Abstract ID: - 64

Abstract Topic: - Molecular effects of genetic variation

Abstract Title: - Comprehensive CytoGenomic study of aplastic anemia

Presenting author name: - Anjali Shah

Presenting author institute: - ICMR-National Institute of Immunohaematology

Co-authors name: - Dr. Chandrakala Shanmukhaiah, Dr. Babu Rao Vundinti

Co-authors institute: - Department of Hematology, King Edward Memorial Hospital, Mumbai, India, ICMR-National Institute of Immunohaematology, Mumbai, India

Aims: - To study the frequency and type of cytogenetic and molecular variations in aplastic anemia subjects Correlation of cytogenetic abnormalities and somatic mutations with response to therapy.

Methods: - We performed high throughput exome sequencing (N=170) and chromosomal copy number variations (CNVs) (N=54) using high resolution array-comparative genomic hybridization (CGH) in AA subjects.

Results: - Genomic profiling of AA showed 101 germline and 32 somatic variants of 63 different genes in 58% AA subjects. A high frequency (13.33%) of variants were observed in MPL gene, correlated with significantly ($p < 0.0037$) elevated plasma THPO levels, followed by telomere regulating genes (RTEL1(11%), TERT (8%), TINF2 (6%)) associated with severe telomere attrition($p=0.002$). The functional implication of frequently identified gene (MPL) using in-silico modelled protein showed structural and functional defects of protein causing trilineage bone marrow failure. Overall, 44 variants identified in ERCC6L2, SAMD9L, RBM8A, MECOM, TRF, TERT, RTEL1, KIR3DL1, etc genes are found to be novel variants. A high frequency (18%) of somatic variants observed in KIR3DL1, followed by BCOR (13%), RUNX1, ASXL1 and TP53 (9%) and are found to be associated with leukemia and myelodysplasia showed poor prognosis/survival (hazardous ratio-2.34). Array CGH analysis of AA, revealed increased CNVs at chromosomal regions, genes encoding interleukin and cytokines mediated apoptosis pathways; MHC systems; Th cell differentiation, immune system and haematopoiesis regulation pathways, which may contribute in tri-lineage marrow aplasia. A good haematological response and progression free survival in absence of somatic changes was observed in subjects treated with IST.

Conclusions: - Genomic profiling of AA is important for appropriate diagnosis and management of the disease, as we have identified genetic alteration (germline and somatic) including novel variants and rare genes, associated with various pathways of bone marrow failure. The frequency of MPL, telomere genes and DNA repair genes are found to be common in our cohort, hence these genes should be studied in large cohort of AA.

Keywords: - Genomic profiling of AA showed 101 germline and 32 somatic variants of 63 different genes in 58% AA subjects. A high frequency (13.33%) of variants were observed in MPL gene, correlated with significantly ($p < 0.0037$) elevated plasma THPO levels, followed by telomere regulating genes (RTEL1(11%), TERT (8%), TINF2 (6%)) associated with severe telomere attrition($p=0.002$). The functional

implication of frequently identified gene (MPL) using in-silico modelled protein showed structural and functional defects of protein causing trilineage bone marrow failure. Overall, 44 variants identified in ERCC6L2, SAMD9L, RBM8A, MECOM, TRF, TERT, RTEL1, KIR3DL1, etc genes are found to be novel variants. A high frequency (18%) of somatic variants observed in KIR3DL1, followed by BCOR (13%), RUNX1, ASXL1 and TP53 (9%) and are found to be associated with leukemia and myelodysplasia showed poor prognosis/survival (hazardous ratio-2.34). Array CGH analysis of AA, revealed increased CNVs at chromosomal regions, genes encoding interleukin and cytokines mediated apoptosis pathways; MHC systems; Th cell differentiation, immune system and haematopoiesis regulation pathways, which may contribute in tri-lineage marrow aplasia. A good haematological response and progression free survival in absence of somatic changes was observed in subjects treated with IST.