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Generalized epilepsy with febrile seizures plus and classical idiopathic generalized epilepsy

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Abstract

The idiopathic generalized epilepsies (IGE) comprise two major groups: the classical IGE and generalized epilepsy with febrile seizures plus (GEFS+). The classical IGE syndromes include childhood absence epilepsy; juvenile absence epilepsy; juvenile myoclonic epilepsy; and epilepsy with generalized tonic-clonic seizures alone. GEFS+ is a familial epilepsy syndrome, characterized by a spectrum of phenotypes. The phenotypes of GEFS+ include febrile seizures (FS), febrile seizures plus (FS+), FS/ FS+ and absences, myoclonic, atonic or partial seizures, myoclonic-astatic epilepsy and severe myoclonic epilepsy of infancy. Our study of 121 individuals in 20 families, where 84 had previously recognized GEFS+ phenotypes, expands the phenotypic spectrum of GEFS+ syndrome to include afebrile generalized tonic-clonic seizures with generalized spike wave or normal EEG in the absence of FS. To date, there are three ion channel genes (SCN1A, SCN1B and GABRG2) confirmed as having a role in GEFS+, but none has been implicated in the majority of patients with GEFS+ phenotypes, such as those found in small families. Indeed it is likely that in most families, GEFS+ is a polygenic disorder resulting from the cumulative effect of a number of genes of lesser effect rather than the genes so far characterized in the few large families ascertained. Small GEFS+ families and bilineal inheritance in some add support for complex inheritance in a significant proportion of families. The phenotypes of classical IGE occur in some GEFS+ families. The percentage of classical IGE phenotypes is 9% (11/121) of affected individuals in our study. This suggests that classical IGE phenotypes and GEFS+ phenotypes overlap in some GEFS+ families. Our study provides new insights into the inter-relationship of GEFS+ and classical IGE, where shared genetic determinants probably account for the overlap of these syndromes in some families.

INTRODUCTION

Generalised epilepsy with febrile seizures plus (GEFS+) is a genetic epilepsy syndrome diagnosed on the basis of a number of family members with phenotypes within the GEFS+ spectrum.[1] The phenotypes of GEFS+ include febrile seizures (FS), febrile seizures plus (FS+), FS/ FS+ and absences, myoclonic, atonic or partial seizures, myoclonic-astatic epilepsy and severe myoclonic epilepsy of infancy (or Dravet syndrome). Although GEFS+ is an idiopathic generalised epilepsy (IGE), it is only rarely seen in association with the classical IGE syndromes of childhood absence epilepsy, juvenile myoclonic epilepsy and juvenile absence epilepsy.[2-5]

There are three ion channel genes (SCN1A, SCN1B and GABRG2) confirmed as having a role in GEFS+. Mutations of these genes have been found in a small number of large multiplex GEFS+ families where the inheritance of seizures is consistent with autosomal dominant inheritance. Small GEFS+ families are more frequent than the large families reported, yet insights into the susceptibility genes for complex inheritance of GEFS+ in smaller kindreds are just beginning to emerge.

Here, we report 20 new GEFS+ families varying in size from 2 affected members to 12 affected individuals. We analyze the phenotypes within these families and compare them with previously reported GEFS+ families. In addition, we examine the overlap of GEFS+ and IGE phenotypes found within a subset of families.

EPILEPSY PHENOTYPES IN GEFS+ FAMILIES

Our study of 121 individuals distributed in 20 families had seizures, 84 with previously recognized GEFS+ phenotypes: FS in 37, FS+ in 16, FS+ with other seizure types (absence, atonic) in 7, myoclonic-astatic epilepsy in 7, and partial epilepsy with or without FS in 17 individuals. In 8 families, an additional 11 individuals had IGE: childhood absence epilepsy in 5, juvenile

myoclonic epilepsy in 5, juvenile absence epilepsy in 1. Twenty six individuals had other phenotypes: afebrile generalized tonic-clonic seizures in 5, Lennox-Gastaut syndrome in 1, unclassified seizures in 17, unconfirmed seizures in 3 individuals.

In studying many families with GEFS+, we have occasionally encountered family members who have isolated or rare afebrile generalized tonic-clonic seizures. In our new families, we found 5 individuals who had afebrile generalized tonic-clonic seizures without preceding FS. The EEG results were normal in 3 patients; no EEG results were available for the other two. Baulac *et al* reported an individual with afebrile generalized tonic-clonic seizures associated with an *SCN1A* mutation in a GEFS+ family.[6] Bonanni *et al* reported 7 GEFS+ families with 39 affected individuals without mutations of known GEFS+ genes.[7] Six individuals in four families had afebrile generalized tonic-clonic seizures. Two of these 6 individuals showed 3 Hz generalised spike and wave on EEG and were classified as IGE with generalized tonic-clonic seizures. These data suggest that isolated afebrile generalized tonic-clonic seizures also form part of the GEFS+ spectrum.

THE PHENOTYPES OF GEFS+ AND CLASSICAL IGE OVERLAP FAMILIES

In 20 GEFS+ families, the phenotypes of GEFS+ and classical IGE overlapped in 8 families. The classical IGE phenotypes in GEFS+ families included five childhood absence epilepsy patients (one twin pair) in 4 families, five juvenile myoclonic epilepsy patients in 4 families, and 1 juvenile absence epilepsy patient in one family. In these 11 classical IGE patients 2 had a history of FS.

This is not the first time that classical IGE have been found in GEFS+ families. Molecular studies have shown that GABAA receptor subunit gene mutations may occur in GEFS+ and classical IGE families. Specifically GABRG2 gene mutations have been reported in a large family with GEFS+ and childhood absence epilepsy phenotypes.[2] Sodium channel subunit mutations more commonly are found in GEFS+ families but classical IGE may also be seen. For example, early-onset absence epilepsy without FS occurred in one member of a GEFS+ family with a SCN1B mutation.[5] Rare individuals in GEFS+ families have been reported with juvenile myoclonic epilepsy. In some cases they carry the familial sodium channel SCN1A mutation[3]; whereas, in others they do not.[8]

EVIDENCE FOR COMPLEX INHERITANCE IN SOME GEFS+ FAMILIES

In 20 GEFS+ families, 10 families were consistent with autosomal dominant inheritance. Bilineal inheritance was present in 8 families, involving 14 affected members. Another 2 GEFS+ families were small, each only had 2 affected members. Bilineal inheritance and small GEFS+ families add support for complex inheritance in a significant proportion of families.

This study expands the phenotypic spectrum of GEFS+ syndrome to include afebrile generalized tonic-clonic seizures with generalized spike wave or normal EEG in the absence of FS. Our findings emphasize the inter-relationship of GEFS+ and IGE; shared genetic determinants probably account for the overlap of these syndromes in some families.

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