

# X-Chromosome Ultra High-Density Microarray, 954 Genes

*TO DETECT LOSS OR GAIN OF DNA ON THE X CHROMOSOME IN PATIENTS WITH UNEXPLAINED INTELLECTUAL DISABILITY, AUTISM, AND OTHER X-LINKED GENETIC CONDITIONS*

## Test Highlights

- The X-array is a custom-designed, X chromosome-specific, ultra high-density oligonucleotide array containing DNA sequences representing specific regions of the human X chromosome. Patient DNA is hybridized to the chip to:
  - Identify unbalanced chromosomal abnormalities (copy-number changes) involving the X chromosome, which are undetectable by conventional chromosome analysis.
  - Define breakpoints for X-chromosome cytogenetic abnormalities identified by conventional cytogenetic methods.
  - Identify very small, exonic-level, intragenic and intergenic deletions and duplications on the X chromosome that may cause specific, X-linked disease in the individual.
- This array uses 720,000 probes, providing very dense coverage of all 954 identified genes located on the X chromosome. At the exonic level, probes are tiled at 15 base-pair (bp) intervals, providing contiguous coverage of each exon of each gene. Probes are spaced 135 bp apart in intronic and flanking regions of each gene, and there is a backbone of probes spaced 525 bp (0.5 kb) apart across the intragenic regions of the chromosome.
- This test will detect copy-number variations within all X-chromosome genes associated with X-linked mental retardation (XLMR) and autism, as well as small, unique deletions and duplications within and between genes associated with other X-linked disorders that may not be identified by conventional sequencing-based technologies.

## Clinical Background

- While the X chromosome contains only 4 percent of all human genes, mutations in these genes account for 10 percent of known Mendelian disorders and 27 percent of intellectual disability.
- Small deletions and duplications have been described as causative mutations in many X-linked disorders.
- Mental retardation:
  - Approximately 25–50 percent of intellectual disability/mental retardation/developmental delay (ID/MR/DD) has a genetic basis.
  - X-linked genetic defects are considered to be important causes of mental retardation, based on the observation that significantly more males than females are affected. Mutations on the X chromosome cause up to 30 percent of all inherited ID.
  - XLMR is a highly heterogeneous condition that can be divided into syndromic XLMR and non-syndromic XLMR depending on the presence or absence of physical abnormalities, dysmorphic features, abnormal laboratory findings, and abnormal brain-imaging studies. Approximately two-thirds of XLMR is considered to be non-syndromic, although the distinction between the two forms is blurred, as variable phenotypes are being described for the same genes.
- Other disorders:
  - The X chromosome contains genes that cause many well-described disorders not involving ID/MR/DD. These disorders fall into several general categories, such as hearing loss, hemophilias, immunodeficiency disorders, metabolic disorders, myopathies, neuromuscular disorders, and skin disorders.

## Indications for Ordering

- Screening of individuals for microdeletions and microduplications associated with clinically diagnosed X-linked syndromes/clinical phenotypes.
- Screening of individuals with disorders following an X-linked pattern of inheritance.
- Screening of individuals with ID/MR/DD.
- To further characterize X-chromosome abnormalities, including marker and ring chromosomes, deletions or duplications, unbalanced translocations, or apparently balanced de novo rearrangements involving the X chromosome in patients with abnormal phenotypes.

## Additional Ordering Notes

A clinical indication for testing must be provided. A patient sample, along with the Patient History for X-Chromosome Ultra High-Density Microarray Form, which can be found on [www.aruplab.com](http://www.aruplab.com), should be completed and submitted.

## Interpretation

- A positive result means that a pathogenic copy-number change was identified.
- A negative result means that no known pathogenic copy-number change was identified.
- A result of unclear clinical significance means that a copy-number change that cannot currently be categorized as either pathogenic or benign was identified.

- Parental testing may be offered free of charge if such testing will be useful for the interpretation of a finding of unclear clinical significance in the patient. However, if parental testing is clinically indicated, such as for recurrence risk, parental testing is available at an additional cost.

### Limitations

- This array will not detect numerical X-chromosome changes, such as Klinefelter, Turner, or triple-X syndromes. This technique will only detect copy-number imbalances within the X chromosome. Balanced rearrangements and base-pair changes will not be detected. Copy-number imbalances for areas of high-sequence similarity may not be detected.
- Genomic imbalances smaller than the resolution of this array, regions of the genome not represented on the array, and mosaicism will not be detected.
- A negative result does not exclude the diagnosis of any of the disorders represented on the microarray.

### Methodology

- The technique involves DNA extraction, labeling, hybridization, washing, array scanning, analysis, and interpretation.
- Copy-number changes are calculated based on hybridization signal ratios between patient sample and controls.
- This X-array test is run on the NimbleGen custom-designed comparative genomic hybridization (CGH) array with 720,000 oligonucleotide probes mapped to specific regions of the X chromosome.
- At the exonic level, these 720,000 probes are tiled at 15 bp intervals, providing contiguous coverage of each exon of each gene. Probes are spaced 135 bp apart in intronic and flanking regions of each gene, and there is a backbone of probes spaced 525 bp (0.5 kb) apart across the intragenic regions of the chromosome.

- This technique will detect imbalances that are extremely small by cytogenetic standards. It is designed to detect single-exon copy-number changes for all 954 genes on the X chromosome.

### Related Tests

- Conventional cytogenetic analysis (karyotyping) will detect large additions, deletions, and rearrangements, including balanced translocations and inversions involving all areas of the genome (including the X chromosome). Conventional cytogenetics generally cannot detect duplications and deletions smaller than approximately 5 Mb (5,000 kb) in size (the average size of a chromosomal band) or larger changes that do not alter the karyotype-banding pattern.
- Whole genome microarray will detect copy-number changes on all other chromosomes in addition to the X chromosome.
- Other molecular techniques (e.g., gene sequencing or other PCR-based assays) are more sensitive than genomic microarray for detecting many intragenic alterations, such as point mutations and very small deletions or duplications (such as a single base pair), but are highly specific and restricted to the genetic site or gene of interest.

### References

1. Ropers HH and Hamel BCJ. X-linked mental retardation. *Nat Rev* 2005;6:46–57.
2. Lisik MZ and Sieron AL. X-linked mental retardation. *Med Sci Monit* 2008;14(11):RA221–9.

## Test Information

### 2004434 X Chromosome Ultra-High Density Microarray, 954 Genes

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).