

Analytical Validation of a SNP-Based Non-Invasive Prenatal Test to Detect the 22q11.2 Deletion

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ABSTRACT

Background: Non-invasive prenatal testing (NIPT) for aneuploidy using cell-free DNA in maternal plasma has been widely adopted. Recently, NIPT coverage has expanded to detect subchromosomal anomalies including the 22q11.2 deletion. Previous validation studies of a SNP-based NIPT for detection of 22q11.2 deletions demonstrated high sensitivity (>95%) and specificity (>99.5%). Here, we validated a revised version of this test in a cohort of pregnancy plasma samples. **Materials and Methods:** Blood samples were obtained from pregnant women with known 22q11.2 status. Ten positive control samples and 390 negative control samples were analyzed using a revised SNP-based NIPT for the 22q11.2 deletion. Samples were amplified and sequenced using pooled primer sets that included 1,351 SNPs spanning a 2.91Mb section of the 22q11.2 region. A risk score was assigned to all samples using a proprietary algorithm. The algorithm's confidence threshold was raised to 0.95 and "high-risk" samples with deletion of the maternal haplotype were reflexively sequenced at high depth of read (14x10⁶ reads/sample). The sensitivity and specificity of the assay were measured. **Results:** Sensitivity of the assay was 90% (9/10), and specificity of 99.74% (389/390), with a corresponding false positive-rate of 0.26% were reported. **Conclusions:** This validation of the revised SNP-based assay in a cohort of pregnancy plasma samples demonstrates a high sensitivity and specificity for detection of the 22q11.2 deletion. Given the benefits of early intervention in patients with the 22q11.2 deletion and the high incidence of the condition, this SNP-based methodology provides a valuable addition to current population-wide prenatal screening approaches.

Congenital Leukemia – A Case Report

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ABSTRACT

Introduction: Congenital and neonatal leukemia rarely occur, yet carry high mortality rates and pose special problems for the obstetricians, perinatologist and hematologist. Although the etiology is unknown, the presence of leukemia at birth suggests a genetic abnormality and possible intrauterine exposure to drugs or other toxin as contributing factors. **Case Presentation:** We describe a case of congenital leukemia of a baby boy born to a 26-year-old multiparous mother, who, apart from being obese, had no other medical problems. The fetus was identified to be larger than gestational age at term, with an estimated birth weight of 4.5 kg, thus delivery was affected via an elective lower segment caesarean section. Sonographic examination done a day before delivery showed an abdominal circumference of 410 mm and HC:AC ratio 0.8 (low). At birth, the baby was noted to have multiple lymphadenopathy, distended abdomen with hepatosplenomegaly and bluish cutaneous nodules. Initial full blood count of the baby was anaemic (haemoglobin level 7 g/dl), had hyperleucocytosis (total white blood cell count 412x10⁹) and thrombocytopenic (platelet count 29x10⁹). A diagnosis of congenital Beta-cell acute lymphoblastic leukemia was suggested by immunophenotyping. The baby received and completed the induction phase of chemotherapy regime in the form of 6 doses of intramuscular L-asparaginase (ASPA). However, there were episodes of relapses during the maintenance phase in March 2017 and he passed on at 4 months of life. **Discussion and Conclusion:** Detecting congenital leukemia in the antenatal period is definitely a challenge to the obstetrician. In situations where the measurement of abdominal circumference is beyond 90th centile and the HC:AC ratio is abnormally low, hepatosplenomegaly should be suspected and further evaluation done. The middle cerebral artery Doppler study may be useful when there is severe fetal anaemia. In such situations, appropriate counselling should be done to the parents and preparation for neonatal care organized.