# Genetic Bio-marker Discovery in *de novo* Myelodysplastic Syndromes

WMMS Bandara[1], AJIS Rathnayake[1], NF Neththikumara[1], HWW Goonasekera[1], VHW Dissanayake[1]

1. Human Genetic Unit, Faculty of Medicine, University of Colombo, Colombo 8, Sri Lanka.

Background: Myelodysplastic syndromes (MDS) are a complex clonal hematopoietic stem cell (HSCs) malignancy where global biomarkers for early diagnosis, prognosis and therapy are lacking. Altered interactions between HSCs and Mesenchymal stem cells (MSCs) in the bone marrow (BM) milieu are implicated in its pathogenesis. Therefore parallel study of HSCs and MSCs should enable greater insights into disease pathobiology. Ethnic variation in MDS biology has also been reported and research into genetics of MDS in South Asians is limited.

Aims: To identify genetic bio-markers having potential for early diagnosis, prognostication and treatment in MDS.

Methods: DNA was isolated from BM-HSCs and BM-MSCs from 11 newly diagnosed untreated *de novo* MDS patients. Next Generation Sequencing was performed by Illumina MiSeq platform, using a panel of 54 genes commonly mutated in myeloid malignancies. Variants were annotated against 1000 Genomes, Exome Variant Server, COSMIC and dbSNP142 databases. Sift and Polyphen software were used to predict the potential effect of mutations.

Results: Out of 54 genes, 37 and 30 genes were mutated in HSCs and MSCs respectively. Both reported and novel mutations were present. Frequently mutated genes in both cell types included *DNMT3A,TET2,KDM6A,STAG2,BCOR/BCORL1,KIT* and *CUX1*. Refractory anaemia with excess blasts had the highest number of mutations in both compartments and Refractory cytopenia with multilineage dysplasia demonstrated more mutations in MSCs. Recurrent novel mutations in HSCs and MSCs included BCOR(C1505W), KTMA(D2488V), SF3B1(Y623N) and KIT(H485P), TET2(L1742W), DNMT3A(H588P), KDM6A(T181P & T833P) respectively. Missense mutations were shown to have deleterious effects on function.

Conclusion: Our findings of altered genome of MSC support the theory of involvement of MSCs in MDS pathogenesis. Detection of distinct mutations in HSCs and MSCs suggest that the origin of mutations in two compartments is independent. Presence of recurrent mutations in genes regulating epigenetic mechanisms and cell signaling pathways raises novel therapeutic perspectives. Further bioinformatics analysis will be done on the novel mutations; detected in this South Asian MDS cohort; to determine their potential as early diagnostic and prognostic markers and as therapeutic targets.

Keywords: Myelodysplastic syndromes (MDS), hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), mutations, next generation sequencing