

Development and evaluation of a cost effective method for the molecular diagnosis of Prader-Willi syndrome (PWS) and Angelman syndrome (AS) in Sri Lanka

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Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are genetic disorders caused by imprinting defects on chromosome 15q11-q13. Prader-Willi syndrome is caused by loss of expression of some paternal genes and Angelman syndrome is caused by loss of expression of some maternal genes on chromosome 15q due to a deletion or uniparental disomy (UPD) of chromosome 15q or methylation centre defects in this region. The methylation specific PCR assay can detect ~99% of cases of PWS caused by deletion or UPD but can miss the 1% of cases caused by imprinting centre defects. The methylation specific PCR can detect around 90% of cases of AS caused by a deletion or UPD but can miss the 10% of cases caused by UBE3A mutation and imprinting centre defects. Objectives of this study were to establish diagnostic testing for PWS and AS among Sri Lankan patients using methylation specific PCR and to develop an in house DNA modification method for use in the methylation specific PCR assay. Forty three patients (suspected PWS = 24, AS = 19) were recruited after ethical clearance and informed consent from parents. DNA was extracted from blood and methylation specific PCR (MS-PCR) performed using control primers (SNRPNF and SNRPNR), maternal (MF1 and MR1) and paternal (PF2 and PR2) primers after the modification of DNA using a sodium bisulfite modification kit while some of the samples were modified using a modified protocol established in our laboratory. Eleven out of twenty four suspected PWS cases and none of the nineteen suspected AS cases were positive on testing. The kit based modification generated consistent reliable results while the in house method requires further optimization. In conclusion, the methylation specific PCR was successful in detecting methylation abnormalities associated with PWS and AS and is a potentially useful test to confirm or refute the diagnosis of suspected cases. The MS-PCR negative, suspected AS cases merit clinical review to determine the need for mutation testing prior to exclusion of AS.

Keywords: Angelman syndrome, Imprinting, Methylation specific PCR, MS-PCR, Prader-willi syndrome

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