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Genomic profiling of plasma cell disorders in a clinical setting: integration of microarray and FISH, after CD138 selection of bone marrow

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ABSTRACT

Aim To evaluate the role of whole genome comparative genomic hybridisation microarray (array-CGH) in detecting genomic imbalances as compared to conventional karyotype (GTG-analysis) or myeloma specific fluorescence in situ hybridisation (FISH) panel in a diagnostic setting for plasma cell dyscrasia (PCD).

Methods A myeloma-specific interphase FISH (i-FISH) panel was carried out on CD138 PC-enriched bone marrow (BM) from 20 patients having BM biopsies for evaluation of PCD. Whole genome array-CGH was performed on reference (control) and neoplastic (test patient) genomic DNA extracted from CD138 PC-enriched BM and analysed.

Results Comparison of techniques demonstrated a much higher detection rate of genomic imbalances using array-CGH. Genomic imbalances were detected in 1, 19 and 20 patients using GTG-analysis, i-FISH and array-CGH, respectively. Genomic rearrangements were detected in one patient using GTG-analysis and seven patients using i-FISH, while none were detected using array-CGH. I-FISH was the most sensitive method for detecting gene rearrangements and GTG-analysis was the least sensitive method overall. All copy number aberrations observed in GTG-analysis were detected using array-CGH and i-FISH.

Conclusions We show that array-CGH performed on CD138-enriched PCs significantly improves the detection of clinically relevant and possibly novel genomic abnormalities in PCD, and thus could be considered as a standard diagnostic technique in combination with IGH rearrangement i-FISH.

Array-comparative genomic hybridisation (CGH) overcomes the need for dividing PCs for conventional GTG-analysis as well as the highly targeted detection of changes in regions by interphase fluorescent in situ hybridisation (i-FISH). Array-CGH, similar to G-banding, detects regions of chromosomal gain or loss throughout the whole genome. Furthermore, array-CGH allows for the detection of gains and losses of genetic material at a much higher resolution. In this study, we demonstrate the superiority of combining the screening methods of array-CGH and IGH translocation i-FISH in detecting genomic changes in PCDs.

PATIENTS AND METHODS

Patients

We studied 20 patients (50% male) with PCD based on WHO criteria.¹ Bone marrow (BM) aspirates were collected after informed consent and were selected based on availability of sufficient sample material.

GTG-analysis

GTG-analysis was performed on unstimulated BM cells after long-term (72h and 120 h) culture. Chromosomes were banded using trypsin digestion pretreatment followed by staining with Giemsa solution. Karyotypes were described according to ISCN 2013.⁹

Immunomagnetic enrichment of CD138 positive cells

PCs were selected to a purity of >90% (as previously tested on a subcohort (results not shown)) by immunomagnetic enrichment of CD138 positive cells using the human CD138 positive selection kit (STEMCELL Technologies Melbourne, Australia). Selected cells were used for both array-CGH and i-FISH.

Interphase fluorescent in situ hybridisation

i-FISH was performed on all samples using a mixture of locus-specific probes for 1q21(S100A10)/8p21(PNOC), 11q23(ZBTB16)/13q14(DLEU1) and 17p13(TP53)/19q13.3(CD37) (Kreatech, The Netherlands) and a break-apart probe for 14q32 (IGH). An additional panel of dual fusion probes was applied to the samples that were positive for an IGH rearrangement (4p16(FGFR3)/14q32(IGH), 11q13(MEYO)/14q32(IGH) and 14q32(IGH)/16q23(MAF)) (Cytocell, UK). According to the UK Haemato-Oncology Best Practice Guidelines, a minimum of 100 interphase nuclei were scored wherever possible. Cut-off values were set at the levels recommended by the European Myeloma Network.¹⁰

Genomic imbalances are the predominant genetic abnormality in monoclonal plasma cell disorders (PCD), a group of disorders that include monoclonal gammopathy of undetermined significance, asymptomatic myeloma and symptomatic myeloma (commonly known as multiple myeloma).¹ Rearrangements of the Immunoglobulin heavy locus (IGH) gene are a common feature of PCDs and are of prognostic importance.^{2,3}

PCDs have heterogeneous clinical and biological features. Chromosomal abnormalities detected at diagnosis provide important prognostic information, and predict initial response to chemotherapy, remission duration and overall survival. Genetic risk stratification can assist in guiding specific chemotherapeutic interventions, such as bortezomib and high-dose therapy for patients categorised into high-risk groups.³⁻⁵ Genetic results are not currently included in the diagnostic criteria for PCDs.⁶⁻⁸



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Array-CGH

Whole genome microarray was performed using an oligonucleotide array (8×60 k oligonucleotide array, CCMC design) (BlueGnome, UK). Labelling and hybridisation of patient DNA was performed as per the Agilent Oligonucleotide Array-Based CGH for Genomic DNA analysis-Enzymatic protocol user manual. Sex-matched reference DNA supplied by Agilent Technologies was used (Agilent Technologies, USA). Scanning of the array was performed on an Agilent Technologies DNA Microarray Scanner. Analysis was performed using BlueFuse Multi V2.5 software (BlueGnome, UK).

RESULTS

Genomic imbalances and rearrangements were detected in 1 (15%) patient using GTG-analysis, 19 (95%) patients using i-FISH and 20 (100%) patients using array-CGH and the combination of array-CGH and IGH rearrangement i-FISH.

The total number of abnormalities detected using array-CGH was 248 (figure 1). Seventy abnormalities were detected using i-FISH and 14 by GTG-analysis. On integration of array-CGH and IGH rearrangement i-FISH techniques, the detection of genomic imbalances and rearrangements reached a total of 257 aberrations.

Comparison of techniques for discordance

GTG-analysis compared with iFISH and array-CGH

GTG-analysis provided metaphases for all cases, of which 95% (19/20) produced apparently 'normal' results (see online supplementary table S1). One case was found to be abnormal in which two clonal populations were identified in a low number of cells (4/51). GTG-analysis detected a rearrangement involving 8q and an unknown partner chromosome. This rearrangement was not completely defined using GTG-banding, but was identified as two derivative 8 chromosomes with the loss of the 8p and a gain of unidentified genetic material (+der(8)t(8;?)(p11.2;?)×2). In this instance, the i-FISH probe located at 8p21(PNOC) identified the loss of this loci in 98% of cells scored, but did not detect a rearrangement. Array-CGH clarified the findings of GTG-analysis and identified the additional material on chromosome 8 as being that of 19p, which included the 19 centromere to produce +der(19)t(8;19)(q11.1;q12)×2. Array-CGH did not detect the rearrangement (see online supplementary table S1).

i-FISH compared with array-CGH

i-FISH detected only 62 copy number aberrations (20% cut-off value) and a total of eight IGH rearrangements (10% cut-off

value) in seven cases. Array-CGH identified 241 genomic aberrations at a 1 Mb resolution and a further seven aberrations at the FISH probe loci that were <1 MB to give a total of 248, of which 69 were whole chromosome changes. The seven copy number changes detected at <1 MB all involved the IGH variable region at 14q32.3 (see online supplementary table S1).

Three copy number change aberrations detected by i-FISH in greater than 20% of cells were not detected using array-CGH. These aberrations were present in 21%, 23% and 28% of cells in cases 2, 6 and 11, respectively, and constituted 1.33% (3/226) of the total loci tested by i-FISH.

Interestingly, case 10 was identified as having a near-tetraploid clone by i-FISH (see online supplementary table S1). The array software normalised the data at a copy number of four (Log₂=0), hence all copy numbers greater or less than four were seen as either a gain or a loss. Near-tetraploid clones generally represent a doubling of the original abnormal clone, hence, all aberrations of the original clone were detected.

Combining IGH rearrangement i-FISH and array-CGH

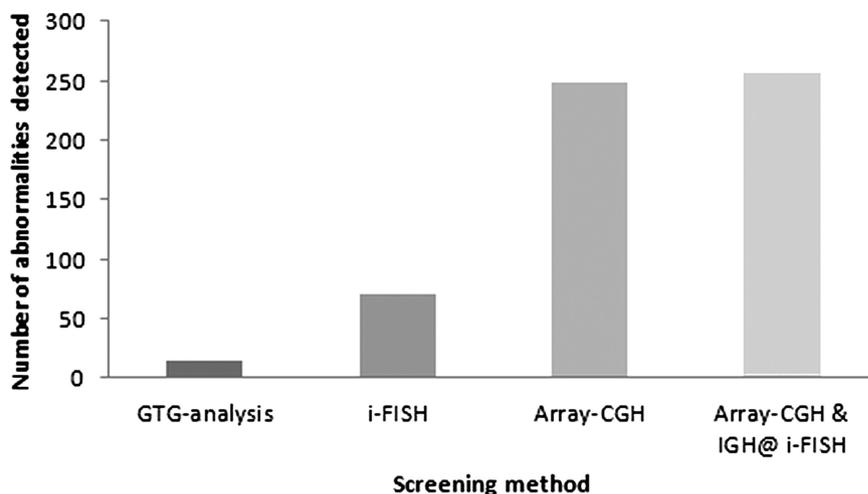
Predictably, array-CGH analysis did not detect IGH rearrangements. However, i-FISH detected rearrangements in 7/20 cases. Of the 7 cases with an IGH rearrangement, 3 involved MYEOV (11q13), 1 FGFR3(4p16), 1 MAF(16q23) and 2 with an unidentified partner chromosome (see online supplementary table S1).

DISCUSSION

GTG-analysis detection rates in myeloma

GTG-analysis for monoclonal PC disorders is inadequate as only one patient showed an abnormal karyotype (case 8) (see online supplementary table S1). This has also been demonstrated in several other studies and is most likely related to the low proliferation rate of PCs.^{11–13} The production of abnormal karyotypes has also been associated with disease progression. Studies have indicated that the earlier stages of disease will be less likely to produce abnormal karyotypes as the abnormal PCs are still stromal dependant and are not able to replicate in situ.^{14–16} This may impact on the availability of dividing PCs for GTG-analysis. Some studies show that stimulation of cultures using various agents such as interleukins, 12-O-tetradecanoylphorbol-13-acetate (TPA), phytohaemagglutinin and granulocyte-macrophage colony-stimulating factor (GM-CSF) may increase the yield of genetically abnormal karyotypes in some cases.^{17–19} The use of stimulants to increase the production of metaphases

Figure 1 Total number of abnormalities detected across 20 patient samples by each individual screening method and the combination of array-CGH and IGH rearrangement i-FISH. i-FISH, interphase fluorescent in situ hybridisation; array-CGH, comparative genomic hybridisation; IGH i-FISH, IGH rearrangement i-FISH.



by PCs is one methodology that may have increased the mitotic yield of abnormal PCs.

Interestingly, a cryptic translocation involving chromosome 8q and unidentified genetic material in case 20 was detected using GTG-analysis, and was further classified with array-CGH to show involvement with chromosome 19p and centromeric regions. This was redefined from $+der(8)t(8;?)(p11.2;?)\times 2$ to $+der(19)t(8;19)(q11.1;q12)\times 2$. To the best of our knowledge, this $t(8;19)$ appears to be a novel translocation in myeloma and there are no known prognostic associations with a gain of 19p in myeloma (see online supplementary table S1).

Genetic risk categorisation of monoclonal PC disorders

Myeloma typically falls into one of two main categories hyperdiploidy or non-hyperdiploidy depending upon the genetic signature of the disease. The hyperdiploid group of myeloma patients (approximately 45% of cases) is associated with standard risk and improved outcome according to the International Myeloma Working Group (IMWG) and Mayo Clinic stratification for myeloma and risk-adapted therapy (mSMART) categorisation.^{3 20 21} The non-hyperdiploid patients (approximately 40%) generally exhibit a translocation involving IGH and losses of either whole chromosomes or chromosome arms. Risk involved in these patients ranges from standard to intermediate to high, depending largely on the translocation partner of the IGH gene. The remaining 15% of cases exhibit traits of both hyper and non-hyperdiploid categories and their associate risk varies depending on which genetic abnormalities are detected.^{8 20 21}

The ploidy status of a patient is achievable using array-CGH; however, the complete risk categorisation can only be determined when array-CGH is combined with IGH rearrangement i-FISH.^{3 8} In our cohort, we determined 7 cases to be hyperdiploid, 12 cases non-hyperdiploid and 1 case to be a combination of both based on copy number changes and the IGH rearrangement status in accordance with the IMWG guidelines. The ability to determine ploidy when using a myeloma-specific FISH panel is somewhat limited, as it is unable to determine if the gain or loss is part of a whole chromosome or a segmental change. Used alone, it is an inaccurate tool in assessment of risk based on current IMWG guidelines.

In addition to the mSMART classification, the IMWG reports that some genetic features are considered to be 'secondary genetic events' being indicators of disease progression, including deletion of TP53 at 17p13 and abnormalities of chromosome 1, typically involving losses on 1p and gains on 1q.^{16 21} It has been demonstrated that TP53 deletions are associated with high risk; however, reports vary as to percentage of cells involved before considered high risk. For instance, some papers describe TP53 deletions as prognostically significant if found in >60% of cells^{8 22} while others do not refer to a tumour burden at all.^{3 6 16 20 23} In this study, we detected a TP53 deletion in three cases using both i-FISH and array-CGH screening methods.

Emerging genomic risk markers, such as chromosome 1 aberrations, del(16q), del(12p), del(22q) and chromosome 5 aberrations are currently being investigated by various microarrays and gene-expression profiling.^{16 24–27} Although our cohort is relatively small, these aberrations were identified by array-CGH in many of the cases.

Chromothripsis is another emerging genomic risk marker associated with PCDs and other cancers.^{28 29} This shattering of chromosomes is not reliably detectable by either GTG-analysis or iFISH, and in some cases may be missed at a 1 Mb resolution. It is expected that this array platform will detect chromothripsis, however, there was no evidence of this in the current cohort of

patients to discuss. The current prognostication guidelines set out by the IMWG and the Mayo Clinic do not refer to chromothripsis as this is a very recent finding in genomics. The mechanisms by which it occurs are not yet understood and there has only been one prospective study of a large cohort associating it with patient outcomes in myeloma.^{28 30–33} As this massive genomic instability generally occurs as a secondary genetic event, it can be assumed to be associated with disease progression, however, it is evident that more studies are required to understand the impact of this phenomenon.

The effect of combining array-CGH with IGH rearrangement i-FISH

In this study, the use of array-CGH increased the aberration detection rate (248) significantly in contrast with i-FISH (70) and GTG-analysis (14) alone. Upon combining the IGH rearrangement i-FISH results with the array-CGH results the detection rate improved (257) and added significant prognostic information. However, while array-CGH is a superior screening method for the identification of copy number changes in PCDs, IGH rearrangement i-FISH is still needed to provide prognostic information.

When comparing the sensitivity of i-FISH to array-CGH, only three aberrations were not detected by array-CGH. These were relatively close to the 20% cut-off value (21–28%). This may be explained by the scoring of single cells while excluding clumps of cells by i-FISH; on the other hand, the DNA from clumps of cells and singular cells were tested on the microarray. This slight difference in cell population may have changed the ratio of normal to abnormal clonal populations enough to mask the aberrations present on the microarray. The introduction of single-nucleotide polymorphism (SNP)-microarrays may overcome some of the sensitivity problems uncovered here, as low mosaic array-CGH calls may be confirmed by SNP calls. They will also provide information on copy-neutral genomic loss of heterozygosity, which may be of prognostic importance.^{16 25}

We show that array-CGH significantly improves the detection of clinically relevant and possibly novel genomic abnormalities in PCD, and thus could be considered as a diagnostic technique in combination with IGH rearrangement i-FISH. However, further prospective studies analysing the prognostic significance of these array-CGH findings are needed.

Take home messages

- ▶ Comparative genomic hybridisation (CGH) arrays are a useful and superior screening method for the identification of copy number changes in plasma cell dyscrasia in a clinical setting.
- ▶ However, due to the prognostic significance of IGH(14q32) rearrangements, it is highly recommended that array-CGH be complemented with IGH translocation FISH.
- ▶ Array-CGH has significantly increased the ability to decipher the complex myeloma genome.

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Contributors Study concepts: NKB, NLB, AKE and PR. Study design: NKB, NLB, AKE and PR. Data acquisition: NKB, NLB, AKE and PR. Quality control of data and algorithms: NKB, NLB, AKE and PR. Data analysis and interpretation: NKB and NLB. Statistical analysis: NKB. Manuscript preparation: NKB, NLB, AKE and PR.

Manuscript editing: NKB, NLB, AKE and PR. Manuscript review: NKB, NLB, AKE and PR.

Competing interests None.

Ethics approval Ethical approval was obtained from the Hunter New England Human Research Ethics Committee (Reference No: 10/07/21/5.07 (SSA Reference No: SSA/10/HNE/158—JHH) John Hunter Hospital, NSW, Australia).

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Data sharing statement An additional cohort of 10 patients was tested to provide information regarding the effectiveness of the CD138 plasma cell enrichment process. The results yielded >90% plasma cell purity as detected by flow cytometry in all 10 cases. This is stated in the methodology text and all data is available upon an email request to the corresponding author: Nadine Berry nadine.berry@hnehealth.nsw.gov.au.

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Table S1 Aberrations detected by GTG-analysis, i-FISH an Array-CGH

Case	GTG-Analysis	i-FISH	Array-CGH compared to i-FISH ≥3 oligo-probe calls	Percent Abnormal by i-FISH	Array-CGH ≥1Mb	Size Mb		
1	46,XY[20]	nuc ish(S100A10x3,PNOCx2)[40/104]	dup 1q21.1q44	38.5	dup 1q21.1q44(142,721,294-247,190,744)	104.5		
		nuc ish(S100A10x4,PNOCx2)[33/104]	dup 1q21.1q44	32				
		nuc ish(FGFR3,IGH)x2[100]	No Change	0				
		nuc ish(MYEOV,IGH)x2[104]	No Change	0				
		nuc ish(ZBTB16x2,DLEU1x1)[68/103]	del 13q11q34	66			del 13q11q34(18,194,574-114,125,318)	95.9
		nuc ish(5'IGHVx2,3'IGHx1)(5'IGHV sep 3'IGHx1)[71/100]	del 14q24.1q32.33	71			del 14q24.1q32.33(68,144,107-105,602,632)	37.5
		nuc ish(IGHx2,MAFx1)[132/254]	del 16q11.2q24.3	52			del 16q11.2q24.3(45,058,272-88,729,431)	43.7
		nuc ish(TP53,CD37)x2[100]	No Change	0				
							del Xp22.33(10,319-2,705,404)	2.7
							dup 3p26.3q29(43,674-199,324,691)	WC
			dup 6p25.3q13(49,943-70,861,955)	70.8				
			dup 15q11.2q26.3(20,060,091-100,155,623)	WC				
			dup 19p13.3q13.11(202,077-37,984,420)	37.8				
2	46,XY[20]	nuc ish(S100A10x3,PNOCx2)[65/107]	dup 1q12q44	61	dup 1q12q44(141,559,496-247,190,744)	105.6		
		nuc ish(ZBTB16x2,DLEU1x1)[90/106]	del 13q11q34	85	del 13q11q34(18,194,574-114,125,318)	WC		
		nuc ish(IGHx1)[96/112]	del 14q11.1q32.33	86	del 14q11.1q32.33(18,149,503-106,358,521)	WC		
		nuc ish(TP53x2,CD37x1)[25/111]	No Change	23				
		nuc ish(TP53x1,CD37x2)[10/111]	No Change	9				
					del Xp22.33(10,319-1,649,586)	1.6		
			del 1p36.33p32.2(6,389-57,211,684)	57.2				
			del 9p24.3p11.1(3,932-47,002,116)	50				
			del 16p13.3q24.3(3,015-88,729,431)	WC				
3	46,XX[20]	nuc ish(S100A10x3,PNOCx2)[88/107]	dup 1q12q44	82	dup 1q12q44(141,559,496-247,190,744)	105.6		
		nuc ish(FGFR3,IGH)x2[102]	No Change	0				
		nuc ish(MYEOV,IGH)x2[100]	No Change	0				
		nuc ish(ZBTB16x2,DLEU1x1)[104/112]	del 13q11q34	93	del 13q11q34(18,194,574-114,125,318)	WC		
		nuc ish(5'IGHVx2,3'IGHx1)(5'IGHV sep 3'IGHx1)[98/106]	del 14q24.1q32.33	92	del 14q24.1q32.33(68,383,642-105,590,671)	37.2		
		nuc ish(IGHx2,MAFx1)[76/105]	del 16p11.2q24.3	72	del 16p11.2q24.3(32,298,921-88,729,431)	56.4		
		nuc ish(TP53,CD37)x2[104]	No Change	0				
					del Xp22.33q28(10,319-154,886,048)	WC		
			del 2p11.2p11.1(88,988,234-91,129,969)	2.1				
4	46,XY[20]	nuc ish(S100A10x2,PNOCx1)[97/102]	del 8p23.3q24.3	95	del 8p23.3q24.3(150,880-146,264,210)	WC		
		nuc ish(ZBTB16x2,DLEU1x1)[98/106]	del 13q11q34	92	del 13q11q34(18,194,574-114,125,318)	WC		
		nuc ish(IGHx1)[90/107]	del 14q11.1q32.33	84	del 14q11.1q32.33(18,149,503-106,358,521)	WC		
		nuc ish(TP53x1,CD37x2)[100/130]	del 17p13.3q21.31	77	del 17p13.3q21.31(13,073-40,519,725)	40.5		
		nuc ish(TP53x1,CD37x3)[23/130]	del 17p13.3q21.31/No Change	18				
					del Xp22.33(10,319-2,705,404)	2.7		
					dup Xp22.33q22.1(2,754,731-98,731,391)	95.8		
					dup Xq22.1q28(98,600,122-154,582,4442)	55.9		
					del 2p25.3p24.1(7,049-20,532,717)	20.5		
					dup 5q23.2q35.3(123,233,694-180,614,669)	57.4		

					dup 9p24.3p11.2(63,679-44,669,621)	44.6
					del 12p13.33q24.33(93,179-132,268,952)	WC
					dup 15q15.2q26.3(40,821,296-100,155,623)	59.3
					del 22q11.1q13.33(14,441,236-49,571,093)	WC
5	46,XX[20]	nuc ish(S100A10x3,PNOCx2)[86/103] nuc ish(ZBTB16x2,DLEU1x1)[100/135] nuc ish(IGHx1)[10/115] nuc ish(TP53x2,CD37x3)[62/112] nuc ish(TP53x1,CD37x3)[17/112]	dup 1q12q44 del 13q11q34 del 14q32.33 dup 19p13.3q13.43 No Change/dup 19p13.3q13.43	83 74 9 56 15	dup 1q12q44(141,559,496-247,190,744) del 13q11q34(18,194,574-114,125,318) dup 19p13.3q13.43(61,720-63,714,244)	105.6 WC WC
					del Xp22.33q28(10,319-154,886,048)	WC
					dup 5p15.33q35.3(132,176-180,658,955)	WC
					dup 7p22.3q36.3(153,877-158,811,298)	WC
					dup 9p24.3q34.3(3,932-140,235,770)	WC
					dup 15q11.1q26.3(18,362,585-100,155,623)	WC
					del 17q11.2q21.31(25,538,030-38,990,118)	13.4
					dup 17q21.31q21.33(39,060,900-46,187,582)	7.1
					dup 17q22q23.2(47,699,730-56,508,953)	8.8
					del 17q24.1q25.3(60,760,558-78,563,591)	17.8
					dup 18p11.32q23(4,346-76,050,727)	WC
					dup 21p11.2q22.3(9,723,492-46,942,609)	WC
6	46,XX[20]	nuc ish(S100A10,PNOC)x2[105] nuc ish(FGFR3x2,IGHx1)[56/103] nuc ish(MYEOVx2,IGHx1)[45/119] nuc ish(ZBTB16,DLEU1)x2[106] nuc ish(IGHx1)[147/337] nuc ish(IGHx1,MAFx2)[46/115] nuc ish(TP53x2,CD37x1)[33/120]	No Change del 14q32.33 del 14q32.33 No Change del 14q32.33 del 14q32.33 No Change	0 54 38 0 44 40 28	 del 15q11.2(18,741,745-20,317,022)	 1.6
7	46,XX[20]	nuc ish(S100A10,PNOC)x2[140] nuc ish(FGFR3,IGH)x2[102] nuc ish(MYEOVx3,IGHx2)(MYEOV con IGHx1)[101] nuc ish(ZBTB16x2,DLEU1x1)[105] nuc ish(5'IGHVx1,3'IGHx2)(5'IGHV con 3'IGHx1)[104] nuc ish(MAF,IGH)x2[100] nuc ish(TP53,CD37)x2[112]	No Change No Change del 14q32.33 del 13q11q34 del 14q32.33 No Change No Change	0 0 100 100 100 0 0	 del 13q11q34(18,194,574-114,125,318) del Xp22.33q28(10,319-154,886,048) del 2p25.3p16.1(724-57,590,450) del 2p11.2p11.1(88,988,234-91,179,436) dup 11q13.2q13.3(68,836,538-69,969,332) del 15q11.2(18,450,592-20,060,091)	 WC WC 57.6 2.2 1.1 1.6
8	55,X,-X,+2,+3,+5,+7,-8 +der(8)t(8;?)(p11.2;?)x2 ,+9,+11,+15,+15,+19[2]/ 55,idem.-19,+20[2]/ 46,XX[47]	nuc ish(S100A10x2,PNOCx1)[100/102] nuc ish(FGFR3,IGH)x2[102] nuc ish(MYEOVx3,IGHx2)[103] nuc ish(ZBTB16x3,DLEU1x2)[100/102] nuc ish(5'IGHVx1,3'IGHx2)(5'IGHV con 3'IGHx1)[100] nuc ish(IGH,MAF)x2[104] nuc ish(TP53x2,CD37x3)[38/113]	No Change/ del 8p23.3p11.1 No Change dup 11p15.5q25/No Change dup 11p15.5q25/No Change del 14q32.33 No Change No Change/ dup 19p13.3q12	98 0 100 98 100 0 34	del 8p23.3p11.1(150,880-43,846,801) dup 11p15.5q25(148,914-134,439,377) dup 19p13.3q12(189,441-32,981,902) del Xp22.33q28(10,319-154,886,048)	43.7 WC 32.8 WC

					dup 2p25.3q37.3(724-242,632,464)	WC
					dup 3p26.3q29(43,674-199,324,691)	WC
					dup 5p15.33q35.3(132,176-180,658,955)	WC
					dup 7p22.3q36.3(153,877-158,811,298)	WC
					dup 8q11.1q24.3(47,087,100-146,264,210)	99.2
					dup 9p24.3q34.3(3,932-140,235,770)	WC
					dup 15q11.1q26.3(18,362,585-100,155,623)	WC
					dup 20p13q13.33(9,037-62,387,676)	WC
9	46,XY[6]	nuc ish(S100A10x3,PNOCx2)[101/110]	dup 1q21.1q44/No Change	92	dup 1q21.1q44(143,781,155-247,190,744)	103.4
		nuc ish(S100A10x4,PNOCx2)[3/110]	dup 1q21.1q44/No Change	3		
		nuc ish(FGFR3,IGH)x2[102]	No Change	0		
		nuc ish(MYEOV,IGH)x2[112]	No Change	0		
		nuc ish(ZBTB16x2,DLEU1x2)[101]	No Change	0		
		nuc ish(5'IGHVx1,3'IGHx2)(5'IGHV con 3'IGHx1)[100/109]	del 14q32.33	99		
		nuc ish(IGH,MAF)x2[108]	No Change	0		
		nuc ish(TP53x2,CD37x3)[101/122]	dup 19p13.3q13.43	83	dup 19p13.3q13.43(183,147-63,714,244)	WC
					dup 5p15.33q35.3(132,176-180,658,955)	WC
					dup 7p22.3q36.3(153,877-158,811,298)	WC
					dup 9p24.3q34.3(3,932-140,235,770)	WC
					dup 10q21.3(68,858,976-70,195,786)	1.3
					dup 15q11.2q26.3(20,010,589-100,155,623)	WC
					del 22q11.23q12.1(23,095,913-24,523,336)	1.4
					del 22q13.32q13.33(47,899,937-49,571,093)	1.7
10★	46,XY[20]	nuc ish(S100A10x5~7,PNOCx4)[118]	dup 1q21.1q44/No Change	100	dup 1q21.1q44(143,778,819-247,190,744)	103.4
		nuc ish(ZBTB16x4,DLEU1x2)[103/114]	No Change/ del 13q11q34	90	del 13q11q34(18,194,574-114,125,318)	WC
		nuc ish(ZBTB16x3,DLEU1x2)[8/114]	No Change / del 13q11q34	7		
		nuc ish(IGHx2)[102]	del 14q11.1q32.33	100	del 14q11.1q32.33(18,149,503-106,358,521)	WC
		nuc ish(TP53x4,CD37x4)[83/107]	No Change	78		
		nuc ish(TP53x4,CD37x3)[16/107]	No Change	15		
		nuc ish(TP53x3,CD37x4)[8/107]	No Change	7		
					del 1p36.33q12(128,255-141,559,496)	141.4
					dup 2p21p16.1(44,313,566-55,684,217)	11.4
					dup 2p15q37.3(63,439,827-242,632,464)	179.2
					del 4p16.3q35.2(6,168-191,223,063)	WC
					del 6q22.1q27(117,005,713-170,780,492)	53.8
					del 10p15.3p13(126,391-12,669,785)	12.5
					del 10p12.1q11.21(26,255,187-43,609,287)	17.4
					del 10q11.21q21.1(44,629,472-56,448,746)	11.8
					del 16p11.2q24.3(31,851,289-88,729,431)	56.9
11	46,XY[20]	nuc ish(S100A10x3,PNOCx2)[23/112]	No Change	21		
		nuc ish(ZBTB16x4,DLEU1x2)[110/118]	dup 11q13.1q25/No Change	93	dup 11q13.1q25(65,916,071-134,439,377)	68.5
		nuc ish(IGH)x2[103]	No Change	0		
		nuc ish(TP53x2,CD37x3)[70/108]	No Change/ dup 19q13.32q13.42	65	dup 19q13.32q13.42(52,299,705-60,957,935)	8.5
					del Xp22.33(348,253-1,649,586)	1.3
					dup 3p26.3q29(43,674-199,324,691)	WC
					dup 4q31.21q35.2(142,089,495-191,219,176)	49.1
					dup 5p15.33q35.3(132,176-180,658,955)	WC
					del 7p22.3p21.2(153,877-15,105,984)	15
					dup 7p21.2p15.2(15,178,655-27,203,053)	12.0

				dup 7p15.2q11.21(27,213,410-61,549,417)	34.3	
				del 7q11.21(62,003,519-65,010,902)	3	
				dup 7q11.22(66,309,177-67,832,293)	1.5	
				dup 8q11.21q24.3(49,178,904-146,264,210)	97.1	
				dup 9p24.3q34.3(3,932-140,235,770)	WC	
				dup 11p15.5p15.1(182,380-20,761,412)	20.6	
				dup 11p14.3q13.1(24,765,745-65,823,737)	41.1	
				dup 15q11.2q26.3(19,465,389-100,155,623)	80.7	
				del 16p13.3p13.2(18,824-6,328,679)	6.3	
				del 16p13.2(7,820,626-9,182,000)	1.4	
				dup 16p13.12p13.11(12,920,046-16,628,303)	3.7	
				dup 16p12.2p12.1(21,192,103-25,033,300)	3.8	
				del 16p12.1(25,417,679-27,422,584)	2	
				dup 16p12.1p11.2(27,465,116-30,308,490)	2.8	
				dup 19p13.3q13.32(61,720-50,807,934)	50.7	
				del 22q11.21q11.23(17,364,490-24,035,286)	6.7	
				del 22q12.1q13.1(25,067,022-37,504,530)	12.4	
				del 22q13.2q13.33(41,629,931-49,571,093)	7.9	
12	46,XY[5]	nuc ish(S100A10x3,PNOcx2)[19/105]	No Change	18		
		nuc ish(FGFR3x2,IGHx3)[103]	No Change	100		
		nuc ish(MYEOV,IGH)x3(MYEOV con IGHx2)[113]	No Change	100		
		nuc ish(ZBTB16x2,DLEU1x1)[108]	No Change/ del 13q11q34	100	del 13q11q34(18,194,574-114,125,318)	WC
		nuc ish(5'IGHVx2,3'IGHx2)(5'IGHV sep 3'IGHx1)[115/119]	No Change	97		
		nuc ish(IGHx3,MAFx1)[118]	No Change/ del 16p11.2q24.3	100	del 16p11.2q24.3(31,851,289-88,729,431)	56.9
		nuc ish(TP53x1,CD37x2)[114/115]	del 17p13.2p13.1/No Change	99	del 17p13.2p13.1(4,691,625-8,959,302)	4.3
					dup Xq23q28(114,437,377-154,886,048)	40.4
					del 1p13.2p12(112,216,670-118,447,882)	6.2
					del 1p12q21.1(120,410,317-143,642,039)	23.2
					del 1q23.3q25.3(161,161,689-179,781,134)	18.6
					del 1q32.1q32.2(203,690,653-205,871,102)	2.2
					del 1q32.2q32.3(207,809,375-211,926,454)	4.1
					del 1q41(212,957,023-213,997,627)	1
					dup 1q42.13q42.2(225,131,010-229,114,603)	4
					del 2p25.3p23.2(724-27,986,709)	28
					dup 3p21.31(47,976,987-50,424,832)	2.4
					del 3p21.31p12.3(50,477,753-79,386,648)	29
					del 3p12.3p12.1(80,571,691-86,581,962)	6
					del 6q16.1q27(92,916,587-170,780,492)	77.9
					del 8q24.21q24.3(128,832,363-146,264,210)	17.4
					del 9p23(10,276,957-12,716,945)	2.4
					del 9q33.1(118,358,837-121,340,663)	3
					dup 9q33.1q34.3(121,432,957-140,202,315)	18.8
					del 10p15.3p12.31(126,391-22,572,688)	22.4
					dup 10p12.31p12.1(22,656,915-25,737,445)	3.1
					del 10p12.1p11.22(26,255,187-32,365,226)	6.1
					del 10p11.21(35,342,572-38,090,915)	2.7
					del 10q23.33q26.3(96,941,867-130,923,085)	34
					del 12p13.33q24.33(93,179-132,268,952)	WC
					del 14q22.2q31.3(53,945,257-87,898,558)	32
					del 15q11.2(18,450,592-20,317,022)	1.9
					del 15q26.1(87,017,337-91,414,509)	4.4

					del 16p13.3p13.2(33,655-9,466,547)	9.4
					del 17p13.3p13.2(13,073-3,835,631)	3.8
					del 17q11.1q11.2(22,963,241-24,108,458)	1.1
					del 17q11.2(24,976,891-26,473,749)	1.5
					del 17q12(29,317,694-31,151,547)	1.8
					del 17q12(31,196,154-33,675,637)	2.5
					del 17q12q21.31(35,320,530-39,414,944)	4.1
					del 22q11.1q13.2(14,441,236-41,693,398)	27.3
13	46,XY[20]	nuc ish(S100A10x3,PNOcx2)[107/131] nuc ish(ZBTB16,DLEU1)x2[121] nuc ish(IGH)x2[104] nuc ish(TP53x1,CD37x2)[99/127]	dup 1p12q41/No Change No Change No Change del 17p13.2p11.2/No Change	81 0 0 78	dup 1p12q41(120,282,290-217,949,659)	97.7
					del 17p13.2p11.2(6,319,486-16,153,452)	9.8
					dup Xq28(150,794,887-154,886,048)	4.1
					dup 1q44(243,292,891-247,190,744)	3.9
					del 4p11q12(49,008,250-55,711,430)	6.7
					del 7q11.21q11.23(63,592,692-73,367,633)	9.8
					dup 9p24.3q34.3(3,932-140,193,696)	WC
					del 14q24.2q32.11(72,639,328-90,078,392)	17.4
					del 17p13.2p11.2(6,319,486-16,153,452)	9.8
					del 20q12q13.2(38,252,937-54,143,777)	15.0
					del 22q11.1q12.3(14,441,236-32,476,978)	18
					del 22q13.31q13.33(46,395,254-48,785,471)	2.4
14	46,XX[20]	nuc ish(S100A10x4~14,PNOcx2)[106/107] nuc ish(FGFR3,IGH)x3(FGFR3 con IGHx2)[102/112] nuc ish(MYEOVx2,IGHx3)[106] nuc ish(ZBTB16x2,DLEU1x1)[99/101] nuc ish(5'IGHVx2,3'IGHx2)(5'IGHV sep 3'IGHx1)[123/134] nuc ish(IGHx3,MAFx2)[116/119] nuc ish(TP53x2,CD37x3~5)[97/113] nuc ish(TP53x3~4,CD37x3~5)[11/113]	dup 1q21.1q23.3/No Change No Change No Change No Change/ del 13q11q34 No Change No Change No Change/ dup 19p13.3q13.43 No Change/ dup 19p13.3q13.43	99 91 100 98 92 97 86 11	dup 1q21.1q23.3(142,721,294-162,863,111)	20.1
					del 13q11q34(18,194,574-114,125,318)	WC
					dup 19p13.3q13.43(61,720-63,714,244)	WC
					del Xp22.33q25(10,319-121,546,453)	121.5
					del 1p33q12(50,455,859-141,559,496)	91.1
					dup 1q21.1q23.3(142,721,294-162,863,111)	20.1
					dup 1q23.3q44(162,866,701-247,190,744)	84.3
					del 4p16.1p12(7,865,068-46,193,547)	38.3
					del 6q16.1q27(94,643,251-170,780,492)	76.1
					dup 8p11.21q11.21(39,937,237-48,650,245)	8.7
					del 8q24.13q24.21(126,419,979-128,672,773)	2.2
					dup 9q32q33.1(114,592,070-121,664,607)	7.1
					dup 9q33.2q34.3(124,930,814-140,151,293)	15.2
					dup 10q26.3(133,386,798-135,275,161)	1.9
					dup 11p15.5p12(175,779-39,125,592)	39
					dup 15q22.31q24.1(64,115,001-73,081,744)	9
					dup 15q26.1q26.3(89,666,037-100,155,623)	10.4
					del 16p11.2(32,187,075-33,527,492)	1.3
					del 17q21.2q21.31(37,193,922-39,678,472)	2.4
					del 17q25.3(75,498,182-77,536,640)	2
					del 20p13p12.2(9,037-10,553,283)	10.5
15	46,XY[20]	nuc ish(S100A10x2,PNOcx1)[75/122]	No Change/ del 8p23.3p11.21	62	del 8p23.3p11.21(150,880-42,014,428)	41.9

		nuc ish(ZBTB16,DLEU1)x2[137]	No Change	0		
		nuc ish(IGH)x3[91/107]	dup 14q32.32q32.33	85	dup 14q32.32q32.33(102,539,856-105,251,496)	2.7
		nuc ish(TP53x3~5,CD37x3)[102/122]	dup 17p13.1/dup 19p13.3q13.43	84	dup 19p13.3q13.43(61,720-63,714,244)	WC
					del 2p11.2p11.1(87,131,092-91,429,639)	4.3
					dup 3q24q25.1(147,954,160-150,751,463)	2.8
					dup 3q25.1q25.2(152,702,584-153,707,027)	1.0
					dup 3q26.1q26.2(168,733,357-171,960,803)	3.2
					dup 3q26.31q27.1(176,951,105-184,728,455)	7.8
					del 3q27.1q29(184,831,327-199,324,691)	14.5
					dup 4p16.3q35.2(6,168-191,258,361)	WC
					dup 7p22.3p11.2(160,671-56,131,904)	56
					dup 7q21.12q34(86,261,174-140,281,470)	54
					dup 7q35q36.3(146,129,853-156,495,930)	10.4
					dup 8q11.1q24.3(47,087,100-146,264,210)	99.2
					dup 9p24.3q34.3(3,932-140,235,770)	WC
					del 14q11.1q11.2(18,149,503-19,851,470)	1.7
					dup 14q31.1q31.2(79,400,146-82,838,080)	3.4
					dup 14q31.3(87,179,588-88,558,206)	1.3
					dup 14q32.13q32.31(93,221,390-100,890,435)	7.7
					dup 17p13.3(282,251-2,250,975)	2
					del 17p13.3(2,257,292-3,462,518)	1.2
					dup 17p13.3p13.2(3,505,113-6,261,330)	2.8
					del 17p13.1p11.2(7,534,488-16,397,656)	8.9
					dup 17p11.2q11.2(16,469,174-24,108,458)	7.6
					dup 17q12(28,908,884-34,829,557)	5.9
					dup 17q21.31q21.32(41,564,438-44,732,420)	3.2
					dup 17q21.33q25.3(46,126,179-78,563,591)	32.4
					del 22q11.21q11.23(20,138,964-21,959,422)	1.8
					dup 22q11.23q12.1(23,033,976-24,678,497)	1.6
					del 22q12.1(25,067,022-26,518,064)	1.5
					dup 22q12.2(28,679,892-29,922,404)	1.2
16	46,XX[20]	nuc ish(S100A10,PNOC)x2[100]	No Change	0		
		nuc ish(FGFR3x2,IGHx4)[29/52]	No Change/dup 14q32.33	56		
		nuc ish(FGFR3x2,IGHx3)[23/52]	No Change/dup 14q32.33	44		
		nuc ish(MYEOV,IGH)x4(MYEOV con IGHx3)[38/65]	dup 11q24.3q25/dup 14q32.33	58	dup 11q24.3q25(129,268,330-130,507,199)	1.2
		nuc ish(MYEOV,IGH)x3(MYEOV con IGHx2)[27/65]	dup 11q24.3q25/dup 14q32.33	42		
		nuc ish(ZBTB16x2,DLEU1x1)[101]	No Change/ del 13q11q34	100	del 13q11q34(18,194,574-114,125,318)	WC
		nuc ish(5`IGHVx1,3`IGHx3)(5`IGHV sep 3`IGHx1)[72/106]	dup 14q32.33	68		
		nuc ish(5`IGHVx1,3`IGHx2)(5`IGHV sep 3`IGHx1)[34/106]	dup 14q32.33	32		
		nuc ish(IGHx4,MAFx2)[31/52]	dup 14q32.33/No Change	60		
		nuc ish(IGHx3,MAFx2)[21/52]	dup 14q32.33/No Change	40		
		nuc ish(TP53,CD37)x2[111]	No Change	0		
					del Xp22.33q28(10,319-152,816,963)	WC
					del 20p13q13.33(9,037-62,387,676)	WC
					del 22q11.1q13.33(14,441,236-49,571,093)	WC
17	46,XX[20]	nuc ish(S100A10x3,PNOCx2)[80/109]	dup 1q12q44/No Change	73	dup 1q12q44(141,559,496-247,190,744)	105.6
		nuc ish(ZBTB16x2,DLEU1x1)[79/111]	No Change/ del 13q11q34	71	del 13q11q34(18,194,574-114,125,318)	WC
		nuc ish(IGH)x2[109]	No Change	0		
		nuc ish(TP53x2,CD37x3)[70/110]	No Change/ dup 19p13.3q13.43	64	dup 19p13.3q13.43(61,720-63,714,244)	WC

						dup 3p26.3q29(43,674-199,324,691)	WC
						dup 7p22.3q36.3(153,877-158,811,298)	WC
						dup 9p24.3q34.3(3,932-140,235,770)	WC
						dup 15q11.1q26.3(18,362,585-100,155,623)	WC
18	46,XY[20]	nuc ish(S100A10x2,PNOCx3)[82/103]	No Change/ dup 8p23.3q24.3	80		dup 8p23.3q24.3(150,880-146,264,210)	146.1
		nuc ish(FGFR3,IGH)x2[100]	No Change	0			
		nuc ish(MYE OVx4,IGHx2)91/101]	dup 11p15.5q25/No Change	90			
		nuc ish(ZBTB16x4,DLEU1x2)[57/104]	dup 11p15.5q25/ dup 13q11q34	55		dup 11p15.5q25(148,914-134,439,377)	WC
		nuc ish(ZBTB16x4,DLEU1x3)[31/104]	dup 11p15.5q25/ dup 13q11q34	30		dup 13q11q34(18,194,574-114,125,318)	WC
		nuc ish(5'IGHVx1,3'IGHx2)(5'IGHV con 3'IGHx1)[59/106]	del 14q32.33	56			
		nuc ish(IGH,MAF)x2[107]	No Change	0			
		nuc ish(TP53x2,CD37x3)[58/109]	No Change/ dup 19p13.3q13.43	53		dup 19p13.3q13.43(61,720-63,714,244)	WC
						dup 3p26.3q29(43,674-199,324,691)	WC
						dup 5p15.33q35.3(132,176-180,658,955)	WC
						dup 6p25.3q27(49,943-170,780,492)	WC
						dup 7p22.3q36.3(153,877-158,811,298)	WC
						dup 9p24.3q34.3(3,932-140,235,770)	WC
						dup 15q11.1q26.3(18,362,585-100,155,623)	WC
						dup 21p11.2q21.2(9,723,492-25,576,176)	15.9
19	46,XX[20]	nuc ish(S100A10x3,PNOCx2)[16/102]	No Change	16			
		nuc ish(FGFR3x2,IGHx3)[78/112]	No Change	70			
		nuc ish(MYE OVx2,IGHx3)[82/125]	No Change	66			
		nuc ish(ZBTB16,DLEU1)x2[108]	No Change	0			
		nuc ish(5'IGHVx2,3'IGHx2)(5'IGHV sep 3'IGHx1)[73/111]	No Change	66			
		nuc ish(IGH,MAF)x3(MAF con IGHx2)[74/110]	No Change	67			
		nuc ish(TP53,CD37)x2[107]	No Change	0			
						del 2p11.2p11.1(88,891,050-91,129,969)	2.2
20	46,XX(20)	nuc ish(S100A10,PNOC)x2[100]	No Change	0			
		nuc ish(ZBTB16,DLEU1)x2[100]	No Change	0			
		nuc ish(TP53,CD37)x2[100]	No Change	0			
		nuc ish(IGH)x2[100]	No Change	0			
						del 16p11.2p11.1(32,187,075-34,584,822)	2.4

★ = Near-tetraploid, dup = duplication, del = deletion, i-FISH = interphase fluorescent in-situ hybridisation, Array-CGH comparative genomic hybridisation microarray, WC = Whole chromosome