MOLECULAR DIAGNOSIS for X-LINKED INTELLECTUAL DISABILITY
Intellectual disability (ID) or mental retardation is characterized by significant limitations in cognitive abilities and social/behavioral adaptive skills. It is estimated that 1-3% of the general population is affected with ID. Intellectual disability is one of the primary reasons for pediatric, neurologic, and genetic referrals.

Intellectual disability can result from both environmental circumstances and genetic causes. Genetic causes, which account for up to 50% of moderate-severe cases, include chromosomal anomalies, specific syndromes, and single gene disorders.

Mutations in genes located on the X chromosome are a common cause of ID and may be responsible for about 10% of the delays found in males. To date, more than 90 genes on the X chromosome have shown clear association with X-linked intellectual disability (XLID) disorders. In a family with multiple affected males, an X-linked pattern of inheritance should be considered. Females in those families may be unaffected carriers of the mutation or may exhibit milder symptoms than males due, in part, to X-inactivation.

**CLASSIFICATION OF XLID**

Approximately 10% of the protein-encoding genes on the X chromosome have been implicated in XLID. Although the numbers of mutations and reported families are small, collectively the impact of these genes is significant.

Based on phenotypic characterization of individuals with pathogenic gene alterations, three classes of XLID presentations exist:

- **Syndromic**
  Individuals may have multiple congenital anomalies, dysmorphic features and/or other abnormal clinical findings.

- **Non-Syndromic**
  Intellectual disability is the only consistent clinical finding. No dysmorphic or neurologic phenotypes are present. This form accounts for approximately 2/3 of all XLID.

- **Neuromuscular**
  No malformations are noted, but there is evidence of neurological or muscular findings in addition to the ID.
For patients with suspected XLID, Emory Genetics Laboratory (EGL), in collaboration with the Greenwood Genetics Center (GGC), has developed a panel providing sequence analysis for all coding exons and flanking intronic sequence of 92 XLID genes.

**XLID TEST PATHWAY**

**Suspected XLID**

Chromosomal Microarray & Fragile X Syndrome Testing

If Negative  If Positive

**XLID Gene Sequencing Panel**  **Diagnosis Confirmed**

*For patients with syndromic XLID, individual XLID gene sequencing should be ordered based on clinical presentation.

**WHAT ARE THE BENEFITS OF TESTING?**

A majority of individuals with XLID are non-syndromic with no other features to assist in the diagnosis. Because of the number of genes involved, it is very difficult to identify which X-linked gene may be responsible for the phenotype in any given patient. Our simultaneous testing of all known XLID genes in a single study provides a significant diagnostic advantage over single gene sequencing. Additional benefits for the patients and families include:

- Providing information for recurrence risk and family planning and allowing for presymptomatic support.
- Helping physicians to determine appropriate follow-up testing and develop a health maintenance plan.
- Predicting better patient prognostic value.
• Assisting researchers in the understanding of the molecular basis of disease in the hope for treatments and cures.
• Assessing the possibility of therapy for some forms of XLID.

APPROPRIATE CANDIDATES FOR TESTING
• Males with ID in the presence or absence of other dysmorphic, neuromuscular, metabolic or behavioral phenotypes that distinguish the proband from unaffected males in the family.
• Males with an X-linked pattern of ID who have negative fragile X and cytogenetic test results.
• At-risk family members of those with a known mutation can have site-specific mutation analysis. In particular are females who are at significant risk for being carriers of identified mutations.

LIMITATIONS OF GENETIC TESTING
• Variants of uncertain clinical significance may be identified.
• This panel can only identify mutations within genes known to be associated with XLID.
• Non-coding RNA genes are not included on this panel.

INTERPRETING TEST RESULTS
• Positive result: A mutation has been identified that is of particular diagnostic and clinical significance.
• Negative result: No mutation has been identified. A negative result does not exclude the presence of a mutation that cannot be identified by the current panel and technology.
• If variants of unknown significance are detected, follow-up testing of available family members is generally recommended. Additional study typically includes the proband’s mother and other appropriate maternally-related males. This additional study helps determine the segregation pattern of the identified variant. When variants of questionable significance are identified in phenotypically normal males, they are deemed benign variations with no clinical significance.
Testing for the *SLC6A8* genes should be performed separately by biochemical analysis.

Testing for *IKBKG* is not currently offered.
SAMPLE REQUIREMENTS/ SHIPPING INSTRUCTIONS

• 5 ml peripheral blood in EDTA tube

• Ship overnight, at room temperature to:
  Emory Genetics Laboratory
  2165 North Decatur Road
  Decatur, GA  30033

• Turnaround time is sixteen weeks

CPT CODES
83891 (x1), 83892 (x1), 83894 (x1), 83898 (x10), 83900 (x1), 83901 (x20), 83904 (x20), 83909 (x20), 83912 (x1)

CONTACT INFORMATION

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Emory Genetics Laboratory (EGL) is a comprehensive clinical genetics testing laboratory specializing in molecular cytogenetics, rare disease testing, and newborn screening confirmatory testing.

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