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Primary Familial Brain Calcification

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Summary

Clinical characteristics

Primary familial brain calcification (PFBC) is a neurodegenerative disorder with characteristic calcium deposits in the basal ganglia and other brain areas visualized on neuroimaging. Most affected individuals are in good health during childhood and young adulthood and typically present in the fourth to fifth decade with a gradually progressive movement disorder and neuropsychiatric symptoms. The movement disorder first manifests as clumsiness, fatigability, unsteady gait, slow or slurred speech, dysphagia, involuntary movements, or muscle cramping. Neuropsychiatric symptoms, often the first or most prominent manifestations, range from mild difficulty with concentration and memory to changes in personality and/or behavior, to psychosis and dementia. Seizures of various types occur frequently, some individuals experience chronic headache and vertigo; urinary urgency or incontinence may be present.

Diagnosis/testing

The diagnosis of PFBC relies on: visualization of bilateral calcification of the basal ganglia on neuroimaging; presence of progressive neurologic dysfunction; and absence of metabolic, infectious, toxic, or traumatic cause. A family history consistent with autosomal dominant inheritance is often found as well. Thus, the diagnosis of PFBC should be left for those cases where other neurologic or systemic disorders potentially associated with ectopic calcium deposits have not been identified after appropriate examinations. A heterozygous pathogenic variant in *PDGFB*, *PDGFRB*, *SLC20A2*, or *XPR1* has been identified in a little more than half of those individuals with a clinical diagnosis of PFBC.

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Management

Treatment of manifestations: Pharmacologic treatment to improve anxiety, depression, obsessive-compulsive behaviors, as well as for movement disorders (e.g., tremors) or dystonia; anticholinergics for urinary incontinence; anti-seizure medication for seizures.

Surveillance: Annual neurologic and neuropsychiatric assessments.

Agents/circumstances to avoid: Cautious use of neuroleptic medications as they may exacerbate extrapyramidal symptoms.

Genetic counseling

PFBC is inherited in an autosomal dominant manner. Most individuals diagnosed with PFBC have an affected parent identified either clinically or by brain CT scan. However, the transmitting parent may be clinically asymptomatic throughout life or may develop disease manifestations that are later in onset or less severe than those in the proband. If a parent of the proband is affected and/or is known to be heterozygous for a PFBC-related pathogenic variant, sibs of a proband are at a 50% risk of inheriting the pathogenic variant; however, the risk to sibs of being clinically affected may be slightly lower due to reduced penetrance. Offspring of an affected individual have a 50% chance of inheriting the pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

Primary familial brain calcification (PFBC) **should be suspected** in individuals who meet the following criteria (modified from Moskowitz et al [1971], Ellie et al [1989], and Manyam [2005]):

- **Progressive neurologic dysfunction,** generally including a movement disorder and/or neuropsychiatric manifestations. Age of onset is typically in the fourth or fifth decade, although this dysfunction may present in childhood or later in life.
- **Bilateral calcification of the basal ganglia** visualized on neuroimaging. Other brain regions may also be affected, including the cerebellum, the brain stem, the centrum semiovale, and the subcortical white matter. Of note, the presence of brain calcifications in asymptomatic individuals is possible.
- **Absence of biochemical abnormalities** and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder
- **Absence** of an **infectious**, **toxic**, or **traumatic cause**
- **Family history** consistent with autosomal dominant inheritance

Imaging studies. The calcifications in PFBC are generally not distinguishable from those due to hypoparathyroidism or to other causes. However, some clues, such as the appearance and localization of the calcium deposits, may point to specific, mostly non-idiopathic causes [Livingston et al 2013].

- **Brain CT scan,** which easily detects calcium, is the preferred method of localizing and assessing the extent of cerebral calcifications. Most frequently affected is the lenticular nucleus, especially the internal globus pallidus. Calcifications in the putamen, thalami, caudate, and dentate nuclei are common. Occasionally, calcium deposits begin or predominate in regions outside the basal ganglia. Calcification appears to be progressive, since these deposits are generally more extensive in older individuals and an increase in calcification can sometimes be documented on follow up of affected individuals.

Cerebellum, the brain stem, centrum semiovale, and subcortical white matter may also be affected [Manyam et al 1992]. Diffuse atrophic changes with dilatation of the subarachnoid space and/or ventricular system may coexist with calcifications.

- **Magnetic resonance imaging (MRI).** Calcified areas in the basal ganglia give a low-intensity signal on T_2-weighted images and a low- or high-intensity signal on T_1-weighted planes. In the cerebellum and cerebral white matter, the lesions may be more heterogeneous, sometimes seen as high signal on both T_1 and T_2, perhaps as a result of reactive gliosis or degenerating tissue within the calcified areas [Avrahami et al 1994].

  MRI provides better anatomic detail than CT but is less sensitive in detecting calcification. Calcified lesions on MRI produce various levels of signal intensities that may be misinterpreted as not representing brain calcification. Kozic et al [2009] reported three individuals with brain calcification easily identified on CT scan for which MRI was interpreted as either completely normal, inconclusive, or wrongly compatible with toxic/metabolic demyelination.

- **Plain skull radiograph.** The calcifications appear as clusters of punctate densities symmetrically distributed above the sella turcica and lateral to the midline. Subcortical and cerebellar calcifications may appear wavy. Although the sensitivity of CT scan largely surpasses that of plain skull radiographs, the latter are still useful to evaluate abnormalities of bone structures suggestive of other diagnoses.

Testing

Normal findings. In order to evaluate for other genetic and acquired causes of brain calcifications, a diagnostic approach has been revised for adults [Bonazza et al 2011]. In individuals with PFBC the following evaluations are typically normal:

- Serum concentration of calcium, phosphorus, magnesium, alkaline phosphatase, calcitonin, and parathyroid hormone (PTH)
- Routine hematologic and biochemical investigations
- Workup for metabolic, inflammatory, and infectious conditions
- Blood and urine heavy metal concentrations
- Ellsworth Howard test (i.e., a 10- to 20-fold increase of urinary cAMP excretion following stimulation with 200 U of PTH)
- Cerebrospinal fluid evaluation for bacteria, viruses, and parasites. However, a slight increase in protein has been described [Boller et al 1977].

Neuropathology

- Gross pathologic examination shows accumulation of a granular material and solid nodules in the striatum, internal capsule, white matter, and cerebellum. Circumscribed calcium deposits may also be seen in the thalamus and cerebral cortex. Mild lobar atrophy is common [Wider et al 2009].
- Histologic examination of affected areas shows concentric calcium deposits within the walls of small and medium-sized arteries and, less frequently, veins [Norman & Urich 1960, Cervos-Navarro & Urich 1995]. Droplet calcifications can be observed along capillaries. These deposits may eventually obliterate the lumina of vessels. Multifocal parenchymal mineral deposits may also be present. The pallidal deposits stain positive for iron [Cervos-Navarro & Urich 1995]. Diffuse gliosis may surround the large deposits, but significant loss of nerve cells is rare. Ischemic changes may be present in the basal ganglia, as well as in cortical and subcortical regions [Wider et al 2009].
- On **electron microscopy**, the mineral deposits appear as amorphous or crystalline material surrounded by a basal membrane. Calcium granules are seen within the cytoplasm of neuronal and glial cells.

Establishing the Diagnosis

The diagnosis of PFBC **is established** in a proband with: bilateral calcification mainly in the basal ganglia; presence of progressive neurologic dysfunction; and absence of metabolic, infectious, toxic, or traumatic causes. Identification of a heterozygous pathogenic variant in *PDGFB*, *PDGFRB*, *SLC20A2*, or *XPR1* (see Table 1) by molecular genetic testing confirms the clinical diagnosis of PFBC.

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Serial single-gene testing** should be performed sequentially based on the relative frequency of pathogenic variants of each PFBC-associated gene (see Table 1). Conventionally, sequence analysis of *SLC20A2* is performed first, and if no causal variants are identified, sequence analysis of *PDGFB*, *PDGFRB*, and then *XPR1* is performed, followed by gene-targeted deletion/duplication analysis if no pathogenic variants are found in any of these genes.
- **A multigene panel** that includes *PDGFB, PDGFRB*, *SLC20A2, XPR1*, and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene varies by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Primary Familial Brain Calcification

Gene [1, 2]	Proportion of PFBC Attributed to Pathogenic Variants [3] in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
PDGFB	~11%	21/22	1/22 [6]
PDGFRB	~2%	6/6	None reported [7]
SLC20A2	~40%	67/74	7/74 [8]
XPR1	~2%	5/5	Unknown [9]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of PFBC Attributed to Pathogenic Variants [3] in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown [10]	~46%	NA	

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene. Variants in these genes have been curated: see *PDGFB*; *PDGFRB*; *SLC20A2*; *XPR1*.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Nicolas et al [2014b] identified a *PDGFB* heterozygous deletion spanning exons 2 to 7 in an affected individual. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. No del/dup variants were found in a total of 52 cases screened for CNVs in *PDGFRB* [Nicolas et al 2014b, David et al 2016, Pasanen et al 2017].
8. Pasanen et al [2017] identified one individual with a large *SCL20A2* deletion that removes the 5' UTR region, the non-coding exon 1, and the putative promoter region of *SLC20A2* as well as the coding regions of six other genes. David et al [2016] identified intragenic deletions of *SLC20A2* in four unrelated patients. Baker et al [2014] identified a family with PFBC with a large genomic deletion affecting multiple genes including *SLC20A2* and the known dystonia-related gene *THAP1*. Grütz et al [2016] identified a heterozygous multiexon *SLC20A2* deletion in several affected members of a family with PFBC.
9. No data on detection rate of gene-targeted deletion/duplication analysis are available.
10. Author, personal laboratory data

Clinical Characteristics

Clinical Description

Since the first description of primary familial brain calcification (PFBC) [Foley 1951], more than 100 affected kindreds (which further highlight the heterogeneous clinical presentation) have been reported [Manyam et al 2001a, Volpato et al 2009, Ashtari & Fatehi 2010, Batla et al 2017].

The clinical manifestations of PFBC are limited to the nervous system. Most individuals with PFBC are in good health during childhood and young adulthood.

Age of onset. Typically, the age of onset is between 30 and 60 years with gradual progression of the movement disorder and neuropsychiatric symptoms.

Variability. Age at onset, clinical presentation, and severity of PFBC are variable both between and within families. No correlation has been identified between age of onset, extent of calcium deposits, and neurologic deficits. In some instances, calcifications precede the clinical manifestations by several years [Manyam et al 1992] while there are other reports of young symptomatic individuals with no changes observed on CT scan who only later develop radiologically visible calcifications [Geschwind et al 1999].

The movement disorder often first manifests as clumsiness, fatigability, unsteady gait, slow or slurred speech, dysphagia, involuntary movements, or muscle cramping [Manyam et al 1992, Manyam et al 2001b]. Neurologic evaluation generally reveals features similar to those seen in Parkinson disease, with variable combinations of bradykinesia, rigidity, festinating gait, hypophonia, mask-like facies, diminished blinking, dystonia, tremor, choreoathetosis, or dyskinesia. Palmomental and other frontal release signs may be elicited.

Pyramidal or cerebellar signs may also be present; in some cases the cerebellar picture predominates.

Dystonia is prominent in a few families [Larsen et al 1985].

Neuropsychiatric symptoms, often the first or most prominent manifestations, range from mild concentration and memory deficits to changes in personality or behavior to psychosis and dementia [Geschwind et al 1999, Benke et al 2004, Shakibai et al 2005, Nicolas et al 2013a]. It has been suggested that those who become symptomatic early in adulthood are more likely to have psychosis.

The pattern of dementia includes frequent frontal-executive dysfunction and resembles that occurring in other disorders affecting subcortical structures, including Wilson disease and Huntington disease [Geschwind et al 1999, Benke et al 2004, Modrego et al 2005, Weisman et al 2007].

Although premorbid psychomotor development is generally normal, low IQ and mild delay in motor or intellectual milestones during school age are described.

Other

- Seizures of various types occur frequently.
- Some individuals experience chronic headache and vertigo [Geschwind et al 1999].
- Urinary urgency or incontinence and impotence may be present [Manyam et al 1992].
- Severe hypertension has been reported in two sisters with basal ganglia calcification with no other neurologic or systemic abnormalities [Puvanendran & Wong 1980]. Whether this represents an unusual association, a rare manifestation of PFBC, or a distinct genetic disorder with basal ganglia calcification is unknown.
- General medical examination, growth, and facial appearance are normal. Strength and sensation are generally intact. Specifically, no abnormalities are detected in the skull, hands, teeth, nails, or skin, and there is no evidence of a parathyroid disorder.
- Neurophysiologic studies are generally normal.

Genotype-Phenotype Correlations

Batla et al [2017] reviewed 137 cases of PFBC published in the literature with a positive genetic test result and characteristic CT scan findings. In these, parkinsonism was more commonly observed in those with *SLC20A2* pathogenic variants and headache was more common in those with *PDGFB* pathogenic variants. Thalamus and dentate nucleus were reported as more frequently involved in association with *SLC20A2* pathogenic variants, while only those with *PDGFB* pathogenic variants were noted to have cysts in the white matter.

In addition, the limited number of affected individuals with *PDGFRB* pathogenic variants showed clinical and radiologic manifestations that are indistinguishable from families with pathogenic variants in *SCL20A2* and from affected individuals with no detected pathogenic variants [Nicolas et al 2013b].

Penetrance

Incomplete and age-related penetrance is reported in PFBC, but the factors that influence clinical manifestations are unknown. The degree of penetrance may depend on whether diagnosis is considered at an anatomic level (presence of calcifications in the brain) or at a clinical level (presence of clinical symptoms).

With respect to calcium deposits, analysis of reported pedigrees indicates about 95% penetrance by age 50 years or older. If clinical manifestations are considered, the penetrance is incomplete and may vary between and within families. The precise clinical penetrance has not been fully established for the different PFBC-related genes and pathogenic variants, but it may be around 70% or even lower [Westenberger & Klein 2014]. This figure can be difficult to establish for late-onset slowly progressive neurologic disorders whose symptoms overlap with common traits such as migraine headache, vertigo, and mild psychiatric manifestations including anxiety or depression.

No reliable correlations exist between age of onset, extent of calcium deposits, and neurologic deficit. Although most individuals with calcifications eventually develop neurologic dysfunction, the type or severity of clinical symptoms cannot be predicted from the pattern of calcification.

Anticipation

Anticipation has occasionally been observed in kindreds with PFBC [Geschwind et al 1999, Shirahama et al 2010, Maeda et al 2012].

Nomenclature

Traditionally described as "Fahr's disease," this disorder has been referred to in the literature by about 35 different names [Manyam 2005], with familial idiopathic basal ganglia calcification (FIBGC) being until recently the preferred term.

With the identification of the first associated genes, following an autosomal dominant trait, the term "idiopathic" (i.e., calcifications of unknown cause) ceased to be appropriate and was replaced by "primary" (as opposed to calcifications secondary to infectious, inflammatory, toxic, or other causes). Therefore, and because calcium deposits are not limited to the basal ganglia but can also be seen in other brain areas (as described in Suggestive Findings), the designation "primary familial brain calcification" (PFBC) has been proposed.

Although the term Fahr's disease is still often used to designate either familial or sporadic basal ganglia calcification, it is unknown whether the nonfamilial cases represent the same disease. The term Fahr's disease is ambiguous and therefore should be avoided.

Prevalence

The prevalence of PFBC is unknown; more than 100 kindreds and sporadic cases have been reported. However, the disorder is probably under-recognized because of insufficient investigation of other family members of individuals presenting with brain calcification.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PDGFB*, *PDGFRB*, *SLC20A2*, or *XPR1*.

Sporadic tumors (including dermatofibrosarcoma protruberans) and some hematologic malignancies in the absence of other findings of PFBC frequently harbor somatic translocations involving *PDGFB* or *PDGFRB* that are **not** present in the germline. In these circumstances predisposition to these cancers is not heritable. For more details, see Cancer and Benign Tumors.

Differential Diagnosis

Parathyroid Disorders

Hypoparathyroidism (HP), idiopathic or postsurgical, is the most common cause of symmetric calcification of the basal ganglia [Illum & Dupont 1985]. HP usually begins in childhood or adolescence (i.e., earlier than what is observed in PFBC). In individuals with HP, decreased serum concentration of parathyroid hormone (PTH) results in hypocalcemia and hyperphosphatemia and their clinical manifestations (i.e., tetany, muscle weakness, paresthesia, seizures, cardiac arrhythmias, and cognitive impairment). Additional features include cataracts, renal dysfunction, and increased bone density [Abate & Clarke 2017]. Genetic forms have been described, both syndromic (e.g., 21q and 22q chromosome abnormalities) and nonsyndromic (e.g., pathogenic variants in *PTH*,

GCM2, *SOX3*, *CASR*, *GNA11*). Because treatment of HP may lead to marked clinical improvement, it is important to evaluate individuals with calcification of the basal ganglia for HP.

Pseudohypoparathyroidism (PHP) and pseudopseudohypoparathyroidism (PPHP) are the phenotypic spectrum caused by germline inactivating (loss-of-function) *GNAS* variants (*GNAS* encodes the alpha subunit of a G-protein involved in signal transduction). PHP and PPHP can occur in the same family. Occasionally, variants of PHP or PPHP may have few or no somatic abnormalities, making diagnosis on clinical grounds difficult. Inheritance is autosomal dominant. See Disorders of *GNAS* Inactivation.

PHP results from end-organ unresponsiveness to PTH. The biochemical hallmarks are hypocalcemia and hyperphosphatemia with an elevated serum concentration of PTH. The average age of onset of PHP is age eight to ten years. Most clinical manifestations are related to hypocalcemia, and thus similar to those in hypoparathyroidism, with intellectual disability being somewhat more common in PHP. Affected individuals may have other manifestations of Albright hereditary osteodystrophy, including short stature, round facies, obesity, soft tissue calcification, short metacarpals or metatarsals, and other hormone resistance, resulting in hypothyroidism and/or hypogonadism. PPHP is characterized by the physical findings of Albright hereditary osteodystrophy with normal serum concentration of calcium and phosphorus and normal response to PTH stimulation.

Kenny-Caffey syndrome type 1 (OMIM 244460) is characterized by growth delay, cortical thickening of the long bones, hypocalcemia, hypoparathyroidism, and calcification of the basal ganglia. It is caused by pathogenic variants in *TBCE*, which encodes a chaperone protein required for proper folding of alpha-tubulin subunits and the formation of alpha-beta-tubulin heterodimers [Parvari et al 2002]. Inheritance is autosomal recessive.

Infectious Diseases

Intrauterine or perinatal infection with toxoplasmosis, rubella, cytomegalovirus, or herpes simplex virus may result in calcification of the basal ganglia and dentate nucleus, as well as irregular masses of calcium distributed throughout the brain. Central nervous system (CNS) infection should be considered when clinical onset occurs soon after birth, especially in the presence of chorioretinitis, microcephaly, or neurologic abnormalities.

Noncongenital, active viral encephalitis should also be considered in individuals with brain calcifications and no family history [Morita et al 1998]. In HIV/AIDS, either opportunistic infections or inflammatory changes may cause symmetric calcified lesions in the basal ganglia, mostly in children.

Bacterial or parasitic infections such as brucellosis, toxoplasmosis, or cysticercosis should be considered, although the appearance and distribution of calcium deposits are generally quite different from PFBC.

- **Brucellosis.** Although cerebral calcification is rare, the detection of basal ganglia calcification in individuals residing in endemic areas should raise the possibility of a CNS brucellar infection.
- **Toxoplasmosis.** The basal ganglia are affected in up to 75% of cases.
- **Parenchymatous cysticercosis.** Calcifications are a manifestation of larval death and are generally rounded, less symmetric, and scattered within the grey matter or grey-white matter junction, sometimes in the basal ganglia or in the deep matter. This diagnostic possibility should be considered in regions where cysticercal infection is common. MRI is more sensitive than CT scan in identifying the parasitic cysts.

Mitochondrial Disorders

Mineral deposits in the basal ganglia and other brain structures are observed in mitochondrial diseases (see Mitochondrial Disorders Overview). Some mitochondrial disorders only affect a single organ (such as the eye in Leber hereditary optic neuropathy), but many involve multiple organ systems and often present with prominent neurologic and myopathic features. Many individuals with mitochondrial abnormalities have a discrete clinical

syndrome such as Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic weakness with ataxia and retinitis pigmentosa (NARP), or Leigh syndrome (LS). However, clinical variability is considerable and many do not fit perfectly into a recognized syndrome.

Inherited Congenital or Early-Onset Syndromes

Calcifications in the basal ganglia and other brain structures are observed in several congenital or early-onset syndromes with normal calcium-phosphorus metabolism and are frequently associated with intellectual disability.

Cockayne syndrome is an autosomal recessive disorder caused by impaired DNA repair resulting from pathogenic variants in *ERCC6* and *ERCC8*; it is characterized by developmental delay, photosensitivity, retinal degeneration, and deafness. Intracranial calcifications, including of the basal ganglia, are observed in some individuals [Rapin et al 2006].

Aicardi-Goutières syndrome is typically an early-onset encephalopathy characterized by severe intellectual and neuromuscular problems associated with calcification of the basal ganglia (particularly the putamen, globus pallidus, and thalamus), leukodystrophy, cerebral atrophy, and chronic CSF leukocytosis. Seven associated genes have been identified: *ADAR*, *RNASEH2A*, *IFIH1*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, and *TREX1*. Inheritance is most frequently autosomal recessive.

Immunodeficiency 38 with basal ganglia calcification (OMIM 616126) is an autosomal recessive immune system disorder caused by a deficiency in the interferon-induced protein ISG15 and associated with basal ganglia calcifications [Zhang et al 2015].

Tuberous sclerosis complex involves abnormalities of the skin (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas), brain (cortical tubers, subependymal nodules, seizures, intellectual disability/developmental delay), kidney (angiomyolipomas, cysts), and heart (rhabdomyomas, arrhythmias). The cerebral hamartomas may be calcified, however, they are mainly periventricular or subcortical. Two associated genes, *TSC1* and *TSC2*, have been identified. Inheritance is autosomal dominant.

Cerebroretinal microangiopathy with calcifications and cysts (OMIM 612199). This autosomal recessive condition, also referred to as Coats plus syndrome, is caused by pathogenic variants in *CTC1* [Anderson et al 2012]. The spectrum of neurologic manifestations is complex and includes cognitive deterioration, seizures, spastic tetraparesis, and cerebellar signs. Neuroimaging features are highly characteristic of an encephalopathy with diffuse intracranial calcifications and formation of parenchymal cysts. Affected individuals also have growth retardation, retinal exudates, and skeletal malformations [Linnankivi et al 2006, Briggs et al 2008].

Pantothenate kinase-associated neurodegeneration (**PKAN**) is a form of neurodegeneration with brain iron accumulation (NBIA). PKAN is characterized by progressive dystonia and basal ganglia iron deposition, with onset that usually occurs before age ten. Commonly associated features include dysarthria, rigidity, and pigmentary retinopathy. About 25% of affected individuals have an "atypical" presentation with later onset (age >10 years), prominent speech defects, psychiatric disturbances, and more gradual progression of disease. Approximately 50% of individuals with a clinical diagnosis of NBIA have pathogenic variants in *PANK2*. To date, all individuals with NBIA and "eye-of-the-tiger" sign on T_2-weighted MRI have at least one pathogenic variant in *PANK2*. Inheritance is autosomal recessive.

Down syndrome. Reports of basal ganglia calcifications in Down syndrome are abundant [Takashima & Becker 1985].

Other. Additional rare conditions associated with brain calcification include lipoid proteinosis, dyskeratosis congenita, carbonic anhydrase deficiency (OMIM 259730), biotinidase deficiency, tetrahydrobiopterin-deficient hyperphenylalaninemia (OMIM 261630), and hereditary folate malabsorption.

Adult-Onset Neurodegenerative Conditions

Neuroferritinopathy, another form of NBIA, typically presents with progressive adult-onset chorea or dystonia and subtle cognitive deficits. The movement disorder involves additional limbs within five to ten years and becomes more generalized within 20 years. Cognitive deficits, behavioral issues, and dysphagia are major problems with time. The diagnosis of neuroferritinopathy is based on clinical findings, including adult-onset chorea or dystonia, and MRI or CT showing excess iron storage or cystic degeneration in the putamina. *FTL* is the only gene currently known to be associated with neuroferritinopathy. Inheritance is autosomal dominant.

DRPLA (dentatorubral-pallidoluysian atrophy). Bilateral calcification of the globus pallidus has also been reported in a large African American family from North Carolina with DRPLA (referred to as the Haw River syndrome [Burke et al 1994a, Burke et al 1994b]). Affected individuals showed a varied combination of gait ataxia, dysarthria, involuntary movements, seizures, psychosis, and dementia, overlapping with the clinical picture of families with PFBC. The diagnosis of DRPLA was based on positive family history, characteristic clinical findings, and the detection of a CAG repeat expansion in *ATN1*.

Spinocerebellar ataxia type 20 (SCA20) is associated with pronounced cerebellar calcifications affecting the dentate nucleus, typically without involvement of the basal ganglia. Inheritance is autosomal dominant and the disease locus has been mapped to chromosome 11 in a single large family.

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL, Nasu-Hakola disease) is characterized by fractures (resulting from polycystic osseous lesions), frontal lobe syndrome, and progressive presenile dementia beginning in the fourth decade. Bilateral calcifications of the basal ganglia, most often in the putamina, are commonly observed in CT scans, and may occur before CNS symptoms appear [Paloneva et al 2001]. Variants in *TYROBP* and *TREM2* are known to cause PLOSL. Inheritance is autosomal recessive.

Diffuse neurofibrillary tangles with calcification (DNTC, or Kosaka-Shibayama disease [Ukai & Kosaka 2016]) is a rare entity, largely observed in individuals of Japanese descent, characterized by dementia, cortical (temporal or frontotemporal) atrophy, neurofibrillary tangles, and symmetric brain calcifications.

Dystonia/parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease is a movement disorder resulting from manganese accumulation in the basal ganglia. This condition results from biallelic loss-of-function variants in *SLC30A10*. Neuroimaging findings in individuals with this condition may mimic those seen in individuals with PFBC [Quadri et al 2012, Tuschl et al 2012].

Other

Calcifications of the basal ganglia may result from the following:

- **Necrosis of neural tissue** caused by traumatic, toxic, or physical insults. These include but are not limited to perinatal anoxia, Rh incompatibility, vitamin D and carbon monoxide intoxication, mercury and lead poisoning, exposure to ionizing radiation, and methotrexate therapy.
- **Systemic lupus erythematosus (SLE).** A subset of patients with cerebral lupus can present brain calcifications, which can be extensive [Raymond et al 1996].
- **Celiac disease.** Although intracranial calcifications have been described, the calcium deposits are mainly occipital. Other neurologic manifestations can include cerebellar ataxia, epilepsy, and peripheral neuropathy.

- **Normal aging.** Calcification of the basal ganglia is an incidental finding in about 0.3%-1.5% of brain CT scans, especially in elderly individuals. Microscopic calcifications can be observed in the globus pallidus and dentate nucleus in up to 70% of autopsy series. These calcifications are generally confined to the globus pallidus and do not have associated clinical findings [Förstl et al 1992]. Basal ganglia calcifications in the elderly have been associated with psychotic symptoms [Ostling et al 2003].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary familial brain calcification (PFBC), the following evaluations are recommended:

- Thorough neurologic and neuropsychiatric assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The following are appropriate:

- Pharmacologic treatment to improve anxiety, depression, and obsessive-compulsive behaviors
- To alleviate dystonia and other associated involuntary movements, pharmacologic therapies as typically used in neurologic practice for the treatment of movement disorders
- For urinary urgency or incontinence, oxybutynin or other anticholinergic medications
- Anti-seizure medication for seizures
- Symptomatic treatment for headaches

Surveillance

Thorough neurologic and neuropsychiatric assessment is indicated annually.

Agents/Circumstances to Avoid

Neuroleptic medications should be used cautiously, since they may exacerbate extrapyramidal symptoms [Cummings et al 1983]. A poor response to neuroleptics was noted in a family with PFBC and mainly psychotic manifestations [Callender 1995]. Extrapyramidal symptoms may also be elicited or worsened by other drugs (e.g., some anti-seizure medications, medications to treat vertigo or dizziness).

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

The response of parkinsonian features to levodopa therapy is generally poor. Manyam et al [2001a] attributed a positive response to levodopa in an affected member of a family with PFBC to the coexistence of PFBC and idiopathic Parkinson disease.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary familial brain calcification (PFBC) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with PFBC have an affected parent identified either clinically or by brain CT scan. However, the transmitting parent may be clinically asymptomatic throughout life or may develop disease manifestations that are later in onset or less severe than those in the proband.
- Some individuals diagnosed with PFBC have the disorder as the result of a *de novo* pathogenic variant [Keller et al 2013, Ferreira et al 2014, Nicolas et al 2014a].

  The proportion of cases caused by a *de novo PDGFB*, *PDGFRB*, *SLC20A2*, or *XPR1* pathogenic variant is unknown. Whether nonfamilial (simplex) cases represent *de novo* pathogenic variants, incomplete penetrance, or non-genetic conditions is also not known.
- Molecular genetic testing, physical and neurologic examination, and CT scan are recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported to date.
- The family history of some individuals diagnosed with PFBC may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected and/or is known to be heterozygous for a PFBC-related pathogenic variant, sibs of a proband are at a 50% of inheriting the pathogenic variant; however, the risk to sibs of being clinically affected may be slightly lower because of reduced penetrance (see Penetrance).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs is approximately 1% because of the theoretic possibility of parental germline mosaicism.
- The absence of clinical symptoms in parents whose genetic status is unknown cannot be used to predict risk to sibs of a proband because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a PFBC-related pathogenic variant has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a PFBC-related pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

A thorough discussion of the implications and limitations of clinical genetic testing, particularly in presymptomatic at-risk individuals, is advisable.

Predictive testing of at-risk asymptomatic adults. Molecular genetic testing is possible if a *PDGFB*, *PDGFRB*, *SLC20A2*, or *XPR1* pathogenic variant has been identified in an affected family member. Since calcium deposits may precede the onset of clinical symptoms by several years, a brain CT scan also serves as a presymptomatic test in at-risk individuals. Thus, psychological and ethical considerations in offering such testing to asymptomatic adults should be similar to those applied for other neurodegenerative disorders in which a curative treatment is not currently available.

Molecular genetic testing and brain CT scan are not useful in predicting age of onset, severity or type of symptoms, or rate of progression in asymptomatic individuals. Molecular genetic testing and testing for calcium deposits using brain CT scan in the absence of definite clinical symptoms of the disease is predictive testing.

Predictive testing of at-risk asymptomatic individuals younger than age 18 years who are at risk for adult-onset disorders for which no curative or preventive treatment exists is not considered appropriate, primarily because it negates the autonomy of the child with no compelling medical benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause. Furthermore, a CT scan will not remove uncertainty in the case of PFBC because penetrance is age dependent, reaching about 95% by age 50 years.

For more information, see also the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

It is appropriate to consider testing symptomatic individuals regardless of age in a family with an established diagnosis of PFBC.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *PDGFB*, *PDGFRB*, *SLC20A2*, or *XPR1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for PFBC are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Primary familial brain calcification
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Fahr's Syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Familial Brain Calcification: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PDGFB	22q13.1	Platelet-derived growth factor subunit B	Coppola Lab - PFBC Variant Database (PDGFB)	PDGFB	PDGFB
PDGFRB	5q32	Platelet-derived growth factor receptor beta	PDGFRB database Coppola Lab - PFBC Variant Database (PDGFRB)	PDGFRB	PDGFRB
SLC20A2	8p11.21	Sodium-dependent phosphate transporter 2	SLC20A2 @ LOVD Coppola Lab - PFBC Variant Database (SLC20A2)	SLC20A2	SLC20A2
XPR1	1q25.3	Solute carrier family 53 member 1	Coppola Lab - PFBC Variant Database (XPR1)	XPR1	XPR1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Familial Brain Calcification (View All in OMIM)

158378	SOLUTE CARRIER FAMILY 20 (PHOSPHATE TRANSPORTER), MEMBER 2; SLC20A2
173410	PLATELET-DERIVED GROWTH FACTOR RECEPTOR, BETA; PDGFRB
190040	PLATELET-DERIVED GROWTH FACTOR, BETA POLYPEPTIDE; PDGFB
213600	BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 1; IBGC1

Table B. continued from previous page.

605237	XENOTROPIC AND POLYTROPIC RETROVIRUS RECEPTOR; XPR1
615007	BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 4; IBGC4
615483	BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 5; IBGC5
616413	BASAL GANGLIA CALCIFICATION, IDIOPATHIC, 6; IBGC6

Molecular Pathogenesis

To date, four genes have been associated with primary familial brain calcification: *SLC20A2* and *XPR1* encode inorganic phosphate transmembrane transporters; *PDGFB* and *PDGFRB* are involved in blood-brain barrier integrity and pericyte survival.

PDGFB

Gene structure. *PDGFB* has six coding exons and an additional noncoding exon at the 3' end of the transcript (NM_002608.2). It encodes a protein with 241 amino acids, including a signal peptide and a propeptide removed in the mature form of the protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Fourteen different *PDGFB* variants have been reported to date, including missense and loss-of-function variants and an in-frame deletion encompassing several exons (coppolalab.ucla.edu/lovd/variants/PDGFB).

Normal gene product. *PDGFB* encodes the platelet-derived growth factor subunit B, the major ligand of PDGFRB. The PDGFB pathway is involved in angiogenesis, pericyte survival, and blood-brain barrier maintenance.

Abnormal gene product. Loss of PDGFRB function results in disease. The lack of PDGFB synthesis in endothelial cells may be the key factor leading to dysfunction of the blood-brain barrier and perivascular calcium deposits [Keller et al 2013]. Hypomorphic *Pdgfb* mice developed brain calcifications that were correlated with the degree of pericyte and blood-brain barrier deficiency [Keller et al 2013].

PDGFRB

Gene structure. The *PDGFRB* transcript (NM_002609.3) has 23 exons and encodes a 1,106 amino acid protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Five *PDGFRB* pathogenic missense variants and one initiation codon variant have been reported to date (coppolalab.ucla.edu/lovd/variants/PDGFRB).

Normal gene product. *PDGFRB* encodes the platelet derived growth factor receptor beta, a cell-surface tyrosine kinase receptor. It is expressed in neurons, choroid plexus, vascular smooth muscle cells, and pericytes of the human brain, mainly in the basal ganglia and the dentate nucleus. It plays a role in angiogenesis and in the maintenance of the blood-brain barrier integrity.

Abnormal gene product. It has been proposed that the loss of PDGFRB function compromises the integrity of the blood-brain barrier, and subsequently induces vascular and perivascular calcium depositions [Nicolas et al 2013b]. *Pdgfrb*-deficient mice lack pericytes, necessary for the formation of the blood-brain barrier, and have increased vascular permeability [Daneman et al 2010].

SLC20A2

Gene structure. The longest *SLC20A2* transcript (NM_006749.4) has 11 exons and encodes a 652-amino acid protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 60 different pathogenic variants including missense, nonsense, frameshift, and splice site variants as well as intragenic deletions have been reported (coppolalab.ucla.edu/lovd/variants/SLC20A2). Several of the pathogenic missense variants reported are within the N-terminal and C-terminal ProDom domains shared by all PiT transporters [Bøttger & Pedersen 2011, Lemos et al 2015].

Normal gene product. *SLC20A2* encodes the type III sodium-dependent inorganic phosphate transporter 2 (PiT2), a transmembrane protein associated with phosphate homeostasis. This transporter is strongly expressed in neurons, but also in astrocytes and endothelial cells of the globus pallidus and other brain regions commonly affected in PFBC [da Silva et al 2013, Inden et al 2013].

Abnormal gene product. Pathogenic variants in PiT2 have been shown to severely impair uptake of phosphate, likely leading to its extracellular accumulation and subsequent deposition of calcium phosphate [Wang et al 2012], and possibly exert dominant-negative effects on normal PiT2 [Larsen et al 2017]. A homozygous *Slc20a2* knockout mouse showed extensive, bilateral calcifications in the thalamus, basal ganglia, and cortex [Jensen et al 2013].

XPR1

Gene structure. The longest *XPR1* transcript (NM_004736.3) has 15 exons, which encodes a 696 amino acid protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Five different missense *XPR1* variants have been reported to date (coppolalab.ucla.edu/lovd/variants/XPR1). They are all located in the SPX putative regulatory domain of *XPR1*.

Normal gene product. *XPR1* encodes a retroviral receptor with a role in phosphate export, therefore directly affecting phosphate homeostasis.

Abnormal gene product. Mutated *XPR1* protein has been shown to cause significantly altered XPR1 cell surface expression and phosphate export [Legati et al 2015, Anheim et al 2016].

Cancer and Benign Tumors

Dermatofibrosarcoma protuberans, a rare type of cancer that causes a tumor in the deep layers of skin, is characterized by a somatic translocation involving *PDGFB* [Simon et al 1997]. In addition, translocations involving its receptor, *PDGFRB,* have been associated with **hematologic malignancies**, with the most common translocation resulting in a ETV6 (TEL)-PDGFRB fusion, while the other numerous fusions are rare and mostly observed in single cases [Appiah-Kubi et al 2017].

The relationship between these two conditions and PFBC-associated genes, and therefore PFBC, is currently unclear.

Chapter Notes

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