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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Chromoanagenesis in Haematological Malignancy: Review of Samples from Patients with Acute Leukemia and MDS

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Background:
Complex chromosome rearrangements (CCRs) include a variety of structural aberrations grouped as chromothripsis, chromoanasynthesis and chromoplexy. Although the underlying mechanisms for these phenomena are unknown and likely to be different, they appear to originate from a single event. While chromothripsis and chromoanasynthesis affect limited genome sites their role and genome associations in haematological malignancy remain to be elucidated.

Aims:
This study aimed to provide clarity on the location, incidence and association with *TP53* gene profile of chromothripsis (cth) and chromoanasynthesis (cha) events in MDS/AML.

Methods:
We analysed data from routine investigations carried out by haematological malignancy diagnostic service (HMDS) at University College London Hospital (UCLH) on 2,506 samples of acute myeloid leukaemia (AML) and myelodysplasia (MDS), including G-banding, FISH (Cytocell), chromosome microarray analysis (CMA, Agilent) and target NGS(Illumina). Analysis of 87 samples with complex bone marrow karyotypes were reported following the ISCN 2020 as: (i) **cth**(alternating disomy and heterozygous loss along a chromosome or chromosomal segment) or (ii) **cha** (deletions and one or two copy number gains in a single chromosome or chromosome region including copy number variants without the clustered breakpoints of chromothripsis). Statistical analysis used RStudio (v 1.4.1106) to carry Pearson's chi-squared (χ^2) and Fisher's exact (2-sided) tests.

Results:
Complex karyotypes harbouring cth and cha type aberrations were detected in 65 out of 727 AML and 22 out of 1779 MDS samples. The cth events were seen alongside cha in 67% of cases, rarely presenting as a sole abnormality (2%), while cha alone was found in 31% of samples. Most frequently cth was mapped at chromosome 21 (17%), chromosome 7 (15%), chromosome 17 and 19 (13%) and chromosome 5 (11%) (Fig.1a). In this cohort of 87cases, chromothripsis was found to be associated with *TP53* deletions ($TP53^{Del/WT}$) in 7 (7%) and with *TP53* mutations ($TP53^{Dpl/mut}$) in 22 (25%), while concurrent *TP53* deletions and mutations ($TP53^{Del/mut}$) were detected in 29 (33%) ($p = 0.0005$). Samples with $TP53^{Del/mut}$ harboured cth in chromosomes 7 (7%), 17 (6%), 8, 9, 19 and 21 (5%) whilst cases with $TP53^{Dpl/mut}$ had cth in chromosomes 21 (9%), 19 (8%), 5 (7%) and 7 (5%). (Fig 1 b).
The cha aberrations generally followed the genome location of cth events with some exception. Firstly, chromosomes X,13 and 21 appear to have only cth and is seen at slightly higher level on chromosome 19 (cth 13% vs cha 9%). Secondly, cha was most frequently seen on 5q (61 %), chromosome 17 (40%) and 7q (34%). However, the same chromosomes also had the greatest number of cases presenting with concurrent cth and cha, seen in 63/87 (72%) for chromosome 5, 46/87 (53%) for chromosome 17 and 43/87 (49%) for chromosome 7.

Importantly, only cases harbouring 5q deletions showed a statistically significant association with *TP53* status ($p = 0.0011$) in this cohort irrespective of cth and cha presence. Notably, 24/29 cases (83%) with *TP53* $^{Del/mut}$ were cth positive and had 5q31 deletion. This finding is an important observation but not in keeping with reports of exclusive association of *TP53* mutations with concurrent 5q and 7q loss (1, 2 and 3). The concurrent recording of cth and cha performed by this study could explain the discrepancy, most likely due to high frequency of cha events in 5q.

Summary

This study highlights issues pertinent to risk stratification in routine diagnostic settings: (i) MDS/AML cases with complex genome harbouring either or both cth and cha share common *TP53* aberrations (del/mut) and (ii) deletion of 5q31 is positively associated with *TP53* aberrations and presence of cth events. (iii) CMA offers a comprehensive, sensitive, fast and financially superior way to detect cth, cha events along with genome complexity compared to G banding complemented by FISH. Overall, combining CMA and *TP53* mutation screening offers a fast, reliable way to detect high risk disease in MDS/AML.

Keywords: Complex genome, CMA, chromothripsis, *TP53* mutations

References:

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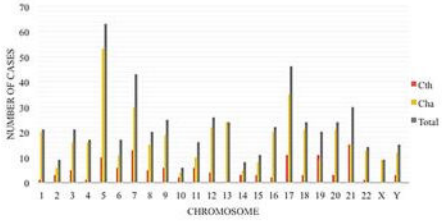
Fig 1 Chromothripsis and chromoanasynthesis number, chromosome location and *TP53* gene status in 87 MDS/AML cases



(a) Chromosome location and number of cth and cha

TP53 Status	Cth+/Cha+	Cth-/Cha+	Cth+/Cha-	Total
TP53$^{Del/mut}$	29	7	0	36
TP53$^{Del/WT}$	7	2	0	9
TP53$^{Dpl/mut}$	21	7	1	29
TP53$^{Dpl/WT}$	2	10	1	13
Total	59	26	2	87

Key: del identifies loss, mut – mutation; WT- wild type, Dpl- diploid status, cth/cha (+) present, cth/cha (-) not identified.

(b) TP53 gene status and presence of cth/cha events

Figure 1

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