GeNeXpreSS

Methylation, Monogenic Disorders and More

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Determining gestational age using genome methylation profile: A novel approach for fetal medicine (Falick Michaeli et al., 2019)

The need for accurate gestational age of a neonate need not be stressed. The available methods have limitations in various settings. In this study, the methylation status was studied using reduced representation bisulfite sequencing (RRBS) in DNA extracted from cord blood and placenta. The investigators identified a set of 332 differentially methylated regions (DMRs) that undergo demethylation in late gestational age and a set of 411 DMRs that undergo de novo methylation in late gestational age. The data of samples used for training (5 less than 33 weeks and 5 more than 33 weeks) was used to evaluate 41 'test' samples of neonates from 25 to 40 weeks. A neonatologist using Ballard criteria, assessed the gestational age of the neonates. This study shows that this novel method (RRBS) of studying methylation levels in DNA of white blood cells in cord blood provides an accurate assessment of gestational age and can be used in clinical settings. It seems the design of the epigenetic clock is working and is useful.

DNA methylation signature for *EZH2* functionally classifies sequence variants in three PRC2 complex genes (Choufani et al., 2020)

Weaver syndrome belongs to the group of overgrowth/intellectual disability syndromes (OGID), and is caused by mutations in *EZH2* gene. *EZH2* codes for a part of the catalytic component of the polycomb repressive complex 2 (PRC2) that regulates genome-wide chromatin and gene expression by methylation of lysine 27 of histone H3. *EED* and *SUZ12* which cause Cohen-Gibson syndrome and Imagawa-Matsumoto syndrome respectively, are other components of PRC2. This study used genome-wide DNA methylation (DNAm) data for 187 cases with OGID and 969 control subjects, and demonstrated that pathogenic variants in *EZH2* produce highly specific and sensitive DNAm signature reflecting the phenotype of WS. The signature identified differentiates loss-of-function from gain-of-function missense variants and to detect somatic mosaicism. Loss-of-function leads to decreased methylation of promotor region thus causing overgrowth phenotype and gain-of-function mutations cause growth restriction due to increase in methylation. This signature identified in *EZH2* helps classify sequence variants in *EED* and *SUZ12* as well, and can predict presence of pathogenic variants in undiagnosed individuals with OGID.

DNA methylation at birth predicts intellectual functioning and autism features in children with Fragile X syndrome (Kraan et al., 2020)

Fragile X syndrome (FXS) has some uncommon characteristics of molecular pathology including dynamic mutation of increase in the number of triplet repeats in the 5´ untranslated region, and silencing of the gene by epigenetic modifications of the *FMR1* promoter including DNA methylation (DNAm). Some other characteristics seen in Fragile X syndrome, that are unusual for a monogenic disorder, are premutation, tissue to tissue variation in number of repeats and methylation

leading to mosaicism including premutation/ mutation mosaicism. The level of DNAm of Fragile X Related Epigenetic Element 2 (FREE2) located to exon1/intron1 of *FMR1* gene has been seen to correlate with FMR protein and intellectual function. This study assessed DNAm of FREE2 by Methylation Specific-Quantitative Melt Analysis (MS QMA) and the EpiTYPER system, in stored newborn blood spots (NBS) and newly created dried blood spots (DBS) from 65 children with FXS. Good correlation was shown between DNAm and neurocognitive function including autism; more so in males than in females. Correlation was also observed between DNAm and FMR mRNA. In males with FXS the change in the level of FREE2m from birth to childhood was not significant but decrease in the level of FREE2m was observed in FXS females. The stochastic changes may be the combined effects of environmental factors, clonal selection and mRNA toxicity. The results have potential for using FREE2M for newborn screening as well as for more accurate prognostication.

MeCP2 links heterochromatin condensates and neurodevelopmental disease (Li et al., 2020)

Rett syndrome is a neuro-developmental disorder seen in females which is caused by mutations in *MECP2* gene associated with DNA methylation regulation. MeCP2 binds methylated DNA, thus regulating transcription and chromatin organization. As per the concept called phase separation, certain molecules form large droplets by which the molecules inside the droplet are separated from the rest of the cell; these droplets are called condensates. By using fluorescent labelled MeCP2 and HP1 proteins, live cell imaging was done which showed that the two proteins occur in the same heterochromatin condensates. Imaging of neurons of mice expressing GFP-tagged MeCP2 protein from the endogenous locus revealed that MeCP2-GFP occurs in Hoechst-dense heterochromatin. These results indicate that MeCP2 is a dynamic component of liquid-like heterochromatin condensates in murine brain cells. The scientists have done various experiments to understand physicochemical properties of MeCP2 and effects of mutations on the heterochromatin condensates. Based on the results the authors propose that a large number of MeCP2 molecules, using multiple weak and dynamic interactions, form membrane-less bodies that can concentrate and compartmentalize additional components engaged in heterochromatin function. Rett syndrome mutations cause decrease in the protein as well as alter the condensate properties. The understanding of molecular pathology may help in development of new approaches to pharmacological modification of condensate behaviors for the treatment of Rett syndrome.

References

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