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1. Schneider SA, Hardy J, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation (NBIA): an update on clinical presentations, histological and genetic underpinnings, and treatment considerations. Mov Disord 2012;27:42–53.
2. Kruer MC, Boddaert N, Schneider SA, et al. Neuroimaging features of neurodegeneration with brain iron accumulation. AJNR Am J Neuroradiol 2012;33:407–414.
3. Schipper HM. Neurodegeneration with brain iron accumulation: clinical syndromes and neuroimaging. Biochim Biophys Acta 2012;1822:350–360.
4. McNeill A, Birchall D, Hayflick SJ, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. Neurology 2008;70:1614–1619.
5. Lehn A, Mellick G, Boyle R. Teaching NeuroImages: neuroferritinopathy. Neurology 2011;77:e107.
6. Vidal R, Ghetti B, Takao M, et al. Intracellular ferritin accumulation in neural and extraneural tissue characterizes a neurodegenerative disease associated with a mutation in the ferritin light polypeptide gene. J Neuropathol Exp Neurol 2004;63:363–380.
7. Li W, Wu B, Batrachenko A, et al. Differential developmental trajectories of magnetic susceptibility in human brain gray and white matter over the lifespan. Hum Brain Mapp 2014;35:2698–2713.

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CLINICAL HETEROGENEITY OF PRIMARY FAMILIAL BRAIN CALCIFICATION DUE TO A NOVEL MUTATION IN *PDGFB*

OPEN

Primary familial basal ganglia calcification (PFBC) (previously known as idiopathic basal ganglia calcification or Fahr disease) is an autosomal dominant neurodegenerative disorder characterized by bilateral cerebral calcification primarily affecting the basal ganglia. Recently, mutations in *SLC20A2*,[1] *PDGFRB*,[2] and *PDGFB*[3,4] have been identified as causing PFBC. However, other than the original study,[3] there has been a paucity of descriptions of families with PFBC.[5]

Herein, we describe 4 cases of PFBC within a family due to a novel mutation in exon 4 of the *PDGFB* gene (c.C3657T:p.P122L) highlighting significant phenotypic heterogeneity.

Cases. ***Patient III.2.*** A 31-year-old woman presented with acute psychosis. She was diagnosed in childhood with mild learning difficulties, but reached normal motor milestones. Over the next 6 years, she had recurrent episodes of psychosis and depression requiring admission. At age 36, a CT scan of her head revealed basal ganglia calcification precipitating neurologic referral (figure, A.b).

Examination revealed jerky ocular pursuit, generalized chorea, and midline ataxia. Investigations revealed a normal full blood count, biochemistry, and autoantibodies. An EEG showed no encephalopathic features.

There was no family history of any neurologic disorder; however, the examining neurologist noted that the patient's mother, accompanying her to clinic, was ataxic (patient II.4).

Patient II.4. A retired shop worker was referred aged 60 years (figure). Both parents died in their 70s with no neurologic symptoms before death. She had 3 siblings, none of whom she remained in contact with.

She had episodic psychosis and depression for more than 20 years, and a 2-year history of falls and unsteady gait. Medical history included hypertension and heavy smoking. Examination revealed a severe midline ataxia with jerky ocular pursuit. There were no cognitive abnormalities or extrapyramidal features.

Serum biochemistry (including calcium and phosphate) was normal. A muscle biopsy showed normal histology, normal mitochondrial biochemical studies, and no mitochondrial DNA deletions. An EEG revealed transient sharp waves in the temporal regions. MRI showed calcium deposition in the globus pallidus and dentate (figure, A.d).

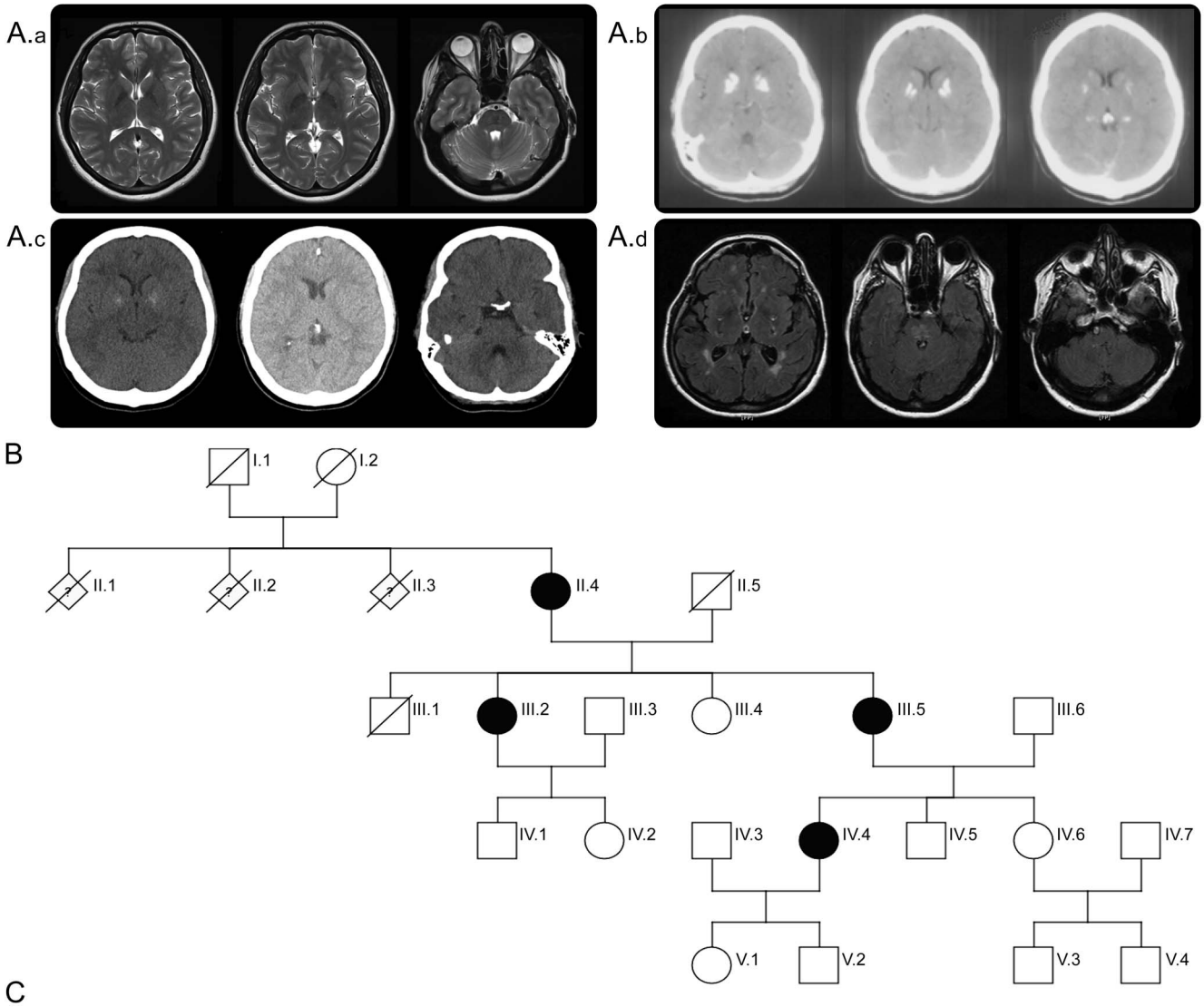
Over the next 5 years, her ataxia progressed but cognition remained normal (Mini-Mental State Examination score 28/30 at age 66).

Patient III.5. A woman aged 40 years was referred with a 2-year history of gait disturbance. She had no psychiatric history, cognitive symptoms, or evidence of abnormal movements. Examination revealed normal cognition, but a midline ataxia. A CT brain scan showed bilateral calcification of the globus pallidus (figure, A.c). Three years later, she developed a complex motor tic, and dystonic posturing of both feet. Formal neuropsychometry remained normal.

Patient IV.4. A 20-year-old woman was referred with a gait disturbance. She had no other medical or psychiatric history. Neurologic examination was normal. Brain MRI revealed small frontal noncalcified white matter changes not in keeping with PFBC, and no evidence of calcium in the basal ganglia even with susceptibility-weighted imaging (figure, A.a).

Supplemental data at Neurology.org

Figure Neuroimaging features and genotype details of affected individuals



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Family	Affected (n)	Gene	Chromosome	Chromosome position	Reference sequence / variant sequence	Protein alteration	InHouse MAF (n=300)	ESP6500 database MAF	1000 genome database MAF	PhyloP prediction	SIFT software	PolyPhen2 software	LRT software	Mutation-Taster software
A	4	PDGFB	22	39627718	G/A	c.C3657T: p.P122L	0	0	0	Conserved	Deleterious (0.00)	Probably damaging (1.00)	Deleterious (1.00)	Disease-causing (0.999)

(A) CT and MRI scans of cases. (A.a) Case IV.4 (age 20 years): T2 MRI scan with no evidence of calcium deposition within the basal ganglia. (A.b) Case III.2 (age 36 years): CT scan showing calcium deposition in the caudate, lentiform nuclei, and thalamus. (A.c) Case III.5 (age 40 years): CT scan showing isolated subtle calcium deposition in the globus pallidus. (A.d) Case II.4 (age 66 years): T1 MRI showing calcification in the globus pallidus together with periventricular and pontine vascular white matter changes. (B) Pedigree of the family with the *PDGFB* p.P122L mutation. Black = affected individuals; clear = unaffected. (C) Details of the mutation found in affected individuals. MAF = minor allele frequency.

Patients III.1 and III.4. Aged 42 and 46 years, respectively, patients III.1 and III.4 were clinically unaffected. Patient III.1 died of a traumatic injury with no evidence of basal ganglia calcification at autopsy. Patient III.4 refused imaging studies.

Exome sequencing. Whole-exome sequencing was performed on patients III.2, II.4, III.5, and IV.4 (appendix e-1 on the *Neurology*® Web site at Neurology.org) revealing a shared novel missense mutation in exon 4 of *PDGFB* (c.C3657T:p.P122L), not seen in the 1000 Genomes or ESP6500 database (figure, C), and predicted to be pathogenic by 4 software programs and conserved across all species (MutationTaster). This mutation was confirmed present in cases and absent in unaffected relatives with Sanger sequencing (III.1 and III.4). The p.P122L mutation is in the same exon as published pathogenic alleles.[3,6]

Discussion. These cases highlight the phenotypic heterogeneity of mutations in *PDGFB*. Two patients exhibited an early psychiatric phenotype followed by

late-onset ataxia or chorea; an isolated movement disorder was identified in a third. All 3 had ataxia, which has been described in isolated cases,[5] but not consistently in *PDGFB* families.[3] In addition, the ataxia in our cases occurred without obvious cerebellar calcification. This suggests that (1) the mechanism may not be primarily mediated by calcium deposition (although we cannot exclude the presence of microcalcification), and (2) there is significant clinical overlap with common neurologic and psychiatric disorders.[5] Our data also show a heterogeneous radiologic phenotype that may be much milder than previously described,[3] and similar to *PDGFRB* families.[7] In keeping with this, case IV.4 showed no basal ganglia calcification and a normal neurologic examination at age 20 years, providing the first evidence of potential incomplete radiologic penetrance for a pathogenic *PDGFB* mutation, highlighting that normal imaging does not exclude the diagnosis of PFBC.

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1. Wang C, Li Y, Shi L, et al. Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nat Genet 2012;44:254–256.
2. Nicolas G, Pottier C, Maltete D, et al. Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification. Neurology 2013;80:181–187.
3. Keller A, Westenberger A, Sobrido MJ, et al. Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice. Nat Genet 2013;45:1077–1082.
4. Nicolas G, Rovelet-Lecrux A, Pottier C, et al. PDGFB partial deletion: a new, rare mechanism causing brain calcification with leukoencephalopathy. J Mol Neurosci 2014;53:171–175.
5. Hayashi T, Legati A, Nishikawa T, Coppola G. First Japanese family with primary familial brain calcification due to a mutation in the PDGFB gene: an exome analysis study. Psychiatry Clin Neurosci 2015;69:77–83.
6. Nicolas G, Jacquin A, Thauvin-Robinet C, et al. A de novo nonsense PDGFB mutation causing idiopathic basal ganglia calcification with laryngeal dystonia. Eur J Hum Genet 2014;22:1236–1238.
7. Nicolas G, Pottier C, Charbonnier C, et al. Phenotypic spectrum of probable and genetically-confirmed idiopathic basal ganglia calcification. Brain 2013;136:3395–3407.