・ 本邦における特発性基底核石灰化症（IBGC）の臨床的・遺伝学的検討（第 2 報）山田恵、田中真生、金子雅幸、二宮勇平、栗田尚佳、位田雅俊、林祐一、石浦浩之、三井純、岩田淳、犬塚貴、辻省次、保住功　第 57 回日本神経学会学術大会で発表予定　平成 28 年 5 月 神戸

（関連発表）

・ 特発性基底核石灰化症（IBGC）の疾患特異的 iPS 細胞を用いた細胞モデル作成　関根信一郎、保住　功、井上治久他　再生医療実現拠点ネットワーク「疾患特異的 iPS 細胞を活用した難病研究」シンポジウム　2015 年 12 月 14 日　東京
・ 家族性特発性基底核石灰化症の患者由来 iPS 細胞の作製と機能解析　亀井孝紀、位田雅俊、関根信一郎、栗田尚佳、柴田　敏之、保住　功　日本薬学会第 136 年会で発表予定　2016 年 3 月 26～29 日 横浜

H. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

厚生労働科学研究費補助金難治性疾患克服研究事業

指定難病 特発性基底核石灰化症(IBGC)
(旧 ファール病) 研究班班会議プログラム

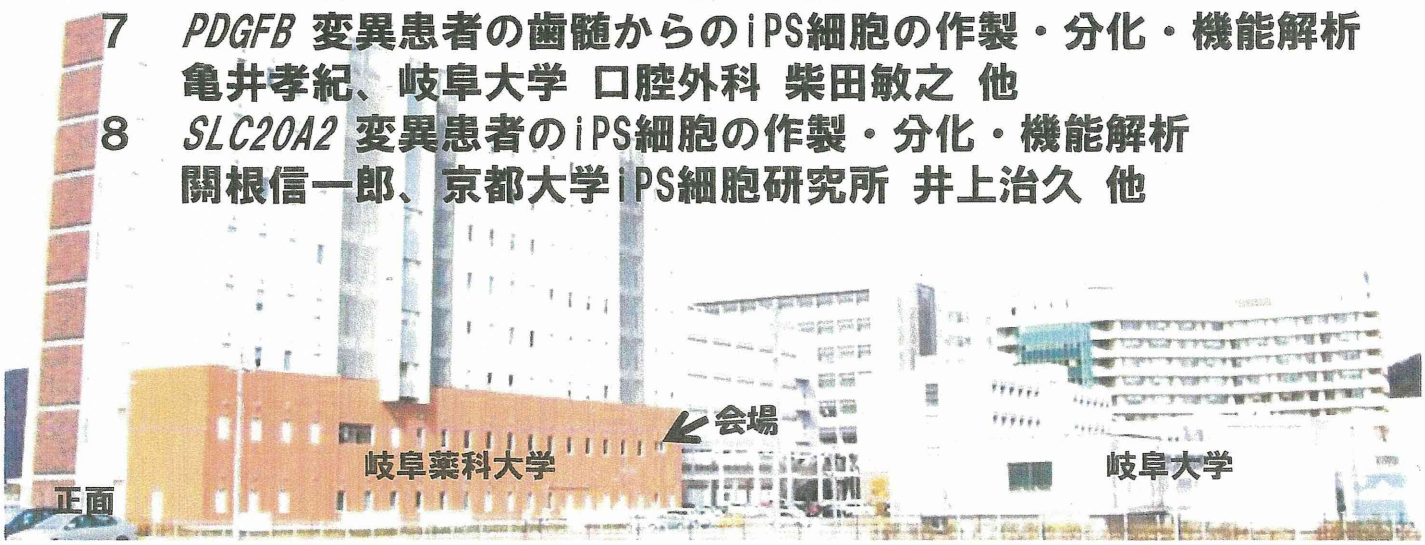
日時：平成28年2月6日(土) 13：00～15：00
場所：岐阜薬科大学大学院講義室 (2F, 医学部との連絡橋渡って左)

進捗状況報告

1　遺伝子検索の現状
　　二宮勇平 他
2　頭痛、生活習慣に関する疫学調査
　　栗田尚佳、獨協医科大学 神経内科 平田幸一
　　岐阜大学 疫学 永田知里 他
3　患者の語りに基づく質的研究
　　井上綾子、富山大学 老年看護 竹内登美子 他
4　総括、診療ガイドラインの作成に向けて
　　保住 功 他

今後の研究戦略について

5　新規原因遺伝子の検索に向けて
　　山田 恵、東京大学 神経内科 田中真生、辻 省次 他
6　創薬にむけての低分子化合物の合成
　　仲川純世、岐阜大学 連合創薬 桑田一夫 他
7　*PDGFB* 変異患者の歯髄からのiPS細胞の作製・分化・機能解析
　　亀井孝紀、岐阜大学 口腔外科 柴田敏之 他
8　*SLC20A2* 変異患者のiPS細胞の作製・分化・機能解析
　　關根信一郎、京都大学iPS細胞研究所 井上治久 他



連絡先：〒501-1196岐阜市大学西1-25-4 岐阜薬科大学 薬物治療学研究室
研究代表者 保住　功 e-mail: hozumi@gifu-pu.ac.jp Tel&Fax: 058-230-8121

Ⅲ.研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
保住　功	Fahr病	別冊 日本臨床	No.30 神経症候群V	750-755	2014
Megumi M, Tanaka M, MD, Takagi M, Kobayashi S, Taguchi Y, Takashima S, Tanaka K, Touge T, Hatsuta H, Murayama S, Hayashi Y, Kaneko M, Ishiura H, Mitsui J, Atsuta N, Sobue G, Shimozawa N, Inuzuka T, Tsuji S, and Hozumi I.	Evaluation of *SLC20A2* mutations that cause idiopathic basal ganglia calcification in Japan.	Neurology	82	705-712	2014

Ⅳ.研究成果の刊行物・別冊

XIII その他の神経疾患

Fahr病

Fahr's disease

保住　功

Key words：ファール病，familial idiopathic basal ganglia calcification(FIBGC)，primary familial brain calcification(PFBC)，特発性脳内石灰化症，リン酸トランスポーター

1. 概念・定義

1930年，ドイツの病理学者Theodor Fahr(1877–1945)が病理学的な症例報告をして[1]，その名前が病名につけられている．しかし，ファール(Fahr)病という病名は疾患概念として曖昧なところがあり，これまでも多くの名称が用いられてきたが[2]，最近，海外ではfamilial idiopathic basal ganglia calcification(FIBGC)，primary familial brain calcification(PFBC)[3]などの名称が使われている．

著者らは，厚生労働省の難治性疾患克服研究事業の一環として，2010年から，従来のファール病を含む特発性脳内石灰化症の調査研究と病態解明・治療薬開発に取り組んできた．調査対象として，①原因不明，②臨床症状の有無を問わない，③頭部CTで両側大脳基底核・小脳歯状核の両方/あるいはどちらかに生理的な範囲を超える，主治医の判断で病的と思われる石灰化を呈している(**図1**)という基準で，症例を

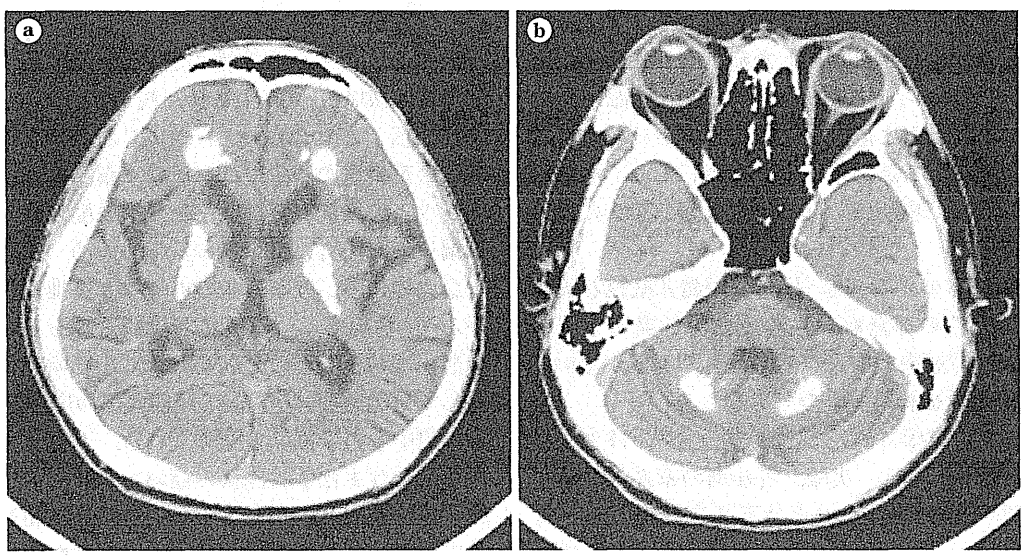


図1　ファール病(=IBGC)31歳，男性の典型的頭部CT画像
a．基底核，大脳白質深部に石灰化を認める．b．小脳基底核に石灰化を認める．

Isao Hozumi: Laboratory of Medical Therapeutics and Molecular Therapeutics, Gifu Pharmaceutical University　岐阜薬科大学大学院 薬物治療学

0047-1852/14/¥60/頁/JCOPY

収集してきたが，2014年3月末まで約200症例の登録があった．

ファール病に関する研究の大きな転機として，2012年2月に，中国から，下記に示す基準を満たすFIBGC症例において，リン酸トランスポーターの一つであるtype III sodium-dependent phosphate transporter 2(PiT2)をcodeする遺伝子*SLC20A2*の変異が報告された[4]．日本人の症例においても，家族例で半数にこの遺伝子変異を認め，病態解明への大きなmilestoneとなった[5]．さらに血小板由来成長因子(platelet-derived growth factor)のレセプターのsubunit βをcodeする遺伝子*PDGFRB*の変異も報告された[6]．続いて，PDGF受容体の重要なligandの一つであるPDGF-Bをcodeする遺伝子*PDGFB*の変異についても報告された[7]．

またdiffuse neurofibrillary tangles with calcification(DNTC)＝小阪・柴山病[8,9]も原因不明の基底核石灰化症という枠では同じくくりには入るが，病理学的には著明な神経原線維性変化を呈する明らかに別個な疾患である．しかし，臨床的には鑑別に苦慮するケースもある．一方，当初孤発例と思われた症例もその後の臨床的検索から，家族例と判明した症例も存在した．家族例すなわちFIBGCの症例では，上記のごとく，半数以上に遺伝子異常が見つかっているが，今後さらなる原因遺伝子が判明していくものと思われる．現状における疾患概念を**図2**に提示した．

FIBGCの診断基準[3]は，①両側基底核石灰化，②進行性の神経症状，③生化学的異常を認めない，④感染，中毒ないし外傷の原因がない，⑤家族歴を満たすものである．

実地の臨床において遭遇する症例のほとんどが孤発例である．実際，各症例の家系内全員の頭部CTを検索することは不可能である．また，著明な石灰化を認めながら，ほとんど無症状の症例も少なからず経験する．以上の現状を考えると，現時点では，家族歴を問わず，ファール病＝特発性基底核石灰化症(IBGC)として，まとめておく方が今後の研究にとって有用であり，また診療上でも実用的であると考えられる．より詳しい説明を加えて，できるだけ臨床的に他疾患が除外できるように，著者らの研究班が提唱した診断基準(**表1**)は岐阜薬科大学薬物治療学のホームページ(HP)上に掲載してある．

[http://www.gifu-pu.ac.jp/lab/yakuchi/Med_Mol_Therp/Fahr_Home.html]

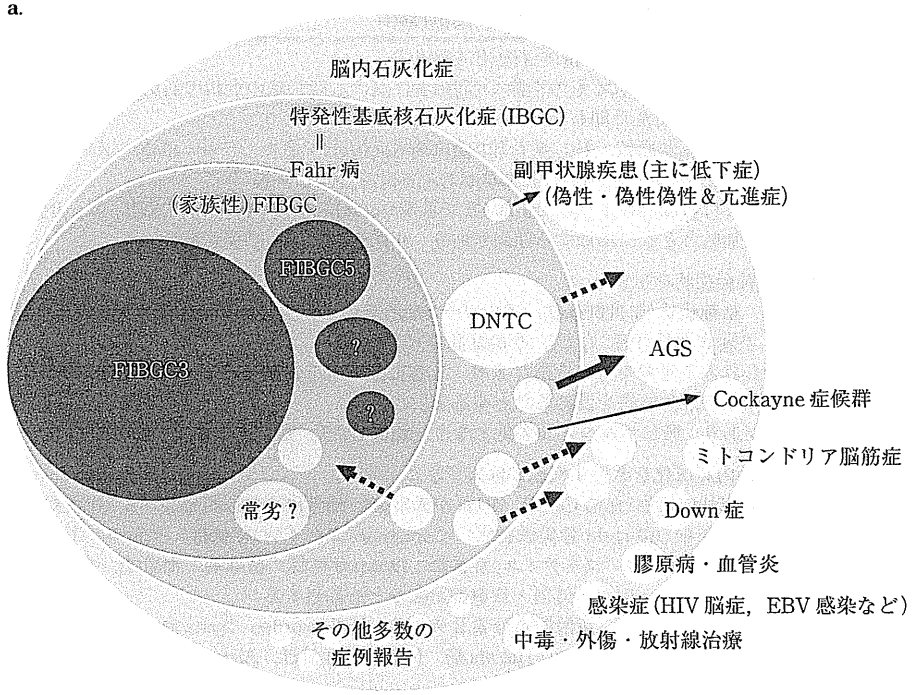
2. 疫　　学

班研究における登録は現在約200人である．しかし，ほとんど無症状にて，頭部外傷などにて頭部CTを撮影した際に，偶発的に異常な脳内石灰化を指摘される症例もまれならず紹介され，少なくともその2-3倍以上の患者は存在すると推定される．著者らが2つの大学病院で施行した1年間の全頭部CT画像の検索では，淡蒼球を主にかなりの高頻度(65歳以上で2.6％，総数で1.6％)で斑状(直径1mm以上)の脳内石灰化を認めている[10]．高齢者では生理的石灰化によるものもあると思われるが，この調査研究からもっと多数の患者が存在する可能性が示唆された．

3. 病因・病態・病理

前述のごとく，家族性のFIBGCの症例において*SLC20A2*，*PDGFRB*，*PDGFB*といった原因遺伝子が見つかった．IBGC患者の3例の髄液の重金属の測定では，亜鉛，銅，鉄，マグネシウムの増加を認め[11]，一方，毛髪の検査では銅を最も顕著に重金属の低下を認め，病態に重金属の代謝，分布異常のあることを推測している[12]．病理では，石灰沈着は淡蒼球を主に，被殻，尾状核などの大脳基底核，小脳歯状核，そして視床(視床枕など)，脳回底部の皮質深部，半卵円中心の深部にも認められる．石灰化をきたす部位は生化学的性状の違い，血管構築，血流のうっ滞などが関与すると思われる．組織学的には主として，細動脈の中膜，毛細血管に沿った周皮細胞，また神経細胞体内，グリア細胞の突起などにも石灰化した顆粒が認められる[13]．石灰化した顆粒は層状構造を呈し，リン酸カルシウムと水酸化カルシウムの複合体である水酸化アパタイトのほか，鉄，亜鉛，銅，マ

a.



b.

分類	遺伝子座	遺伝子	codeされるタンパク質
FIBGC1	14q	*MGEA6?*	MGEA6
FIBGC2	2q37	—	—
FIBGC3	8p11.21	*SLC20A2*	PiT2
FIBGC4	5q32	*PDGFRB*	PDGFRB
FIBGC5	22q13.1	*PDGFB*	PDGFB

図2 ファール病の疾患概念

a. IBGCとして収集した症例には，二次，三次調査で，副甲状腺機能低下症，Cockayne症候群が疑われた症例，また遺伝子検査でAGSと考えられた症例もあった．またDNTCも同じIBGCに入ってくる可能性があるが，病理学的には独立した疾患である．当初IBGC，孤発例と思われた症例も臨床的検索で，家族例と判明した症例も存在した．FIBGCの症例では，現在約半数に遺伝子異常が見つかっている．

IBGC: idiopathic basal ganglia calcification，FIBGC: familial IBGC，DNTC: diffuse neurofibrillary tangles with calcification=小阪・柴山病，AGS: Aicardi–Goutières症候群．

b. FIBGCにおいて報告されている原因遺伝子とデータ．

グネシウムなどの重金属が含まれる．他の脳内石灰化をきたす副甲状腺機能低下症などでも同じような病理像を呈する．また腎不全による続発性副甲状腺機能亢進症において，著明な石灰化を呈する症例もあり，疾患感受性遺伝子や何らかの環境因子が石灰化を促進している可能性も考えられる．

4. 診断と鑑別診断

無症状からパーキンソン症状など錐体外路症

表1　診断基準

1. 頭部CT上，両側基底核に明らかに病的な石灰化を認める．
加齢に伴う生理的石灰化と思われるものを除く(高齢者における淡蒼球の点状の石灰化など)
小脳歯状核などの石灰化の有無は問わない．
注1　原因によらず，大脳基底核，特に淡蒼球内節は最も石灰化をきたしやすい部位であり，特発性の症例で，1症例を除いてすべて両側性に基底核に石灰化を認めている．
注2　下記の文献における調査のように，頭部CTで淡蒼球の石灰化は，約20％に点状，2～3％に斑状に認め，頻度も加齢とともに増加する傾向があり，年齢を考慮する必要がある．

2. 何らかの進行性の神経症状を呈する．
具体的には，頭痛，精神症状(脱抑制症状，アルコール依存症など)，てんかん，精神発達遅延，認知症，パーキンソニズム，不随意運動(PKCなど)，小脳症状などがある．
注1　無症状と思われる若年者でも，問診により，しばしば頭痛を認めることがある．またスキップができないなど軽度の運動障害を認めることもある．
注2　脱抑制症状があり，時にアルコール多飲となり，頭部CTで，脳萎縮が目立つ症例がある．

3. 下記に示すような脳内石灰化をきたす疾患が除外できる．
主なものとして，副甲状腺疾患(血清Ca，P，iPTHが異常値)，偽性副甲状腺機能低下症(血清Ca低値)，偽性偽性副甲状腺機能低下症(Albright骨異栄養症)，Cockayne(コケイン)症候群，ミトコンドリア脳筋症，Aicardi-Goutières(アイカルディ・ゴーティエ)症候群，Down症候群，膠原病，血管炎，感染(HIV脳症など，EBウイルス感染症など)，中毒・外傷・放射線治療などを除外する．
さらに文献上，まれなものとして，炭酸脱水酵素II欠損症，Hallervorden-Spats病，oculodentodigital dysplasia(ODDO)，lipoid proteinosis，Nasu-Hakola病，Moebius症候群，Alexander病などの報告がある．

4. 家族歴の有無は問わない．家族歴のある症例ないし*SLC20A2*などの原因遺伝子異常が判明した症例は症状，画像所見を問わずFIBGCに分類する．

注1　上記診断基準においては，初老期に前頭・側頭型の認知症をきたす小阪・柴山病(diffuse neurofibrillary tangle with calcification(DNTC))との鑑別が困難であるが，確定診断は病理診断に基づくものであり，その原因遺伝子やバイオマーカーが確定しない現状においては，分類が困難な症例も多く，あえて区別しない．ただし，DNTC疑いありの注釈を添える．
注2　家族例においては，近年，約5割で，リン酸トランスポーターであるPiT-2をcodeする遺伝子*SLC20A2*の遺伝子異常が判明し，またPDGFの重要なligandの一つであるPDGF-Bをcodeする遺伝子*PDGFB*の遺伝子変異も認められた．国際的にはFIBGCは1-5型に分類されている．他疾患の除外診断も考え，可能なかぎり，遺伝子検査が望まれる．

ファール病＝特発性基底核石灰化症(IBGC)の診断基準をHP上に掲載した．

状，小脳症状，精神症状(前頭葉症状など)，認知症症状をきたす症例まで極めて多様性がある．若い人で頭痛，てんかんを認めることも少なくない．本疾患は若年発症例もあり，緩徐進行性である．また偶発的に頭部CT所見から見つかることもある．発作性運動誘発性舞踏アテトーゼ(paroxysmal kinesigenic choreoathetosis: PKC)を症状とする場合もある[14]．なかには，中年以降に認知症を呈するDNTCと鑑別に苦慮する症例も少なくない．DNTCは剖検では側頭葉，前頭葉に高度な脳葉萎縮をきたすが，典型的なIBGCでも前頭葉の血流低下を呈する症例が散見される．DNTCでは頭部CT画像上の石灰化は点状から斑状のものまで報告されているが，IBGCで報告されているような際立った石灰化の報告，また家族例の報告はまだない．鑑別診断を**表2**に提示した．

5. 治療と予後

根本的な治療法はまだ見つかっていない．遺伝子変異を認めた患者の疾患特異的iPS細胞やPiT2，PDGFを軸に創薬の研究がなされている．対症療法ではあるが，不随意運動や精神症状にquetiapineなど抗精神病薬[15]が用いられている．また病理学的にもパーキンソン病を合併する症例があり，抗パーキンソン病薬，PKCではcar-

表2 鑑別診断

1) 副甲状腺疾患(副甲状腺機能低下症，腎不全などによる続発性副甲状腺機能亢進症など)
血清 Ca，P，iPTH の測定は必須である．偽性，偽性偽性副甲状腺機能低下症もあり，偽性偽性では Albright 徴候(円形顔貌，短躯，肥満，皮下骨腫，第4中手骨・中足骨の短縮など)のみ．

2) ミトコンドリア脳筋症
症状は低身長，知能低下，筋力低下，難聴，嘔吐，皮質盲，痙攣など．診断は筋生検，遺伝子診断．

3) Aicardi-Goutières(アイカルディ・ゴーティエ)症候群
症状は小頭症，痙縮，ジストニア姿勢，高度の精神発達遅延など．髄液リンパ球増多，凍瘡，髄液中のインターフェロン α とネオプテリンの増加．5つの原因遺伝子，常染色体劣性遺伝．

4) Cockayne(コケイン)症候群
症状は低身長，低体重，小頭症，白内障，網膜色素変性症，難聴，日光過敏症，精神運動発達遅滞，老人様顔貌など．DNA 修復遺伝子の異常，常染色体劣性遺伝．

5) Down 症候群

6) diffuse neurofibrillary tangles with calcification(DNTC)(=小阪・柴山病)
初老期に前頭・側頭型の認知症を呈する．石灰化は点状から斑状，IBGC で報告されているような際立った石灰化の報告，また家族例の報告はまだない．

7) 生理的石灰化
特に高齢者では淡蒼球に，点状～斑状の石灰化が認められる．

8) 感染症
子宮体内あるいは周産期におけるトキソプラズマ，風疹，サイトメガロウイルス，単純ヘルペスウイルスなどの感染症によるものがある．また，HIV 脳症，ウイルス性脳炎，EB ウイルス感染症，ブルセラ症，胞中症(cysticercosis)など．

9) 膠原病(SLE)，血管炎

10) 代謝性疾患
pantothenate-kinase-associated neurodegeneration(PKAN)(=Hallervorden-Spats 病)：淡蒼球に鉄の沈着(eye of the tiger sign)，neuroferrinopathy：被殻に鉄の沈着，Wilson 病：基底核に銅の沈着．

11) 腫瘍
急性リンパ性白血病など．

12) 組織壊死後
中毒(一酸化炭素，有機水銀，鉛)，外傷，無酸素症，Rh 不適合，放射線治療後など．

13) その他(症例報告)
carbonic anhydrase II 欠損症，polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy(PLOSL)(=Nasu-Hakola 病)，Moebius 症候群，Kenny-Caffey 症候群 type 1，autosomal dominant dystonia-plus syndrome with brain calcinosis など．

主に淡蒼球を中心に脳内石灰化をきたす疾患を示した．鑑別上，重要と思われる順に並べた．鑑別のポイントとなる症状などを記載した．

bamazepine が効果を認めている．アルコールを多飲する症例では，精神症状や脳萎縮をきたしやすい．原因遺伝子などによって，脳内石灰化の進行や予後は変わってくると予測される．

[謝辞] 本疾患に関する検討は平成26年度厚生労働科学研究費補助金(難治性疾患等政策研究事業(難治性疾患政策研究事業))(H26-難治等(難)-一般-01)の研究助成で行われた．

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Evaluation of *SLC20A2* mutations that cause idiopathic basal ganglia calcification in Japan

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ABSTRACT

Objective: To investigate the clinical, genetic, and neuroradiologic presentations of idiopathic basal ganglia calcification (IBGC) in a nationwide study in Japan.

Methods: We documented clinical and neuroimaging data of a total of 69 subjects including 23 subjects from 10 families and 46 subjects in sporadic cases of IBGC in Japan. Mutational analysis of *SLC20A2* was performed.

Results: Six new mutations in *SLC20A2* were found in patients with IBGC: 4 missense mutations, 1 nonsense mutation, and 1 frameshift mutation. Four of them were familial cases and 2 were sporadic cases in our survey. The frequency of families with mutations in *SLC20A2* in Japan was 50%, which was as high as in a previous report on other regions. The clinical features varied widely among the patients with *SLC20A2* mutations. However, 2 distinct families have the same mutation of S637R in *SLC20A2* and they have similar characteristics in the clinical course, symptoms, neurologic findings, and neuroimaging. In our study, all the patients with *SLC20A2* mutations showed calcification. In familial cases, there were symptomatic and asymptomatic patients in the same family.

Conclusion: *SLC20A2* mutations are a major cause of familial IBGC in Japan. The members in the families with the same mutation had similar patterns of calcification in the brain and the affected members showed similar clinical manifestations. *Neurology*® 2014;82:705–712

GLOSSARY

DNTC = diffuse neurofibrillary tangles with calcification; **FIBGC** = familial idiopathic basal ganglia calcification; **IBGC** = idiopathic basal ganglia calcification; **MMSE** = Mini-Mental State Examination; **PDGF** = platelet-derived growth factor; **PDGFRB** = platelet-derived growth factor receptor-β; **Pi** = inorganic phosphate; **PiB** = Pittsburgh compound B; **PiT** = type III sodium-dependent phosphate transporter; **PKC** = paroxysmal kinesigenic choreoathetosis.

Idiopathic basal ganglia calcification (IBGC), also known as Fahr disease, is thought to be a rare neuropsychiatric disorder characterized by symmetrical calcification in the basal ganglia and other brain regions. Clinical manifestations range widely from asymptomatic to variable symptoms including headaches, psychosis, and dementia.[1] The diagnosis of IBGC generally relies on the visualization of bilateral calcification mainly in the basal ganglia by neuroimaging and the absence of metabolic, infectious, toxic, or traumatic causes.[2,3]

The mode of inheritance of familial IBGC (FIBGC) has been thought to be autosomal dominant and, to date, 4 responsible chromosomal regions have been identified, namely 14q (IBGC1), 2q37 (IBGC2), 8p11.21 (IBGC3), and 5q32 (IBGC4).[3–14] The causative gene at the IBGC3 locus was identified as *SLC20A2* encoding type III sodium-dependent phosphate transporter 2 (PiT-2). Screening of a large series of patients with IBGC revealed that mutations in *SLC20A2* are a major cause of FIBGC[10]; moreover, other mutations in *SLC20A2* have recently been reported in China and Brazil.[11–13] The mutations of *PDGFRB* encoding platelet-derived growth factor

Supplemental data at www.neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

(PDGF) receptor-β (PDGFRB) and *PDGFB* have recently been reported to cause calcification in the brain.[14,15]

We have collected clinical information of patients with IBGC in a nationwide survey in Japan. Here, on the basis of a mutational analysis of *SLC20A2*, we aim to establish the molecular epidemiology of IBGC3 and evaluate clinically and genetically *SLC20A2* mutations in Japan.

METHODS Subjects and samples. We collected clinical information on patients with IBGC in a nationwide study. The criteria for the selection of patients in the initial survey were as follows: 1) conspicuous calcification is observed in the basal ganglia and/or dentate nucleus by CT scan; 2) calcification is bilateral and symmetrical; and 3) idiopathic (absence of biochemical abnormalities, and an infectious, toxic, or traumatic cause).[2,3] Neurologists enrolled patients in the survey. They examined the medical charts and performed the neurologic examinations again if necessary. The survey was approved by the Ethics Committee of the Gifu University Graduate School of Medicine. During the survey, some patients were found to have hypoparathyroidism, Aicardi-Goutières syndrome, and Cockayne syndrome, and these patients were excluded. For the genetic study, a total of 69 subjects from 41 hospitals provided written informed consent and were enrolled in the project. Of these patients, 46 came from families with a single affected member, and the other 23 came from 10 families with multiple affected members. We defined the former as sporadic patients and the latter as familial patients. The patients' mean age ± SD was 41.3 ± 23.6 years at registration. The patients comprised 32 males and 37 females.

Standard protocol approvals, registrations, and patient consents. All experiments on human DNA were approved by the Ethics Committees of both Gifu University and the University of Tokyo. After written informed consent was obtained, peripheral blood samples were collected.

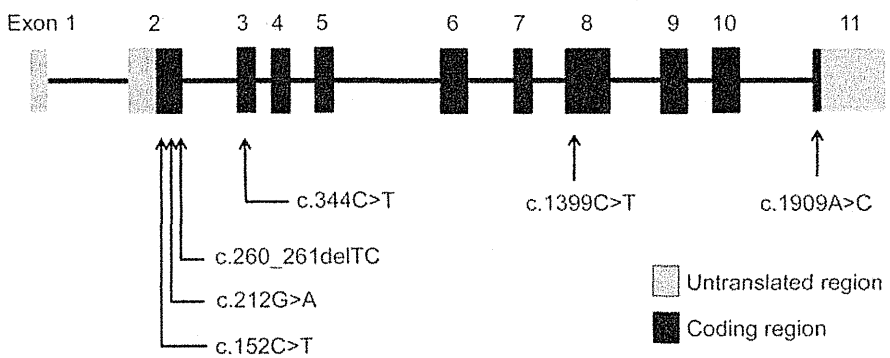
Mutational analysis. Genomic DNA was extracted from the whole blood samples. *SLC20A2* analysis was performed by Sanger sequencing of all coding regions, as described in detail in e-Methods and table e-1, A and B, on the *Neurology*® Web site at www.neurology.org. The pathologic potential of the identified variants was predicted using PolyPhen-2 (*http://genetics.bwh.harvard.edu/pph/*).[16]

RESULTS Mutational analysis. We screened a total of 69 subjects including 23 subjects from 10 families in which multiple affected subjects were observed and 46 subjects in sporadic cases, all of whom were Japanese. Six new mutations in *SLC20A2* were found: 4 missense mutations, 1 nonsense mutation, and 1 frameshift mutation (figure 1). Electropherograms showed the individual heterozygous mutations (figure e-1). None of them were present in an in-house exome sequencing data set (358 Japanese control subjects), dbSNP 137 (www.ncbi.nlm.nih.gov/snp/), or the National Heart, Lung, and Blood Institute "Grand Opportunity" Exome Sequencing Project (ESP6500SI-V2). *In silico* analysis predicted deleterious consequences, as determined from the residue changes in figures 1 and e-1. When confined to the FIBGC patients, 5 of the 10 families (50.0%) showed mutations in *SLC20A2*. In contrast, 2 of the 46 patients (4.3%) with sporadic IBGC carried mutations in *SLC20A2* in this study.

Clinical manifestations. The clinical manifestations are summarized in table 1. A positive family history of IBGC was present in 5 families. Families 1 and 2 had the same mutation.

Familial cases. ***Case 1 (in family 1).*** The proband in family 1 was a 64-year-old woman who had dysarthria and gait disturbance for 5 years. She showed no dementia. Her neurologic examination revealed dysarthria, small steppage gait, rigidity at bilateral wrist joints, bradykinesia, and a pyramidal sign. Her CT images revealed severe calcification at the bilateral globus pallidus, caudate nuclei, thalamus, subcortical white matter, and dentate nuclei (figure 2C). Her son's CT showed similar brain calcification (figure 2D), although he was clinically asymptomatic. His DNA study revealed the

Figure 1 **Schematic representation of causative mutations in *SLC20A2* in idiopathic basal ganglia calcification**



Six new causative mutations in exon 2 (c.152C>T, c.212 G>A, c.260_261delTC), exon 3 (c.344C>T), exon 8 (c.1399C>T), and exon 11 (c.1909A>C) were found in this study.

Table 1 Clinical features of 6 individuals (probands) with *SLC20A2* mutations

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Mutation	c.1909A>C	c.1909A>C	c.344C>T	c.212G>A	c.1399C>T	c.152C>T	c.260_261delTC
	S637R	S637R	T115M	R71H	R467X	A51V	L87Hfs*6
Zygosity	Hetero	Hetero	Hetero	Hetero	Hetero	Hetero	Hetero
Exon	11	11	3	2	8	2	2
Proband information							
Age at detection of calcification, y	60	51	60	73	23	71	74
Age at onset, y	58	50	60	71	15	71	57
Onset symptom	Dysarthria	Dysarthria	Dementia	Parkinsonism	PKC	Dementia	Athetosis
Neurologic findings							
Cognitive impairment (MMSE)	27	24	20	16	30	22	22
Pyramidal sign	+	+	−	−	−	−	−
Extrapyramidal sign	+	+	−	+	−	−	+
Family information (except the proband)							
No. of other individuals with calcification	1	2	5	1	1	0[a]	0[a]
No. of other individuals with confirmed mutations	1	NE	5	NE	1	NA	NA
No. of other symptomatic individuals	0	0	2	0	0	NA	NA
Other symptoms (no.) in the family	—	—	Mental disorder (1), alcoholism (1)	—	—	NA	NA

Abbreviations: MMSE = Mini-Mental State Examination; NA = not applicable; NE = not examined; PKC = paroxysmal kinesigenic choreoathetosis.
[a] Because there was no other family member who had any neurologic symptoms, brain CT screening of other family members was not performed.

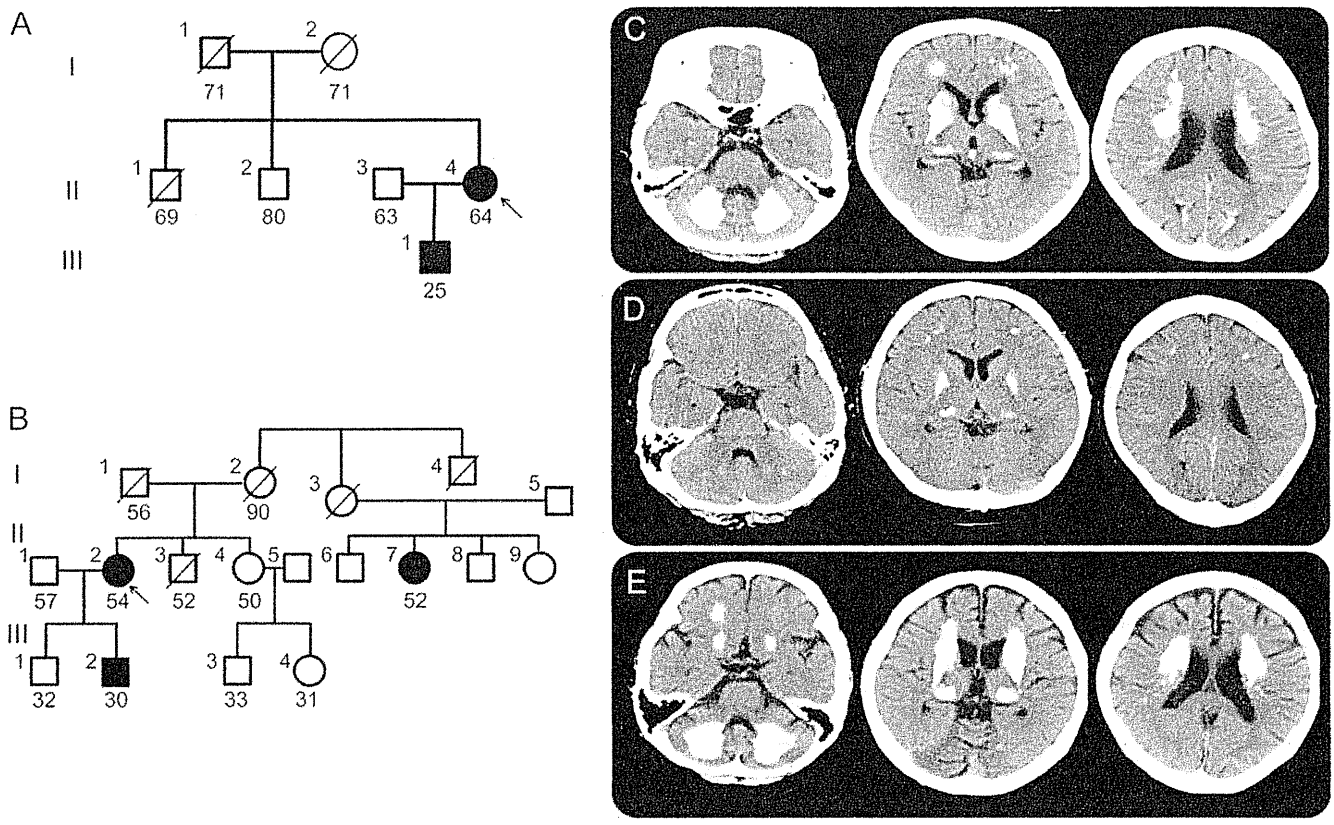
same mutation in exon 11 that had been found in his mother.

Case 2 (in family 2). The proband in family 2 was a 54-year-old woman who had dysarthria and gait disturbance for 4 years. She showed mild mental deterioration in Mini-Mental State Examination (MMSE) score of 24 points, frontal signs, dysarthria, mild parkinsonism (rigidity of bilateral wrist joints and bradykinesia), adiadochokinesis, spasticity, and small steppage gait. Her CT images revealed severe calcification at the bilateral globus pallidus, caudate nuclei, thalamus, subcortical white matter, and dentate nuclei (figure 2E). Although her son and cousin also showed calcification in CT images, they were asymptomatic. Her DNA analysis revealed the same mutation as that in family 1.

Case 3 and other symptomatic individuals (in family 3). The proband was a 69-year-old woman (II-1 in the pedigree in figure 3). She was admitted to a hospital at the age of 65 because of forgetfulness since the age of 60 years. Her MMSE score was 20, which indicated a possibility of dementia (MMSE score below 22). Decreased blood flow was detected in the bilateral basal ganglia and thalamus and the right frontal lobe in particular by SPECT. She had a positive family history of brain calcification, as shown in figure 3A. The initial clinical diagnosis had been diffuse neurofibrillary tangles with calcification (DNTC),[17] although to our knowledge familial cases of DNTC have not been reported. Her son had psychological disorders including violent behavior; unfortunately, no brain CT had yet been performed on him. In the patients in family 3, the degree of calcification was mild compared with that observed in the other families (figure 3, B–G). Her brother with calcification in the brain (II-7) had a mental disorder and another (II-8) presented with alcoholism. The 3 other relatives with calcification were asymptomatic (II-5, II-9, and III-3). The symptomatic patients (II-1, II-7, and II-8) showed more apparent brain atrophy than the others (figure 3, B, D, and E, respectively). The individuals with calcification on the CT images (II-1, II-5, II-7, II-8, II-9, and III-3) had the same mutation in exon 3 in *SLC20A2*. However, the individuals with no calcification (III-2, III-5, and IV-1) revealed no mutation in *SLC20A2*. In summary, 6 patients had calcification among the 10 individuals examined by CT scan in family 3 and all of them carrying the *SLC20A2* mutation exhibited similar calcification on CT images. However, persons without the mutation did not show calcification.

Case 4 (in family 4). Family 4 had a mutation in exon 2. The proband developed clumsiness of her hands and gait unsteadiness at the age of 71 years, and she was diagnosed as having Parkinson disease. Visual

Figure 2 CT images and family trees of families 1 and 2



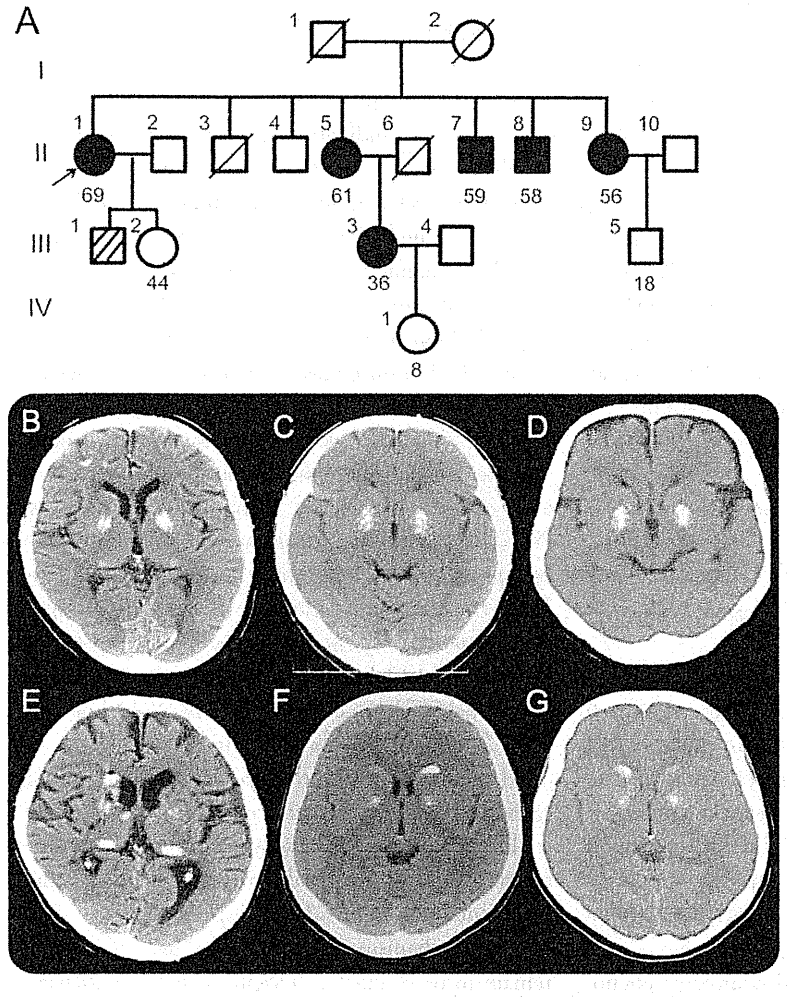
(A) Family tree of family 1. (B) Family tree of family 2. The arrow indicates the index subject. Filled symbols represent patients affected by brain calcification. We show the ages of persons under symbols in the family tree for those we could obtain. (C) CT images of proband (II-4 in pedigree of family 1, part A). (D) CT images of the proband's son (III-1 in pedigree of family 1, part A). (E) CT images of the proband (II-2 in pedigree of family 2, part B). All have mutation of S637R.

hallucinations started with the initiation of medication. She showed parkinsonism (rigidity, bradykinesia, and postural instability), which responded to levodopa. Her MMSE score was 16. Her brain CT images revealed calcification at the globus pallidus, caudate nuclei, and dentate nuclei, and her daughter, who was asymptomatic, also had intracranial calcification (figure e-2C). Brain CT was not performed in her other children. Her SPECT images showed decreased perfusion in the bilateral frontal, temporal, and parietal regions of the brain. She died of pneumonia at the age of 79. Neuropathologic examination revealed neuronal loss and Lewy bodies in the substantia nigra, locus ceruleus, amygdala, and parahippocampal gyrus indicative of Parkinson disease, and prominent deposition of calcium in the parenchyma and the wall of arteries in the globus pallidum and dentate nuclei compatible with the pathologic findings of IBGC.

Case 5 (in family 5). The proband was a 24-year-old man who had paroxysmal kinesigenic choreoathetosis (PKC). His laboratory data were normal except for CT findings. He presented with an attack of PKC after exercise and his symptom responded well to carbamazepine. His CT images revealed calcification at the globus pallidus, thalamus, subcortical white matter, and dentate nuclei (figure e-2B [A]). We had an opportunity to examine his parents, who had no symptoms or signs. Mutational analysis of *SLC20A2* of his parents with their informed consent revealed the same mutation in exon 8 in his mother as he had. Brain CT scan of his mother confirmed calcification at the globus pallidus, subcortical white matter, and dentate nuclei.

Sporadic cases. *Case 6.* The patient had a mutation in exon 2. She was a 72-year-old woman who noticed forgetfulness at the age of 71. She had no motor deficits. Her MMSE score was 22, and her score on the revised Hasegawa Dementia Scale was 24. Her Frontal Assessment Battery score at bedside was 5, indicating a frontal lobe deficit (cutoff score, 11/12). The index scores of the revised Wechsler Memory Scale were as follows: attention and concentration, 86; verbal memory, 89; general memory, 85; attention/concentration, 71; and delayed recall, 75. Her brain CT images revealed calcification at the globus pallidus, caudate nuclei, thalamus, subcortical and periventricular white matter, and dentate nuclei (figure e-2B [B]). Her SPECT images showed decreased perfusion in the left frontal,

Figure 3 Pedigree and CT images of family 3



(A) Pedigree of family 3. The arrow indicates the index subject. Filled symbols represent patients affected by brain calcification. We show the ages of persons under symbols in the family tree for those we could obtain. The striped symbol represents a symptomatic patient, although his CT image and DNA sample were not available for the study. (B) CT image of the proband (II-1 in pedigree of family 3). (C) CT image of asymptomatic II-5. (D) CT image of symptomatic II-7. (E) CT image of symptomatic II-8. (F) CT image of asymptomatic II-9. (G) CT image of asymptomatic III-3. All have mutation of T115M.

temporal, and parietal regions of the cerebrum and bilateral cerebellum. [^{11}C] Pittsburgh compound B (PiB) retention was not observed by [^{11}C]PiB PET. There were no other family members presenting with similar neurologic symptoms. CT scan was not performed for other individuals in the family.

Case 7. The patient was a 78-year-old man who had a frameshift in exon 2. Involuntary movement of the left thumb and index finger like "pill-rolling" began in his sixth decade. His family first noticed memory impairment at the age of 75. Gait disturbance appeared at the age of 77 and oral dyskinesia and left shoulder shrugging appeared at the age of 78. His scores on the MMSE and Frontal Assessment Battery were 22 and 10, respectively. His brain CT images showed calcification at the globus pallidus, thalamus, subcortical and periventricular white matter, and dentate nuclei (figure e-2B [C]). His SPECT images showed decreased perfusion in the bilateral (predominantly in the left) frontal and temporal regions of the cerebrum and bilateral cerebellum. [^{11}C]PiB retention was not observed by [^{11}C]PiB PET, which was performed at the age of 81. There were no other family members presenting with similar neurologic symptoms. CT scan was not performed for other individuals in the family.

DISCUSSION We have obtained clinical information of 161 patients with brain calcification in a nationwide study. We discovered that 3 patients had hypoparathyroidism, Aicardi-Goutières syndrome, and Cockayne syndrome during the survey. CT images revealed varying degrees of calcification, from marked calcification in the basal ganglia to patchy calcification in various regions, suggesting diversity in the etiologies. Some patients were incidentally found to have calcification by CT performed for head injury caused by accidents. Because our previous survey revealed a considerable frequency (1%–2%) of patchy calcification in the CT images of all patients in 2 university hospitals in Japan,[18] more asymptomatic IBGC patients with patchy calcification may exist than the number that we had previously assumed to be present in the population in Japan. After the examination by neurologists, we collected 69 DNA samples from patients who met the criteria for IBGC.[2,3] Symptoms and neurologic findings varied widely from asymptomatic to variable symptoms including headaches, psychosis, and dementia.

In this study, we investigated mutations in *SLC20A2* in 69 patients with IBGC in Japan and identified 4 new mutations in 10 familial cases (the same mutation in 2 families) and 2 other new mutations in 46 sporadic cases. The frequency of families with mutations in *SLC20A2* was 50% (5 of the 10 families), and that of sporadic patients was 4.3% (2 of the 46 patients). The frequency of the mutations in *SLC20A2* in FIBGC in Japan was as high as in other countries in a previous report.[10] Case 5 indicates that it is difficult to reliably determine sporadic cases without brain CT scans and genetic studies of all members in the family.

The mutations in our study existed in exons 2, 3, 8, and 11. One of these mutations (R467X) in exon 8 resulted in a substitution to a TGA stop codon, and the other (c.260_261delTC) in exon 2 was a frameshift. None of the mutations were reported previously, indicating heterogeneities of the mutations in *SLC20A2*. Taken together with other reports, causative mutations identified in *SLC20A2* include 6 mutations in exon 2, 1 in exon 3, 3 in exon 4, 1 in exon 5, 1 in exon 7, 10 in exon 8, 2 in exon 9, 4 in exon 10, and 4 in exon 11.[9–12] It does not seem that there

are mutation hot spots in *SLC20A2*. The in silico analysis using PolyPhen-2 for the missense mutations predicted all to be likely damaging, as determined from the residue changes. We drew the structure model of the PiT-2 protein using the TOPO2 software (http://www.sacs.ucsf.edu/TOPO/top.html). The schematic structure of the PiT-2 protein with the mutations is shown in figure 4.

Although the clinical features varied widely among the families with IBGC with *SLC20A2* mutations, the patients in families 1 and 2 with the same *SLC20A2* mutation exhibited similar clinical manifestations including dysarthria, mild cognitive decline, pyramidal signs, and extrapyramidal signs as well as similar ages at detection of calcification and onset of symptoms. Of note, the CT images among the affected individuals in the 2 families are similar (figure 2). In family 3, in contrast, 3 symptomatic patients presented with dementia, psychological disorder, and alcoholism, accompanied with brain atrophy in CT images. None of them showed movement disorders such as those in families 1 and 2.

Although mutational analysis and CT scan were not performed in other familial members of cases 6 and 7, concordance of the presence of mutations of *SLC20A2* and brain calcification were confirmed in 15 individuals, and we did not observe any individuals who carried the mutation and did not show brain calcification. These observations strongly support a high penetrance of the *SLC20A2* mutations regarding brain calcification.

Correlations of genotypes and neurologic phenotypes, however, have been controversial. *SLC20A2* mutations in patients with FIBGC have been described to show variability in clinical manifestations among the families. In the present study, the 2 affected individuals in families 1 and 2, who carried the same mutation, exhibited quite similar neurologic manifestations and clinical courses, suggesting a genotype-phenotype correlation of the S637R mutation. Of note, 2 individuals aged 56 and 61 years in family 3 did not exhibit any neurologic manifestations despite carrying the mutation and having brain calcification, indicating that penetrance regarding the neurologic manifestations is incomplete.

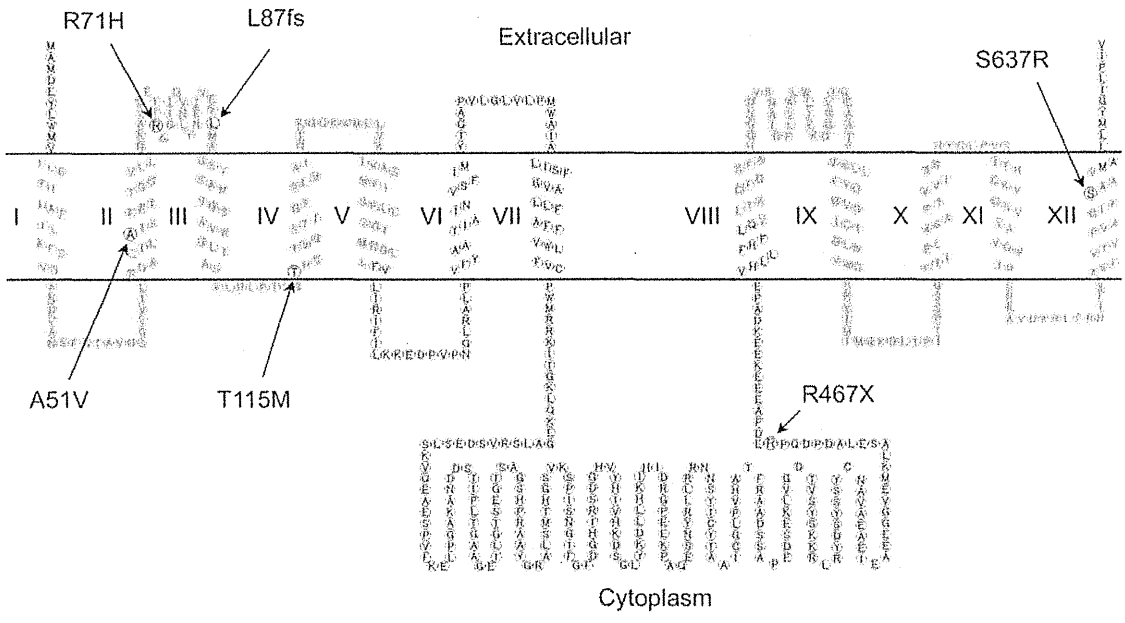
In case 4, interestingly, the proband showed pathologic findings of both IBGC and Parkinson disease. Because Parkinson disease is a common disorder in aged people, there remains a possibility that the presence of IBGC and Parkinson disease is coincidental.

Case 5 had a mutation that leads to a premature stop codon, making an incomplete structure of PiT-2. His neurologic symptom was PKC controllable by carbamazepine. Intriguingly, several patients with IBGC have been reported to present with PKC or paroxysmal nonkinesigenic dyskinesia.[19,20] For these cases of PKC or paroxysmal nonkinesigenic dyskinesia, mutational analyses of not only *SLC20A2* but also *PRRT2* and MRI will be indispensable.[21,22]

Herein, we have reported 5 cases of FIBGC and 2 cases of IBGC with *SLC20A2* mutations in Japan. We could not find any characteristic features of Japanese patients, although we had discovered that each case has a new mutation in *SLC20A2*, respectively.

The mechanisms of calcification and cell damage remain to be elucidated. Despite that the expression of PiT-2 encoded by *SLC20A2* is distributed widely in the human body,[23] mutations in *SLC20A2* cause

Figure 4 **Schematic structure of PiT-2 (type III sodium-dependent phosphate transporter) with the mutations**



calcification only in the brain. Mutations in *SLC34A2* have been reported to cause pulmonary alveolar microlithiasis.[24] Because Npt2b encoded by *SLC34A2* is the only phosphate transporter that is highly expressed in the lungs,[25] the mutations in *SLC34A2* are compatible with the lesion of the alveolar type II cells in the lungs.[24] Because the limitation of calcification to the brain cannot be explained by only the mutation in *SLC20A2* followed by abnormalities of inorganic phosphate (Pi) transport via PiT-2, there might be some other genes responsible for calcification in the brain, or the mutations in *SLC20A2* may take some toxic gain of function. The dysfunction of Pi transport can explain the accumulation of various metals in regions of the brain and the abnormal distribution of metals, which we observed in CSF[26] and hair in the patients with IBGC.[27] We have recently shown that PiT-2 immunopositivity was expressed predominantly in neurons, astrocytes, and vascular endothelial cells in the mouse brain.[28] PDGF-B is expressed in endothelial cells and neurons.[29] PDGF-B homodimer (PDGF-BB) enhanced the expression of PiT-1 mRNA encoded by *SLC20A1* in human aortic smooth muscle cells.[30] The hypomorph of PDGF-B in mice has recently been revealed to cause brain calcification through pericyte and blood-brain barrier impairment.[15] Recently, simple knockout of *SLC20A2* has also been shown to lead to calcification in the mouse brain.[31] PiT-2, PDGF, and as yet undetermined other molecules are considered to have pivotal roles in blood vessel–associated calcification and neuronal death in patients with IBGC. Elucidation of the molecular basis underlying IBGC will contribute to the development of therapeutic measures for patients with calcification in the brain.

AUTHOR CONTRIBUTIONS

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ACKNOWLEDGMENT

The authors thank the patients and their families who supported this research. The authors also thank Societas Neurologica Japonica and the Japanese Society of Child Neurology (Professor Hideo Sugie, Jichi Medical University) for cooperation of collecting patients. The authors thank the Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS) and Japan MSA research consortium (JAMSAC) for kindly providing the exome sequencing data of controls.

STUDY FUNDING

This study was sponsored by a grant from the Ministry of Health, Labour and Welfare of Japan (H23-Nanbyo-Ippan-106 and H25-Nanchitoh [Nan]-Ippan-002).

DISCLOSURE

M. Yamada, M. Tanaka, and M. Takagi report no disclosures. S. Kobayashi received research funds from Research Funding Shionogi Pharma Inc., Mochida Pharmaceutical Co., Ltd., and Eli Lilly Japan K.K. Y. Taguchi and S. Takashima report no disclosures. K. Tanaka received funds from the University of Toyama, Otsuka Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Sanofi Co., Ltd., GlaxoSmithKline Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. T. Touge reports no disclosures. H. Hatsuta received a fund from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Young Scientists [B] 24700371). S. Murayama received research funds from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grants-in-Aid for Comprehensive Scientific Research Network for Brain Bank: Basic Research B for Parkinson Disease), National Center for Geriatrics and Gerontology (Brain Bank), the Ministry of Health, Labour and Welfare of Japan (Grant-in-Aid for Neurodegenerative Disease, Prion Disease and Amyotrophic Lateral Sclerosis), and National Center for Neurology and Psychiatry (Brain Bank). Y. Hayashi reports no disclosures. M. Kaneko received funds from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Young Scientists [B] 23790095, Grant-in-Aid for Scientific Research on Priority Areas 22020032, and Grant-in-Aid for Scientific Research [B] 21300142), Takeda Science Foundation, the Research Foundation for Pharmaceutical Sciences, Niigata Brain Institute, and Japan Amyotrophic Lateral Sclerosis Association. H. Ishiura received funds from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Young Scientists [Start-up] 24890044) and the Cell Science Research Foundation. J. Mitsui received a fund from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Young Scientists [B] 25860700). N. Atsuta is funded by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (grant number 25461277) and the Inochinoiro Foundation of Japan. G. Sobue serves on the scientific advisory board for the Kanae Science Foundation for the Promotion of Medical Science, Takeda Science Foundation, and serves as an advisory board member of *Brain*, an editorial board member of *Degenerative Neurological and Neuromuscular Disease*, the *Journal of Neurology*, and *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, and is funded by the Ministry of Education, Culture, Sports, Science and Technology of Japan; the Ministry of Welfare, Health and Labor of Japan; the Japan Science and Technology Agency, Core Research for Evolutional Science and Technology. N. Shimozawa reports no disclosures. T. Inuzuka received research funds from the Ministry of Health, Labour and Welfare of Japan (H23-Nanbyo-Ippan-106, H22-Nanbyo-Shitei-002, H23-Nanbyo-Shitei-001, H23-Nanti-Ippan-039), and the Ministry of Education, Culture, Sports, Science and Technology of Japan (Basic Research [C] 24591256), and Eizai Co., Ltd., Dainippon Sumitomo Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and GlaxoSmithKline, LSE: GSK, NYSE: GSK. S. Tsuji received research funds from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grants-in-Aid for Scientific Research on Innovative Areas [22129001 and 22129002]), the Ministry of Health, Labour and Welfare of Japan (Grant-in-Aid H23-Jitsuyoka [Nanbyo]-Ippan-004), Sanofi K.K., Japan Blood Products Organization, Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Ono Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Kowa Pharmaceutical, Co., Ltd., and GlaxoSmithKline, K.K. I. Hozumi received funds from the Ministry of Health, Labour and Welfare of Japan, the Ministry of Education, Culture, Sports, Science and Technology of Japan (Basic Research [C] 24590664), Niigata Brain Institute, the Community for Communication of Technology of Gifu University, and Eizai Co., Ltd. Go to Neurology.org for full disclosures.

Received May 18, 2013. Accepted in final form November 15, 2013.

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