Professional Issues

Genetic Counseling for Fragile X Syndrome: Updated Recommendations of the National Society of Genetic Counselors

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These recommendations describe the minimum standard criteria for genetic counseling and testing of individuals and families with fragile X syndrome, as well as carriers and potential carriers of a fragile X mutation. The original guidelines (published in 2000) have been revised, replacing a stratified pre- and full mutation model of fragile X syndrome with one based on a continuum of gene effects across the full spectrum of FMR1 CGG trinucleotide repeat expansion. This document reviews the molecular genetics of fragile X syndrome, clinical phenotype (including the spectrum of premature ovarian failure and fragile X-associated tremor-ataxia syndrome), indications for genetic testing and interpretation of results, risks of transmission, family planning options, psychosocial issues, and references for professional and patient resources. These recommendations are the opinions of a multicenter working group of genetic counselors with expertise in fragile X syndrome genetic counseling, and they are based on clinical experience, review of pertinent English language articles, and reports of expert committees. These recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. The professional judgment of a health care provider, familiar with the facts and circumstances of a specific case, will always supersede these recommendations.

KEY WORDS: fragile X syndrome; genetic counseling; genetic testing; premature ovarian failure; FXTAS; premutation; FMR1; prenatal diagnosis; National Society of Genetic Counselors; practice guidelines.

PURPOSE

To present practice recommendations for genetic counselors and other health care professionals who provide genetic counseling and risk assessment for patients with suspected or confirmed fragile X syndrome and their families.

DISCLAIMER

The genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist practitioners and patients in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current.
as of the submission date and are subject to change as advances in diagnostic techniques, treatment, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments, or procedures alternative to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient.

METHOD

The authors consisted of experts in the field of genetic counseling for fragile X syndrome. Review and input was also sought from medical specialists with expertise in fragile X syndrome and patient advocacy groups. The authors searched the MEDLINE and PsycINFO databases for relevant English language medical and psychosocial literature between 1999 and 2004, including seminal articles from earlier dates. Key words included: fragile X syndrome, genetic counseling, psychosocial assessment, genetic testing, premature ovarian failure, prenatal diagnosis, carrier testing, and preimplantation diagnosis. Guidelines and policy statements published by the American College of Medical Genetics (Sherman, Pletcher, and Driscoll, 2005; Maddalena et al., 2001), and genetic counseling guidelines developed by genetic counselors in the state of Washington (Marymee et al., 1998) were also reviewed. This literature is based on clinical experience, descriptive studies and/or reports of expert committees. The literature was reviewed and evaluated for quality according to the categories outlined by the U.S Preventive Services Task Force (1995). The rating of supporting literature for this recommendation is class III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

A draft document was made available to the 2072 members of NSGC for comment. The NSGC membership includes genetic counselors, physicians, nurses, attorneys, doctors of philosophy, and students. The revised document was reviewed by the NSGC attorney and the NSGC Ethics Subcommittee and no conflicts with the NSGC Code of Ethics or issues regarding legal liability were identified in the final document. The NSGC Board of Directors reviewed and approved the final document in March, 2005.

INTRODUCTION TO FRAGILE X SYNDROME

In 1969 Lubs reported the presence of an abnormal “marker X” chromosome in a family with males with mental retardation following an X-linked pattern (Lubs, 1969). It was not until 1977 that Sutherland was able to show that the expression of the marker X chromosome was inextricably linked to low folate concentrations in the cell culture medium (Sutherland, 1977). With this riddle solved, a relatively reliable cytogenetic test soon became available to distinguish the subgroup of males with the newly-named fragile X syndrome. Throughout the 1980s, as molecular advances put researchers within reach of the exact location of the fragile X gene, linkage analysis allowed relatively accurate carrier and prenatal testing for some families (Shapiro et al., 1988). In 1991 the gene responsible for fragile X syndrome was identified (Oberle et al., 1991; Verkerk et al., 1991; Yu et al., 1991), allowing highly reliable diagnostic, prenatal, and carrier testing. Despite these advances, several aspects of genetic counseling for fragile X syndrome remain challenging, including the interpretation of intermediate alleles and the widely variable clinical prognosis, particularly in females with fragile X mutations. Apart from the certainty that there is no male-to-male transmission of the fragile X mutation, genetic counselors should be wary of citing absolutes. As the understanding of the clinical phenotype in both males and females continues to evolve, the previously sharp clinical distinctions between pre- and full mutations have become more fluid. Recently, Hagerman and Hagerman (2004) proposed replacing the stratified pre- and full mutation model of fragile X syndrome with one based on a continuum of gene effects across the full spectrum of repeat expansion.

FMR1 Gene and FMR1 Protein (FMRP)

The FMR1 (Fragile X Mental Retardation-1) gene is characterized by a repetitive CGG trinucleotide sequence located in the 5' promoter region, which, in most people in the general population, is repeated from 6 to 50 times. Two abnormal FMR1 states have been identified in association with fragile