Fragile X syndrome

CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

PROTOCOLS

Principal investigators

Jonathan Down, MB, MHSc, FRCPC, Developmental Paediatrician, Vancouver Island Health Authority, Queen Alexandra Centre for Children's Health, 2400 Arbutus Rd., Victoria BC V8N 1V7; tel.: 250-519-6745; fax: 250-519-6931; jonathan.down@viha.ca

Gudrun Aubertin, MD, MSc, FRCPC, Clinical Geneticist, Vancouver Island Medical Genetics/University of British Columbia, Victoria General Hospital, Victoria BC V8Z 6R5; tel.: 250-727-4419; fax: 250-727-4295; gudrun.aubertin@viha.ca

Co-investigators

Tanya Nelson, PhD, University of British Columbia
Gail Graham, MD, Ottawa University
Carlo Paribello, MD, Fragile X Research Foundation of Canada, Toronto
Marianna Ofner, PhD, University of Toronto, Public Health Agency of Canada

Background

Fragile X syndrome (FXS) is the most common form of inherited intellectual and developmental disability and is characterized by a behavioural phenotype that may include symptoms of autism and attention deficit hyperactivity, in addition to mild physical features.

FXS results from an expansion of a CGG trinucleotide repeat in the *FMR1* gene located on the X chromosome. Expansions of CGG repeats above ~200 lead to methylation of the *FMR1* gene and are designated full mutations. The prevalence of FXS has been estimated at 1 in 4,000 in males[1,2] and 1 in 5,000 to 8,000 females.[3,4] These estimates are based on screening children with special needs and may not reflect the true prevalence of FXS in the general population or the possible differences in mutation frequency amongst different ethnic groups. More recent prevalence figures of 1 in 5,161 males with methylated *FMR1* alleles were obtained from a large cohort of de-identified newborn screening samples in the Southern United States.[5] A Canadian study screened 12,418 newborn males and 12,032 newborn females; the prevalence for the full mutation was 1 in 6,209 males and 0 in 12,032 females.[6] Diagnostic testing for fragile X syndrome is recommended in the evaluation of a child presenting with developmental delay by the American Academy of Pediatrics, the American College of Medical Genetics, and the American Academy of Neurology. The average age at diagnosis of FXS is three years of age, occurring on average two years after concerns are first identified by the family, and did not decrease following published diagnostic testing recommendations.[7] One quarter to one third of children with FXS attending public schools were diagnosed after the age of 10 years.[3] This is concerning because a late diagnosis may delay early intervention services for these children, but more importantly, it delays accurate genetic counseling on the recurrence risk and availability of prenatal diagnosis. Approximately one third of parents have another child before a diagnosis of FXS is made, in many cases leading to the birth of a second child with FXS. Delayed diagnosis may be attributable to decreased awareness and/or to wait times associated with referrals to subspecialists, including geneticists, developmental paediatricians, or paediatric neurologists.

There is limited information in the medical literature on the demographics of FXS in Canada. It is currently unclear if the prevalence is similar to published rates in other populations, whether there is a delay in obtaining a diagnosis or there is a significant number of individuals with FXS without access to specialty care.

A better understanding of the characteristics of the fragile X patient population in Canada is essential, given two recent developments in the field. First, population screening, including newborn screening, is increasingly being advocated within the fragile X community and is being endorsed by the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) in the United States. Second, advances in the understanding of the molecular pathways underlying FXS have lead to novel pharmaceutical agents that are being studied in clinical trials and have given rise to speculation that targeted therapies will be available to patients in the next few years.

This study will investigate the incidence of new diagnoses of FXS in order to obtain information about the demographics, clinical features, geographic distribution and management of FXS in Canada.

Methods

Through the established methodology of the CPSP, over 2,500 paediatricians and paediatric subspecialists, including geneticists, will be actively surveyed on a monthly basis for new cases of FXS. For each reported case, participants will be asked to complete a detailed clinical questionnaire to ensure that the case definition is met.

Case definition

Report any new patient less than 18 years of age with diagnosed fragile X syndrome (FXS) meeting the following criteria:

1) **Genetic criteria:** Males or females, with laboratory confirmation of a CGG repeat allele in the full mutation size range (>200 repeats), including mosaicism
   AND
2) **Clinical criteria, one** of the following:
   - Global developmental delay, manifesting as the clinical impression of delays in two or more domains of development **or**
   - Intellectual disability, mild, moderate or severe, diagnosed through standardized psychological testing **or**
   - Asymptomatic infant, tested because of a positive family history, including prenatally diagnosed cases

Exclusion criteria

Clinical evidence of global developmental delays or intellectual disability with laboratory confirmation of a CGG repeat allele in the normal or premutation size range.

Objectives

Primary objective

Ascertain the incidence of new diagnoses of FXS in Canada.

Secondary objectives

1) Describe the demographics, regional and ethnic variations of FXS
2) Describe the clinical features, age at diagnosis and comorbid conditions (e.g., autistic spectrum disorder) associated with FXS

3) Improve professional awareness of FXS
4) Determine the access and availability of medical and laboratory services for FXS
5) Compare Canadian data with other published epidemiological incidence estimates and improve overall global knowledge of FXS

Duration

April 2012 to March 2014

Expected number of cases

In British Columbia, the detection rate of FXS full mutation between 2006 and 2009 was 5–10 cases per year, or less than 1% of total samples.[8] It is estimated that 50–100 new cases will be reported each year in Canada.

Ethical approval

Vancouver Island Health Authority Research Ethics Board, Victoria

Analysis and publication

Data will be undertaken using basic statistical analyses. Validation of cases will be done by contacting regional genetic laboratories across Canada (and USA where indicated) to determine, anonymously, how many genetic tests were performed confirming FXS cases with full mutation (>200 repeats) in the years of the study investigation. This number will then be cross-referenced against the provincial/ territorial reporting to CPSP during the same years.

Completed study results will be presented at national and international scientific meetings and submitted for publication in scientific peer-reviewed journals.

References

1. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. *Am J Med Genet* 1996;64:196–7.
2. Murray A, Youings S, Dennis N et al. Population screening at the FRAXA and FRAXE loci: molecular analyses of boys with learning difficulties and their mothers. *Hum Mol Genet* 1996;5:727–35.
3. Crawford D, Meadows K, Newman J, Taft L, Scott E et al. Prevalence of the fragile X syndrome in African Americans. *Am J Med Genet* 2002;110:226–33.
4. Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. *Genet Med* 2001;3:359–71.
5. Coffee B, Keith K, Albizua I, Malone T, Mowrey J et al. Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. *Am J Hum Genet* 2009;85:503–14.
6. Levesque S, Dombrowski C, Morel ML et al. Screening and instability of FMR1 alleles in a prospective sample of 24,449 mother-newborn pairs from the general population. *Clin Genet* 2009;76:511–23.
7. Bailey D, Raspa M, Bishop E, Holiday D. No change in the age of diagnosis for fragile X syndrome: Findings from a national parent survey. *Pediatrics* 2009;124:527–33.
8. Nelson T. Personal communication, unpublished data. 2011.