Letter to the Editor

Identical twins with Idiopathic Basal Ganglia Calcification (“Fahr’s Disease”) presenting with a remarkably similar pattern of neuroimaging findings

There is a growing interest in defining the genetic background of autosomal dominant inherited Familial Idiopathic Basal Ganglia Calcification (FIBGC), a neuropsychiatric condition often described as “Fahr’s Disease” [1–3].

However, the current debate about the nosology of this heterogeneous phenotype demands a search for standard diagnostic criteria and the identification of loci or mutations responsible for FIBGC that might help to elucidate this intriguing neuropsychiatric condition [4].

The clinical profile includes a variable combination of both motor and cognitive impairment, such as parkinsonism, dystonia, tremor, chorea, ataxia, dysphagia, progressive cognitive impairment, psychosis and changes in mood. Neuroimaging may identify calcifications not only in the basal ganglia but also in the thalamus, cerebral white matter, cerebellum and internal capsule, which are always associated with normal biochemical and endocrine screening [1].

Previous neuroradiological analysis in familial brain calcinosis showed that some individuals may have been symptom free despite the presence of extensive findings on neuroimaging; however, studies measuring the total volume of calcification suggest a significantly larger number of deposits in symptomatic individuals compared to asymptomatic subjects [4].

Linkage of FIBGC to a 13.3-cM critical region on chromosome 14 was described for a large American multigenerational family and this locus (IBGC1) is currently being fully sequenced. Another small kindred, from Spain, has also been reported as possibly linked to this locus (IBGC2) [5].

The issue of differential levels of penetrance has already been addressed in other movement disorders such as primary torsion dystonia (PTD) and Huntington Disease (HD). While both these conditions are characterized by autosomal dominant inheritance, they also present with variable penetrance. Compared with the HD carrier state, only a minority of mutated dystonia gene carriers ever develops clinical symptoms. Abnormal metabolic findings in the brains of asymptomatic carriers show that our definition of genetic penetrance based only on visual clinical examinations might be flawed, when dealing with hereditable movement disorders with probable metabolic endophenotypes [5].

We conclude that it is necessary to consider two levels of penetrance in IBGC: one for the calcification formations and another for the clinical manifestation. A crucial step towards the definition of this hypothesis will be the identification of a gene or genes involved in FIBGC.

We suggest that the presence of extensive bilateral calcifications in basal ganglia and cerebellum may be related to the absence of clinical symptoms in IBGC. A crucial step towards the definition of this hypothesis is the identification of a gene or genes involved in FIBGC.

We would like to see a follow-up of asymptomatic subjects with FIBGC in order to detect the exact timing of the appearance of the first symptoms and to define the limits of brain resilience to calcifications. Considering that a significantly greater amount of calcification is present in symptomatic individuals, even among subjects from the same pedigree, we might infer that there is a differential level of penetrance for the formation of calcifications and the manifestation of the first symptoms [4].

The search for genetic loci associated with IBGC is currently ongoing. Further studies measuring the total volume of calcification suggest a significantly larger number of deposits in symptomatic individuals compared to asymptomatic subjects [4].

We conclude that it is necessary to consider two levels of penetrance in IBGC: one for the calcification formations and another for the clinical manifestation. A crucial step towards the definition of this hypothesis will be the identification of a gene or genes involved in FIBGC.

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References


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Fig. 1. The axial head computerized tomography showing calcifications in cerebellum, basal ganglia and white matter in the brains of the identical twins in both up and bottom rows.

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