



All-Chromosome Telomere Analysis for Patients with Idiopathic Mental Retardation

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IN THE UNITED STATES, approximately 3% of the population are mentally retarded or have some degree of developmental delay. There are various causes; these include pre- or postnatal agent exposure, birth trauma, biochemical genetic defects and cytogenetic abnormalities. Even with the cytogenetic, biochemical, and molecular diagnostic tests currently available, an explanation for cognitive delay is identified in less than one-third of referred patients. Family history information, in addition, indicates that although specific testing is not available, additional cases appear to be due to either autosomal dominant, autosomal or X-linked recessive, or unbalanced chromosomal inheritance.

Development of FISH (fluorescent in situ hybridization) technology is now allowing the gap between molecular diagnostics and conventional cytogenetic analysis to be closed. This technique allows detection of rearrangements that have been proven to be below the limits of cytogenetic resolution.

A new set of DNA FISH probes has been developed and is now available for clinical use at the Sacred Heart Medical Center/PAML cytogenetics laboratory. These probes are specific for the telomeric region of both the short arm and long arm of each of the human chromosomes, including the sex chromosomes. Analysis using this probe set will allow molecular visualization of cytogenetically undetectable deletions or translocations at the ends of all the chromosomes.

Evidence has been mounting over the past decade that indicates that small chromosome rearrangements involving the terminal bands of chromosomes may be an important unrecognized cause of mental retardation in humans.¹ Recent articles in the peer-reviewed literature support this; in properly selected patient populations, a sub-telomere FISH probe set may allow diagnosis in up to 18% of individuals that heretofore have remained without a causative diagnosis (95% confidence interval 1-18%).² More specific figures from patients studied to date indicate that an abnormal result may be found in approximately 8% of patients with moderate to severe mental retardation and in about 1% of patients with mild mental retardation.³

The probability of obtaining an abnormal test result depends on choosing the proper patients for testing. Once an abnormality is identified in a patient, follow-up parental FISH studies are recommended; this further analysis allows differentiation between de novo aberrations and chromosome rearrangements that are segregating within a given family. The latter situation would be associated with a significant recurrence risk for those and possibly other family members.

Selection of patients for testing

There are several recommendations for patient selection. These include the following:

- Occurrence within several generations of a family of more than one affected individual, not necessarily with the same abnormal clinical phenotype.
- Lack of another clinical diagnosis; this would include having a prior documented normal result from a routine or high-resolution cytogenetic analysis on the patient. A copy of the prior cytogenetics result is requested and should accompany the specimen.
- Presence of developmental delay/MR, but not necessarily the presence of dysmorphic features or other physical findings upon exam.

Features

- ▶ Probes are specific for the telomeric region of both the short and long arm of each human chromosome.
- ▶ Analysis with the probe set allows molecular visualization of cytogenetically undetectable deletions or translocations at the ends of all chromosomes.
- ▶ Data indicate that approximately 8% of individual patients with moderate to severe MR have cryptic sub-telomeric chromosome rearrangements.

For more information, please contact Client Services.

Test Information

The specimen required for this analysis is 5 mL whole blood in a green-top sodium heparin Vacutainer tube. Do not spin or freeze the specimen. It is stable up to 72 hours at room temperature or refrigerated. The turnaround time is 2-4 weeks. The CPT codes charges are 88271, 88272×23, and 88291.

References

1. Ledbetter, David H., "Minireview: Cryptic Translocations and Telomere Integrity" Am. J. Hum. Genetics 1992, 51:451-456.
2. Flint, J., et al. "The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation" Nature Genetics 1995, 9:132-140.
3. Knight, S.J.L., et al. "Subtle chromosome rearrangements in children with unexplained mental retardation" The Lancet 1999, 354:1676-1681.

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