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ORIGINAL ARTICLE

Detection of complex genomic signatures associated with risk in plasma cell disorders

Nadine K. Berry [a,b,c,*], Amanda Dixon-McIver [d], Rodney J. Scott [c,e], Philip Rowlings [a,b], Anoop K. Enjeti [a,b]

[a] *Department of Hematology, Calvary Mater Hospital, Newcastle, New South Wales, Australia;* [b] *School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia;* [c] *School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, New South Wales, Australia;* [d] *IGENZ, Auckland, New Zealand;* [e] *Department of Molecular Medicine, Pathology North Newcastle, Rankin Park, New South Wales, Australia*

Plasma cell disorders (PCD) range from benign to highly malignant disease. The ability to detect risk-stratifying aberrations based on cytogenetic and molecular genetic assays plays an increasing role in therapeutic decision making. In this study, 58 patients were chosen for screening by comparative genomic hybridisation microarray (aCGH) to identify the new high-risk prognostic markers of chromothripsis and chromoanasynthesis. All patients had an unequivocal clinical diagnosis of a plasma cell disorder (plasma cell myeloma (PCM)(n = 51) or monoclonal gammopathy of undetermined significance (MGUS)(n = 7)) and an abnormal FISH result. There were a total of 17 complex genomic events identified across 9 patient samples, which were selected for further investigation by high definition single nucleotide polymorphism (HD-SNP) microarray. Each event was analysed and characterised for chromothripsis, chromoanasynthesis or a complex stepwise chromosomal event. We describe an effective method to identify the new high-risk prognostic markers of chromothripsis and chromoanasynthesis in plasma cell disorders.

Keywords Plasma cell disorders, myeloma, microarray, chromothripisis, chromoanasynthesis

Introduction

Monoclonal plasma cell disorder (PCD) is a spectrum of disorders that include monoclonal gammopathy of undetermined significance (MGUS), smouldering multiple myeloma (SMM) and symptomatic myeloma (PCM) (1,2). Heterogeneous clinical and biological features characterise PCD. Genomic abnormalities detected at diagnosis provide important prognostic information and are among the most important factors in predicting initial response to chemotherapy, remission duration and overall survival. Genetic risk stratification can assist in guiding specific chemotherapeutic interventions, such as the use of Bortezomib and high dose therapy (HDT) or novel agents, for patients categorised into high-risk groups (2–4).

Current genetic risk stratification guidelines have been established by the International Myeloma Working Group (IMWG), which also incorporates the Mayo Clinic's stratification approach—stratification for myeloma and risk adapted therapy (mSMART—see methods section) and is regularly reviewed (2,3,5). These guidelines have been used to provide a risk estimate based on genomic data from traditional karyotype and fluorescent in-situ hybridization (FISH) results. However, the incorporation of microarray findings may provide a more accurate disease classification for the treatment of these patients.

The use of microarray technology in the evaluation of haematological malignancies has rapidly gained popularity in response to the need for significantly greater molecular resolution of the whole genome to aid in diagnostic, prognostic and individualised patient treatment (6–8). In many cases it has begun to replace the need for conventional karyotyping and the use of extensive FISH panels for haematological malignancies (9,10). The value of aCGH in a clinical setting compared to traditional karyotype and multiple FISH analysis has been previously reported (6,10–13).

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* Corresponding author.
E-mail address: Nadine.berry@hnehealth.nsw.gov.au

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In this study we screened a series of PCD patient samples by interrogating their molecular genetic profile utilizing aCGH. Further interrogation of complex genomic signatures was performed on a subgroup using a HD-SNP microarray platform. The aim was to characterise these complex findings, which may have significant clinical relevance especially with respect to treatment failure and or recurrence risk.

The use of aCGH has revealed new and emerging genetic risk factors that had hitherto remained undiagnosed, such as chromosome 1 aberrations, 12p deletions, 5q gains and evidence of the recently described phenomenon of chromothripsis and chromoanasynthesis (7,14–17). Chromothripsis is a phenomenon whereby a localised chromosome, chromosome arm or segment is shattered and repaired in a one-off catastrophic event that occurs at one time point rather than being acquired over many cell cycles such as a "step-wise" event. This event results in significant DNA rearrangements of which its genomic signature using microarray based analysis appears as an oscillation between two to three copy number states with loss of heterozygosity (LOH) (7,18–22). Chromoanasynthesis also appears to be acquired in a one-off event, however it is characterised by gained or amplified segments that retain heterozygosity (23,24).

Whilst these phenomena have been described as having a strong association with high-risk disease in myeloma and other haematological diseases, there has been no definitive mechanism by which to characterise these changes identified predominantly with the use of microarray technology (7,14,23,25). From a clinical diagnostic perspective, we sought to further investigate complex genomic events identified using CGH array analysis by HD-SNP microarray analysis to better characterise these multifaceted alterations.

Materials and methods

Patients and specimen ascertainment

58 samples from patients with a clinical diagnosis of PCD (based on the WHO criteria) were positively selected for microarray studies according to an abnormal interphase FISH (iFISH) result and DNA availability. The samples were comprised of a mix of diagnostic or relapsed bone marrow cells. A comprehensive iFISH panel analysis was performed on all samples and a diagnostic report issued. DNA was then extracted and a microarray analysis was performed.

The patient cohort characteristics are shown in Table 1 and the specific PCD classification is provided.

Table 1 Patient characteristics

Basic characteristics of patients in this study		
Patients (n = 58)		
Median age at diagnosis, years (range)	68	(43-93)
Female sex, N (%)	17	29%
WHO diagnosis		
PCM	51	88%
MGUS	7	10%

Abbreviations: WHO: World Health Organisation; PCM: Plasma cell myeloma; SMM: Smouldering multiple myeloma; MGUS: Monoclonal gammopathy of uncertain significance.

Enrichment of CD138 positive cells

Enrichment of CD138+ plasma cells was performed on all patient samples before testing using the EasySep methodologies as previously published (6).

Interphase FISH studies

i-FISH was performed using a break-apart probe for 14q32(*IGH*) and dual fusion probes for 4p16(*FGFR3*) / 14q32(*IGH*), 11q13(*MYEOV*) / 14q32(*IGH*) and 14q32(*IGH*) / 16q23(*MAF*) (Cytocell, UK) according to the UK Haemato-Oncology Best Practice Guidelines. Measurements of uncertainty were set at the levels recommended by the European Myeloma Network (10% for break-apart and dual fusion probes and 20% for locus specific probes) (26).

DNA extraction & quality assessment

DNA was initially extracted using either a QIAsymphony (Qiagen, USA) robot or a QIAcube (Qiagen, USA) robot using the relevant protocols. Clean up of the DNA was performed using a Zymo DNA Clean & Concentrator™ kit (no. 04004) (Zymo Research, USA) according to the manufacturer's instructions. DNA quality was assessed using a NanoDrop 2000 spectrophotometer.

Microarray analysis

Whole genome microarray analysis was performed using an oligonucleotide array (8x60k oligonucleotide array, CCMC design) (BlueGnome, UK). Labelling, hybridization and scanning were performed as per the Agilent Technologies user manuals. For comparison, sex-matched reference DNA supplied by Agilent Technologies was used (Agilent Technologies, USA). Analysis was performed using BlueFuse Multi v2.5 software (BlueGnome, UK).

Results were visualised using the BlueFuse Multi v2.5 software program (BlueGnome, UK). The nucleotide positions listed in BlueFuse are based on the UCSC Genome Browser's February 2009 human reference sequence (hg19; NCBI Build 37).

Data was analysed using a 3-probe calling criteria for Log2 values of >0.3 and <-0.3 and a smoothing of 2. Additional criteria for low mosaic calls of ≥ 10-probes with a Log2 value of 0.10 for gains and -0.10 for losses, was also applied.

Accurate alignment of genomic data for oligonucleotide microarray data where large amounts of the genome were lost or gained was impeded by the software's fundamental

Table 2 Cytogenetic Risk Classification

High Risk	Standard Risk
t(14;16)(q32;q23)	All others including;
t(14;20)(q32;q11)	Hyperdiploidy
del (17)(p13)—TP53 *	(≥47 chromosomes with trisomies
t(4;14)(p16;q32) *	of odd numbered chromosomes)
Non-Hyperdiploid	t(11;14)(q13;q32)
Gain 1q21	t(6;14)(p21;q32)
Deletion 1p	

* Patients' risk may be reduced with the choice of therapy.

Table 3 Features of chromothripsis, chromoanasynthesis and complex stepwise events identifiable by SNP-microarray genomic profiles

Chromothripsis	Chromoanasynthesis	Complex Step-wise alterations
• Interspersed loss and preservation of heterozygosity • Clustering of breakpoints • Event occurs on one or a few of chromosomes • Most often involves a chromosome arm, but in MM it has been observed to extend across the whole chromosome • Oscillation between 2 copy number states, but may occasionally involve 3 copy number states • ≥ 10 changes per chromosome • Neighbouring segments to be roughly the same size	• Segments oscillate to show increased copy number states • Retention of heterozygosity	• Multiple high copy-number states due to the overlapping of tandem duplications. Often resulting in a gradient of copy number change at breakpoints. • Extensive variation of copy-number states across the derivative chromosome • Non-oscillating patterns of copy-number changes

algorithm design. For samples where a large proportion of the genome was lost or gained, the automatic alignment of data was incorrect and had to be manually adjusted. The copy number result obtained from *IGH* FISH probe was used as a reference point.

Due to the limited resolution of oligonucleotide arrays those samples that revealed a complex chromosomal signature and were suspected of being chromothripsis or chromoanasynthesis (cases 12, 13, 17, 23, 25, 27, 30, 48 and 58) according to the criteria listed in Table 2 were subjected to more accurate analysis using high-density single nucleotide polymorphism (HD-SNP) arrays (Figures 1 and 2).

High density SNP array analysis was undertaken using the CytoScan® HD SNP microarrays according to the manufacture's protocols. Results were analysed using the Affymetrix Chromosome Analysis Suite (ChAS) v2.0.0.195(r5758) software program (Affymetrix, Santa Clara CA). HD-SNP microarray data was aligned correctly without manual adjustment. A 20-probe calling criteria was applied for each gain or loss identified.

Molecular cytogenetic classification

Genomic results were classified and assigned a risk estimate according to our interpretation of the IMWG and mSMART risk categorisation guidelines (Table 3) (2,3,5). Whilst the importance of chromosome 1 aberrations has been contentious, more recent data showing the negative implications of both 1q21 gains and 1p losses (4,27–33) were also included in the classification system as a high-risk feature.

Molecular cytogenetic characterisation of complex genomic signatures

The characterisation of these events into chromothripsis, chromoanasynthesis or a complex step-wise event was confirmed and better delineated using the CytoScan® HD SNP microarray platform according to the parameters detailed in Table 2 (7,17,18,21,23,24,34,35).

Ethics

Approval for the study was obtained from the Institutional Review Board of 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) in accordance with the declaration of Helsinki.

Results

From the 58 patients enrolled in this study, there was an evidence of 17 complex genomic events identified across 9(16%) patients using aCGH, which could be classified as chromothripsis, chromoanasynthesis or a complex step-wise event (case # 12, 13, 17, 23, 25, 27, 30, 48 & 58) (Figure 1). These were further investigated utilising the CytoScan® HD SNP microarray platform (Figure 2).

Each event was classified according to the criteria set out in Table 2 with the majority (13/17) showing evidence of a complex step-wise event (Table 4). Chromothripsis was observed in 2 events (case 13: chromosome 1 and case 58: chromosome 16), whereas chromoanasynthesis was

Table 4 Summary of the characterisation of complex genomic events observed using the CytoScan HD SNP microarray

Case #	Chromosome #	Characterisation of genomic event
12	16	Complex step-wise
	22	Complex step-wise
13	1	Chromothripsis
	3	Complex step-wise
	10	Complex step-wise
	17	Complex step-wise
17	3	Complex step-wise
	14	Chromoanasynthesis
	17	Complex step-wise
23	1	Complex step-wise and Chromoanasynthesis
25	20	Complex step-wise
27	8	Complex step-wise
30	1	Complex step-wise
48	4	Complex step-wise
	10	Complex step-wise
	17	Complex step-wise
58	16	Chromothripsis

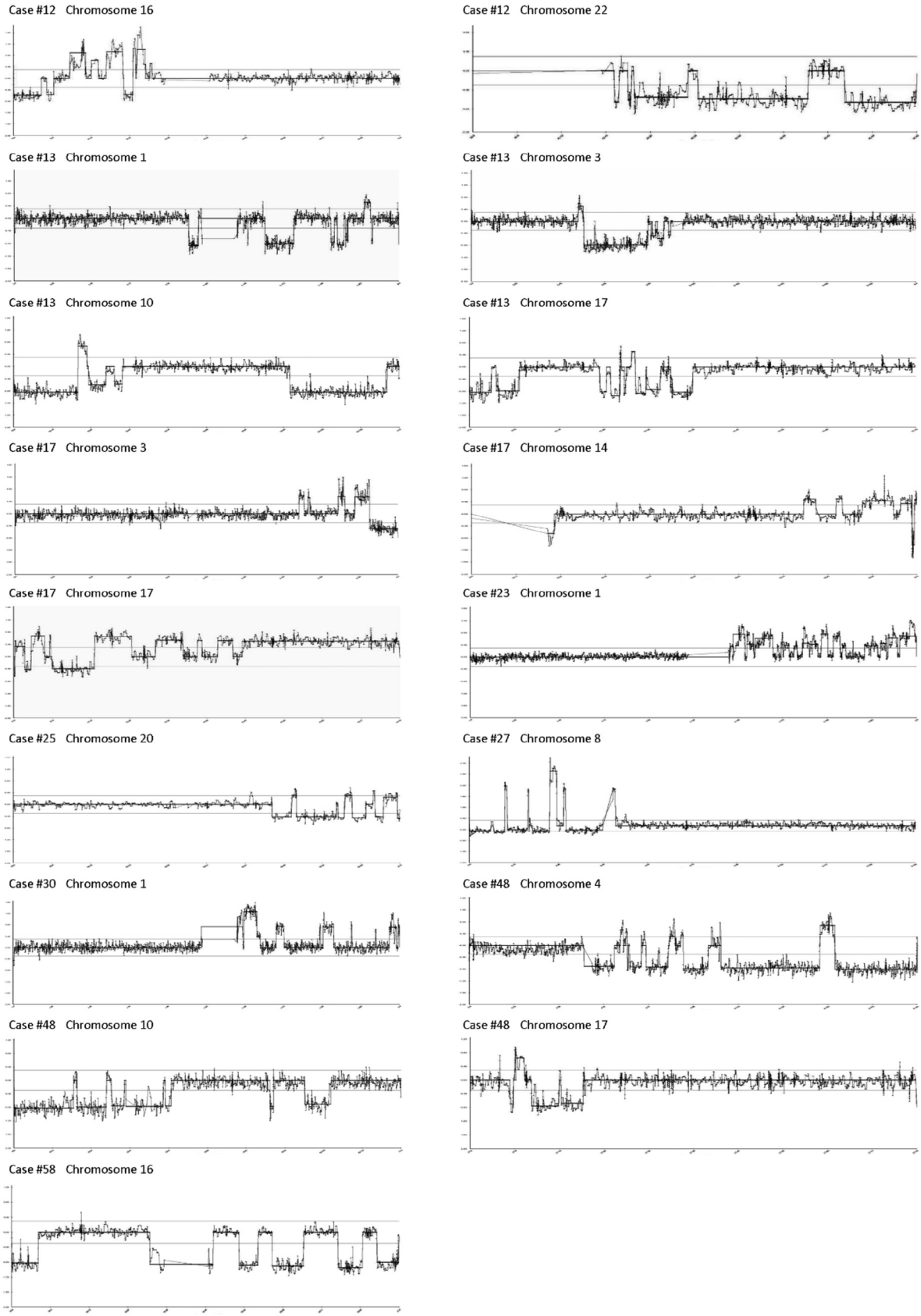

Figure 1 Copy-number profiles of complex genomic events representing chromothripsis, chromoanasynthesis or other complex stepwise events as detected by CGH microarray.

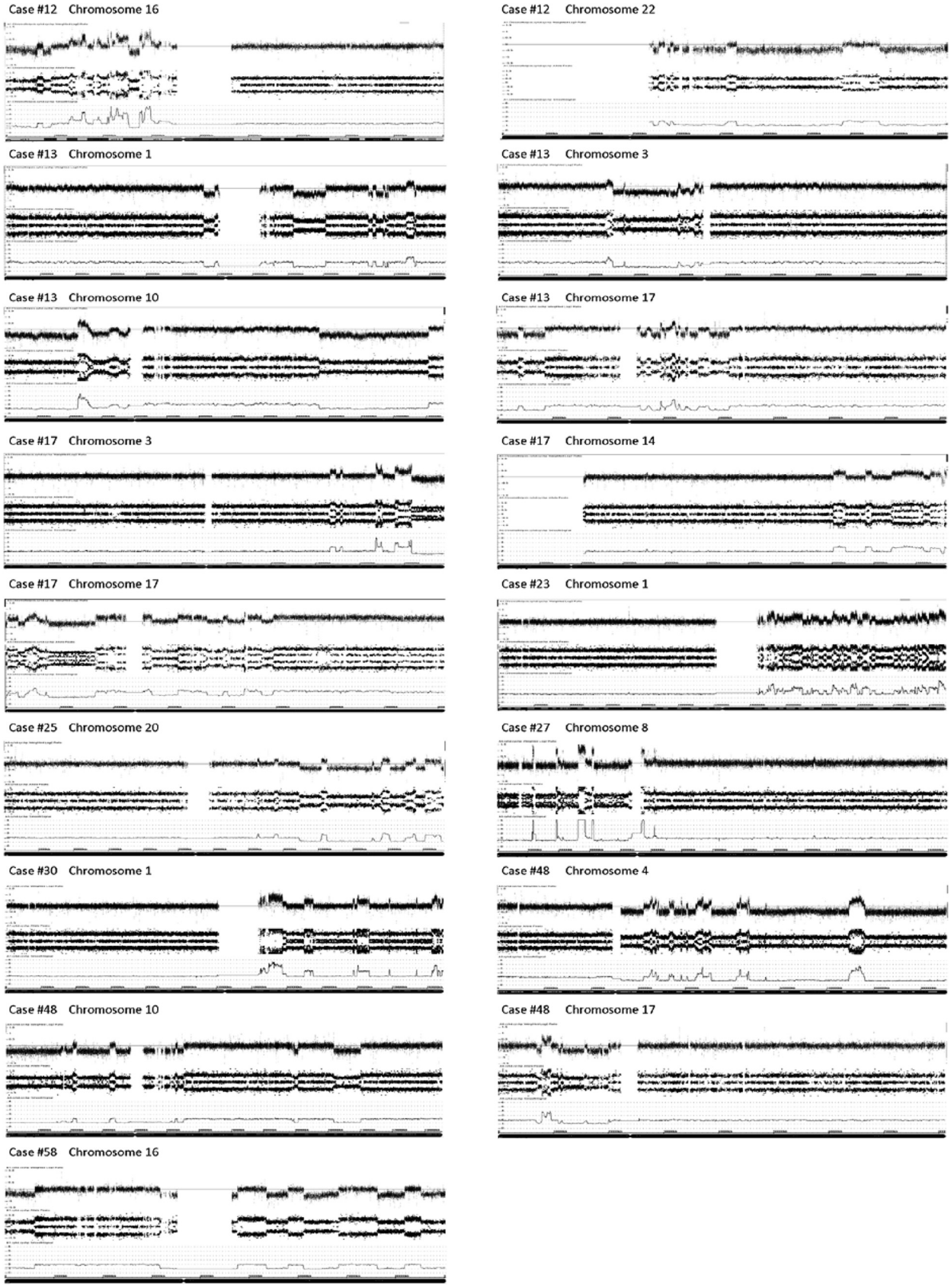

Figure 2 Copy-number profiles of complex genomic events representing chromothripsis, chromoanasynthesis or other complex stepwise events detected on the CytoScan HD-SNP microarray platform.

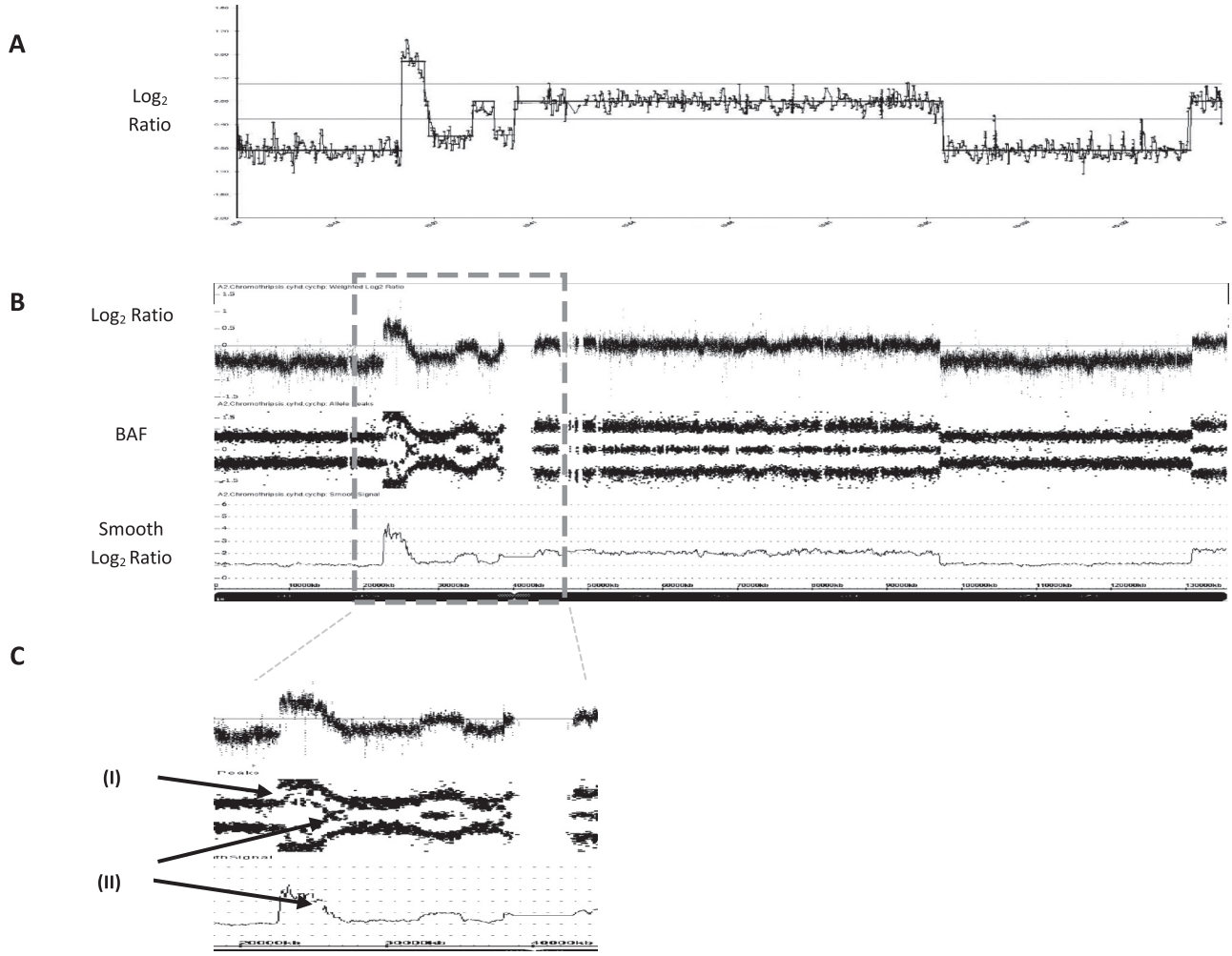

Figure 3 Complex step-wise event on chromosome 10 (case #13). **(A)** Whole chromosome 10 view ratio plots derived from aCGH 8x60k oligo data of MM patient (#13) showing a complex genomic pattern. The Y-axis represents the $\log_2$ ratio values and the X-axis illustrates all the probes in the array for chromosome 10, which are sorted by physical mapping positions. **(B)** Whole chromosome 10 view ratio and B-allele frequency (BAF) plots derived from HD-SNP microarray data of MM patient (#13) showing a complex genomic pattern highlighted by the grey box. The Y-axis represents the $\log_2$ ratio values, the B-allele frequency values and the smoothed $\log_2$ ratio indicating copy number values. The X-axis illustrates the probes in the array for chromosome 10, which are sorted by physical mapping positions. **(C)** Enhanced view of the complex genomic event identified by HD-SNP microarray on chromosome 10 (#13). From left to right, a well-defined breakpoint **(I)** is observed followed by a less well-defined breakpoint **(II)** that appears to show a gradual change in copy number. It is this gradual change that cannot be easily identified on a low-density oligo array platform, which is most likely to represent the overlapping of tandem duplications that are prevalent in a complex step-wise event. This gradual change also indicates progressive acquisition of copy number change states over each cell cycle and not at one-time point as is the case in chromoanasynthesis.

observed in one event on chromosome 14 of case 17. Characterisation of complex genomic events identified by HD-SNP microarray can be challenging. This was evident in case 23 where chromosome 1q exhibits a mass of breakpoints across the whole arm with varying amplification (Figure 3). The complexity is extreme and the breakpoints show a mixture of clear breaks and gradients of copy number change as well as several levels of amplification. This may be due to a two-step process of chromoanasynthesis followed by a series of complex step-wise events over subsequent cell cycles or vice versa.

All 9 cases were classified as high risk prior to the observance of these events (Supplementary Table S1). There was a high correlation (7/9 cases) with chromosome 1q21 gains. Three cases also contained a *TP53* deletion. More than one complex event was observed in 4/9 cases whilst chromosome 1 and 17 were the most commonly involved with 3 events detected on each (Table 4). None of these complex genomic events were detectable using FISH methodology alone (Supplementary Table S1).

Given the small sample size and low percentage of cases with complex genomic events we were unable to determine,

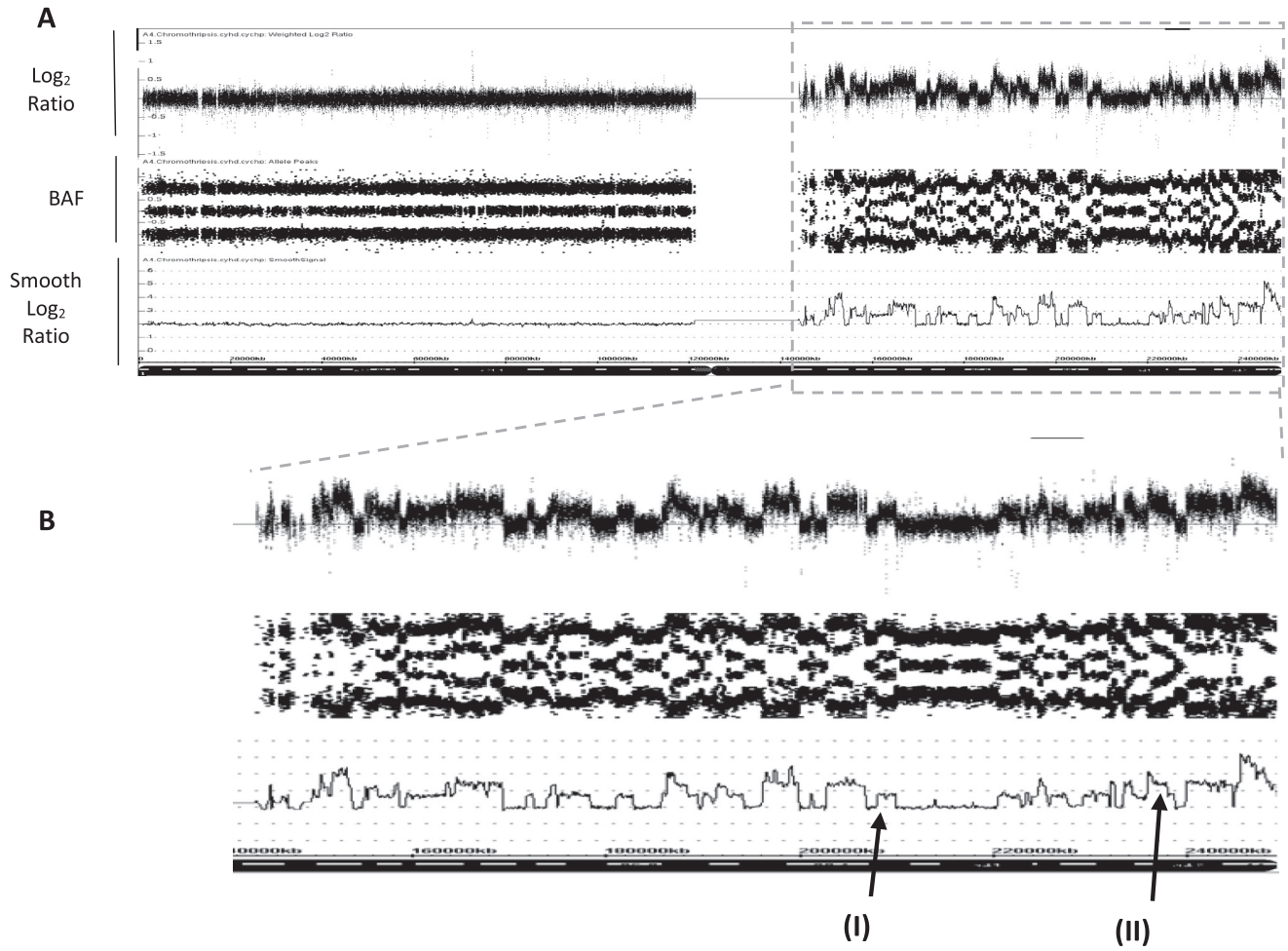

Figure 4 Possible chromoanasynthesis and a complex step-wise event on chromosome 1q (case #23). **(A)** Whole chromosome 1 view ratio and B-allele frequency (BAF) plots derived from HD-SNP microarray data of MM patient (#23) showing a complex genomic pattern highlighted by the grey box. The Y-axis represents the $\log_2$ ratio values, the B-allele frequency values and the smoothed $\log_2$ ratio indicating copy number values. The X-axis illustrates the probes in the array for chromosome 1, which are sorted by physical mapping positions. **(B)** Enhanced view of the complex genomic event identified by HD-SNP microarray on chromosome 1q (#23). From left to right, a well-defined breakpoint **(I)** is observed and can be seen at many breakpoints along the q arm, which is a signature of chromoanasynthesis. These breakpoints are interspersed with less well-defined breakpoints **(II)** that appear to show a gradual change in copy number. It is this gradual change that cannot be easily identified on a low-density oligo array platform, which is most likely to represent the overlapping of tandem duplications that are prevalent in a complex step-wise event. This gradual change also indicates progressive acquisition of copy number change states over each cell cycle.

with statistical significance, whether these complex events were associated with a poor outcome. Nevertheless, from the 9 patients diagnosed with a complex event one has not survived and 6 had relapsed.

Discussion

The detection of chromothripsis and chromoanasynthesis in haematological malignancies is becoming increasingly important with evidence of their involvement signifying a high-risk disease status. SNP-microarray analysis has now become the method of choice used to identify these events due to its cost effectiveness, reproducibility and simplicity in comparison with whole genome sequencing. The need for clarification of the identification of these phenomenon is now necessary in a clinical setting (7,18,21). Our attempt to classify complex genomic events into three different categories 1) chromothripsis, 2) chromoanasynthesis and 3) a complex step-wise event has been a challenge and has yielded unexpected results with the majority of genomic variation appearing to be complex step-wise events.

The data revealed an increase in the number of breakpoints detected as well as clarification of each oscillation breakpoint (Figures 1 and 2). However, the characterisation of these three complex aberrations remained challenging, since their occurrence may not be mutually exclusive blurring their classification boundaries.

The HD-SNP microarray analysis revealed significantly more complex genomic patterns supporting changes that occur over several cell cycles such as that shown in Figure 4. The most prevalent feature that is consistent with this is the gradual change in copy number, more clearly seen on the B-allele frequency (BAF) plot, which is likely to represent the overlapping of tandem duplications rather than the well-defined breakpoints that would be a result from either chromothripsis or chromoanasynthesis.

The oscillating pattern of regular copy number change, which is a signature of chromothripsis and chromoanasynthesis was observed in 4 cases (#13, #17, #23 and #58). Chromothripsis, which is described as being an oscillation of 2 to 3 copy number states with LOH and >10 clustering breakpoints, was observed in case 13 on chromosome 1 and in case 58 on chromosome 16 (Figure 2). Here the segment copy number states are clear and the breakpoints are well defined, suggesting the population of cells affected by these breaks are in equal quantities throughout the sample. Had they been acquired over many cell cycles and therefore in unequal quantities, the likelihood is that their representation would indicate multiple breaks and a gradient of copy number change.

Throughout the analysis and classification process many questions were raised as to whether or not there is a need for the specific classification of these complex events in relation to genomic risk. Do all three complex events infer a high-risk due to their complex nature or does the mechanism involved play a specific role?

Whilst chromothripsis has been associated with a poor outcome in multiple myeloma (7), there remains a need for prospective clinical trials to evaluate other complex genomic events in order to confirm their prognostic implications and to clarify their characterisation. The clinical interpretation of these complex genomic events remains challenging as there is currently a) limited information available to explain the mechanisms behind these phenomenon and b) restricted information about the implications for disease risk and or recurrence.

Conclusion

The genetic complexity of processes acquired at one time point such as chromothripsis and chromoanasynthesis appear to be somewhat different to other step-wise events, which are acquired over several cell cycles. Some of these events may be integral to the disease progression and to specific genetic changes that relate to targets for drug-therapy and prognostic indicators, all of which are important in contributing to the pathogenesis of the disease and to the improvement of our understanding of it.

Authorship

NKB and AKE were the principal investigators and takes primary responsibility for the paper; AKE and PR recruited the patients; NKB performed the laboratory work for this study; NKB, AD-M, PR, RS and AKE wrote the paper.

Disclosures

Nothing to disclose. All authors report no conflicts of interest.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.cancergen.2017.08.004.

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