11-759F15
RP11-816A17
RP11-21P4
CTD-2591F3
CTD-2191F5
CTD-3145L21
CTD-2524A7
RP11-125M23
RP11-1150B17
CTD-3245C7
CTD-3017F12
RP11-270I13
RP11-939022
RP11-547I3
RP11-423J18
RP11-1101H9
CTD-3142O11
CTD-2540B15
UCSC Known Genes (June, 05) Based on UniProt, RefSeq, and GenBank mRNA
BC006108
GPATC1
LRP3
LRP3
BC063874
CEBPA
CEBPG
PEPD


der(14)
der(19)


19q13.11 CCAGTACCACACTGTCTTGAATACCTTTGCTTTGTAGTAAGTTTTGGAATCAGGAAGTTTAAGTCCTCCA
G1 CCAGTACCACACTGTCTTGAATACCTTTGCTTTGTAGTCACCGTCTCCTCAGGTGAGTCCTCACAACCTC
IGH J4 TGTGACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGTGAGTCCTCACAACCTC

IGH@-CEBP family

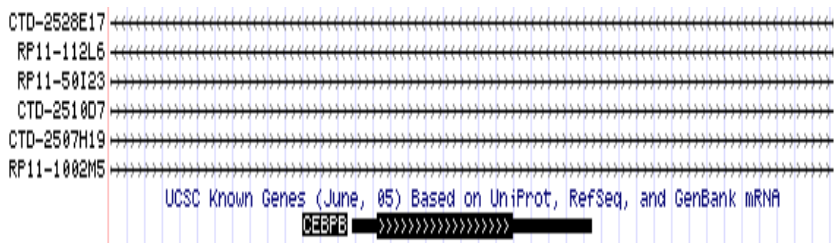
t(14;14)(q11;q32) **inv(14)(q11q32)**



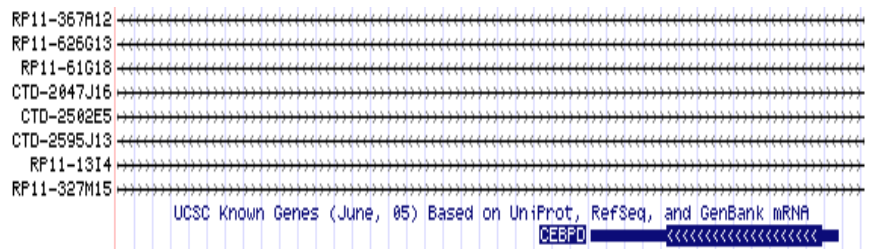
t(14;19)(q32;q13)

***IGH@* translocations**

t(14;20)(q32;q13)

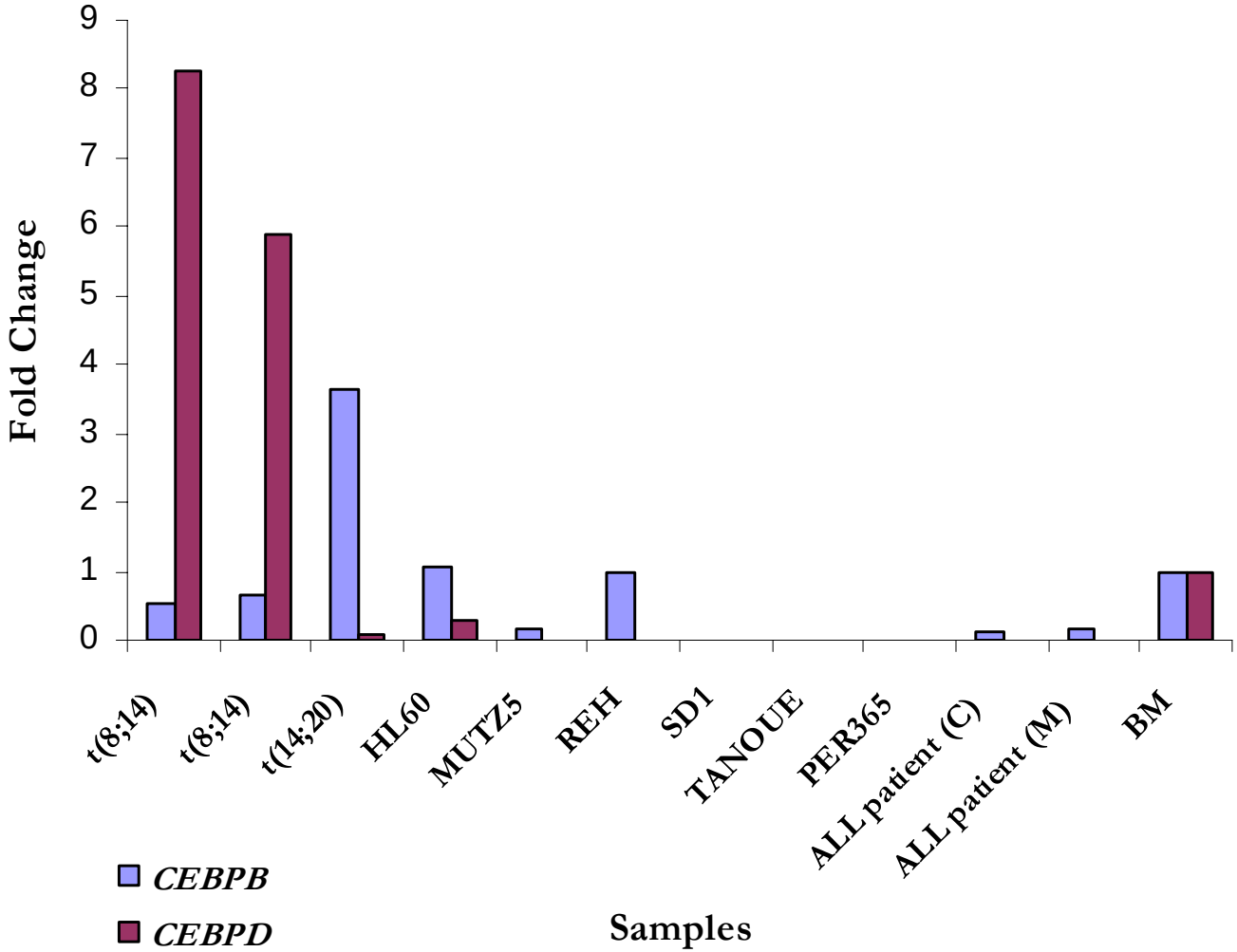


t(8;14)(q11;q32)



IGH@-CEBP family

qRTPCR



IGH@-CEBP family

Translocation	M:F ratio	Age range (median)	WBC range x10^9/L (median)	Current status where available
t(14;19)(q32;q13)	2:7	10-44 (19)	1-71 (5)	1 dead 4 CR
t(14;19)(q32;q13)	0:1	32	94	NA
t(14;20)(q32;q13)	1:2	13-35 (15)	3-103 (75)	2 CR
t(8;14)(q11;q32)	5:5	3-49 (14)	2-375 (7)	1 dead 2 CR
t(14;14)(q11;q32) inv(14)(q11q32)	4:0	15-45 (20)	1-24 (13)	3 CR

Summary – *IGH@-CEBP* family

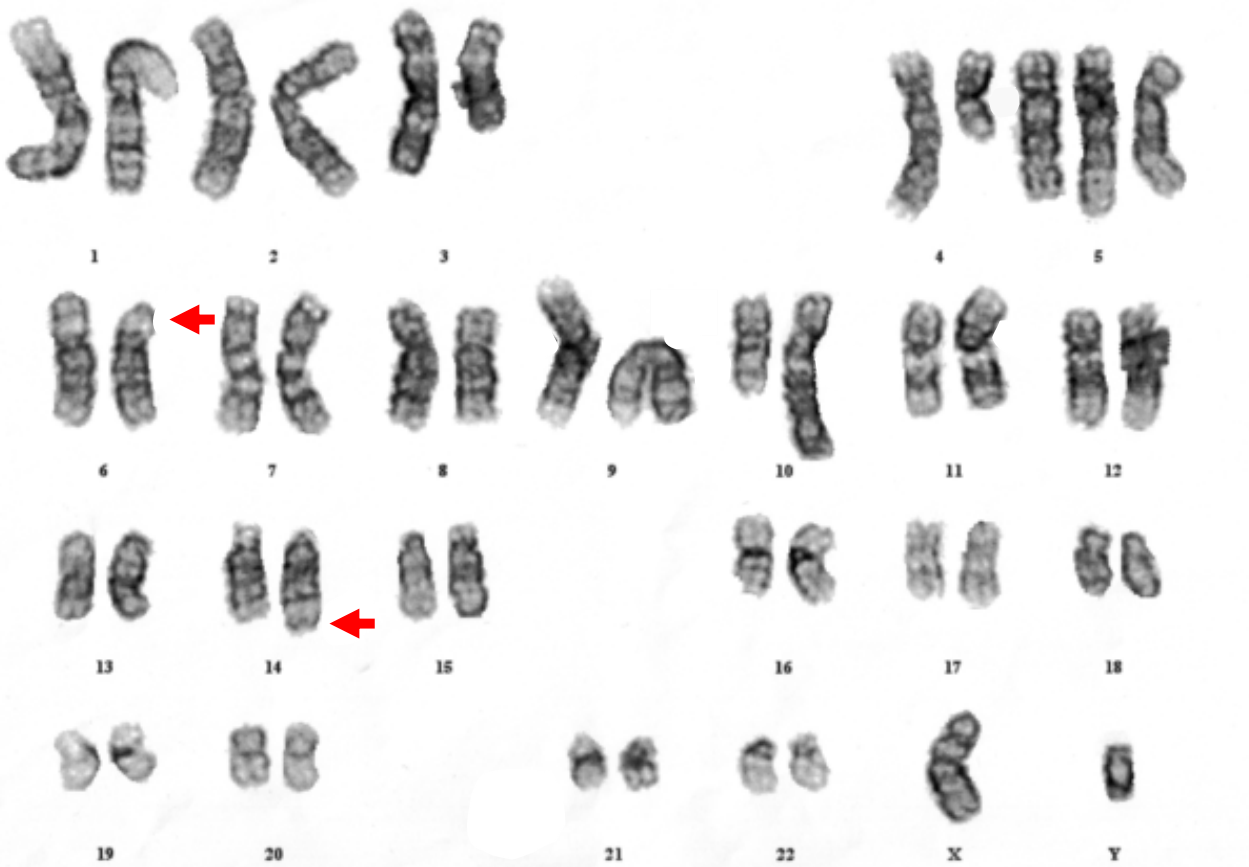
- Four *IGH@* translocations
- Involve five partner genes from the same gene family – CCAAT enhancer binding-proteins
- One subtype of haematological disease, B-cell precursor ALL in older children and young adults
- Basic leucine zipper transcription factors implicated in proliferation and differentiation
- Expressed in haematopoietic system – control of myeloid differentiation
- Tumour suppressor and oncogenic effects in leukaemogenesis

Brief report

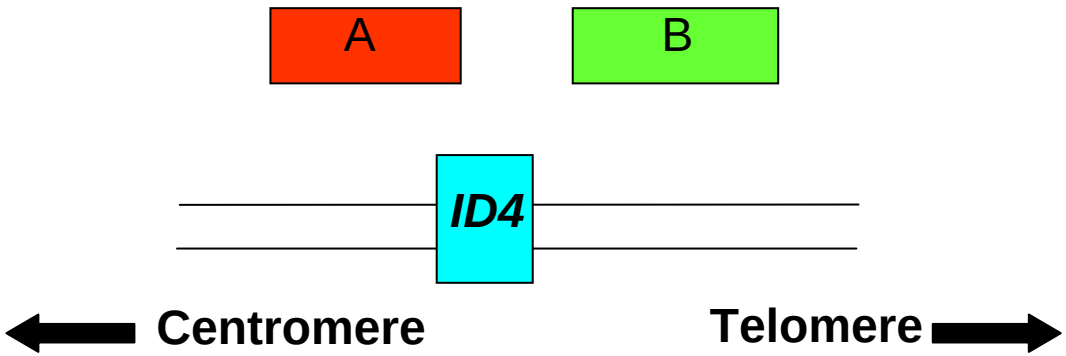
t(6;14)(p22;q32): a new recurrent *IGH@* translocation involving *ID4* in B-cell precursor acute lymphoblastic leukemia (BCP-ALL)

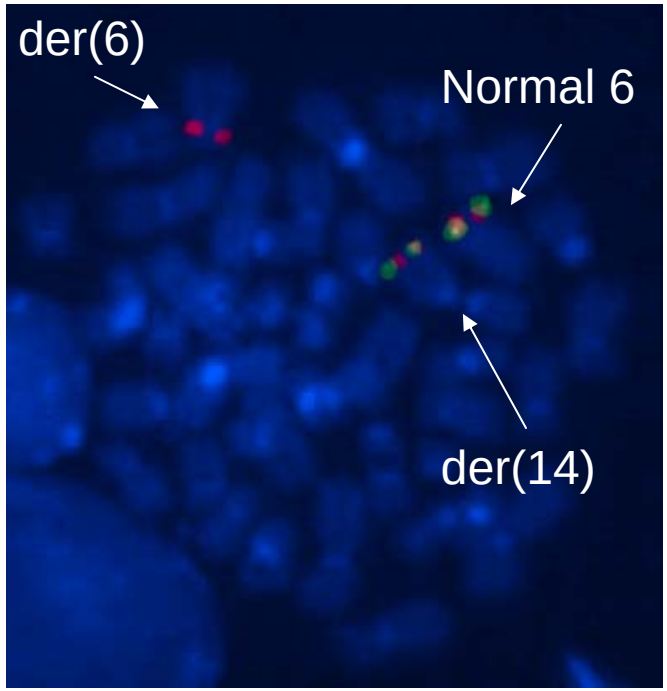
Lisa J. Russell,[1] Takashi Akasaka,[2] Anoela Majid,[2] Keiji Sugimoto,[2] E. Loraine Karran,[3] Inga Nagel,[3] Lana Harder,[3] Alexander Claviez,[4] Stefan Gesk,[3] Anthony V. Moorman,[1] Fiona Ross,[5] Helen Mazzullo,[6] Jonathan C. Strefford,[1] Reiner Siebert,[3] Martin J. S. Dyer,[2] and Christine J. Harrison[1]

[1]Leukaemia Research Cytogenetics Group, Cancer Sciences Division, University of Southampton, Southampton General Hospital, Southampton, United Kingdom; [2]Medical Research Council (MRC) Toxicology Unit, University of Leicester, Leicester, United Kingdom; [3]Institute of Human Genetics and [4]Department of Pediatrics, University-Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [5]Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury, United Kingdom; and [6]Department of Haematology and Blood Transfusion, University College Hospital, London, United Kingdom



IGH@-ID4

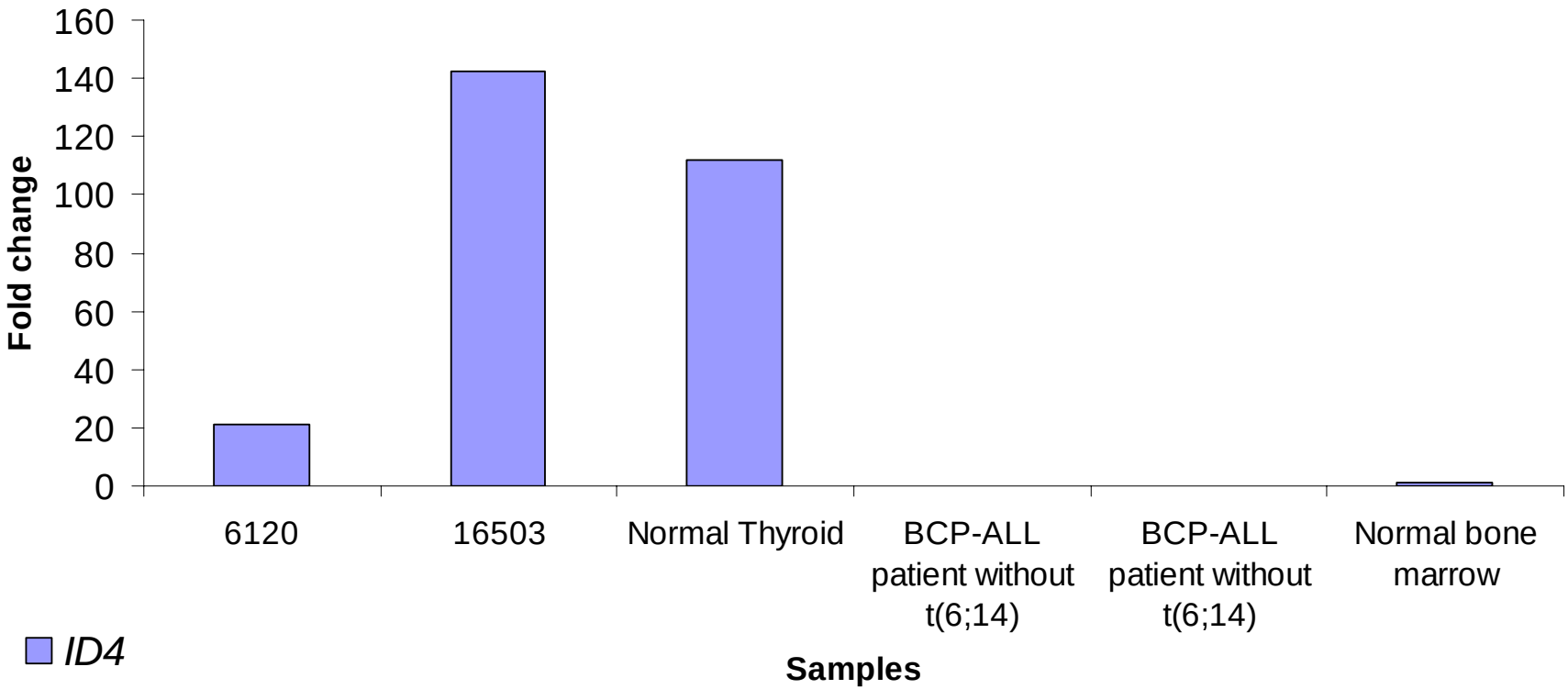




bHLH family of transcription factors – inhibitory proteins which regulate growth, differentiation, senescence and apoptosis

IGH@-ID4

- qRTPCR



IGH@-ID4

Patients

- 13 BCP-ALL patients – recurrent translocation
- Low WBC (median $3x10^9$/l, range $1\text{-}11x10^9$/l)
- Age higher than expected for BCP-ALL (median 16 yrs, range 6-48 years)

IGH@-EPOR

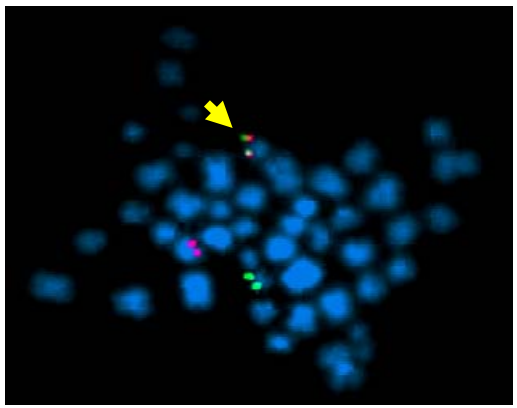
Leukemia (2008), 1–4

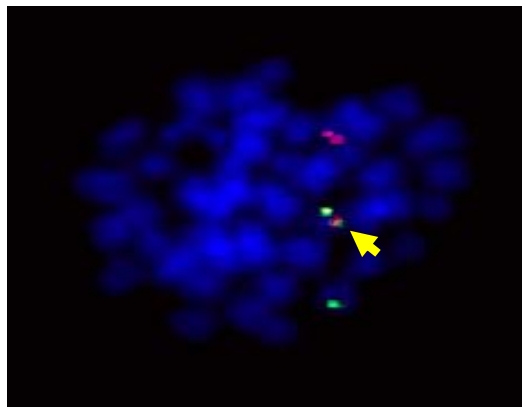
www.nature.com/leu

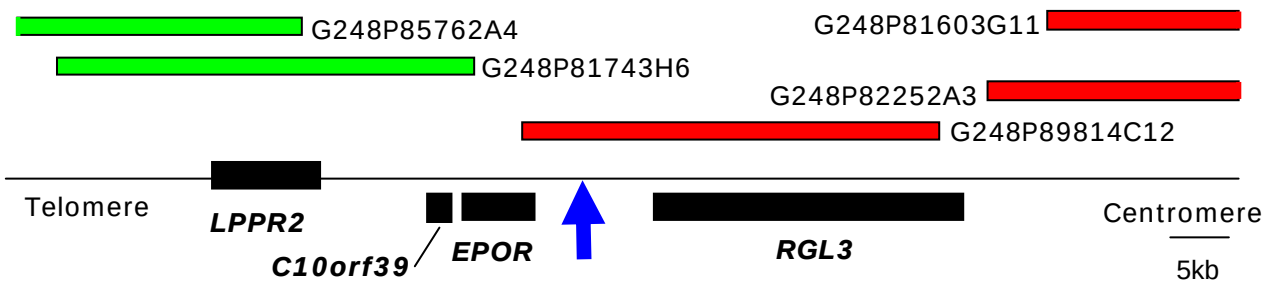
LETTER TO THE EDITOR

A novel translocation, t(14;19)(q32;p13), involving *IGH@* and the cytokine receptor for erythropoietin

der(14) der(19)

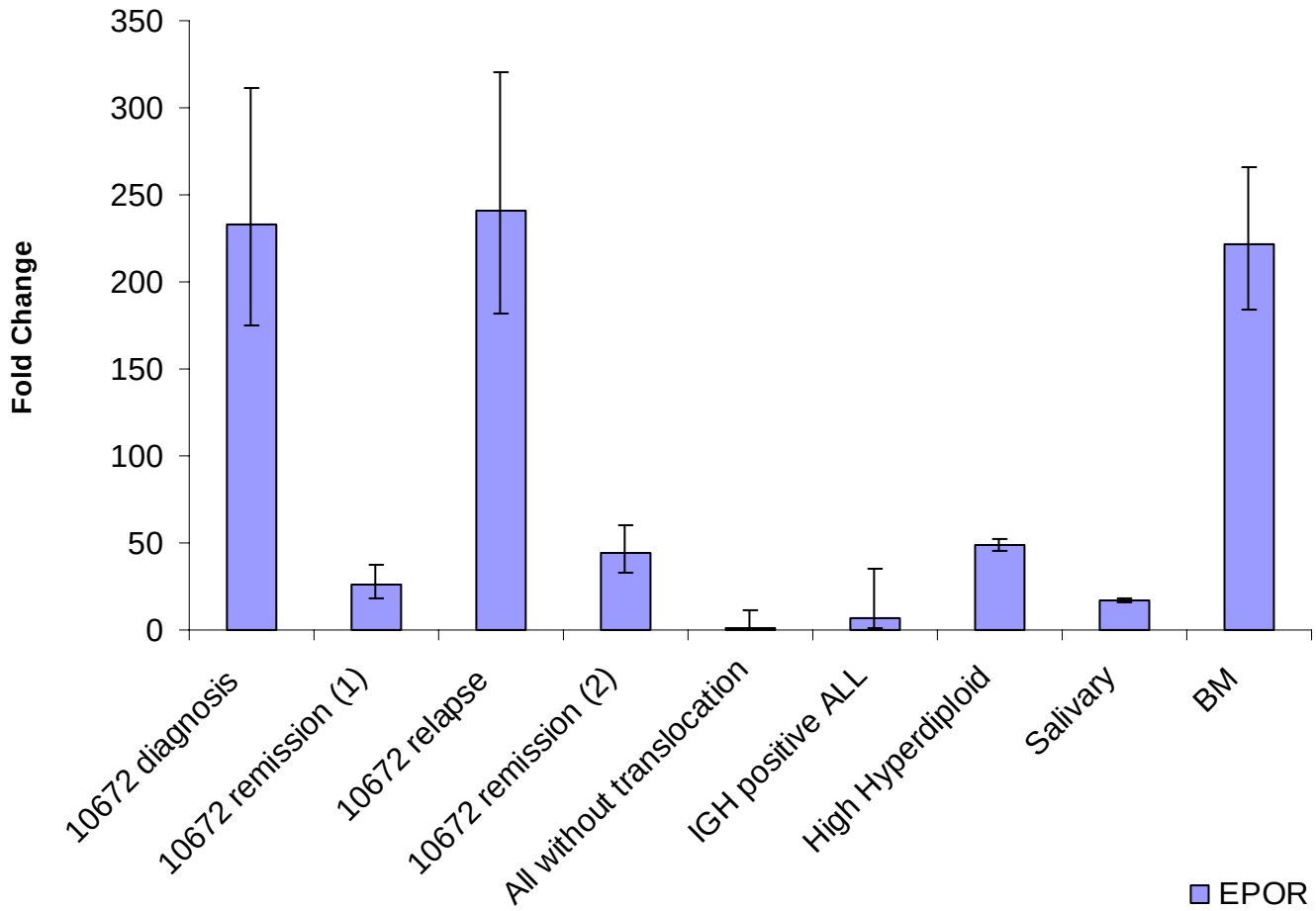






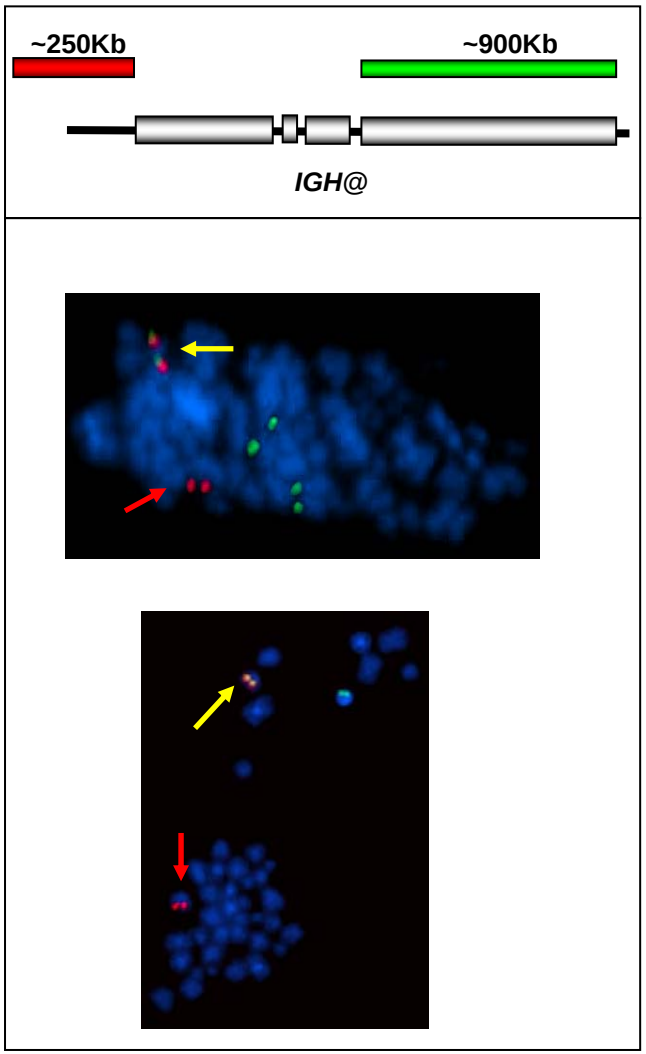
IGH@-EPOR

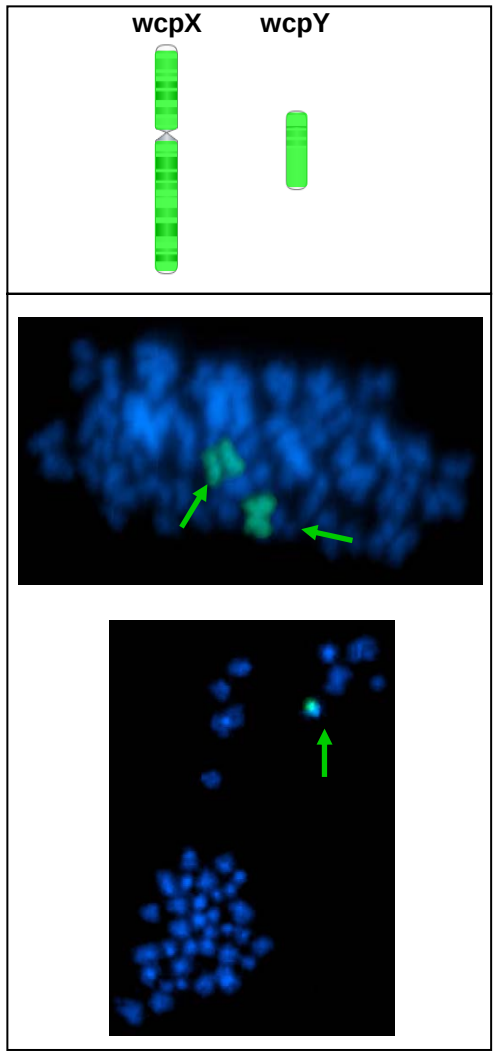
- qRTPCR

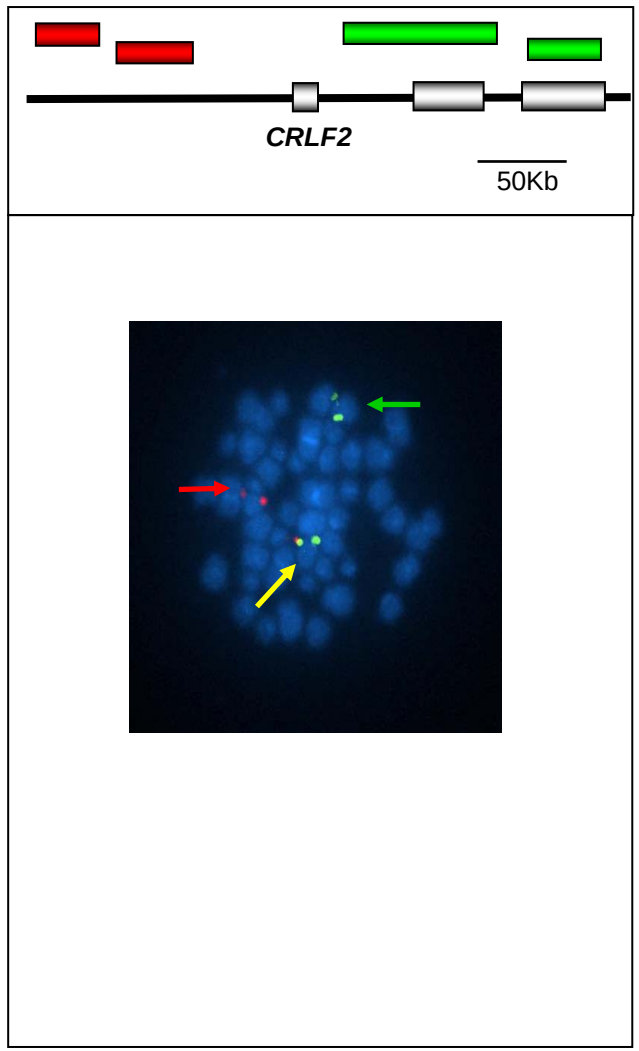


IGH@-CRLF2

TSLP (thymic stromal derived lymphopoietin)

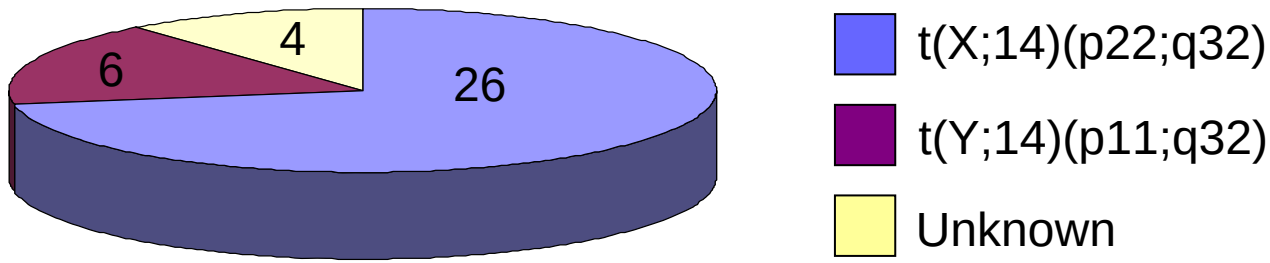






IGH@-CRLF2

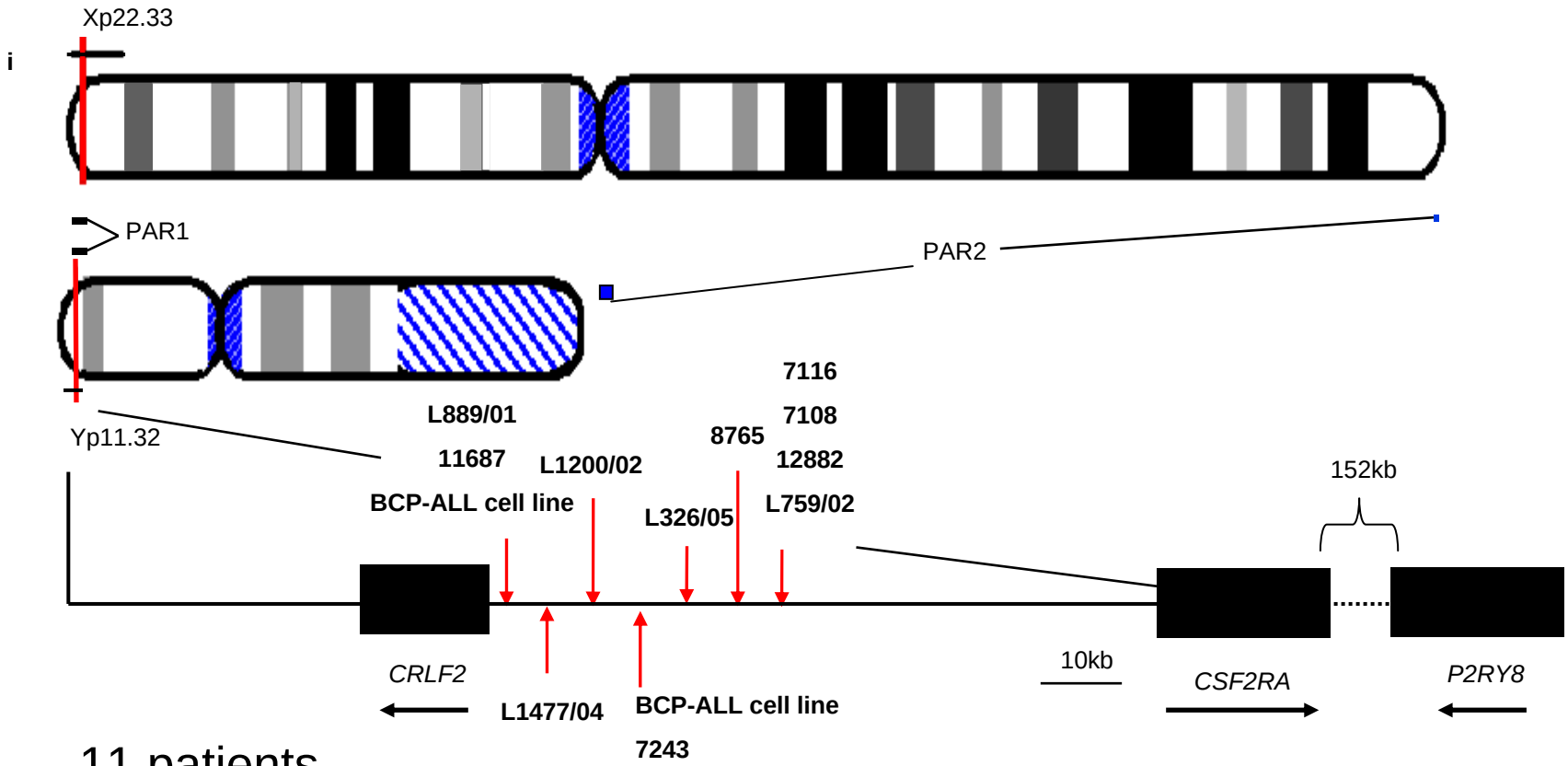
- 33 patients



- BCP-ALL
  - CD34+ and CD33+
- Median age 16yrs (range 3-76yrs)

IGH@-CRLF2

- LDI-PCR

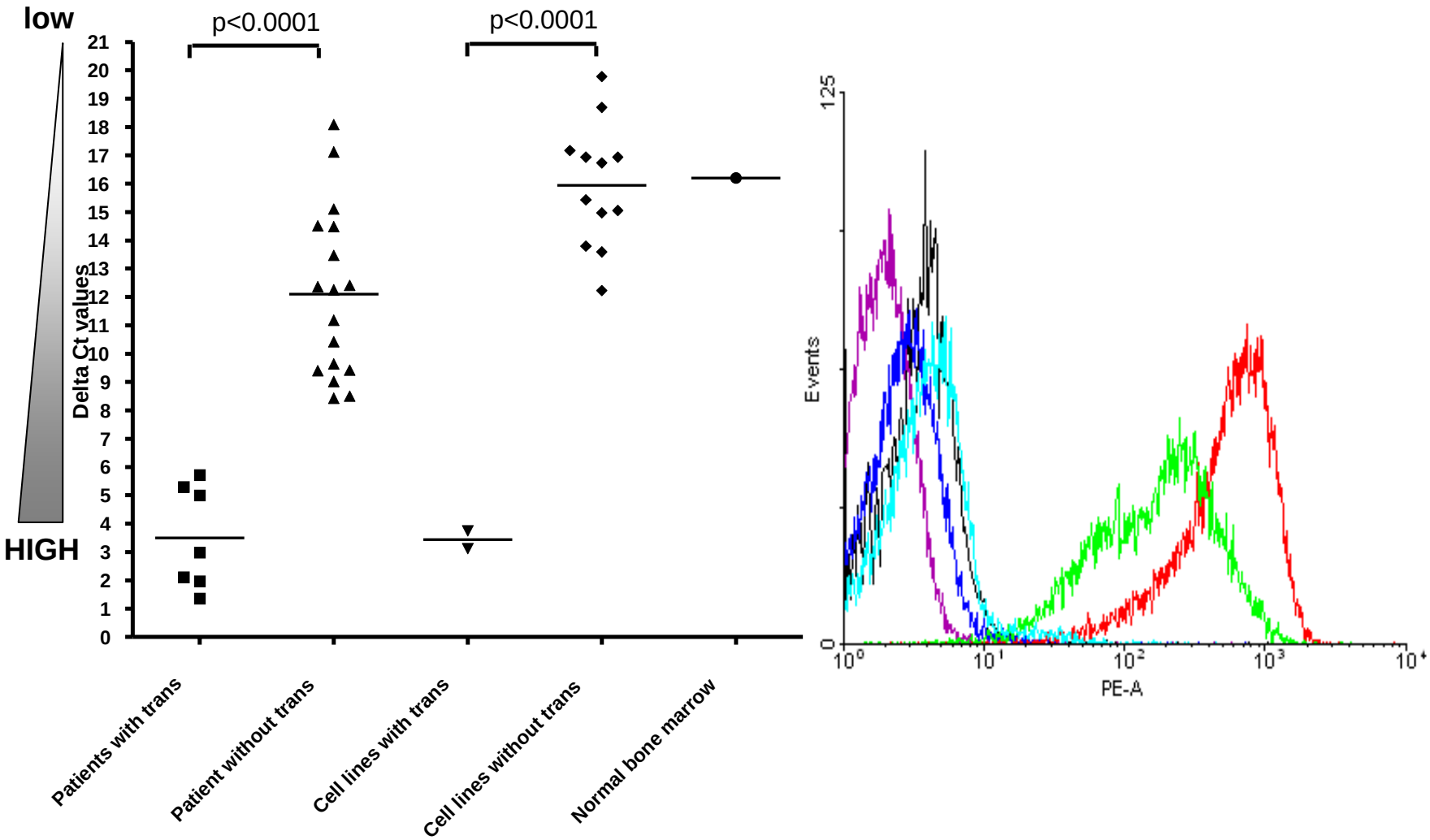


11 patients

27 BCP-ALL cell lines – 2 with t(Y;14)

IGH@-CRLF2

- Expression

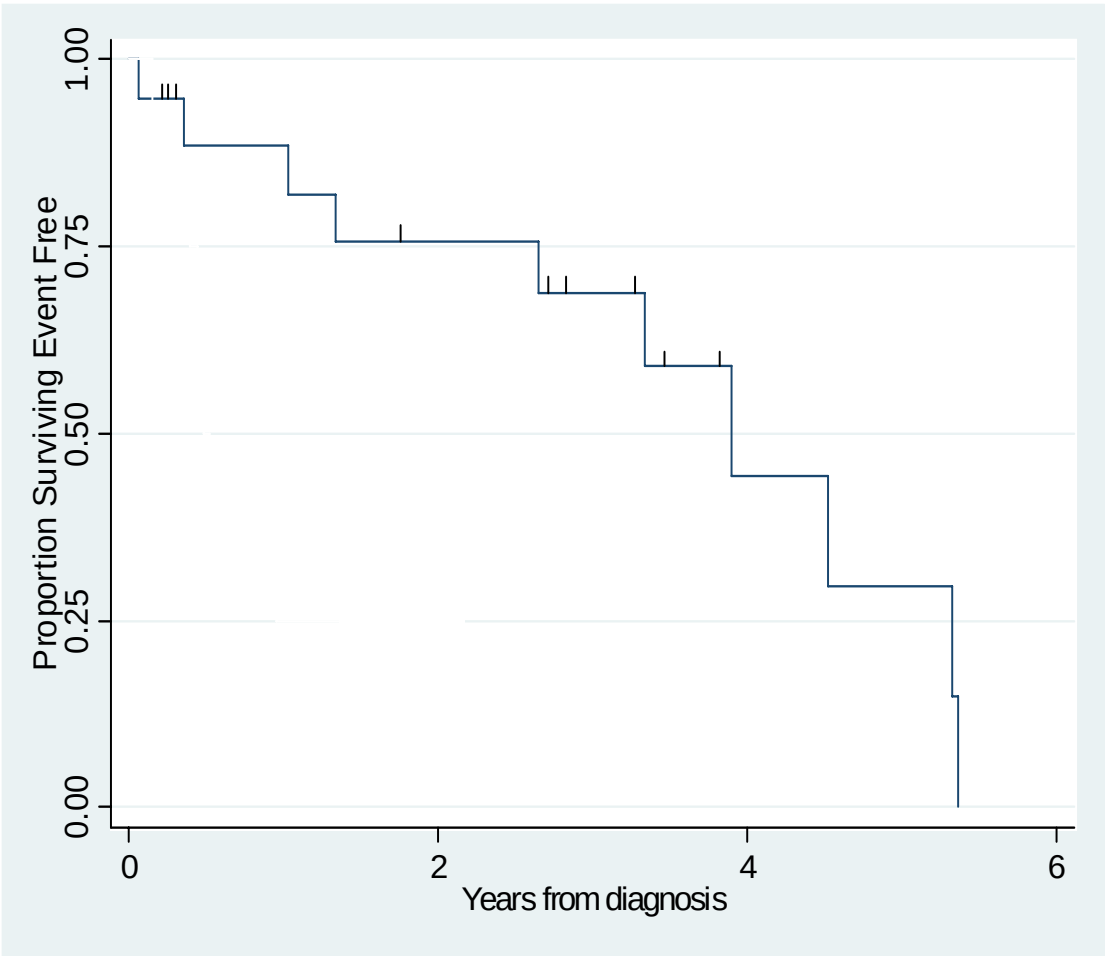


IGH@-CRLF2

Children (n=19)

10 events: 8 relapses (7 died);
2 non-remitter/early death

9 patients on ALL2003 – all in 1st CCR



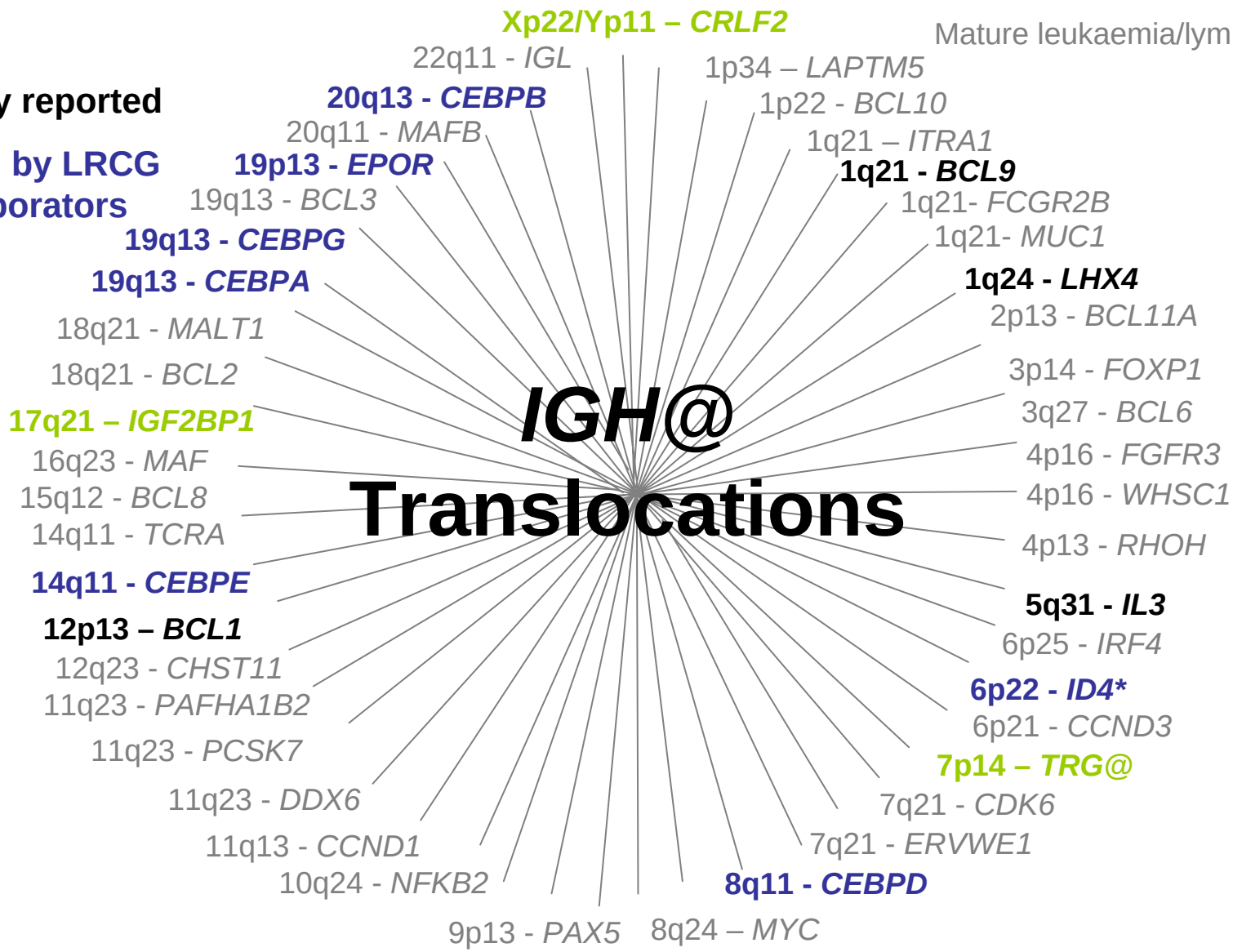
IGH@ Partners

BCP-ALL

Previously reported

Published by LRCG and collaborators

On-going



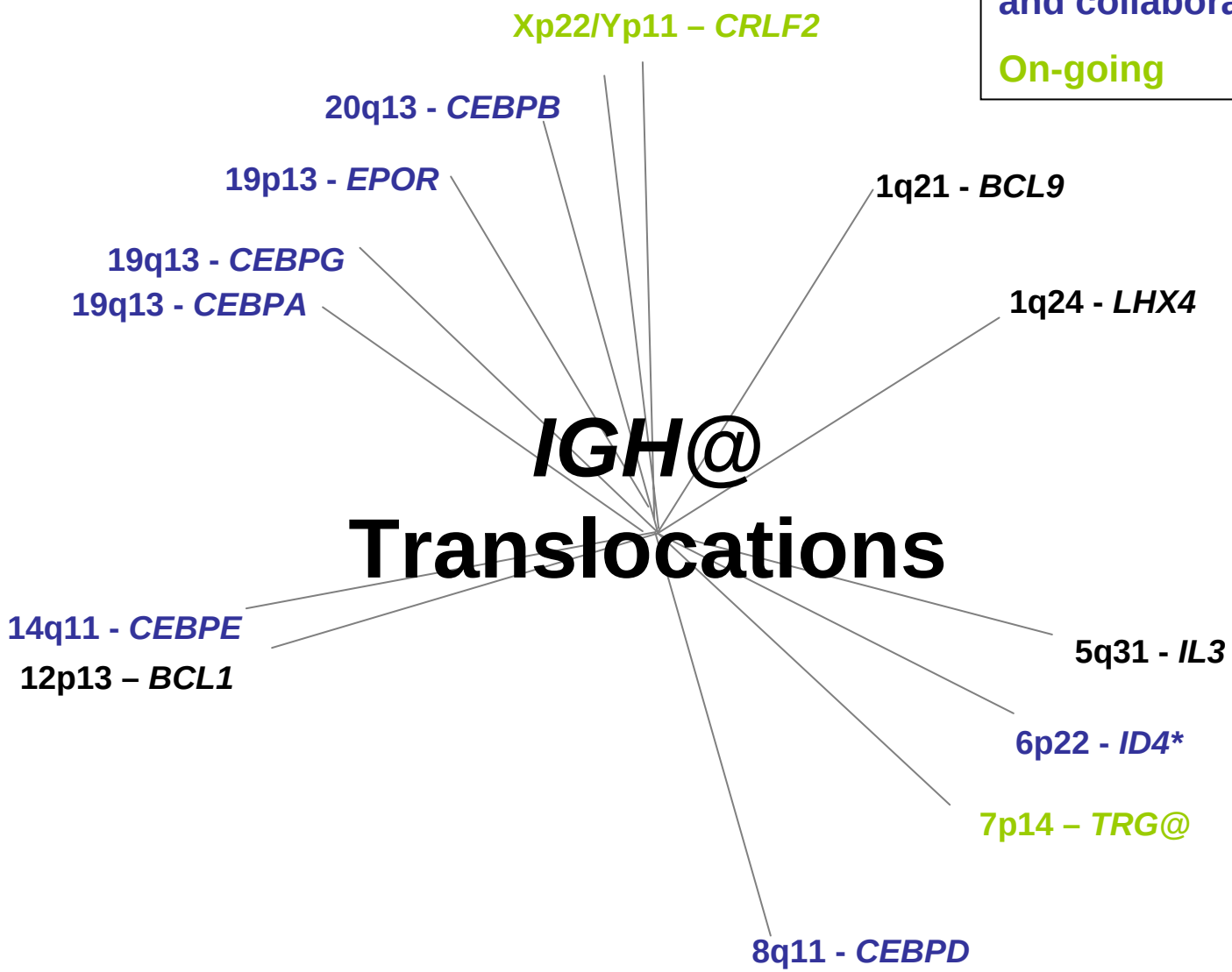
IGH@ Partners in BCP-ALL

BCP-ALL

Previously reported

Published by LRCG and collaborators

On-going



IGH@ translocations

- *IGH@* is a promiscuous locus: common link to the genes involved and their interrelated pathways
- Majority of patients are older children or adolescents
- Cytogenetics still identifies new translocations and subgroups

Conclusions to genetics of AYA

- They show abnormalities in common with childhood ALL, although the incidences are different
- There are some novel abnormalities emerging which are common in this age group
- Detailed analysis may highlight some as these as specific targets for therapy

Acknowledgements

Newcastle, UK

- Anthony Moorman
- Leukaemia Research Cytogenetics Group

LEUKAEMIA RESEARCH
HODGKIN'S | LYMPHOMA | MYELOMA

Leicester, UK

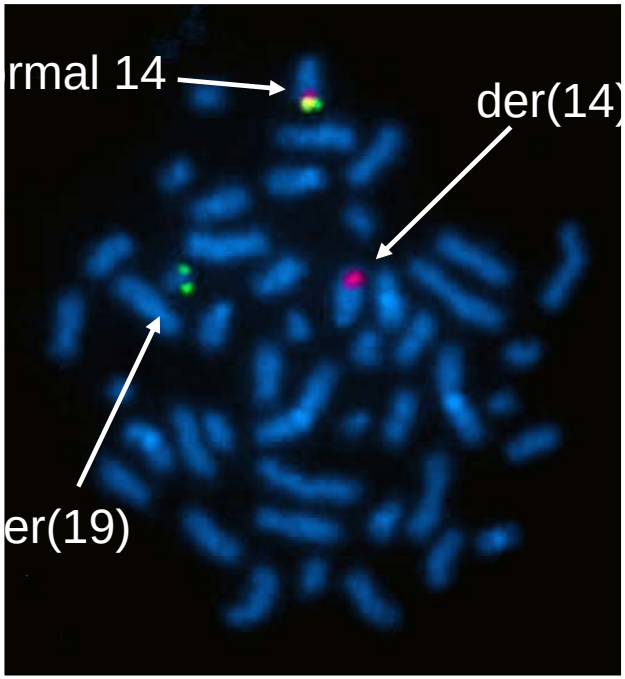
- Martin Dyer

Kiel, Germany

- Reiner Siebert

Paris, France

- Olivier Bernard



To find *IGH@* positive cases

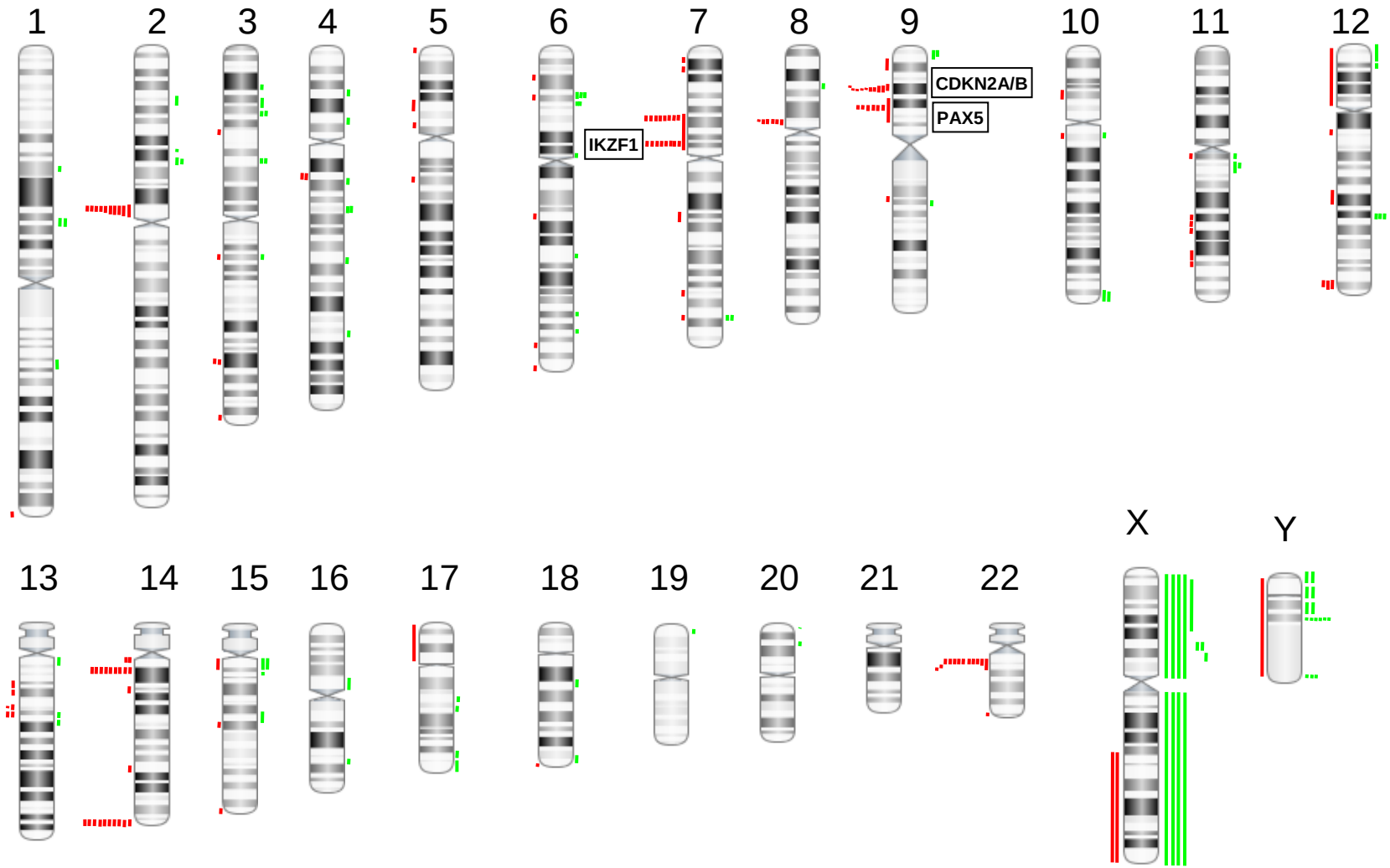
Screen by FISH with *IGH@* breakapart probe

Not:

- *ETV6-RUNX1* positive
- High hyperdiploidy
- *BCR-ABL1*
- t(1;19)

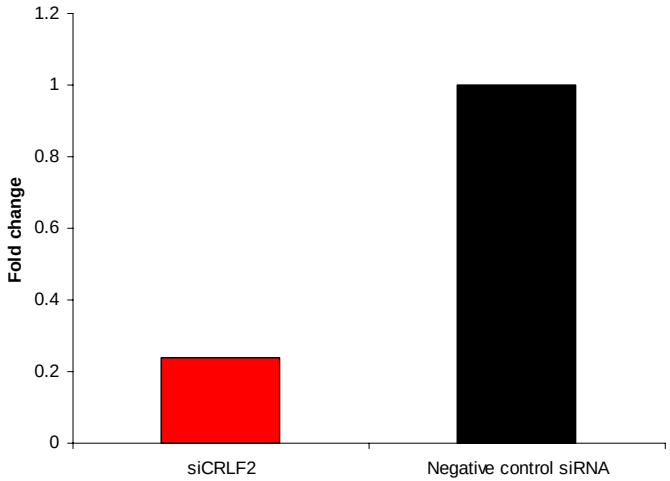
IGH@-CRLF2

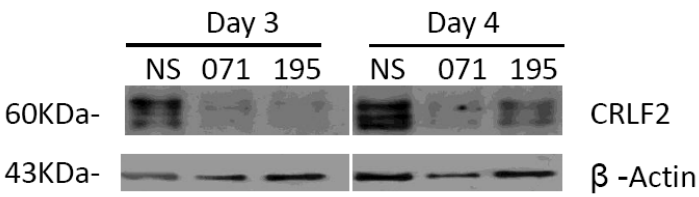
- aCGH

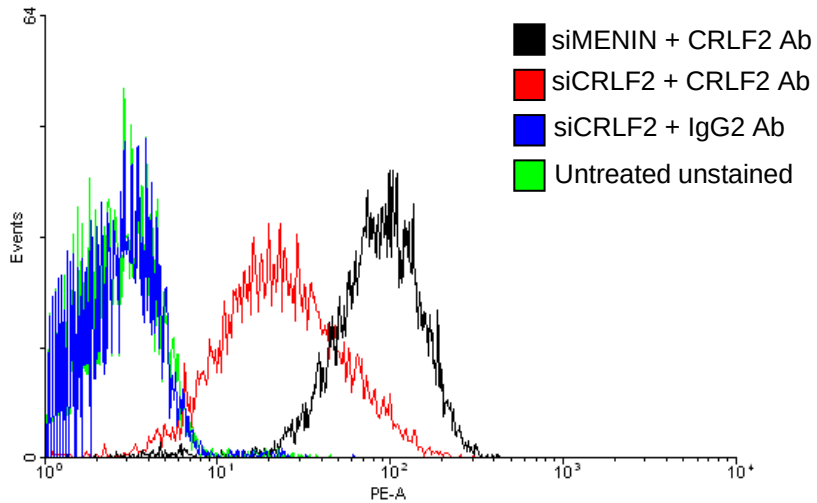


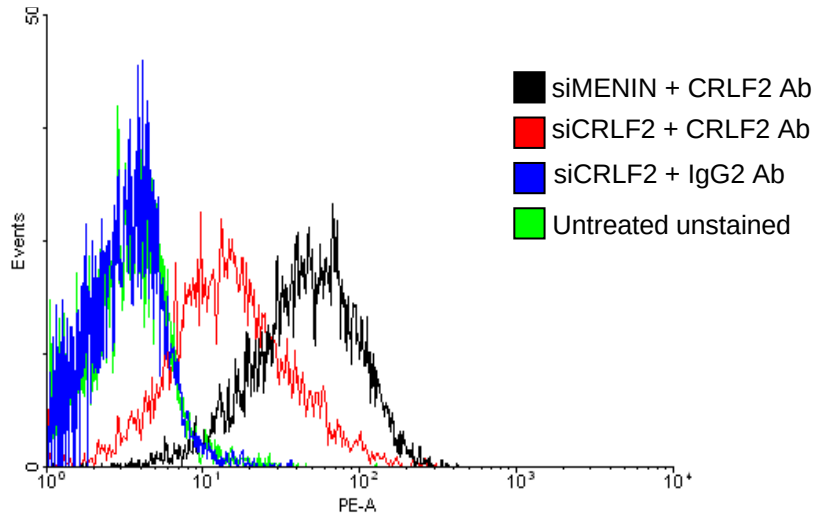
IGH@-CRLF2

- Knockdown



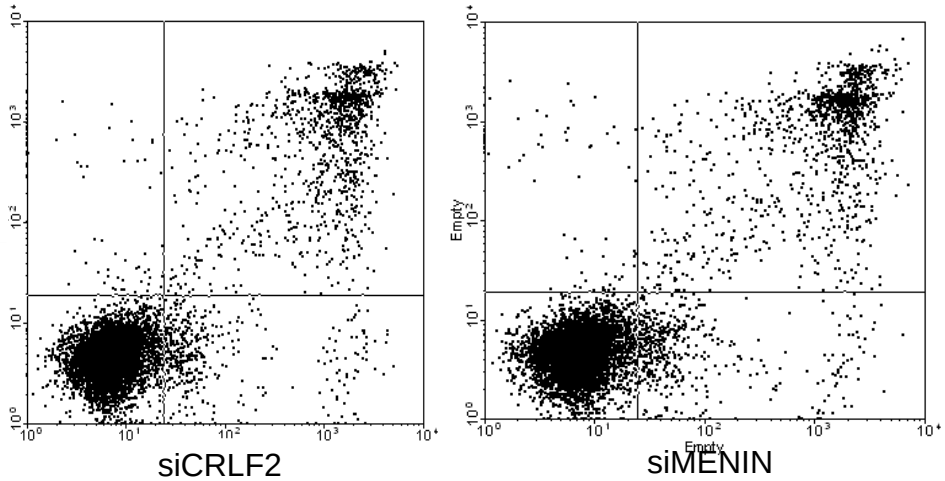


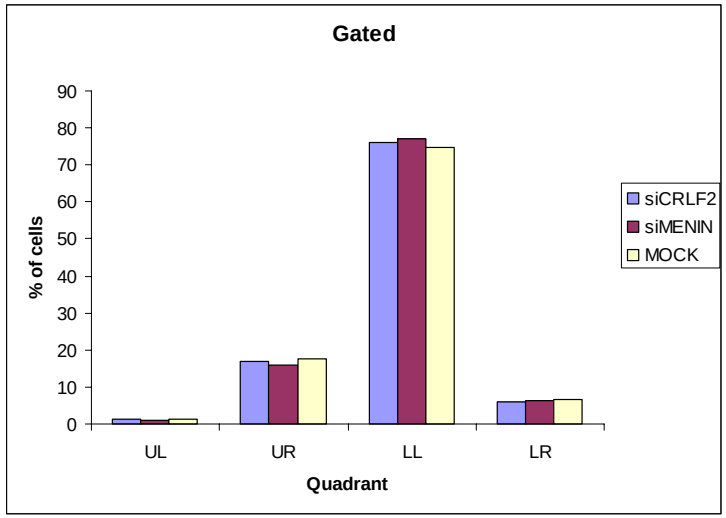


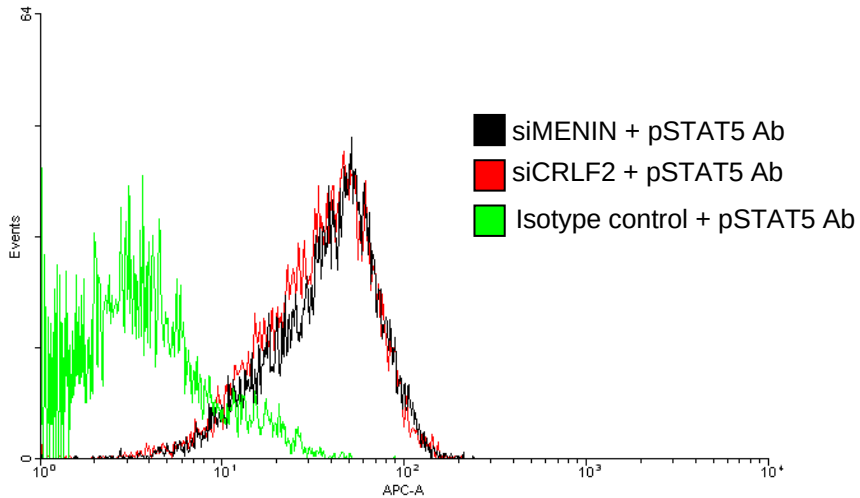


IGH@-CRLF2

- Biological consequences







No difference in;

Apoptosis

pSTAT5

Cell cycle

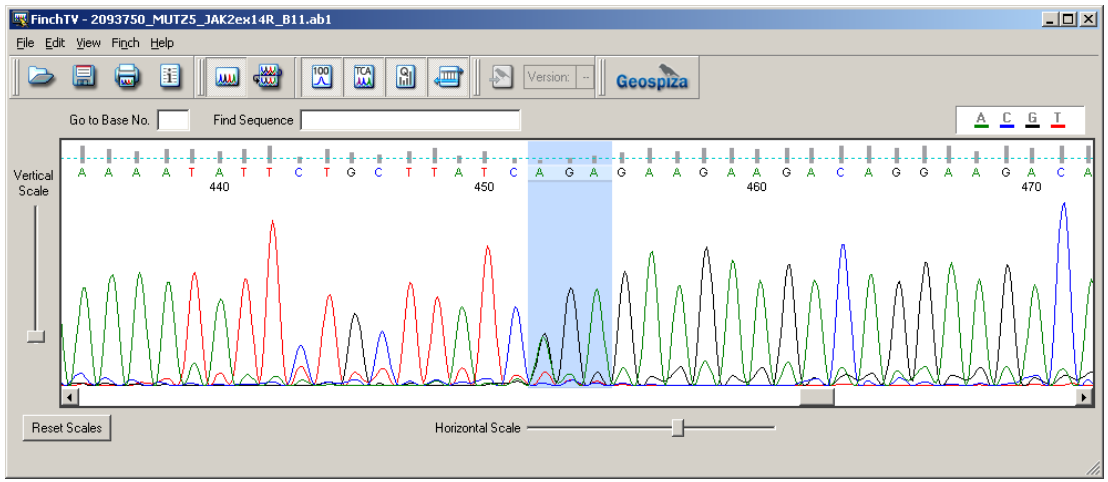
} Why?

IGH@-CRLF2

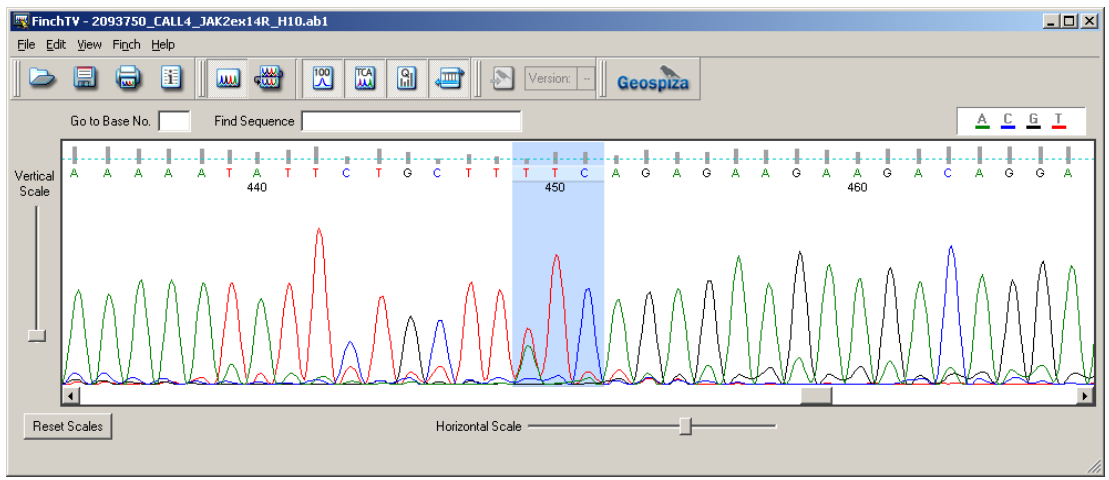
WT - TTCTGCTTATCAGAGAAGAA

- JAK2 mutation?

GGA - R683G



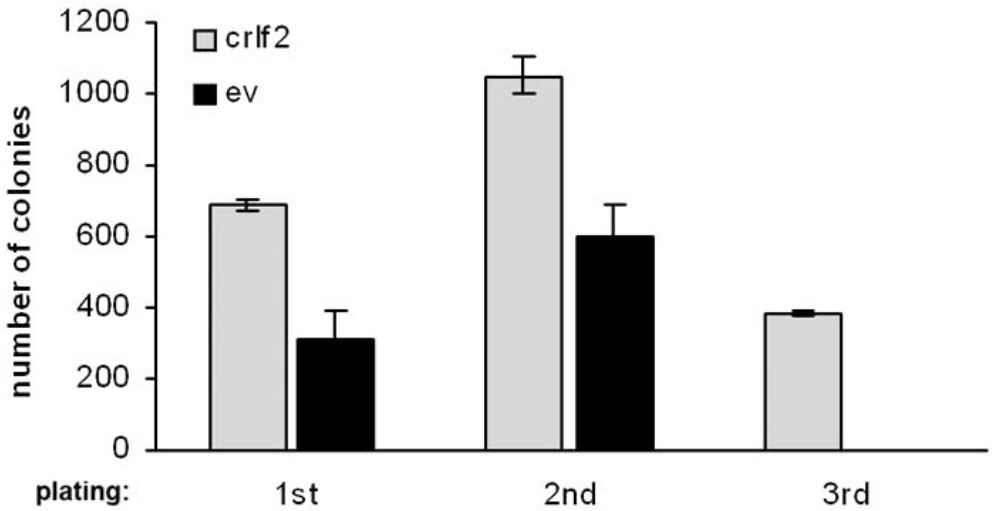
TTC - I682F

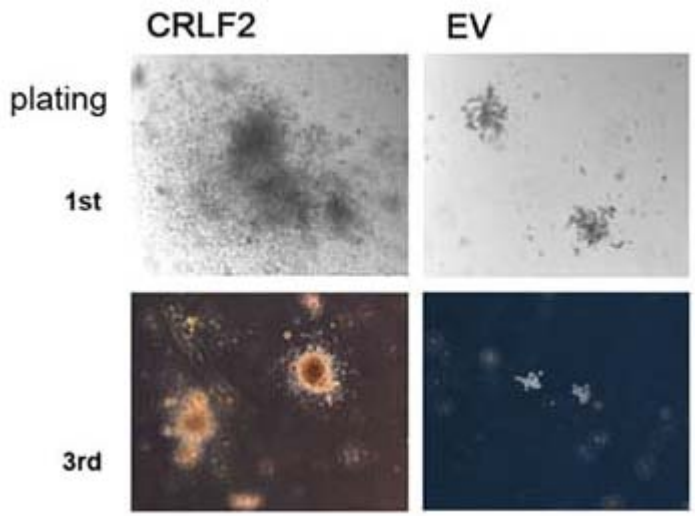


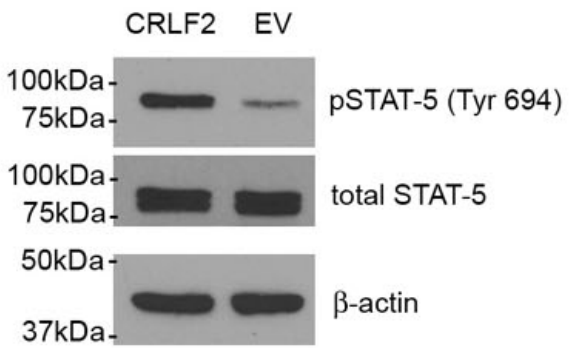
IGH@-CRLF2

- Retroviral transfection

Mouse fetal liver cells





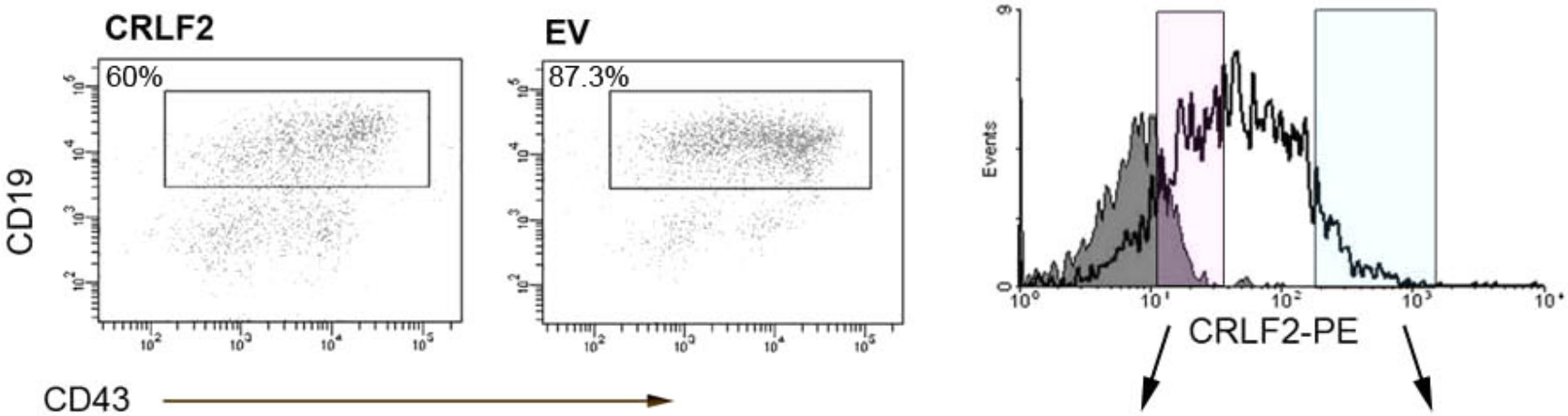


hCRLF2 – ↑number and ↑diameter

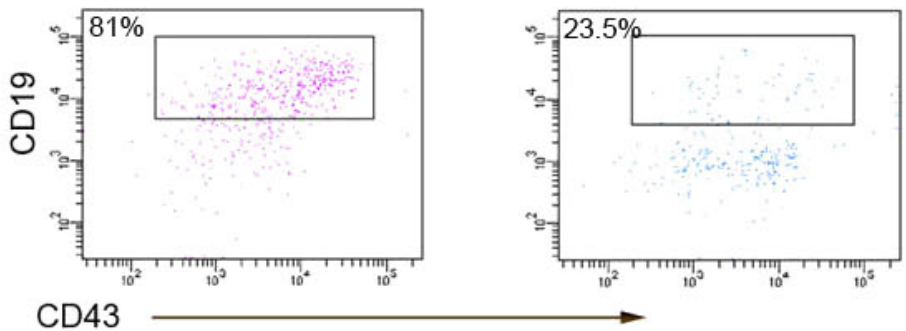
Data from Dr Melania Capasso

IGH@-CRLF2

CD43+/CD19+



- CRLF2 expressing cells are less differentiated compared to EV cells
- Low CRLF2 expressing cells are more differentiated than high CRLF2 expressing cells



Data from Dr Melania Capasso

Numbers of AYA by Trial and Year of diagnosis (N=1,179)