

Genomic Approaches to the Diagnosis of Mental Retardation in Adults

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Introduction: Mental retardation (MR) is a common and costly **birth defect** affecting 1-3% of the population and 1 in 10 families. MR is frequently due to genetic factors, which must be identified if recurrence risk counseling and prevention measures are to occur. Sadly, however, a diagnosis is made in only 50% of MR cases. For adults with MR, a rapidly growing group, a comprehensive genetic evaluation is lacking in the majority of cases and there is **substantial room for improvement in the diagnostic approach to MR in adults.**

Recent studies in children have clearly shown that 'submicroscopic' chromosomal defects (microdeletion syndromes and subtelomeric rearrangements), often undetectable by traditional chromosome studies, account for as much as 20% of MR. **The prevalence of these defects in MR patients surviving to adulthood is not known.** We are working with a novel, state-of-the art chromosomal microarray (Ch-MA) technology with high sensitivity for detecting submicroscopic chromosomal defects.

Public Health Impact: Many adults with genetic forms of MR can have children, and these children are at high risk to have MR as a birth defect. With respect to the goal of 'preventing birth defects' a comprehensive genetic evaluation of adults with MR is critical. The **long-term objective** of this research proposal is to improve our ability to diagnose genetic forms of *mental retardation in adults* with the goal of improving the health of these *patients and their families* and reducing the incidence of MR as a birth defect.

Project: We have received funding the by March of Dimes to explore two '**Research Hypotheses**':

- 1) that 20% of mentally retarded adults who lack an explanation (diagnosis) for their mental retardation have sub-microscopic chromosomal defects detectable by Ch-MA, and
- 2) that these chromosomal abnormalities are *causal* of the mental retardation phenotype in the majority of cases. A third, '**Translational/ Clinical Hypothesis**'
- 3) is that Ch-MA technology poses additional challenges for delivering understandable and effective genetic counseling.

Methods: Adults with MR from our established Adult Medical Genetics clinic will be evaluated by a clinical geneticist (PI) and enrolled in an MR Registry (n=130). Adults with unexplained MR and normal standard genetic studies (high resolution chromosomes and Fragile X analysis) will be studied using Ch-MA (Hypothesis 1). Our CH-MA platform tests for subtelomeric defects and over 40 syndromes. Positive results will be studied in available relatives (parents) to assess causality of each defect in MR (Hypothesis 2). Genetic counseling for Ch-MA will be videotaped, studied, and formal methods for genetic counseling in setting of Ch-MA technology will be developed. The impact of genetic counseling on patient/family understanding, reproductive decision-making, and recurrence of birth defects will be studied (Hypothesis 3).

Study outcomes: Data from this project will

- 1) determine the prevalence of submicroscopic chromosomal defects in adults with MR,
- 2) identify new genetic MR syndromes,
- 3) lead to optimal genetic counseling methods for Ch-MA, 4) improve the management of pregnancies affected by a family history of MR, 5) assess the impact of Ch-MA testing on patients, families, and the recurrence of MR as a birth defect, and 6) lead to clinical counseling guidelines for use in Ch-MA testing.