Mother and maternal grandmother were heterozygous for the F8 variant. It is possible that the two additional variants were either de novo mutations or inherited from the father.

Conclusions: The clinical phenotype noted may represent a compound heterozygous state associated with atypical lyonization and characterised by a novel mutation in the F8 gene accompanied by two additional mutations also associated with low factor VIII levels on the alternate allele.

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CRITICAL ILLNESS IN PRETERM INFANTS IS ASSOCIATED WITH DIFFERENTIAL EXPRESSION OF STRESS-ACTIVATED PROTEIN KINASE SIGNALLING AND DRUG METABOLIZING CYP450 GENES

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Background: Preterm infants often suffer from critical conditions involving stress that requires advanced treatment including increased oxygen supply. We aimed to examine the influence of critical illness at the molecular level represented by gene expressions.

Methods: 20 premature infants in a level III NICU at Oslo University Hospital, Rikshospitalet, were studied. Inclusion criteria was critical illness defined by conditions requiring surgical procedures and severe drop in oxygen saturation, SaO₂ (< 60%), following more than 80% oxygen supply. For peripheral blood preparation we used RiboPure™-Blood, GLOBINclear™-Human protocol, and NugeneOvation RNA-Amplification system. Gene expressions were assessed using GeneChip Human Genome-U133 Plus2.0-arrays from Affymetrix. Ethical approval was granted by the Regional Committees for Medical and Health Research Ethics in Norway.

Results: A total of 107 peripheral blood samples were assessed. Thirteen samples at the time of critical illness from 7 infants showed significant

differential expression for 6000 genes. Further investigation identified higher expression levels in a group of genes related to oxidative stress and stress activated protein kinase (SAPK) signalling pathway. We also found significant differential expression of CYP450 genes involved in drug metabolism, including CYP1A2, CYP2D6, and CYP3A4. Interestingly, CYP1A2 was standing out with more than a 6 fold increased level.

Conclusion: This is the first study on simultaneously expressed genes in preterm babies. Our results highlight the significance of critical illness, pathophysiological mechanisms following stress and their effect on gene expression levels. Thus, molecular biomarkers are important to understand the impact of stress on gene expression, including CYP450 genes, in preterm infants.

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EXPRESSION OF CYTOCHROME P450 METABOLIZING ENZYMES IN PRETERM INFANTS DEPENDS ON AGE, BUT NOT GENDER

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Background: The neonatal period is a critical time for premature born infants. Variability in drug response may be due to differences in expression of the metabolizing CYP450 genes. Comprehensive studies of CYP450 gene expression at clinical relevant time points are lacking. We aimed to compare the gene expression levels of all CYP450 genes simultaneously in relation to gestational age (GA) and gender.

Materials: Peripheral blood at subsequent time points was withdrawn from premature born infants between GA 25.2-37.0, in a level III NICU at Oslo University Hospital, Rikshospitalet. We used the RiboPure™-Blood-, GLOBINclear™-Human protocol, NugeneOvation RNA Amplification system, and GeneChip Human Genome U133 Plus 2.0 arrays from Affymetrix to analyse global gene

expression patterns. Ethical approval was granted by the Regional Committees for Medical and Health Research Ethics in Norway.

Results: CYP450 gene expression was significantly altered about 6 weeks postnatally between preterm infants (n=18) born at early (GA 25.2-28.6 wks) versus late (n=23) GA (29.0-33.6). Thirteen CYP450 genes, including those metabolizing commonly used drugs, such as CYP1A2 (p=0.0112) and CYP3A4 (p=0.0424), differed in expression levels. No significant differences in CYP450 gene expressions among preterm males and females were found.

Conclusion: We identified significant differences in CYP450 gene expression levels in preterm infants 6 weeks postnatally depending on GA. In particular CYP1A2 and CYP3A4 are interesting candidates for explaining variable drug response in preterm infants. Further investigation is needed to explore the role of these differences related to drug metabolism.

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ASSOCIATION OF MATRIX METALLOPROTEINASE 2 AND TIMP-2 GENE POLYMORPHISMS WITH DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS

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Background and aims: Bronchopulmonary Dysplasia (BPD) is considered to be a consequence of prematurity, pulmonary baro/volutrauma, hyperoxia and inflammation. Increased inflammatory response and lung repair with impaired alveolarization and vascularisation are largely determined by genetic variability. Metalloproteinases are endopeptidases with key role in extracellular matrix remodeling as occurs during lung development and repair after injury. The aim of this study was to assess the influence of MMP-2 and TIMP-2 genetic polymorphisms on the risk of BPD.

Methods: 95 preterm neonates with a gestational age of ≤ 32 weeks and birth weight ≤ 1500 g were

included in this prospective study. For the evaluation of phenotypic effect 215 term healthy neonates were additionally included. Out of 95 premature infants 47 developed BPD according to NIH criteria. 7 neonates died before time of assessment presenting severe lung damage. Using SNP TaqMan assays -1306C/T MMP-2 and +853G/A TIMP-2 polymorphisms were genotyped in DNA extracted from blood samples.

Results: Analysis of genetic variability in preterm neonates showed difference in distribution of genotypes at -1306C/T MMP-2 position. C/T and T/T genotypes were more frequent in neonates developing BPD or in those who died. Additionally T allele presence was associated with prolonged ventilation time and hospitalization duration at NICU. No difference in +853G/A TIMP-2 polymorphism frequency was found between tested groups.

Conclusions: Based on presented data and multigenetic background of BPD, genetic variability of MMP-2 may be one of the contributory factors in development of bronchopulmonary dysplasia.

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PROGRESSIVE MUSCULAR DYSTROPHY: CLINICAL AND GENETICAL STUDY

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Background and aims: Progressive muscular dystrophies represent a group of genetic diseases with insidious onset in childhood; they are characterized by muscle fatigue associated with pseudohypertrophy of the muscles, high level of creatin kinase; electrophysiological, histological and molecular biology studies distinguish the primary disorder of the muscles.

Methods: Prospective study that included 16 patients (1-5 years old) in a period of 2 years (2006-2008). Patients were evaluated clinically, functionally, paraclinical (muscle enzyme), neurophysiology. In all patients muscle biopsy was performed and in 8 cases genetic tests.

Results: In this trial 12 children (75%) had pseudohypertrophy of calf muscles, 8 children (50%) had signs of muscular disease (the weakness of proximal muscles, a positive Gowers's sign), 5 children (31.25%) had increased