Background: SRS is a typical epigenetic disease. 38-62% patients show a hypomethylation in the imprinting control region 1 in 11p15. 7%-10% SRS individuals carry a maternal uniparental disomy of chromosome 7(UPD7)mat. Approximately 40% of patients can not be detected genetic and epigenetic disturbances.

Objective: To analysis whether there is unknown genes or imprinted genes associated with pathogenicity of SRS and to detect the fine mapping SRS hypomethylation position through the Illumina Methylation 450K chip to detect genome-wide methylation differences.

METHODS

To detect genome-wide methylation sites through the Illumina 450K Infinium Methylation BeadChip chip in 7 cases (two cases were MLPA positive and five cases were negative) of SRS diagnosed in Beijing Children’s Hospital and 5 controls matched age. The two methods were validated by using the classical method of sequencing with focal phosphate and digital PCR.

Methylation site probe screening standards meet the following 2 points: (1) adjust Pval < 0.05, if adjust Pval=0.05, the Pval requires less than 0.05 before correction; (2) case vs control Beta-Difference should be not less than 0.2. That is |Beta-Difference| ≥ 0.2.

RESULTS

Screening out 116 differential methylation sites in 484821 probes. Through the GO Pathway enrichment analysis, found the cg25963939 site of OSBPL5 was the most significant methylation difference in case group and normal control group (P=0.023, β=-0.243). The 2 methods were validated by using the classical method of sequencing with focal phosphate and digital PCR. And the gene is located on 11p14 5’UTR region, it is quite possible pathogenic.

This study also found that TGF beta 3, HSF1, GAP43, NOTCH4, MYH14 these 5 genes have some sites which were significant methylation changes of SRS are located in 5’UTR area. The two methods were validated by using the classical method of sequencing with focal phosphate and digital PCR.

CONCLUSIONS

Through whole genome methylation chip detection, we found the imprinted gene OSBPL5, located on chromosome 11p14, which was detected a significant differential hypomethylation site in 5’UTR area. The two methods were validated by using the classical method of sequencing with focal phosphate and digital PCR. So OSBPL5 may be related to the pathogenicity of SRS. Through the detection of Illumina 450K Infinium high density microarray methylation, we confirmed that the most important epigenetic methylation changes of SRS are located in the 11p1. This is consistent with traditional classical methods such as MS-MLPA.

References