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Genetic heterogeneity in familial idiopathic basal ganglia calcification (Fahr disease)

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Abstract—Familial idiopathic basal ganglia calcification (IBGC, Fahr disease) is an inherited neurologic condition characterized by basal ganglia and extra-basal ganglia brain calcifications, parkinsonism, and neuropsychiatric symptoms. The authors examined six families for linkage to the previously identified genetic locus (IBGC1) located on chromosome 14q. The authors found evidence against linkage to IBGC1 in five of the six families supporting previous preliminary studies demonstrating genetic heterogeneity in familial IBGC.

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Fahr disease or familial idiopathic basal ganglia calcification (IBGC) is an inheritable occurrence of bilateral calcifications of the basal ganglia and extrastriate regions. IBGC is manifested by a variable combination of dystonia, parkinsonism, ataxia, cognitive impairment, and behavioral changes and most cases display autosomal dominant transmission.[1] A large multigenerational family with autosomal dominant pattern of inheritance (FY1) of IBGC was found to have significant linkage to the long arm of chromosome 14 (IBGC1).[2] A second pedigree, in which clinical criteria consisting of diverse neuropsychiatric phenotypes instead of imaging were used to determine affection status, was excluded from the IBGC1 locus, suggesting genetic heterogeneity.[3] In order to narrow the IBGC1 locus and to define the extent of genetic heterogeneity in IBGC, we have ascertained additional families using strict diagnostic criteria and examined for linkage to IBGC1.

Patients and methods. *Subject recruitment and assessment.* Six IBGC pedigrees with an autosomal dominant pattern of inheritance were ascertained as previously described[2] under protocols approved by the institutional review boards of participating institutions (figure). Brain CT scans were undertaken to determine positive or negative calcium deposition. Biochemical investigation was used to rule out abnormalities of calcium regulation and metabolic disorders that could underlie brain calcifications in at least one affected member of each family (www.geneclinics.org).[1,2]

Three families (FB2, FZ3, and FP5) had been previously reported in the literature.[4-6] Neurologic examination was performed in family members when possible (D.H.G., J.K., J.G., Z.K.W., D.B.C., A.J.S., B.V.M., F.B., M.B.). Defining affected individuals is complicated by the heterogeneity in clinical presentation, age dependent penetrance, and the fact that many asymptomatic individuals have positive CTs.[1-3] We therefore defined affected individuals as those with positive CTs, since clinical criteria are neither sensitive nor specific for IBGC.[2] Individuals with negative CTs who are over the age of 50 are defined as unaffected, while those at earlier ages are classified as unknown, as in previous linkage studies.[2] The main clinical features observed in each family are summarized in table 1. (Additional information can be found in the appendix on the *Neurology* Web site at www.neurology.org.)

Molecular genetics and analytic methods. DNA was extracted from peripheral blood lymphocytes using the Puregene kit (Gentra Systems). Published primer pairs were used to amplify STR markers across the IBGC1 region (http://www.gdb.org). The markers used and map positions are listed in table 2 (http://www.cephb.fr, http://genome.ucsc.edu, and http://www-genome.wi.mit.edu). Microsatellites cover the IBGC1 locus (32.9 cM–46.8 cM) at relatively high density (about 4 cM average). Slightly different marker sets were used for different families due to availability of markers at the time of examination and non-informative markers in given families. Genotyping was performed as previously described.[2]

Two-point linkage analysis was performed with the MLINK program in the LINKAGE package assuming a dominant pattern of inheritance with 95% penetrance, a disease gene frequency of 0.001, and equal marker allele frequencies.[7] Pedigree generated allele frequencies were also tested with inconsequential differ-

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Table 1 *Main clinical and neuroimaging findings*

Family	Origin	Number of affected	Main clinical symptoms	CT finding	Ancestry
FB2	North America	11	Dementia, chorea, slurred speech, palilalia, gait disturbance, 5 asymptomatic (ref. 4)	Extensive BBGC, white matter, and cerebellum	North American Swedish decent
FZ3	North America	11	Dystonia, chorea, ataxia, postural tremor (ref. 5), 7 asymptomatic	Extensive BBGC, white matter, and cerebellum	North American probable Irish-English decent
FP5	North America	9	Parkinsonism and dystonia, 3 asymptomatic (ref. 6)	Extensive BBGC, thalamus, and white matter	North American Irish-English decent
FE12	Germany	6	Dizziness, epilepsy, headaches	Extensive BBGC	German
FL20	China	6	Dizziness, dementia, muscle spasms, and cramps, 2 asymptomatic	Extensive BBGC and cerebellum	North American Chinese decent/Chinese
FS4	Spain	4	Parkinsonism, psychomotor slowing, seizures, and behavioral changes, 2 asymptomatic	Extensive BBGC among the 3 oldest patients, punctate in a child (8 y)	Spanish

BBGC = bilateral basal ganglia calcifications; asymptomatic = individuals with calcifications but not symptoms on neurologic examination.

ences (excluding Family FZ3 due to unavailable data). Marker distances were determined as described above. Simulations were performed on Family FS4 using SLINK resulting in maximum estimated lod scores after 10,000 replications.[8]

Results. The major clinical features and pedigree structures of the six families are presented in table 1 and the figure. More detailed clinical summaries are available as supplemental material (see appendix at www.neurology.org). Pathologic study has been performed in two families (FB2, FP5), confirming the typical pattern of calcification observed in IBGC[6] (unpublished results). Patients with significant calcifications were clinically asymptomatic in several families, as has been previously noted,[1-3,9] consistent with the need to use radiologic findings to classify patients.

Linkage analysis. Families FB2, FZ3, FP5, and FE12 display lod scores < -2 at $\theta = 0.0$ across the candidate region, therefore excluding linkage to the IBGC locus (see table 2). The lod scores across the region in FL20 do not reach -2 but are suggestive of exclusion of linkage in this region. The lod score for Family FS4 in the IBGC1 region was 0.5 using the observed allele frequencies and 0.7 using

Table 2 *(Top) two-point lod scores of the families FB2, FZ3, FL20, FP5, FE12 at $\theta = 0.0$ across the IBGC1 candidate region; (Bottom) two-point lod scores of the family FS4 at $\theta = 0.0$ across the IBGC1 candidate region*

Markers	cM	FB2	FZ3	FE12	FP5	FL20
D14S1040	26.2	−0.08	−∞	−4.99	−0.56	—
D14S596	34.0	−3.25	—	—	—	−1.80
D14S1014	35.3	−5.72	−∞	−4.79	−1.29	—
D14S278/D14S306	36.3/36.5	−5.18	−∞	−5.09	−4.82	−1.78
D14S976	41.9	−5.62	−∞	−4.79	−3.38	0.0001
D14S259	42.0	—	−3.01	−5.12	—	—
D14S587/D14S989	46.0/46.2	−4.77	−∞	−4.79	−2.20	−1.76

Markers	cM	FS4
D14S1014	35.3	−2.87
D14S75	36.3	0.66
D14S288	39.1	0.48
D14S259	42.0	0.42
D14S989	46.2	0.70
D14S276	47.0	0.65
D14S1064	48.1	0.62
D14S285	50	−2.65

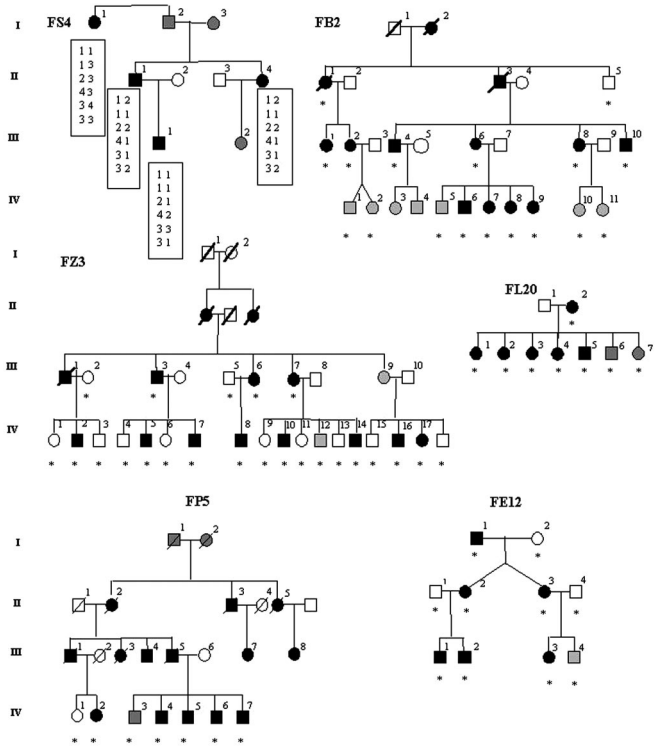

Figure. Pedigree of the FS4 family showing affected members sharing a common haplotype across the region. Markers loci from top to bottom are D14S75, D14S288, D14S259, D14S989, D14S276, D14S1064. Pedigrees of the families FB2, FE12, FL20, FP5, and FZ3. Squares represent males, circles represent females. Black filled represents affected, gray filled represents unknown, unfilled represents unaffected. Asterisk denotes availability of DNA.

equal allele frequencies. Although this is not a significant lod score, in each case it is the expected maximum lod score for this family. All affected members share a haplotype across the region including markers D14S75 to D14S1064. Overlapping of the minimal region of the Families FS4 and FY1 (IBGC1 locus) could narrow down the chromosome 14 region by 3.0 cM to 10.9 cM bounded by markers D14S14 and D14S989.

Discussion. The IBGC1 locus was excluded in five of six families with IBGC. Therefore, IBGC1, the first locus identified for this disorder, is not the major locus. This genetic heterogeneity is not surprising, given the extensive clinical heterogeneity observed among families. Within the same family some individuals may present with a predominantly parkinsonian syndrome, while others manifest predominantly hyperkinetic movement disorders. In other kindreds, most individuals are largely asymptomatic.[9] Within the FY1 family, to our knowledge the largest reported to date, variable symptoms such as frontal executive dysfunction, psychosis, dystonia, and parkinsonism are observed, suggesting that even diverse phenotypes can be caused by a single gene.

We were unable to exclude Family FS4, including four affected individuals, from the IBGC1 locus. In fact, the lod score was equal to the maximum expected lod score obtained in linkage simulations. This is consistent with possible linkage and could narrow the IBGC1 critical region to 10.9 cM between markers D14S1014 and D14S989, or it may be a spurious false positive linkage signal. This family shows a high level of clinical heterogeneity, including asymptomatic subjects, despite extensive calcifications in the basal ganglia and white matter. Thus, as we have suggested previously, it is likely that the calcifications themselves are a marker of disease, rather than the cause of clinical symptoms.[1-3] However, it is critical to use CT scans to classify patients, so as to avoid misclassification based on symptoms or signs alone.

The IBGC1 region contains over 100 known genes, ESTs, and predicted genes.[10] The identification of additional families with IBGC linked to chromosome 14q will be helpful in narrowing the candidate region to allow more efficient gene-by-gene searching. Finding genes in families with basal ganglia calcification will likely help to define the basic pathogenic mechanism of this rare form of focal neurodegeneration and will also provide insight about the different pathways that lead to dysfunction of the basal ganglia, such as parkinsonism, dystonia, and neurobehavioral disorders.

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Appendix

Database information: http://www.geneclinics.org, GeneReviews: Genetic Disease Online Reviews (Sobrido MJ, Hopfer S, Geschwind DH: Idiopathic basal ganglia calcification); http://www.gdb.org, The Genome database; http://www.cephb.fr, Centre d'Etude du Polymorphisme Humain—Jean Dausset Foundation; http://genome.ucsc.edu, University of California, Santa Cruz—Genome Browser; http://www-genome.wi.mit.edu, Center for Genome Research.

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