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SHORT COMMUNICATION

Comprehensive cytogenomic profile of the in vitro neuronal model SH-SY5Y

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Abstract The widely studied SH-SY5Y human neuroblastoma cell line provides a classic example of how a cancer cell line can be instrumental for discoveries of broad biological and clinical significance. An important feature of the SH-SY5Y cells is their ability to differentiate into a functionally mature neuronal phenotype. This property has conferred them the potential to be used as an in vitro model for studies of neurodegenerative and neurodevelopmental disorders. Here, we present a comprehensive assessment of the SH-SY5Y cytogenomic profile. Our results advocate for molecular cytogenetic data to inform the use of cancer cell lines in research.

Keywords SH-SY5Y · Neuroblastoma · Cytogenomic · Neuronal Model · Molecular cytogenetics · Karyotype

Introduction

Cancer cell lines are extensively used as models to investigate the genetics and behaviour of specific tumours. More generally, they are an important resource for basic research on diverse aspects of cellular biology, differentiation and pathology. The widely studied SH-SY5Y human neuroblastoma cell line provides a classic example of how a cancer cell line can be instrumental for discoveries of broad biological and medical significance.

Neuroblastoma is a paediatric malignancy of neuroectodermal origin, characterised by genetic heterogeneity and variable clinical progression. The SH-SY5Y cell line is a third successive sub-clone of the SK-N-SH line, originally established from a bone marrow biopsy of a metastatic neuroblastoma patient [1]. The SK-N-SH parental line comprises at least two morphologically and biochemically distinct phenotypes: neuroblastic (N-type), that led to the sub-cloning of SH-SY5Y (neuroblast-like), and substrate adherent, non-neuronal form (S-type), that led to the sub-cloning of SH-EP (epithelial-like). Different theories have been postulated with regard to the possible biological phenomenon behind the co-existence of those two different cellular phenotypes. Trans-differentiation or the ability of neuroblastoma cells to interconvert bi-directionally, in vitro, from a neuroblast (N) to a non-neuronal (S) form was the initial explanation [2]. Later, "clonal expansion", or the ability of one of the clones co-existing in the parental cell line to expand over the other, was advanced as an alternative explanation [3].

Unquestionably, the most important characteristic of the SH-SY5Y cells is their ability to differentiate into a functionally mature neuronal phenotype in the presence of various agents, for example sequential exposure to retinoic acid and brain-derived neurotrophic factor in serum-free medium [4], and when cultured three-dimensionally [5]. Upon differentiation, they stop proliferating and a constant cell number is subsequently maintained.

This property has conferred the SH-SY5Y cell line with the potential to provide an alternative to the experimental limitations caused by the inability of primary neurons to

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propagate in vitro. Consequently, the SH-SY5Y cell line has been extensively used as a neuronal model since the early 1980s in experimental neurological studies, including analysis of neuronal function, growth and damage in response to insult, degeneration and differentiation.

Differentiated and undifferentiated SH-SY5Y cells have become a popular in vitro cell model for Parkinson disease as they possess many characteristics of dopaminergic neurons [6–9]. Because upon differentiation the SH-SY5Y cells have been found to express mature tau isoforms, this cell line has also gained a status as an in vitro model for research into Alzheimer's disease [10]. The repertoire of biological research that relies on the use of the SH-SY5Y cells has been rapidly expanding and has recently included investigations on autism-spectrum neurodevelopmental disorders [11, 12], studies of mitochondrial metabolism and antioxidant defences upon neuronal differentiation [13] and research of productive varicella-zoster virus infection of neuronal cells [14].

Neuroblastoma, like most human cancers, is characterised by non-random chromosomal abnormalities, to include large-scale chromosomal imbalances, with diagnostic and prognostic significance [15–19]. The first cytogenetic analysis of the SH-SY5Y cell line was performed by Spengler and collaborators in 1983 [2] and a revised G-banded karyotype subsequently published by the same authors in 2002 [20]. Those first classical cytogenetic studies succeeded in describing with certain accuracy some, but obviously not all, of the chromosomal abnormalities that were subsequently to be identified in the SH-SY5Y cell line by means of higher-resolution molecular cytogenetic techniques. In 2001, Van Roy and collaborators published a detailed description of genetic alterations in 16 neuroblastoma cell lines, to include the SH-SY5Y parental cell line SK-N-SH [21]. In 2003, by applying fluorescence in situ hybridization (FISH) with gene- and chromosome-specific probes, to include a SKY multi-colour labelling kit for spectral karyotyping, Cohen and collaborators [3] published a comparative cytogenetic analysis of the parental SK-N-SH cell line and SH-EP and SH-SY5Y, highlighting karyotypic similarities and differences between the three lines. Further molecular cytogenetic insights specifically into the karyotype of the SH-SY5Y cell line were gained by Do and collaborators [22] by means of comparative genomic hybridization on a custom-designed 4000 bacterial artificial chromosomes microarray, covering the whole human genome. That study allowed the identification of unbalanced chromosomal changes—gains and losses—at a resolution of 1 Mb. More recently, Kryh and collaborators [23] published the first high-density single-nucleotide polymorphism (SNP) array study on the SH-SY5Y, revealing the presence of previously undetected allelic imbalances and copy-neutral loss of heterozygosity (LOH).

In the present study, by means of a comprehensive molecular cytogenetic approach, including single-probe FISH, multi-colour karyotyping by M-FISH and MCM-banding, and microarray analysis for copy number variants (CNV) and LOH, we carried out a detailed re-assessment of the chromosomal complement and genomic profile of the SH-SY5Y. Given the common use of this neuroblastoma cell line as an in vitro model for studies of neurodegenerative and neurodevelopmental disorders, our aims were to resolve previous inconsistencies and provide the definitive SH-SY5Y karyotype description.

Materials and methods

The SH-SY5Y cell line was purchased from the European Collection of Cell Cultures, a Health Protection Agency Culture Collection. Chromosome preparations were obtained from unsynchronised cultures of early passage cells upon receipt from the repository following standard procedures.

Karyotyping by multiplex fluorescence in situ hybridization (M-FISH) was performed as recommended by the 24XCyte mFISH probe kit manufacturer (MetaSystems, Germany, http://www.metasystems-international.com). Directly labelled chromosome-specific probes used for validation FISH experiments were: Aquarius® Whole Chromosome Painting Probes for chromosome 17 (FITC) and chromosome 15 (Texas Red) (Cytocell), Poseidon™ Whole Chromosome 22 Probe (blue, Platinum Bright 415) (Kreatech), classical 1qh satellite (FITC) and classical D9Z3 satellite (Rhodamine) (Qbiogene). FISH and M-FISH experiments were analysed on a CytoVysion system (Genetix, UK, http://www.genetix.com), consisting of an Olympus BX-51 epifluorescence microscope coupled to a JAI CVM4+ CCD camera.

Multi-colour mBand FISH imaging (MCM-banding) and analysis were performed as recommended by the XCyte1 mBand probe kit manufacturer (MetaSystems, Germany, http://www.metasystems-international.com), utilizing a Carl Zeiss AxioImager.Z2 epifluorescence microscope coupled to a MetaSystems CoolCube camera and MetaSystems ISIS software.

Analysis of copy number (CN) changes and LOH was performed on Affymetrix Cytogenetics Whole-Genome 2.7 M Arrays. Genomic DNA from the SH-SY5Y cell line was extracted from unsynchronysed cultures of early passage number cells upon receipt from the repository (and in parallel with chromosome preparations) using a Qiagen Blood & Cell Culture DNA kit. After ethanol precipitation, the DNA was resuspended in TE buffer (10 mM Tris, pH 8.0, 1 mM EDTA) at a final concentration of 33 ng/μL. Whole genome amplification, fragmentation and labelling

Table 1 SH-SY5Y: Summary of karyotypic findings

Authors, techniques	Chromosome 1	Chromosome 2	Chromosomes 4 and 5	Chromosome 7	Chromosomes 9 and 10	Chromosome 14	Chromosome 16	Chromosomes 15, 17 and 22
Spengler et al. [20], G-banding	der(1)(1pter → 1q25::1q25 → 1q11::1q44 → 1q25::1q25 → 1qter)			+ 7	der(9)(9pter → 9q34::7q22 → 7qter)			der(22)(22pter → 22q13::17q21 → 17qter)
Cohen et al. [3], G-banding and SKY	dup(1)(q12q25)			+7 t(7;8)(q34; q24.2)	der(9)t(2;9) (p15;q34)			der(22)t(17;22) (q21.3;q13)
Do et al. [22], Array-CGH ((4000) BAC clones)	1q12-1q44 Gain	2p25.3-2p16.3 Gain		+7		14q21.1-14q21.3 Loss		17q21.32-17q25.3 Gain; 22q13.1-22q13.2 Loss
Kryh et al. [23], SNP-Array	1q12-1q44 Gain	2pter-2p16.3 Gain	5q34.1 Loss	+7	9p21.2-9p21.1 Gain	14q CN-LOH 14q Loss	16q22.2-16q22.3 Loss	17q Gain 22q CN-LOH
This study[a], SNP-Array, MC-banding, FISH and M-FISH	1q12-1q44 der(1) (1q12→1q31::1q31→1q12::1q44→1q31::1q31→1q44)	2p25.3-2p16.3 Gain/Mosaic	4q28.3 Loss 5q34 Loss 5q14.3 Loss	+7 t(7;8)(q34; q24.2)	9p21.2-9p21.1 Gain; der(9) t(2;9)(p15;q34)/ Mosaic; 10q26.13 Gain	14q13.3-14q21.3 Loss; 14q21.3-14q32.33 CN-LOH	16q22.2-16q22.3 Loss	17q21.33-17q25.3 Gain; 22q12.3 Loss ; 22q13.1-22q13.2 Loss; der(15)t (15;17;22); der (22)t(15;22)

CGH comparative genomic hybridization, *BAC* bacterial artificial chromosome

[a] Additional information on CN data in Table 2

were performed following the array manufacturer instructions. Briefly, after incubation at 50 °C in a GeneChip Hybridization oven with rotation at 60 rpm for 19 h, the arrays were stained in the Gene Chip Fluidic Station 450 and scanned with Affymetrix Gene Chip Scanner 3000. For data analysis, the CEL files were imported into Chromosome Analysis Suite software v.1.2.2. Array quality was evaluated as per manufacturer's instructions and only arrays with SNP-QC>1.1 and MAPD<0.27 were accepted for further data analysis. The analysis was based on the assembly hg19 of the human genome. Parameters were set at minimum filter values of 60Kb, 35 marker count and 0.85 confidence for both gains and losses, and minimum filter values of 100 Kb and 35 marker count for mosaicism. All copy number changes observed were compared to CNVs catalogued in the Database of Genomic Variants (DGV) (http://projects.tcag.ca/variation/) and the UCSC genome browser (http://genome.ucsc.edu/).

Results and discussion

We have applied an all-inclusive cytogenomic approach to re-evaluate the karyotypic profile of the SH-SY5Y, a neuroblastoma cell line widely used as an in vitro neuronal model. By combining FISH-based techniques, which retain information on a per cell basis, with high-resolution microarray-based techniques, we were able to report thus far unnoticed karyotypic features of the SH-SY5Y cell line. Our findings are summarised in Table 1 together with findings from previous investigations.

M-FISH analysis confirmed the presence of a set of previously reported chromosomal abnormalities that in combination define the cytogenetic identity of the SH-SY5Y cell line (Fig. 1), consisting of chromosome 7 trisomy, a duplication of the entire q arm of chromosome 1, a balanced translocation involving chromosomes 7 and 8, a derivative 9 t(2;9), and a derivative 22 believed to be the result a of a t (17;22). Another distinctive karyotypic trait of the SH-SY5Y is the lack of amplification of the N-myc proto-oncogene.

In our study, the derivative chromosome 9, resulting from a translocation of extra chromosome 2p material to chromosome 9, appeared in only 50 % of metaphases analysed by M-FISH and dual-colour FISH analysis with chromosome-specific probes (data not shown). This observation ties with the mosaic status of the detected imbalance (gain) on the short arm of chromosome 2 (2p25.3-2p16.3), as shown by

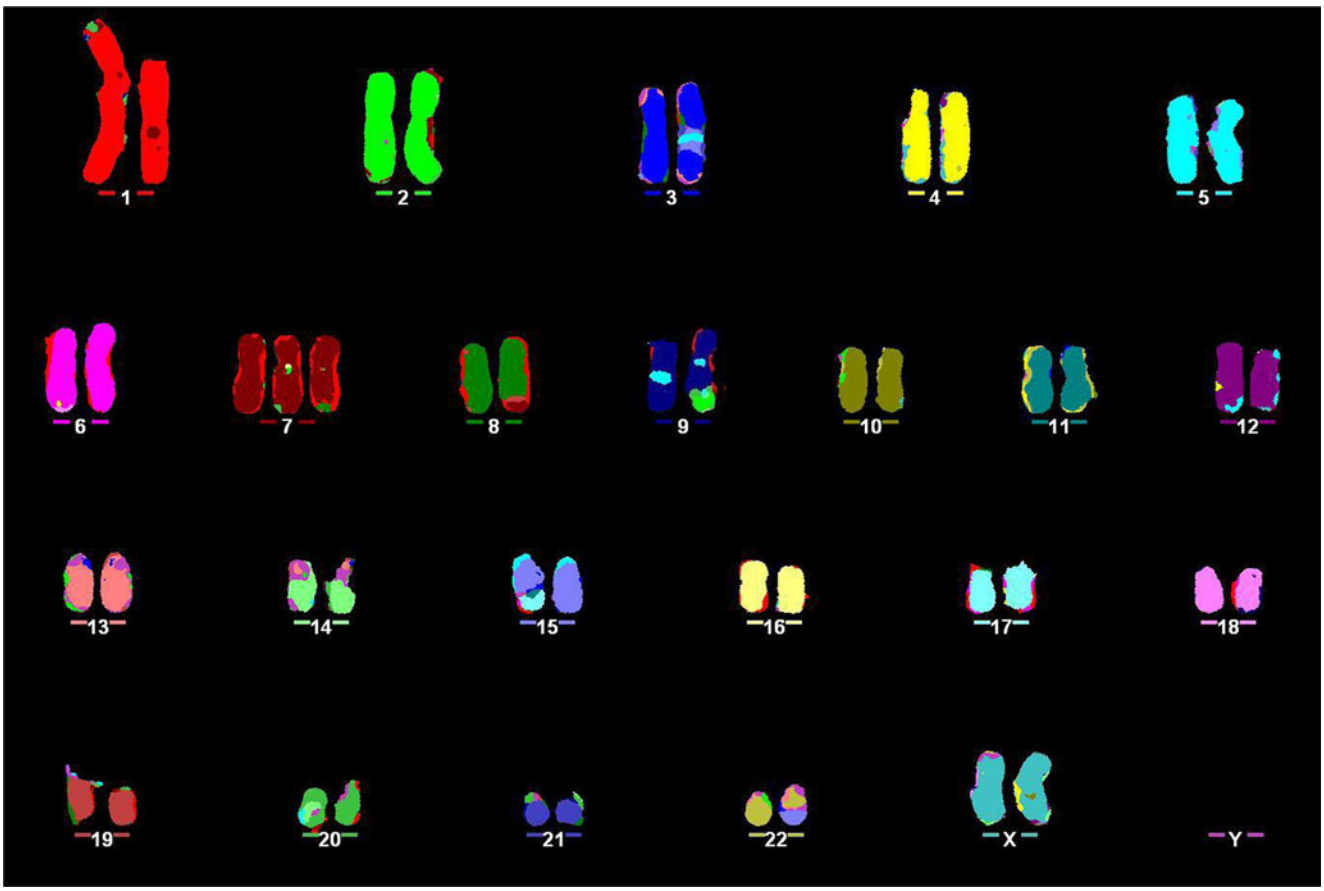

Fig. 1 Representative example of M-FISH analysis. The karyotypic identity of the SH-SY5Y cell line is confirmed by multi-colour karyotyping

Table 2 SH-SY5Y: gains and losses identified in this study by microarray analysis

Chromosome	Type	CN state	Min	Max	Size (kbp)	Cytoband	Genes	Other
1	Gain	3	145,388.014	247,906.738	102,519	1q21.1-1q44	Large number	1q Trisomy
2	Gain	3	234.052	48,165.786	47,932	2p25.3-2p16.3	Large number	Mosaic
4	Loss	1	134,926.438	135,186.391	260	4q28.3	PABPC4L	DGV
5	Loss	1	168,029.695	168,226.333	197	5q34	SLIT3, MIR218-2	DGV/segm.dupl.
5	Loss	1	83,782.541	83,907.654	125	5q14.3	None	DGV/segm.dupl.
7	Gain	3	46.845	159,118.443	159,071	7p22.3-7q36.3	Large number	7 Trisomy
9	Gain	3	26,628.228	28,223.980	1,595	9p21.2-9p21.1	C9orf82, PLAA, IFT74, LRRC19, TEK, NCRNA00032, C9orf11, MOBKL2B, IFNK, C9orf72, LINGO2	DGV/segm.dupl.
10	Gain	3	123,334.116	123,541.044	207	10q26.13	FGFR2, ATE1	DGV
14	Loss	1	37,139.362	49,563.020	12,424	14q13.3-14q21.3	Large number	DGV/segm.dupl.
14	Copy-neutral LOH	2	48,216.230	107,242.027	59,026	14q21.3-14q32.33	Large number	14q CN-LOH
16	Loss	1	72,558.134	73,017.684	460	16q22.2-16q22.3	ZFHX3	DGV/segm.dupl
17	Gain	3	43,825.911	81,004.770	37,179	17q21.33-17q25.3	Large number	DGV/segm.dupl.
22	Loss	1	32,411.007	32,472.930	62	22q12.3	SLC5A1	no
22	Loss	1	38,337.611	44,222.693	5,885	22q13.1-22q13.31	Large number	DGV/segm.dupl

our CNV microarray data (Table 2). A high incidence of unbalanced "jumping" translocations involving a gain of chromosome 2 short arm material with a minimum region of overlap 2pter-2p22 and various partner chromosomes had been previously observed in a panel of 18 neuroblastoma cell lines, including the parental SK-N-SH [21, 24]. Recent SNP array studies had indicated the gain on chromosome 2p to be an aberration shared by the SK-N-SH parental line and its neuroblast-like sub-clone SH-SY5Y, but not its epithelial sub-clone SH-EP [23]. Given that the three cell lines were found in general to be very similar, sharing many of the chromosome aberrations, it could be argued that most of the chromosomal alterations seen in the daughter cell lines were present in a mosaic form in the parental cell line (and perhaps also in the original tumour), and that the karyotypes of the daughter cell lines are the result of the combined effect of the initial sub-cloning and subsequent cell line evolution over time.

An intriguing finding emerging from our investigations was the nature of the rearrangement(s) involving chromosome 17 and 22, which were revealed to be more complex than previously reported. Structural abnormalities of chromosome 17 resulting in gain of material are the most frequent genetic abnormalities in neuroblastoma and powerful independent predictor of poor outcome, commonly found in primary tumours and cell lines. Our SNP array analysis showed in the SH-SY5Y cell line a gain on chromosome

Fig. 2 Three-colour FISH shows a complex rearrangement involving chromosomes 15, 17 and 22. Three-colour FISH with directly labelled chromosome-specific "paints" for chromosome 15 (*red*), 17 (*green*) and 22 (*blue*) on reverse-DAPI banded chromosomes confirms the presence of a der(22)t(15;22) (*top arrow*) and a der(15)t(15;17;22) (*bottom arrow*)

17q (17q21.33-17q25.3) and two distinct losses on chromosome 22q (22q12.3 and 22q13.1-22q13.31). Differently from what reported previously, our M-FISH and validation FISH experiments with chromosome-specific probes revealed the derivative 22 to be the result of a translocation involving not chromosome 17, as initially thought, but chromosome 15. We also identified a der(15)t(15; 17; 22) (Figs. 1 and 2).

The Affymetrix Cytogenetics Whole-Genome 2.7 M Array used in this study provides high-density coverage across the genome, with 2.7 million markers, including 400,000 SNPs, spaced throughout at a median inter-marker distance of ~1 kb. Indeed, multiple areas of LOH and copy number gain were identified in this analysis of the SH-SY5Y cell line (Table 2). Although most of the gains and losses overlap with polymorphic CNVs documented in the DGV, it is nevertheless interesting that the list of genes concerned by the imbalances includes a number of transcription factors involved with cancer and neuronal differentiation, like ZFHX3 on chromosome 16q, SLIT 3 on chromosome 5q and FGFR2 on chromosome 10q. Loci of neuro-biological interest, also mapping on structurally re-arranged chromosomal regions in the SH-SH5Y cell line, are the Parkinson's-associated LINGO2 gene on chromosome 9p, the MAPT gene (encoding TAU) on chromosome 17q, PSEN1 gene on 14q, and the 15q11-13 chromosomal region.

Almost all of the regions of LOH resulted from copy number loss. However, we also observed extensive copy-neutral LOH on chromosome 14q (14q21.3-14q32.33). LOH on the long arm of chromosome 14—with a consensus region in 14q23-q32—has been consistently observed in primary neuroblastomas, suggesting the deletion of this region to be a common abnormality in these tumours [25]. UPD or LOH with neutral copy number of chromosome arm 14q was also reported in primary neuroblastoma tumours and derivative early-passage cell lines [26].

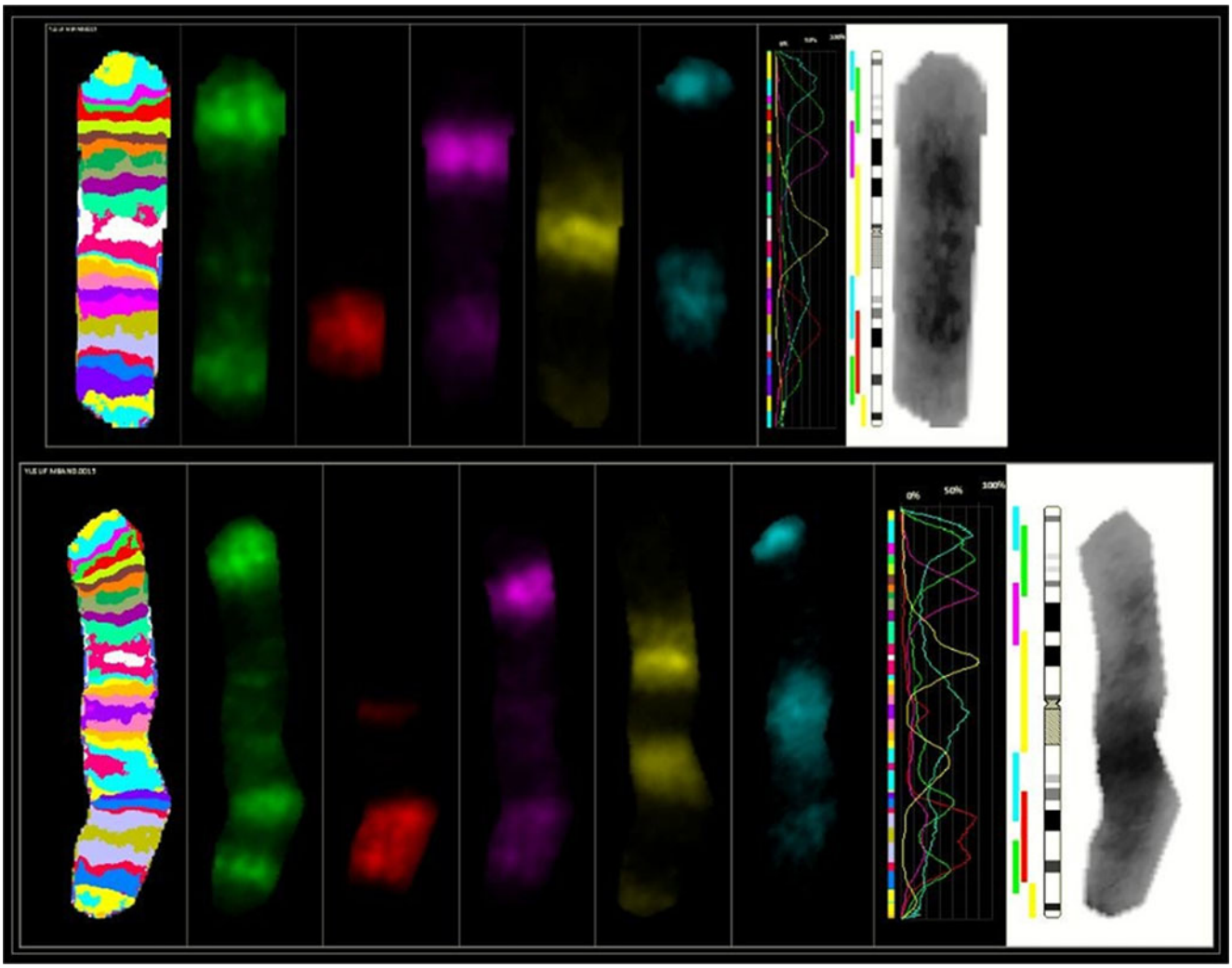

Fig. 3 High-resolution multi-colour chromosome banding provides new clues on complex 1q rearrangement. A duplication of the entire long arm appears to have been followed by a paracentric inversion

Our investigations by high-resolution multi-colour chromosome banding on the long arm of chromosome 1 suggest a complex rearrangement arising from a duplication of the entire chromosome arm—as confirmed by our SNP-array analysis—followed by a paracentric inversion, resulting in a der(1)(1q12→1q31::1q31→1q12::1q44→1q31::1q31→1q44) (Fig. 3). Duplication of the juxtacentromeric heterochromatic area was confirmed by FISH analysis with a D1Z1 probe for the classical satellite DNA (data not shown).

In the light of what previously published and confirmed by us, and what newly identified by us, we would like to suggest an updated karyotypic description for the SH-SY5Y cell line to imply the existence of two cytogenetically related subclones (stemline and sideline), as follows: 47,XX, der(1)(1q12→1q31::1q31→1q12::1q44→1q31::1q31→1q44), +7, der(7)t(7 ;8)(q34 ;q24.2), der(8)t(7 ;8)(q34 ;q24.2), der(15)t(15;17;22), der(22)t(15;22)[54]/47, idem, der(9)t(2;9)[46]. The number of cells for each sub-clone in our sample is given in square brackets. Additional CN variation array data are summarised in Table 2. M-FISH observations on SH-SY5Y cells at a higher passage number (data not shown) would suggest the sideline karyotype to become prevalent, with most of the metaphases analysed presenting the der(9)t(2;9) as well as new chromosomal aberrations resulting from the extended culture.

Given the importance acquired by the SH-SY5Y cell line as a neuronal in vitro model, a thorough understanding of its genetic background is of paramount importance. We believe that information on the SH-SY5 cytogenomic profile should be factored in when designing experimental studies based on these cells. In particular, the interpretation of the results should be passage number- and karyotype-informed, especially with regard to gene expression data and genome architecture of genetic loci linked to cancer or neurological diseases which coincidentally map to chromosomal regions that are highly re-arranged in this cell line. For instance, biomedical research relying on the use of the SH-SY5Y cells for highly topical diseases like Parkinson and Alzheimer's and autism-spectrum developmental disorders, should take into account possible dosage effects or position effects on loci like the Parkinson's-associated LINGO2 gene on chromosome 9p, the MAPT gene (encoding TAU) on chromosome 17q, PSEN1 gene on 14q, and the 15q11-13 chromosomal region.

Our results demonstrate the impact of an integrated molecular cytogenetic approach on the ability to resolve complex karyotypes and underline the importance for the cytogenomic profiling of cancer cell lines to inform their use in research.

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Conflicts of interest The authors declare that they have no conflict of interest.

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