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High incidence of pediatric idiopathic epilepsy is associated with familial and autosomal dominant disease in Eastern Newfoundland

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Summary
Purpose: To describe the incidence and epidemiology of pediatric idiopathic epilepsy (IE) in Newfoundland and Labrador.
Methods: All children in Newfoundland and Labrador aged 0—15 years with IE were ascertained through the provincial neurology clinic at the Janeway Child Health Centre. Family history, medical history and blood samples were obtained from probands and relatives. Two genes, *SCN1A* and *KCNQ2*, were screened for mutations by direct sequencing.
Results: The mean annual incidence of IE for the population of children living in the Avalon region of Newfoundland from 2000 to 2004 was 107 per 100 000. This rate is approximately three-fold greater than rates reported in other developed countries. Of 117 families with IE eligible for study, 86 (74%) provided detailed pedigree data. Multiple different epilepsy phenotypes were identified. Fifty-five families (64%) had a positive family history. Eight of these had family histories compatible with autosomal dominant (AD) inheritance and these families lived in five different geographic isolates. DNA was obtained from 21 families (79 individuals). The two

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previously identified mutations in Newfoundland families with epilepsy were sequenced and excluded as pathogenic sites in all but one family which had a mutation in *SCN1A*.
Conclusion: The incidence of IE is high in the Avalon Peninsula of Newfoundland and the rate of familial disease is high throughout the province of Newfoundland and Labrador. The distribution of familial and AD IE in different geographic isolates, together with the clinical heterogeneity of disease suggests substantial genetic heterogeneity. It is likely that other novel mutations will be identified in this population.

Introduction

Epilepsy is a common, chronic neurological disorder characterized by clinical and genetic heterogeneity. The incidence of epilepsy in children is 40—80 per 100 000 (Freitag et al., 2001; Olafsson et al., 1996; Zarrelli et al., 1999; Forsgren et al., 2005). Approximately half of all cases are idiopathic and are presumed to have a predominantly genetic basis (Annegers et al., 1996; Andrade and Minassian, 2007). The rest are symptomatic, resulting from an underlying structural or metabolic cause, and cryptogenic, in which an underlying cause is suspected but not identified (1989).

Family studies in idiopathic epilepsy (IE) have shown that a first degree relative of an affected individual has a 2.5—4 fold increased risk of being affected than the general population, and twin studies have shown more than 40% monozygotic concordance rates (Annegers et al., 1996; Weissbecker et al., 1999). Most cases of IE are inherited in a complex manner, involving the interaction of several genes and unknown environmental factors (Berkovic et al., 1998). Mendelian conditions are thought to account for only 1% of heritable cases of epilepsy (Robinson and Gardiner, 2004; Gardiner, 2000). These rare mendelian cases are clinically and genetically heterogeneous with 11 causal genes (*KCNQ2*, *KCNQ3*, *CHRNA4*, *CHRNA2*, *CHRNB2*, *SCN1B*, *SCN1A*, *SCN2A*, *GABRG2*, *GABRA1*, and *LGI1*) identified to date (Berkovic et al., 2006; Baulac and Baulac, 2009). All but one of the causative genes identified in IE encode components of neuronal ion channels (voltage-gated sodium, potassium, and chloride channels) or neurotransmitter receptors (acetylcholine nicotinic receptor and $GABA_A$ receptor). Mutations in two neuronal ion channel genes have been identified in the province of Newfoundland and Labrador: a missense mutation in exon 6 of a potassium channel gene (*KCNQ2*) was previously shown to be associated with Benign Familial Neonatal Convulsions in another Newfoundland family (Singh et al., 1998) and a missense mutation in *SCN1A* was identified in a family with GEFS+ (Family A in this study) (Mahoney et al., 2009). The only non-ion channel gene associated with mendelian epilepsy, *LGI1* (leucine-rich glioma inactivated 1), was identified as a cause of autosomal dominant lateral temporal epilepsy (Kalachikov et al., 2002).

Few population-based studies of the familial basis of childhood epilepsy have been undertaken. Two previous epidemiological studies of childhood epilepsy in northern Sweden and Hong Kong found that 9.6% and 9.7% of patients had a first degree relative with a history of epilepsy, respectively (Sidenvall et al., 1996; Kwong et al., 2001) and an Estonian study found that 14.8% of patients had a family history of epilepsy amongst first and second degree relatives (Sidenvall et al., 1996; Kwong et al., 2001; Beilmann et al., 1999a,b). Though several previous studies have included family history data (Sidenvall et al., 1993, 1996; Beilmann et al., 1999a,b; Freitag et al., 2001; Kwong et al., 2001; Mullins et al., 2007), there are no previous reports giving detailed family histories in a population-based study.

The population of Newfoundland and Labrador is predominantly of English and Irish extraction and has grown primarily by natural increase within small, isolated communities, resulting in multiple founder effects (Rahman et al., 2003). Currently, the population of the province is approximately 509 200; about 50% of the population live in rural communities of fewer than 2500 inhabitants and approximately half the population (257 223) live in the Avalon Peninsula region (http://www.statcan.gc.ca) (Bear et al., 1987). The Avalon Peninsula is a predominantly urban region and is the location of the provincial capital, St. John's. A provincial study of Bardet—Biedl Syndrome, an autosomal recessive disorder, demonstrated that the condition occurred in multiple geographic isolates, but the genetic cause differed from region to region. In fact, 6 different genes were identified in which 10 different mutations were the cause of this syndrome (Webb et al., 2009). In autosomal dominant Lynch Syndrome, the genetic cause of this cancer syndrome also varied across geographic isolates (P.S. Parfrey, personal communication). The aim of the current study was to determine the incidence of IE in the Avalon Peninsula region, describe the clinical causes of IE in the province and identify families with IE compatible with monogenic inheritance.

Methods

Patients

Patients were ascertained through the provincial pediatric neurology clinic at the Janeway Child Health Centre, the only children's hospital in the province. Inclusion criteria were: residents of Newfoundland and Labrador aged 0—15 years with a clinical diagnosis of IE made between 1999 and 2006. IE was defined as two or more unprovoked asymptomatic seizures occurring more than 24 h apart in accordance with the International League Against Epilepsy (1993). Diagnoses were confirmed by pediatric neurologists (DB, MA). Children with a single unprovoked seizure or febrile seizures were excluded from the study.

Three-hundred ninety-five cases of childhood epilepsy, presenting to the neurology clinic between 1997 and 2006, were reviewed, yielding 121 cases (117 families) who met eligibility criteria for the study. Ninety-seven of the 117 families were contacted and 86 agreed to participate, giving a response rate of 74%. The 11 families who did not participate in the family study either refused (6),