Methylation status of X inactivation-escape genes in controls and females with X chromosome rearrangements

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Introduction and objective

• X chromosome inactivation (XCI) is a process in which one of the two X chromosomes in females is randomly inactivated in order to correct the imbalance of gene dosage between males and females. However, about 15% of genes on the inactivated X chromosome escape from XCI1).
• The mechanism of inactivation and escape remains to be revealed.
• The promoter regions of escape genes are hypomethylated compared to those of the inactivated genes2).
• The objective of this study is to reveal the influence on the methylation status of escape genes’ promoters in patients with X chromosome rearrangements.

Methods

Subjects

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<td>Four patients (XX) with X chromosome rearrangements and 11 female and 12 male controls</td>
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Methods

We performed the array-based methylation analysis with genomic DNA from leukocytes of the patients and controls using Infinium MethylationEPIC BeadChip.

Extract escape genes

• Within 1 kb up and downstream of transcription start sites
• Hypermethylation in both sexes (β levels < 0.15)
• Methylation differences between males and females (Δ(β)) < 0.1

When the above items are satisfied with 2 probes or more per a gene, the gene was regarded as an escape gene.

Methylation status in patients with X chromosome rearrangements

We evaluated 34 genes that were predicted to be escape genes by our criteria and also reported as escape genes in the previous report1).

We extracted escape genes in patients satisfying the following conditions:
• β levels > 0.25
• SD > 2.0 (compared with female controls)
• The above items are satisfied with 2 probes or more per a gene

Results

The methylation status of the promoters of the escape genes in the patients with X chromosome rearrangements

Patient 1 showed hypermethylation in 5 escape genes at the duplicated region on short arm.

Discussion

Specific X chromosome rearrangements is likely to affect the methylation status of promoter regions of some escape genes.