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Fluorescence *in situ* hybridisation assays designed for del(7q) detection uncover more complex rearrangements in myeloid leukaemia cell lines

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ABSTRACT

Chromosome 7 abnormalities are associated with poor prognosis in myeloid leukaemia. The pathogenetic mechanisms that arise from chromosome 7 rearrangements and lead to malignancy are still poorly understood. The use of leukaemia-derived cell lines might be a useful tool to shed some light on these mechanisms. The cytogenetic characterisation of these cell lines is therefore important for the understanding of the genetic alterations leading to the disease. We carried out fluorescence *in situ* hybridisation (FISH) on three different myeloid leukaemia-derived cell lines (GDM-1, GF-D8 and K562). These were selected on the basis of harbouring rearrangements of chromosome 7. The probes used in these experiments were whole and partial chromosome paints, Multiplex-fluorescence *in situ* hybridisation (M-FISH) probes as well as locus specific probes for the 7q22, 7q31 and 7q36 regions. Our study confirmed the chromosome 7 abnormalities previously reported in the cell lines GDM-1 and GF-D8. We refined one of the rearrangements of chromosome 7 in the K562 cell line and reported some discrepancies with the data published in earlier reports. With this study, we confirm the importance of using a series of FISH probes to characterise chromosomal abnormalities in detail, as some rearrangements might go under-detected or mis-interpreted. Moreover, we highlight the importance of monitoring cell lines broadly used in research, as these can lose or acquire characteristics as they evolve in time in different laboratories.

KEYWORDS: fluorescence *in situ* hybridisation, chromosome 7, chromosome abnormalities, myeloid leukaemia, leukaemia cell lines, GF-D8, GDM-1, K562

INTRODUCTION

The identification of chromosomal abnormalities is of crucial importance in cancer in general and especially in leukaemia. Non-random chromosomal rearrangements have been associated with specific leukaemia subtypes and have been shown to impact on prognosis [1]. It is broadly accepted that rearrangements of chromosome 7 confer a poor prognosis in all types of leukaemia. This is particularly true when considering deletions of the long arm of chromosome 7, del(7q), that are reported frequently in myeloid leukaemia in both paediatric and adult cases, as well as *de novo* and therapy related disorders [2]. The extent of the genomic loss in del(7q) is variable. A number of studies have focused on the delineation of a possible critical region common to all cases in order to pinpoint

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a tumour suppressor gene (TSG) responsible for the pathogenesis of del(7q) leukaemias [3]. The understanding of chromosome 7 biology was enhanced by the publication of the DNA sequence and annotation of the entire chromosome 7 [4]. This had a direct impact on the discovery of disease-associated genes and allowed the production of a wide range of clones spanning chromosome 7. These clones proved useful tools to be applied in fluorescence *in situ* hybridisation (FISH) experiments. In fact, with the development of FISH in the nineties, a number of groups used this approach to produce a comprehensive map of the deleted regions in 7q [5-8]. These studies resulted in the delineation of several non-overlapping regions along 7q, excluding the presence of a single TSG. FISH also enabled the characterisation of translocation breakpoints as well as the identification of cryptic rearrangements that were previously unidentifiable by conventional cytogenetic methods [9, 10]. Today FISH is still broadly used in the diagnostic sector as well as in research, alongside new approaches such as array based methods and next generation sequencing. Together with advance in technology, the use of cell lines is crucial to the development of cancer research. Cancer-derived cell lines are exploited as a model for the understanding of different aspects of pathobiology and to test cancer treatment [11]. To date, more than 600 different leukaemia and lymphoma cell lines have been carefully characterised and are made available to a range of laboratories [12]. It is envisaged that cell lines will continue to play a crucial role in leukaemia research.

This study focuses on the validation of two sets of commercially available probes designed to detect deletions in the most commonly reported chromosome 7 regions: 7q22, 7q31 and 7q36. The aim of this work is twofold: 1. to confirm the chromosome 7 abnormalities previously detected in a number of myeloid leukaemia cell lines and 2. to highlight the importance of FISH in monitoring the karyotypic evolution of cell lines *in vitro*.

MATERIALS AND METHODS

Fluorescence *in situ* hybridisation (FISH) has been carried out on four different cell lines. These are listed in Table 1. The cell lines were grown using the following conditions. The GF-D8 cell line was originally cultured in the presence of recombinant granulocyte-macrophage colony-stimulating factor as previously described [13]. However, no cell culture was carried out for the purpose of these experiments as archival fixed cells and chromosome suspensions were available from the same aliquots used in [8, 14]. The remaining cell lines (Farage, GDM-1 and K562) were grown in RPMI 1640 medium with addition of 10% foetal calf serum. Probes used in the FISH experiments were obtained from MetaSystems Gmbh and are commercially available. These are listed in Table 2. Maps of single locus probes are

Table 1. Cell lines used in this study.

Cell line	Origin	Reference
Farage	non-Hodgkin's lymphoma	[15]
GDM-1	Acute myeloid leukaemia	[16]
GF-D8	Acute myeloid leukaemia	[13]
K562	Chronic myeloid leukaemia	[17]

Table 2. List of probes used in this study.

Probe name	Targets	Labelling
XL 7q22/7q31	7q22 region including the *MLL5* gene	Orange
	7q31 region including the *MET* proto-oncogene	Green
	Chromosome 7 centromere	Blue
XL 7q22/7q36	7q22 region including the *MLL5* gene	Orange
	7q36 and including the *EZH2* gene	Green
	Chromosome 7 centromere	Blue
HLXB9	Regions flanking the *HLXB9* gene in 7q36	Green
XCP 7	Whole chromosome 7	Orange
XCAP 7 short	Short arm of chromosome 7	Orange
XCAP 7 long	Long arm of chromosome 7	Green
M-FISH	Whole chromosomes	Combinatorial

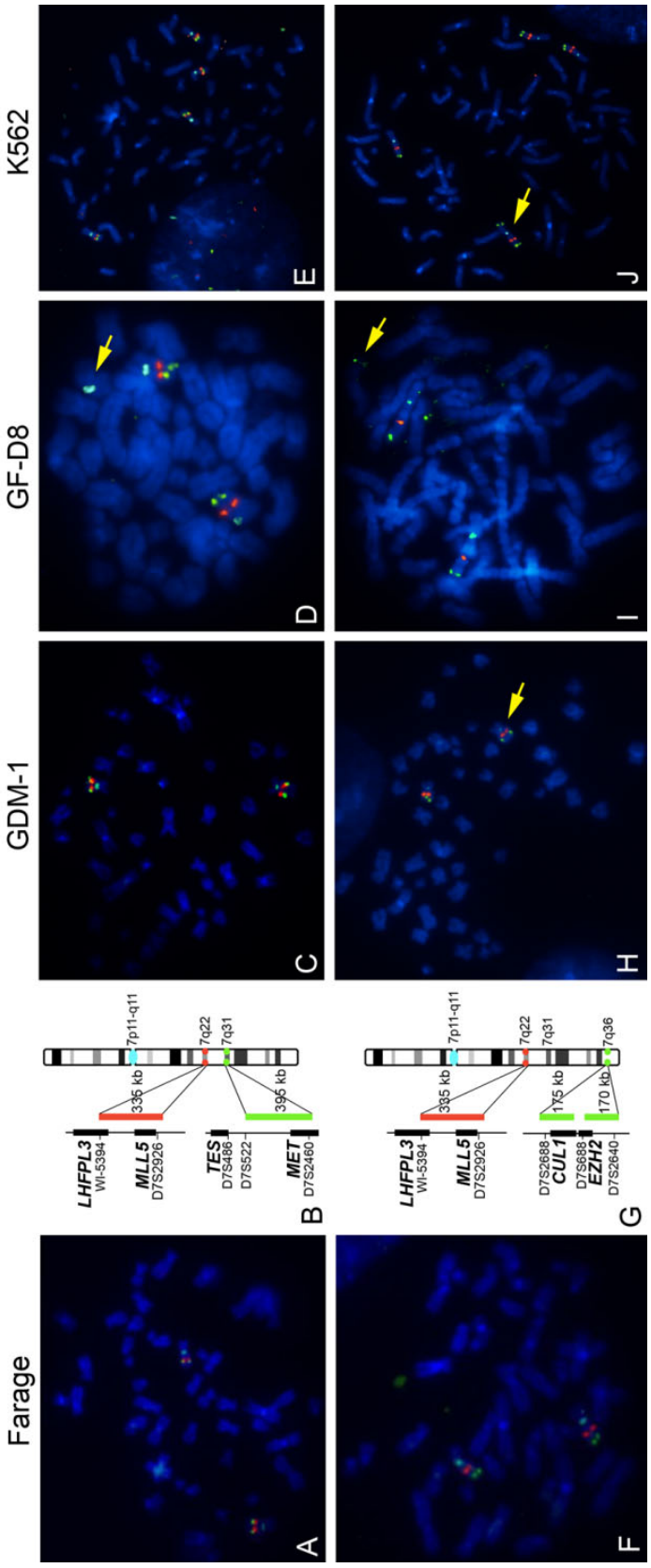

Figure 1. Hybridisation patterns of 7q locus specific probes on metaphase chromosomes from different cell lines. Examples of FISH on metaphase spreads using probes for 7q22 and 7q31 regions (upper row) and for the 7q22 and 7q36 regions (lower row). Metaphase chromosomes from the Farage cell line have been used to show normal localisation of the probes (A and F) as shown in the schematic representations (B and G). These probe sets show an unaltered position of hybridisation signals also in the chromosomes of the GDM-1 cell line (C and H), although the der(7)t(6;7) is identifiable for carrying additional material distal to the 7q36 hybridisation signals (H). In the GF-D8 cells, three copies of chromosome 7 are visible through the centromere-specific hybridisation signals visible in blue (D and I). Of these, two copies carry also signals for 7q22 and 7q31 probes (D), although they are positioned far apart compared to the control. The third copy carries only centromere-specific signals (indicated by the yellow arrow). Hybridisation signals specific for the 7q36 region are found on two copies of chromosome 7 as well as on another chromosome (indicated by the yellow arrow in panel I). The K562 chromosomes display four sets of hybridisation signals, showing the presence of four full copies of chromosome 7 using the 7q22-7q31 probe set (E). However, when using the 7q22-7q36 probe set, in one of the four homologues (indicated by the yellow arrow) 7q36 signals are also present on the short arm to indicate a possible intrachromosomal rearrangement (J).

shown in Figures 1B, 1G and 5A. FISH experiments were carried out according to the manufacturer's instructions. The FISH protocols used here have been described previously [18]. 24-colour karyotyping achieved by M-FISH was used to paint the K562 cell line using a modified method of the Metasystems™ protocol as described previously [19]. Digital images were captured using a charge-coupled device (CCD) camera (Photometrics Sensys CCD) coupled to and driven by ISIS (Metasystems™). Structural chromosomal abnormalities were identified as colour-junctions down the length of individual chromosomes and/or by the presence of chromosome fragments. The M-FISH paint composition was used to identify the chromosomes involved in the abnormality and the abnormalities were described according to International System of Cytogenetic Nomenclature [20].

RESULTS AND DISCUSSION

FISH analysis using 7q22/7q31 and 7q22/7q36 probes

The use of these three-colour FISH probe-sets enabled us to achieve information on three critical regions along chromosome 7 in a total of three myeloid leukaemia-derived cell lines. We used the lymphoma-derived cell line Farage as control, since no abnormalities of chromosome 7 were observed by us or reported by others. The expected hybridisation patterns using the 7q22/7q31 and 7q22/7q36 probes on Farage chromosomes are shown in Figure 1A and 1F. A summary of all the data obtained on the different cell lines are shown in Table 3.

GDM-1 cell line

According to previous report [21], the GDM-1 cell line harbours a balanced rearrangement t(6;7)(q23;q36) with a breakpoint on chromosome 7, distal to the *HLXB9* gene, that is localised in 7q36. Our experiments are in agreement with data previously reported as signals specific for the 7q36 probe used in this study correspond to the *EZH2* region, which is proximal to *HLXB9* and retained in the der(7) (see Figure 1H and Figure 2C and 2D). A similar pattern is shown with the 7q22/7q31 probe set, whose signals are both retained in the der(7) (see Figure 1C and Figure 2A and 2B).

GF-D8 cell line

Two of our previous works described the characterisation of chromosomal abnormalities in the GF-D8 cell line using various FISH approaches [14] and with particular focus on chromosome 7 [8]. In this study we confirm all the rearrangements reported previously, with the 7q22/7q31 probe set highlighting only the presence of the centromere in the der(7) with no signals being found other than on the two copies of the inv(7). Moreover, the same probe set confirmed the inversion to affect the positioning of the 7q31 probe (see Figure 1D and Figure 3A and 3B). The 7q36 probe confirms the translocation of this region to the short arm of the der(12) (see Figure 1D and Figure 3C and 3D).

K562 cell line

This cell line is broadly used in the scientific community and has been characterised by two independent groups using a range of FISH

Table 3. Summary of data relative to the cell lines presented in this study.

Cell line	Published chromosome 7 status	Ref.	This study
Farage	Two normal copies	[15]	confirmed
GDM-1	One normal copy + der(7)t(6;7)(q23;q36)	[21]	confirmed
GF-D8	inv(7)(q31.1q35-36) (two copies) + der(7)t(7;15)(q22;q22.3)del(7)(q22q33)del(15)(q13q22.3) + der(12)t(7;12)(q33;p11.2)del(12)(p11.2p13)	[8, 14]	confirmed
K562	One normal copy + mar 4: inv(7) mar 5: del(7)(p15) mar 6: der(7)rea del(7)	[22]	Three apparently normal copies + one new marker refined

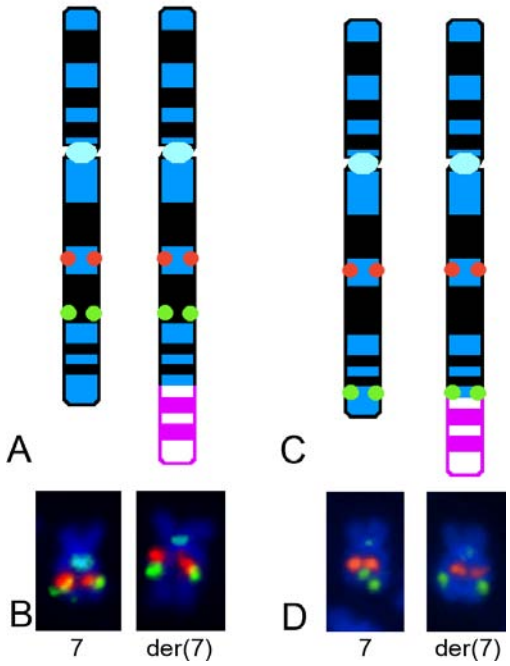

Figure 2. Hybridisation patterns of 7q locus specific probes in GDM-1 chromosomes. Ideograms representing localisation of hybridisation signals for the 7q22/7q31 probe set are shown in (A) in correspondence to the hybridised chromosomes (B). The distribution of signals is where expected in both the normal chromosome 7 and the der(7). Ideograms representing localisation of hybridisation signals for the 7q22/7q36 probe set are shown in (C) in correspondence to the hybridised chromosomes (D). The distribution of signals is where expected in both the normal chromosome 7 and the der(7), showing that additional material is present distal to the 7q36 hybridisation signal on the der(7).

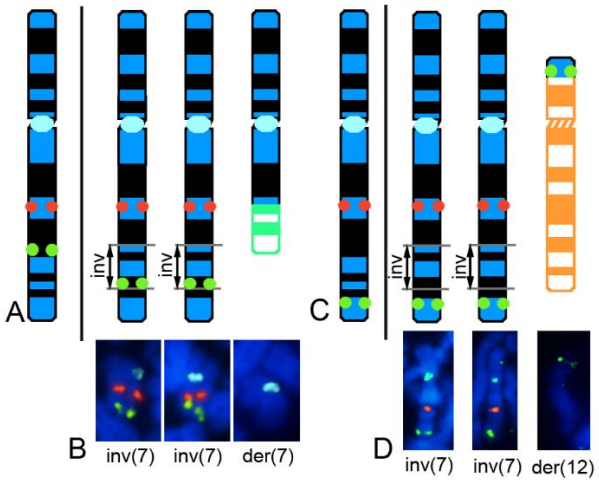

Figure 3. Hybridisation patterns of 7q locus specific probes in GF-D8 chromosomes. Ideograms representing localisation of hybridisation signals for the 7q22/7q31 probe set are shown in (A) in correspondence to the hybridised chromosomes (B). The 7q22/7q31 signals are positioned more far apart than expected, due to the presence of an inversion affecting bands 7q31.1 and 7q35-36. There are two copies of the inv(7) chromosome. A third chromosome 7, der(7), lacks 7q22 and 7q31 signals altogether due to loss of material between 7q22 and 7q36. Ideograms representing localisation of hybridisation signals for the 7q22/7q36 probe set are shown in (C) in correspondence to the hybridised chromosomes (D). The distribution of signals is where expected in both the inv(7) chromosomes as the inversion does not affect the 7q36 region covered by the probe. Hybridisation signals corresponding to 7q36 are present on the der(12) as a result of a translocation. Because there is no normal chromosome 7 in the GF-D8 cell line, a chromosome 7 ideogram is shown as reference at the left hand side in both (A) and (C).

approaches [22, 23]. The cell line has always been described as quasi-triploid containing three or four copies of chromosome 7. The number and the nature of the rearrangements of chromosome 7 vary according to the different descriptions (see Table 4). In our study, the use of these specific probe sets for chromosome 7 regions has shown that in the K562 cells in our laboratory three copies might be consistently normal whereas one copy is rearranged and carries signals for 7q36 on both 7q and 7p (see Figure 1E and 1J and Figure 4).

Refining the chromosome 7 rearrangement in K562 cells

The unusual and unexpected result seen on the rearranged chromosome 7, prompted us to carry out further investigations to elucidate the mechanisms that generated such a rearrangement. At first, we contemplated the possibility that the rearrangement could be a translocation between two homologues with complete loss of the short arm and retention of 7q material only. This would be plausible when looking at the hybridisation pattern generated by the use of chromosome 7 paint in combination with the *HLXB9* specific probe (Figure 5B). A further FISH experiment using partial chromosome paints specific for the short arm and the long arm visible in different fluorochromes, revealed the presence of a portion of 7q juxtaposed to the terminal portion of 7p (see Figure 5C).

Table 4. Reports of different rearrangements of chromosome 7 in K562 cells.

[24]	[25]	[23]	[22]	This study
Two normal copies	Three normal copies	One normal copy	One normal copy	Three normal copies
inv(7)(pter-~p21: : p11--~p21: : p11--~qter)	inv(7)(p11.2p22)		inv(7p)	
			del(7)(p15)	
			der(7)rea del(7)	
		i(7)(q10)		
		del(7)(q21q36)		
		del(7)(q31.2:q36)		
				add(7)p(22).ish dup(7)(q36)(HLXB9+)

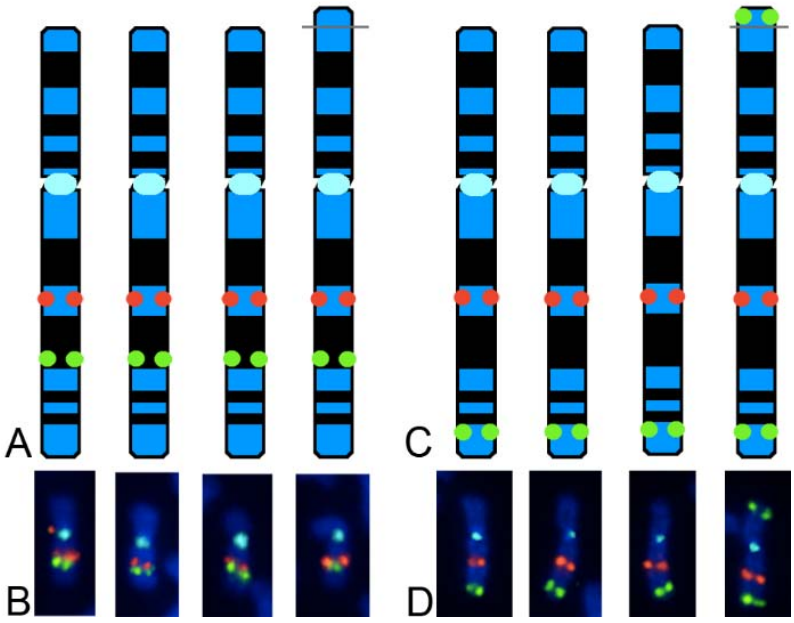

Figure 4. Hybridisation patterns of 7q locus specific probes in K562 chromosomes. Ideograms representing localisation of hybridisation signals for the 7q22/7q31 probe set are shown in (A) in correspondence to the hybridised chromosomes (B). The distribution of signals is where expected in the four copies of chromosome 7. It is noted that one of these chromosomes has a slightly longer p arm (first from the right in A and B). Ideograms representing localisation of hybridisation signals for the 7q22/7q36 probe set are shown in (C) in correspondence to the hybridised chromosomes (D). The distribution of signals is where expected in three copies of chromosome 7. The fourth copy shows 7q36 signals on both the long arm and the short arm (first from the right in C and D).

This might be due to an intrachromosomal rearrangement or to a translocation with its homologue. However, in the cell line in our laboratory, the other three copies of chromosome 7 do not seem to be affected (see Figure 6). We contemplated the possibility that in the original karyotype described by Naumann *et al.* [22], this rearranged chromosome was already visible and was indicated as inv(7). The other two abnormal copies of chromosome 7 disappeared due to clonal

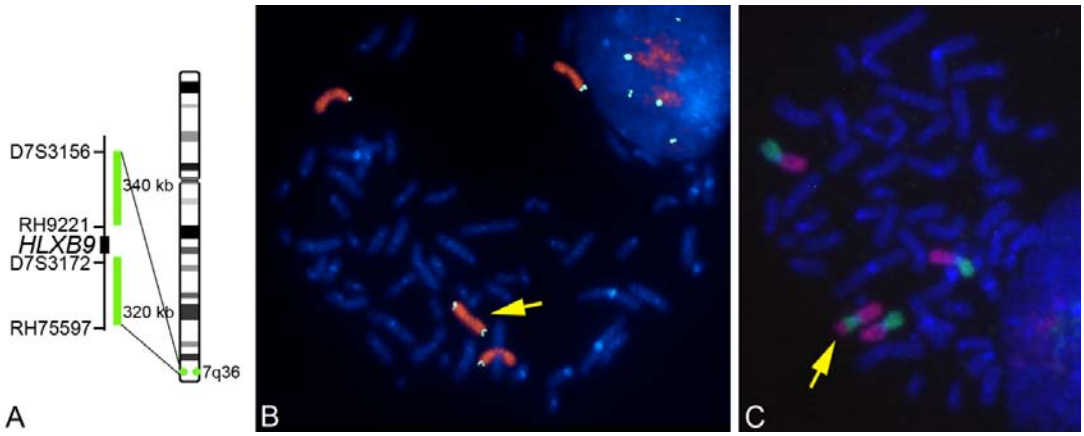

Figure 5. Chromosome 7 paint patterns in K562 chromosomes. (A) Mapping details of the HLXB9 probe used in dual-colour FISH. (B) Whole chromosome paint shows that all four chromosomes 7 are fully painted (in red), and they carry signals specific for the *HLXB9* region in 7q36 (in green). The chromosome 7 indicated by the yellow arrow shows additional *HLXB9* signals on the short arm. (C) Dual colour chromosome paint shows 7q material in red and 7p material in green. The yellow arrow indicates an intrachromosomal rearrangement that involves translocation of a portion of 7q on the distal region of 7p.

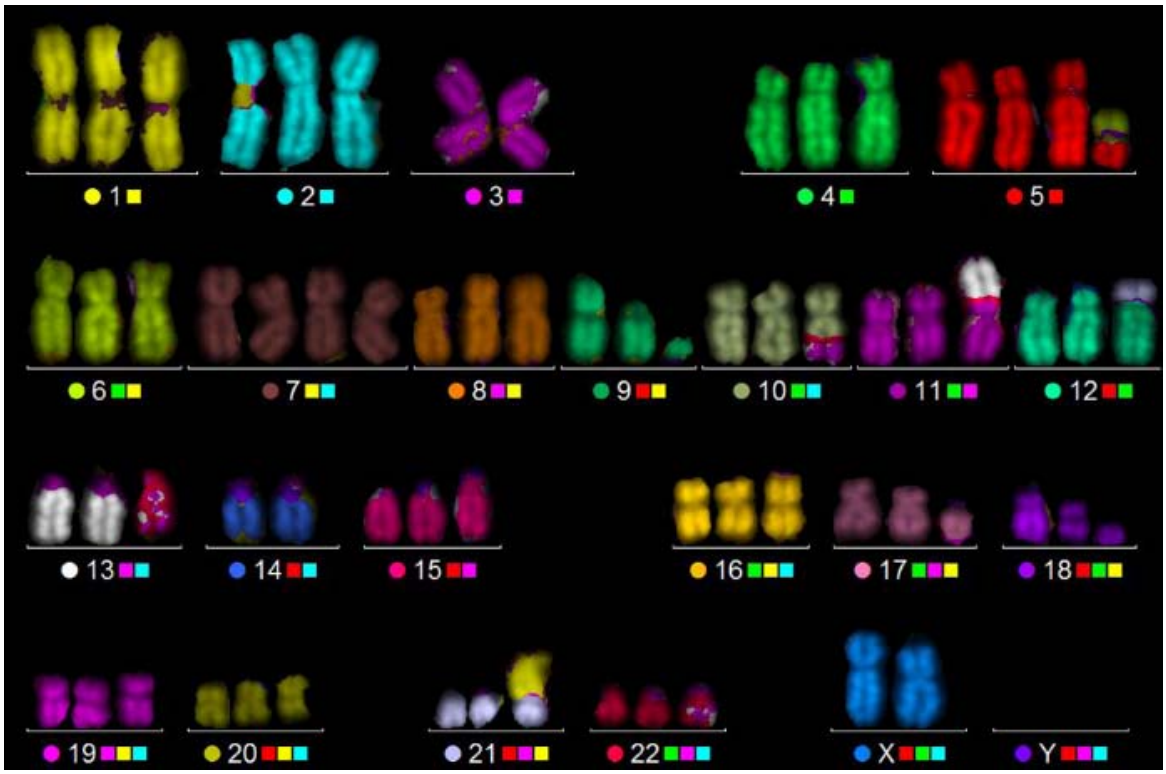

Figure 6. Representative M-FISH karyotype of K562 cell. The karyotype shown here is described as 69,XX,X,-3,+der(5)t(5;6),+7,-9,del(9),ace(9),der(10)t(3;10),der(11)t(11;13),der(12)t(12;21),14,-17,ace(17),-18,del(18),ace(18),der(21)t(1;21). The cell line is near-triploid with cell-to-cell variation in both number of chromosomes and structural abnormalities observed giving ~64-68,XX,-X,-3,+der(5)t(5;6)+7,-9,del(9),ace(9),der(10)t(3;10),der(11)t(11;13),der(12)t(12;21),-14,16,der(17)t(9;17),-18,der(18)t(1;18),ace(18),der(21)t(1;21),-22 [cp10].

evolution and were replaced by duplications of the normal copy. It has to be noted that the presence of an inv(7) has already been mentioned in previous reports [24, 25] (see Table 4). The M-FISH karyotype published by Gribble *et al.* [23] shows a pattern of chromosome 7 rearrangements comparable to what observed by Naumann *et al.* [22] in copy number and chromosome size. However, the interpretation of these rearrangements is different for the two groups of authors. By looking closely at all the reports of inv(7) in K562, we can exclude the possibility that these could have been mis-interpretations. It remains to be established whether the rearrangement here reported is novel, hence occurred *in vitro* independently, or if it was previously undetected due to the limited range of probes used. Assuming we are describing a novel rearrangement, Figure 7 illustrates the series of events that might have led to the situation here reported.

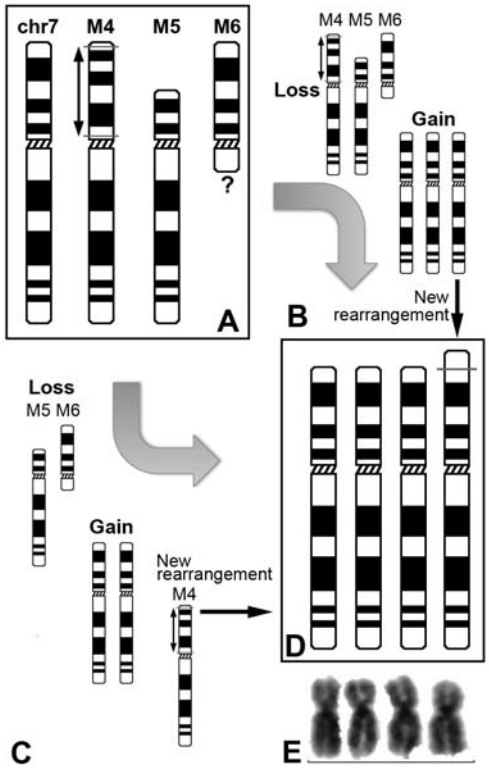

Figure 7. Possible mechanisms for the arising of new 7p rearrangement in K562 cells. (A) shows the status of different copies of chromosome 7 as described by Naumann *et al.*, with an inv(7p) corresponding to marker M4. This karyotype might have evolved with the loss of all chromosome 7 markers (M4, M5 and M6) that were replaced by three copies of the normal chromosome 7 (B). Alternatively, only M5 and M6 might have disappeared from the karyotype, and these might have been replaced by two copies of normal 7. According to this hypothesis, marker M4 should be involved in the rearrangement visible on 7p (C). In any case, either one normal copy of chromosome 7 or the inv(7p) might have acquired a further rearrangement *in vitro* (D). A G-banded partial karyotype showing all copies of chromosome 7 observed in this study is also represented (E).

Importance of cell lines and their characterisation in cancer research

Cancer cell lines are used in many research laboratories and considerable progress in the understanding of cancer and leukaemia biology to date has been possible through the use of cell lines. Cell lines derived from myeloid leukaemia in particular, provide model-systems to study normal and altered myeloid development with the ultimate aim to test appropriate therapies. The three cell lines chosen in this study are all characterised by the presence of abnormalities of chromosome 7. The extent of the abnormality as well as the complexity of the karyotype varies. However, for different aspects these cell lines may contribute to the understanding of the chromosome 7 biology in the leukaemia phenotype, as it has already been demonstrated in some studies [14, 21, 26]. It is very common that cell lines are established in one laboratory and then passed to other research groups. When exposed to new environment, and also when undergoing through a number of passages, cell lines may be subjected to variations. In the long run, cell lines might lose their characteristics and might evolve differently from the samples they originated from [27]. Furthermore, it has been estimated that the changes observed in up to 15% of leukaemia and lymphoma cell lines are due to cross contamination [28]. It is therefore important to carry out a thorough characterisation and regular monitoring of the cell lines used in the laboratory. Cytogenetics and DNA fingerprinting are commonly used for the authentication of cell lines, and with the use of FISH it is possible to target specific regions of interest in the genome in order to confirm the presence of certain chromosomal characteristics.

In the cell lines handled in this study, we focused on the analysis of chromosome 7 using a series of

ready-made probes. We confirmed previous data obtained by FISH and previously published on two cell lines, GDM-1 and GF-D8. Of the three cell lines, K562 is more extensively used in research laboratories in different contexts. The change in the chromosome 7 abnormalities found in this cell line is more likely to be due to clonal evolution than cross contamination. This is suggested by the M-FISH karyotype (see Figure 6) that shows most of the characteristics of the original karyotype reported by others [22, 23].

Examples of the generation of new cell lines with different characteristics from the parent cell line by clonal evolution have been reported in the literature [29, 30]. The situations observed in cell lines might mimic those occurring *in vivo* creating further models for study. Furthermore, it has been shown that a possible coexistence of two clones *in vitro* from the same original specimen might be beneficial for the understanding of tumour heterogeneity [31].

CONCLUSIONS

In this study we employed a series of FISH probes commercially available to confirm and refine the rearrangements of chromosome 7 in three myeloid leukaemia-derived cell lines. This approach enabled us to uncover an unusual rearrangement in K562 that was not reported previously. This feature, together with the normal appearance of the remaining copies of chromosome 7 led us to think that the cell line has evolved from the one originally described. In conclusion, FISH using a more targeted approach than previously adopted for the characterisation of K562 chromosomes, has enabled us to better understand the contribution of chromosome 7 to its karyotype.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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