Abstract ID:- 72

Abstract Topic:- Prenatal, perinatal and developmental genetics

Abstract Title:- Understanding the contribution of maternal telomere homeostasis genes in spontaneous preterm birth.

Presenting author name :- Divyank Varshney

Presenting author institute:- National Institute of Biomedical Genomics, Kalyani, West Bengal, India

Co-authors name:- Esha Bhattacharjee, Jagyashila Das, Indranil Bagchi, Shekhar Ghosh, Ramachandran Thiruvengadam, Nitya Wadhwa, Pallavi Kshetrapal, GARBH-Ini study group, Shinjini Bhatnagar, Partha Pratim Majumder, Arindam Maitra

Co-authors institute:-National Institute of Biomedical Genomics, Kalyani, West Bengal, India, Pondicherry Institute of Medical Sciences, Kalapet, Puducherry, India, Translational Health Science and Technology Institute, Faridabad, India, John C. Martin Center for Liver Research and Innovation, Kolkata, West Bengal, India,

Aims:-Preterm birth is a significant global health concern and is associated with neonatal mortality and long-term health complications. India contributes the highest number of preterm births worldwide. Despite extensive research, the underlying mechanisms leading to preterm birth remain incompletely understood. Recent findings from our group indicated that maternal telomere dysfunction, might be involved. We undertook targeted genomic and epigenomic investigations to identify the genetic and epigenetic alterations in telomere homeostasis genes that might contribute to spontaneous preterm birth outcomes.

Methods:- We recruited 1,563 pregnant women from the GARBH-Ini (Interdisciplinary Group for Advanced Research on Birth Outcomes - DBT India Initiative) cohort in a 1:2 matched case-control design for genetic association analysis. Peripheral blood DNA samples from these women were collected and extracted for genotyping of 700,604 SNP markers. Additionally, in a subset of 44 pairs of preterm and term-delivering women, DNA samples were collected at three time points during pregnancy (11-14 weeks, 18-20 weeks, and 26-28 weeks) and used for DNA methylation analysis. We also conducted methylation quantitative trait loci (meQTL) analysis to understand whether the significantly associated genetic variants of telomere homeostasis genes alter DNA methylation levels.

Results:- From the genetic study, we identified 10 maternal SNPs with significant association with spontaneous preterm birth (sPTB) (Bonferroni corrected p-value < 3.6×10-4).

We ultimately homed in on rs78731121, an intronic variant of the TNKS gene, as the most significantly associated SNP (p-value = 9.37×10-5). Furthermore, we observed that the minor allele (C) of rs78731121 was associated with alteration in DNA methylation of TNKS gene. We identified a CpG site, cg00538229, which was significantly associated with preterm birth at 11-14 weeks of pregnancy (Bonferroni corrected p-value = 2.7×10 -4). This specific CpG site is located in the TSS-1500 region of the TAL1 gene.

Conclusions:- From our genetic and meQTL analysis, we observed that minor allele of rs78731121 result in hypermethylation at TSS-200 (timepoint 1) and hypomethylation at gene body (timepoint 3) of TNKS, both leading to decreased expression of TNKS, thereby shortening telomere length and ultimately resulting in increasing the risk of sPTB.

From epigenetic study, we observed that at CpG site cg00538229 located in TSS 1500 region of TAL1, there is hypomethylation leading to higher expression of TAL1 which decreases expression of telomerase enzyme resulting in reduction of telomere length and hence enhancing risk of sPTB delivery.

Keywords:- Spontaneous preterm birth, India, Telomere, Minor allele, Methylation quantitative trait loci.