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Abstract Topic: - Epigenetics

Abstract Title: - Genetics and Epigenetics study of Fanconi Anemia phenotype and cancer predisposition

Presenting author name: - Merin George

Presenting author institute: - Department of Cytogenetics, ICMR-National Institute of Immunohematology, K.E.M. Hospital Campus, Parel, Mumbai, Maharashtra. India.

Co-authors name: - Aruna Rajendran, Sandeep Nemani, Deendayalan Munirathnam, Sangeeta Murlidar, Pranoti kini, Mamta Manglani, Chandrakala Shanmukhaiah, Babu Rao Vundinti,

Co-authors institute: - Department of Pediatric Hematology, Institute of ChildHealth and Hospital for children, Chennai, Tamil Nādu, India., Usha Hematology Center, Sangli, Maharashtra, India., Kanchi Kamakoti Childs Trust Hospital, Tamil Nādu, India., Bai JerbaiWadia Hospital for Children, Mumbai Maharashtra,India., Comprehensive Thalassemia Care Center and Bone Marrow Transplantation Center, Mumbai Maharashtra, India., Comprehensive Thalassemia Care Center and Bone Marrow Transplantation Center, Mumbai Maharashtra, India., King Edward Memorial Hospital, Maharashtra, India., Department of Cytogenetics, ICMR-National Institute of Immunohematology, K.E.M. Hospital Campus, Parel, Mumbai, Maharashtra, India.,

Aims: - Genotyping of FA and study the role of epigenetic factors in cancer predisposition

Methods: - The study was carried out in 70 FA subjects diagnosed by chromosomal breakage investigations. Mutational analysis was done using NGS, MLPA and Sanger sequencing. Whole Genome methylation sequencing using Infinium Methylation EPIC BeadChip, Expression of histone modifying enzymes by qPCR.

Results: - A high frequency of chromosomal breakages was observed in all FA subjects and median age was 8.9 years. Molecular study characterized 68 subjects and identified 9 complementation groups. In our cohort, the genotype-phenotype correlation revealed skin pigmentation, short stature, and skeletal abnormalities as the common clinical features among all FA complementation groups. However, FANCD2 complementation group subjects presented with additional clinical abnormalities such as renal anomalies, organ deformities, and genital anomalies. Four patients revealed VACTERL-H association. Global methylation in 16 FA subjects revealed 135 significant differentially methylated genes. These genes belonged to different functions like immunity, DNA repair, tumor suppressor, apoptotic, developmental, transcription factors, and metabolic. Most BMF genes (DKC1, FANCB, and WAS) were seen to be hypermethylated in FANCA patients as compared to FANCG and FANCL patients, suggesting an early BMF in FANCA patients as compared to the others. We further validated top 10 significantly methylated genes in 60 FA patients and age matched healthy controls; FAM65B and CDKN1B genes were significantly down regulated in patients as compared to controls and may be associated with cancer progression. Out of 16 histone modifying genes were studied; SETD6, DNMT1, PRMT1, CIITA and DNMT3a expression were significantly (<0.05) down regulated in FA subjects compared to the controls. The reduced expression of

these genes in FA, suggests that these patients have altered epigenetic regulation, which may be involved in the neoplastic complications of this disease.

Conclusions: - The FANCA, G, L complementation groups should be studied in Indian FA as these are account for more than 90% of FA subjects. Our study highlights the abnormal methylation and histone modifications in FA which may be considered as cancer predisposition.

Keywords: - A high frequency of chromosomal breakages was observed in all FA subjects and median age was 8.9 years. Molecular study characterized 68 subjects and identified 9 complementation groups. In our cohort, the genotype-phenotype correlation revealed skin pigmentation, short stature, and skeletal abnormalities as the common clinical features among all FA complementation groups. However, FANCD2 complementation group subjects presented with additional clinical abnormalities such as renal anomalies, organ deformities, and genital anomalies. Four patients revealed VACTERL-H association. Global methylation in 16 FA subjects revealed 135 significant differentially methylated genes. These genes belonged to different functions like immunity, DNA repair, tumor suppressor, apoptotic, developmental, transcription factors, and metabolic. Most BMF genes (DKC1, FANCB, and WAS) were seen to be hypermethylated in FANCA patients as compared to FANCG and FANCL patients, suggesting an early BMF in FANCA patients as compared to the others. We further validated top 10 significantly methylated genes in 60 FA patients and age matched healthy controls; FAM65B and CDKN1B genes were significantly down regulated in patients as compared to controls and may be associated with cancer progression. Out of 16 histone modifying genes were studied; SETD6, DNMT1, PRMT1, CIITA and DNMT3a expression were significantly (<0.05) down regulated in FA subjects compared to the controls. The reduced expression of these genes in FA, suggests that these patients have altered epigenetic regulation, which may be involved in the neoplastic complications of this disease.