SickKids | Genome Diagnostics

X Chromosome Inactivation

In females one of the two X chromosomes becomes randomly inactivated early in embryogenesis to allow for dosage compensation of X-linked genes. In any one female somatic cell the inactive X may be either the paternal or maternal X chromosome. If the paternal X chromosome is inactivated more frequently than the maternal X chromosome or vice versa, the X inactivation pattern is skewed. If a woman carries a disease-causing mutation on just one of her X chromosomes, she normally would not show signs of the disease. However, skewed X inactivation may result in symptoms of an X-linked disease if the chromosome carrying the mutation is preferentially active. X inactivation is considered skewed if the ratio of the active to inactive X chromosome is less than 10 per cent or greater than 90 per cent.

Genetics

The highly polymorphic androgen receptor (CAG)n repeat region, located on the X chromosome (Xq11-q12), is used to detect X inactivation. Methylation sensitive enzymes are used to cut the androgen receptor repeat region on the DNA strand. These enzymes digest DNA on the active X but do not cut sites on the inactive X. The quantitative PCR of androgen receptor repeats is compared with and without digestion to determine X inactivation ratio.

Who Should Be Tested?

- Females clinically suspected of being manifesting carriers of X-linked disorders

Test Methods

- PCR across the CAG repeat of the androgen receptor (*AR*) gene both before and after digestion with methylation sensitive enzymes Hha I and Hpa II.

Test Limitation

- This test will detect the methylation status of X chromosomes, but will not determine if the X inactivation pattern is linked to any mutations in genes on the X chromosome.

- The test will also assess the X inactivation pattern in the sample type submitted, however X chromosome patterns can differ in different tissues.

Potential Outcomes & Interpretation of Test Results

Sex of Patient	X Inactivation Ratio	Explanation
Female	Less than 90% inactivation of one allele	This result does not support skewed X inactivation in the sample type received from this patient
Female	Greater than 90% inactivation of one allele	This result supports skewed X inactivation in the sample type received from this patient

For More Information

To locate a genetics center near you, visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

SickKids

This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.