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Genome wide high density SNP-based linkage analysis of childhood absence epilepsy identifies a susceptibility locus on chromosome 3p23-p14

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Summary: Childhood absence epilepsy (CAE) is an idiopathic generalised epilepsy (IGE) characterised by typical absence seizures manifested by transitory loss of awareness with 2.5—4 Hz spike-wave complexes on ictal EEG. A genetic component to the aetiology is well recognised but the mechanism of inheritance and the genes involved are yet to be fully established.
A genome wide single nucleotide polymorphism (SNP)-based high density linkage scan was carried out using 41 nuclear pedigrees with at least two affected members. Multipoint parametric and non-parametric linkage analyses were performed using MERLIN 1.1.1 and a susceptibility locus was identified on chromosome 3p23-p14 ($Z_{mean} = 3.9$, $p < 0.0001$; HLOD = 3.3, $\alpha = 0.7$). The linked region harbours the functional candidate genes *TRAK1* and *CACNA2D2*. Fine-mapping using a tagSNP approach demonstrated disease association with variants in *TRAK1*.

Introduction

The absence epilepsies are a group of idiopathic generalised epilepsies (IGEs) which differ in their seizure frequency, age of onset and pattern of evolution. A typical absence seizure manifests as a transitory loss of awareness with 2.5—4 Hz spike-wave complexes on ictal EEG. Many patients also have generalised tonic—clonic seizures (GTCS), myoclonic seizures or febrile seizures in addition and a variety of 'atypical' absence seizures are recognised. The International League Against Epilepsy (ILAE) classification recognises a number of distinct absence epilepsy syndromes including childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), epilepsy with myoclonic absences, juvenile myoclonic epilepsy (JME) and eyelid myoclonia with absences as a seizure type (Engel, 2001). However, it is still unclear whether these syndromes represent a 'biological continuum' or distinct entities. Frequency of absence seizures per day is greater in CAE than JAE, and the occurrence of GTCS is greater in patients with JAE than CAE. However, there is evidence that CAE and JAE share a close genetic relationship allowing them to be considered as one phenotype in genetic studies (Berkovic et al., 1987; Marini et al., 2004).

Twin studies have demonstrated that the IGEs, including those in which absence seizures occur, have a significant heritability (Berkovic et al., 1998), with regards to both occurrence and type of seizure and syndrome with concordance rates for monozygotic twin pairs far higher than for dizygotic twin pairs (Kjeldsen et al., 2003). Absence epilepsies, along with the other common forms of IGE, show a complex pattern of inheritance. In keeping with other common genetic disorders, this is expected to result from the action of a few or many genes of small to moderate effect.

Genome-wide linkage analysis of IGE-multiplex families has demonstrated evidence for susceptibility loci on chromosomes 2q36, 3q26, and 14q23 (Sander et al., 2000). Furthermore, loci for three similar forms of absence epilepsy have been identified on chromosomes 8q24 (*ECA1*), 5q31.1 (*ECA2*) and 3q26 (*ECA3*) (Fong et al., 1998; Robinson et al., 2002; Sugimoto et al., 2000; Wallace et al., 2001). We have previously shown evidence for linkage and association to chromosome 16p12-p13.1, the region containing the calcium channel gene *CACNG3* (Everett et al., 2007). An association in humans has been documented between polymorphisms in *CACNA1A* (chromosome 19p13.2-p13.1) and IGE including CAE (Chioza et al., 2001). Twelve missense mutations in