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Network Neurological Diseases (ERN-RND)

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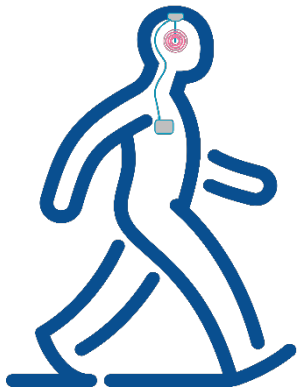
Webinar – 13th June 2023

‘Dissecting Fahr’s disease’

by Amit Batla and Francesca Magrinelli

Institute of Neurology, University College London, UK



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Learning objectives

By the end of this webinar you will be able to:

- Discuss the clinical features of Fahr‘s disease
- Explain the difference between Fahr‘s disease and Fahr‘s syndrome
- Define the diagnostic approach to brain calcifications
- State therapeutic approaches
- Outline the genes hitherto associated with Fahr‘s disease

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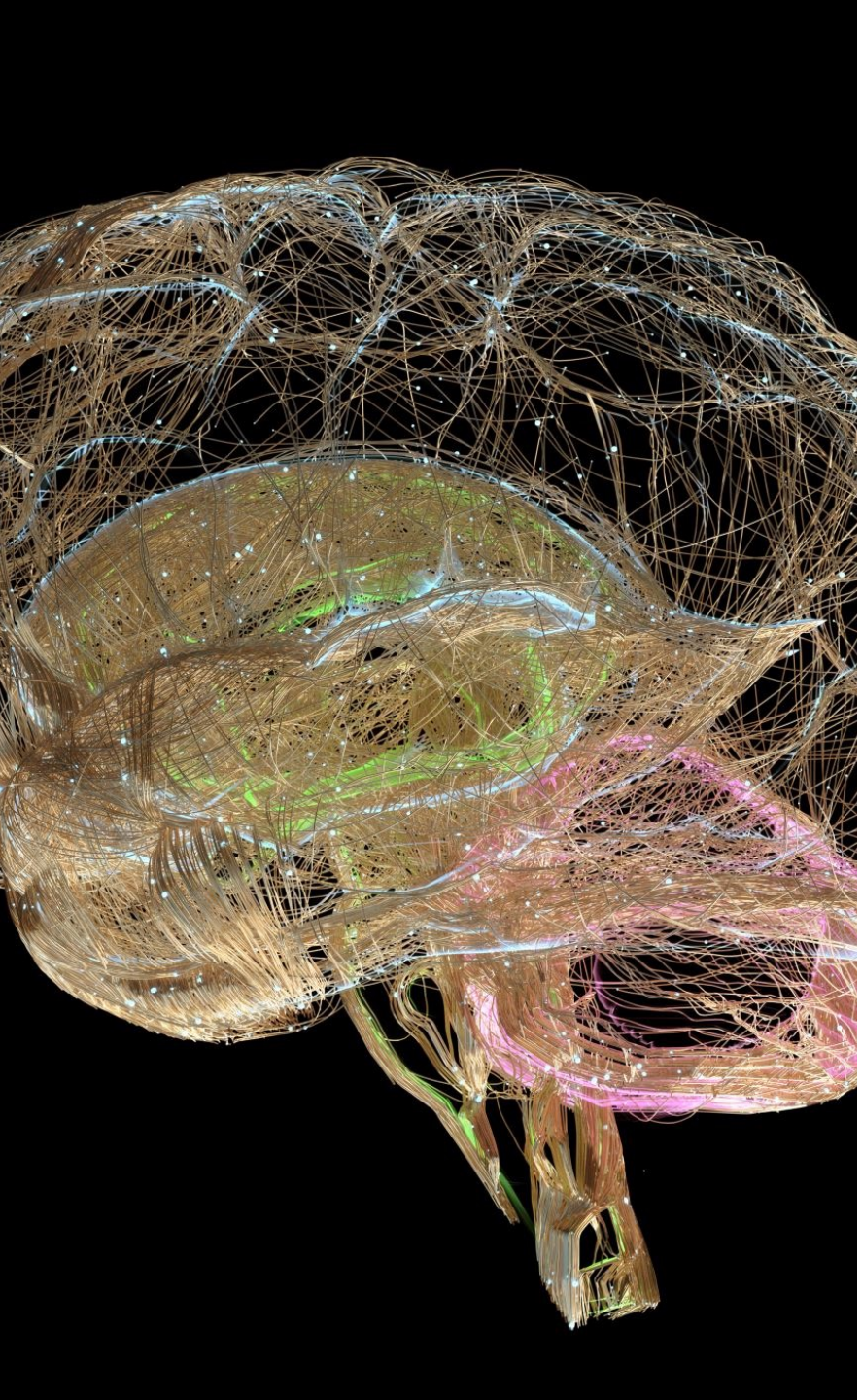
Webinar outline

1) Clinical approach to Fahr's disease

Causes of Brain Calcification
Clinical situations
An update on clinical appraisal of individual genes
Investigations
Treatment/supportive care

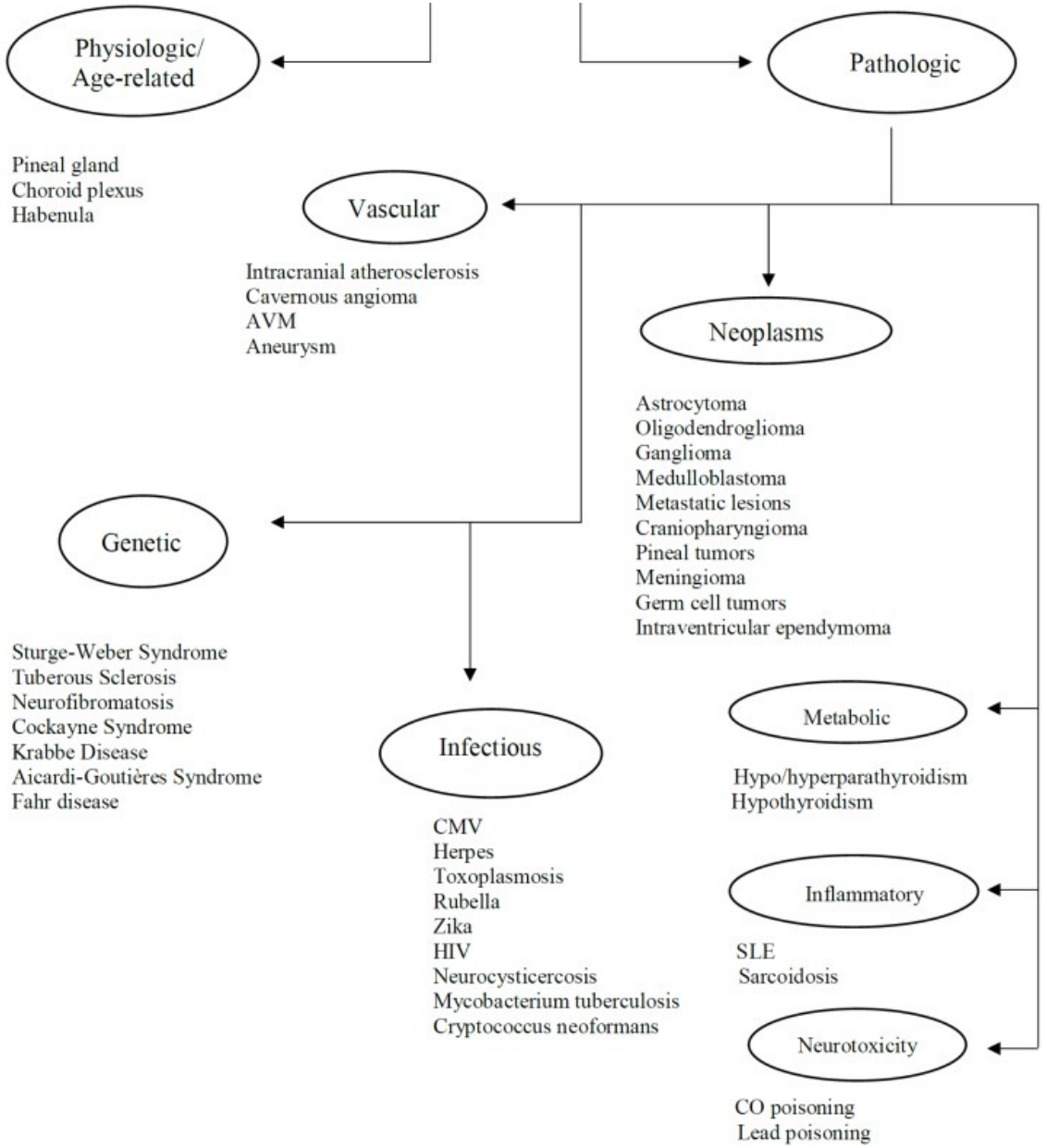
2) Genetics of Fahr's disease



Clinical approach to Fahr’s

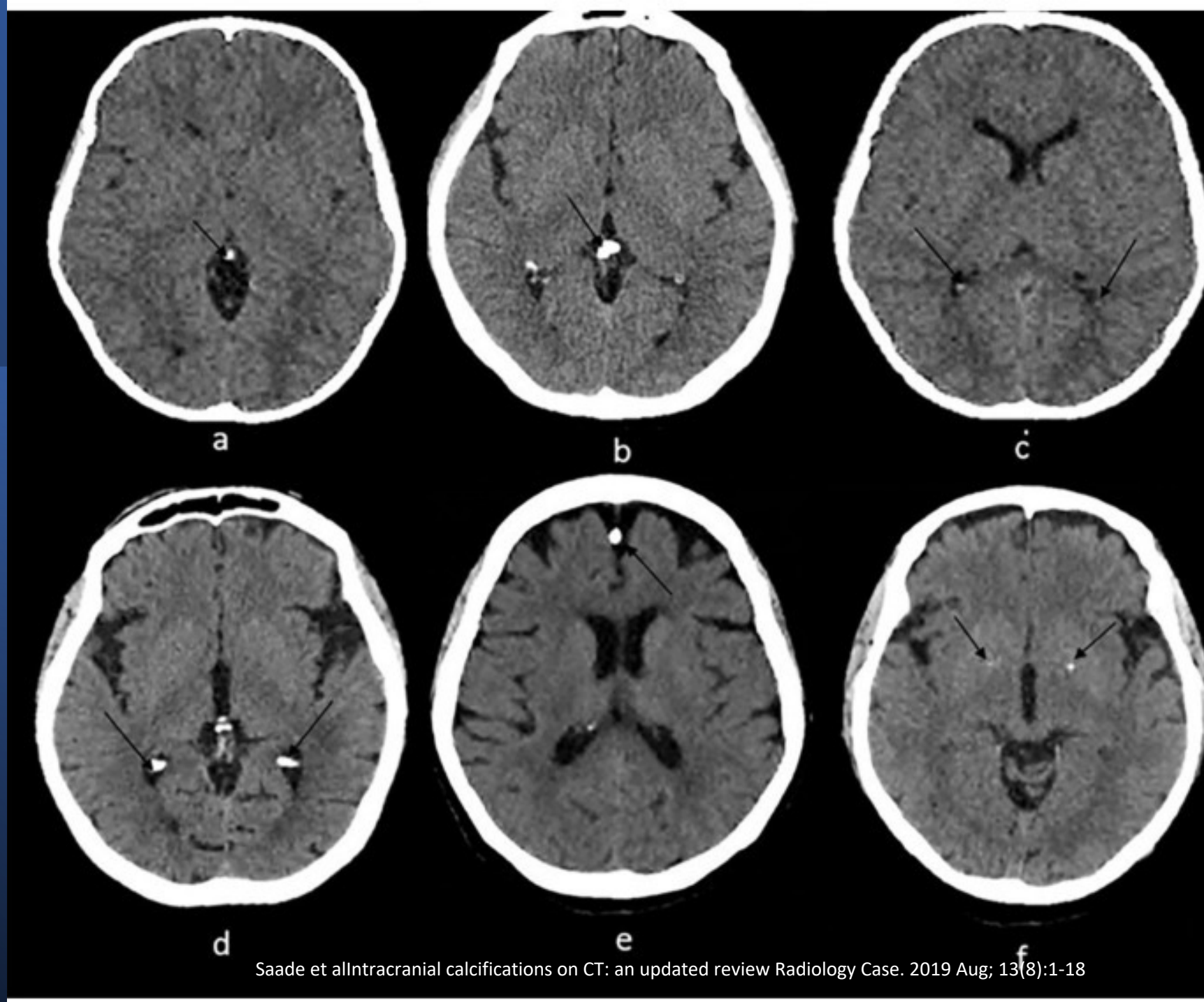
- Causes of Brain Calcification
- Clinical situations
- An update on clinical appraisal of individual genes
- Investigations
- Treatment/supportive care

Causes of brain calcification

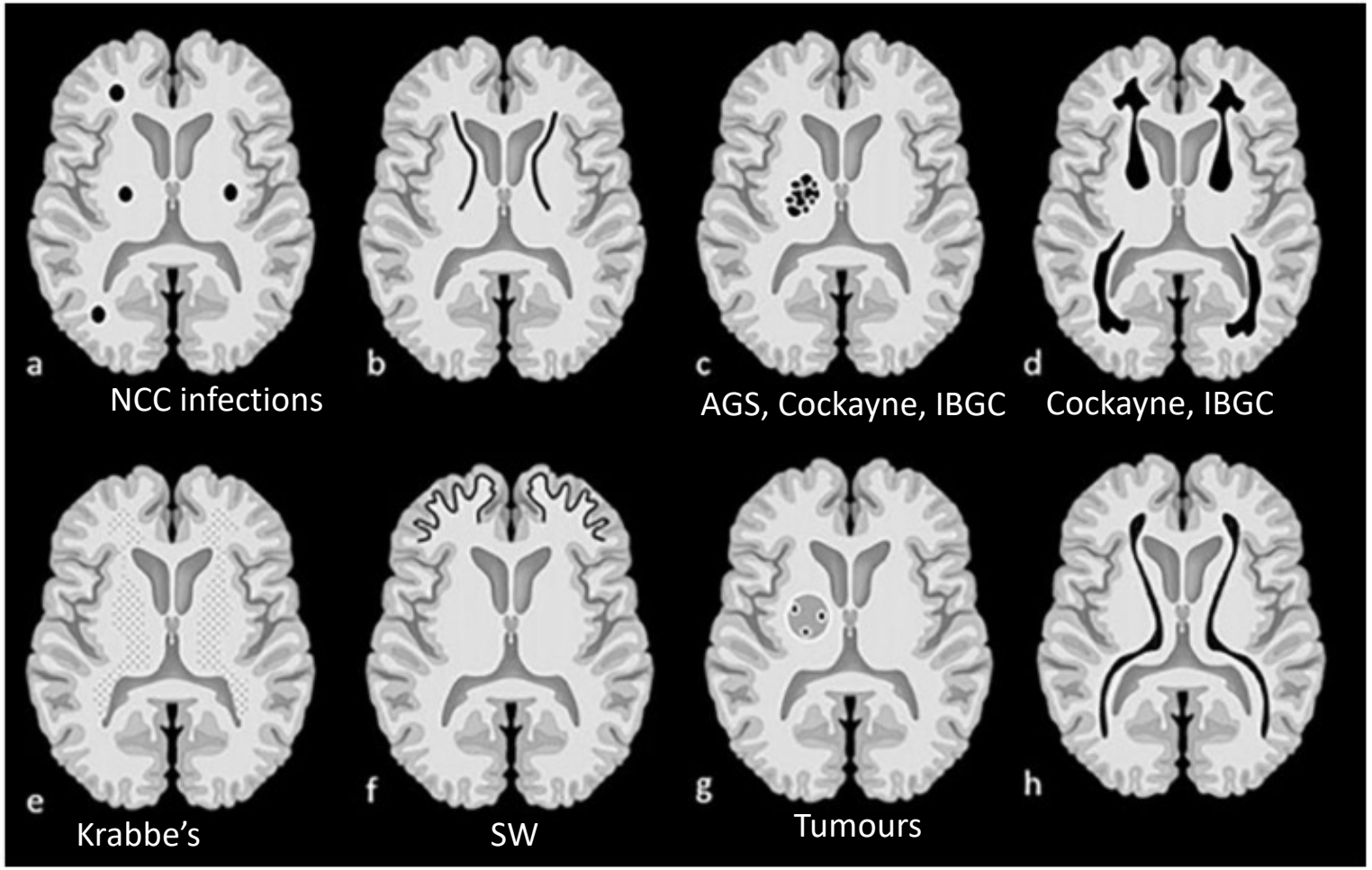


Saade et alIntracranial calcifications on CT: an updated review Radiology Case. 2019 Aug; 13(8):1-18

1. Incidental brain calcification



Saade et alIntracranial calcifications on CT: an updated review Radiology Case. 2019 Aug; 13(8):1-18



Examples of patterns of calcification and related terminology. (a) dots, (b) lines, (c) conglomerate or mass-like, (d) rock-like, (e) blush, (f) gyriform/band-like, (g) stippled (h) reticular.

NCC- neurocysticercosis, AGS Aicardi Goutiere's , IBGC - Fahrs SW Sturge Weber

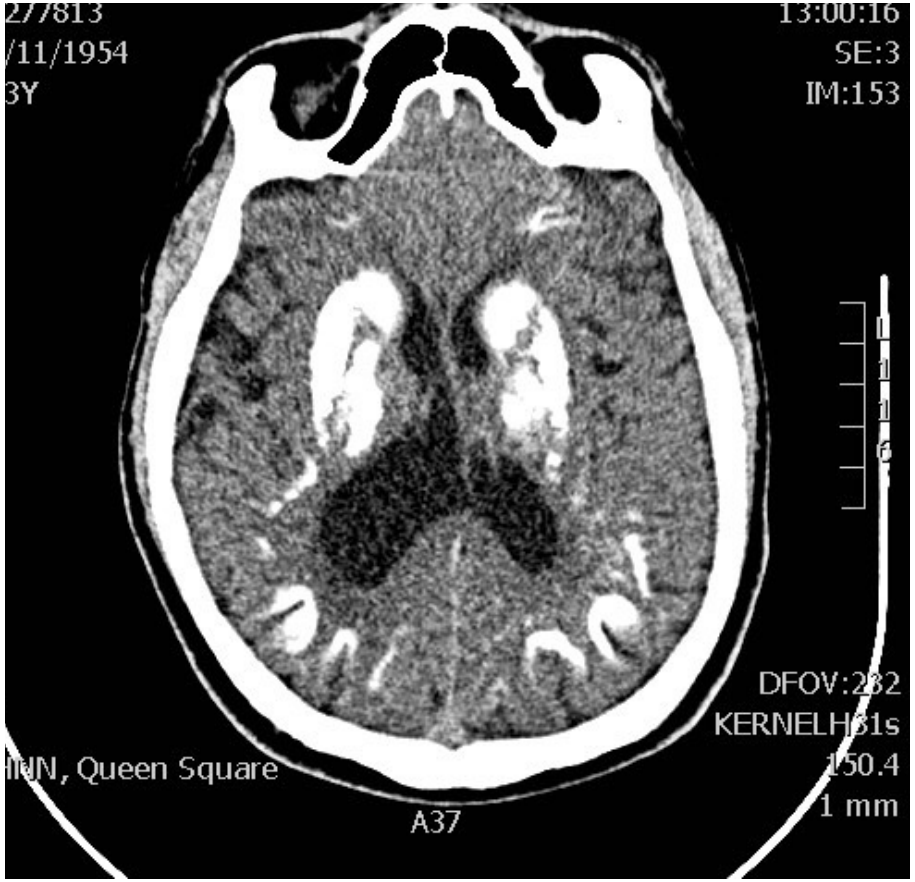
Saade et alIntracranial calcifications on CT: an updated review Radiology Case. 2019 Aug; 13(8):1-18

2. Parkinsonism

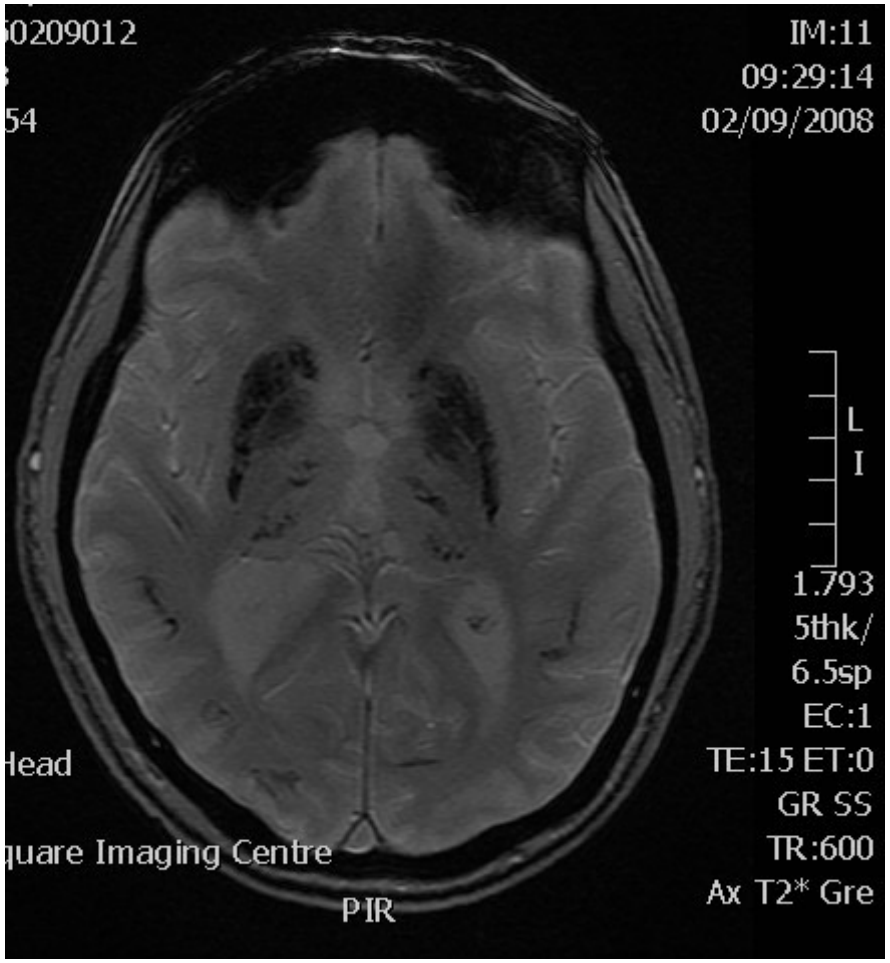
- Experienced particular difficulty turning
- In the last year he has started stuttering
- Hand writing has deteriorated and become scruffy, has felt some benefit since starting Madopar
- He was previously very sociable, the ‘life and soul’ of the party, but has become increasingly withdrawn, lacking in confidence and depressed

Stamelou M, et al. Ability to cycle despite severe freezing of gait in atypical parkinsonism in Fahr's syndrome. Mov Disord. 2011 Sep;26(11):2141-2.

CT head



MRI GRE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02/09/2008
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L
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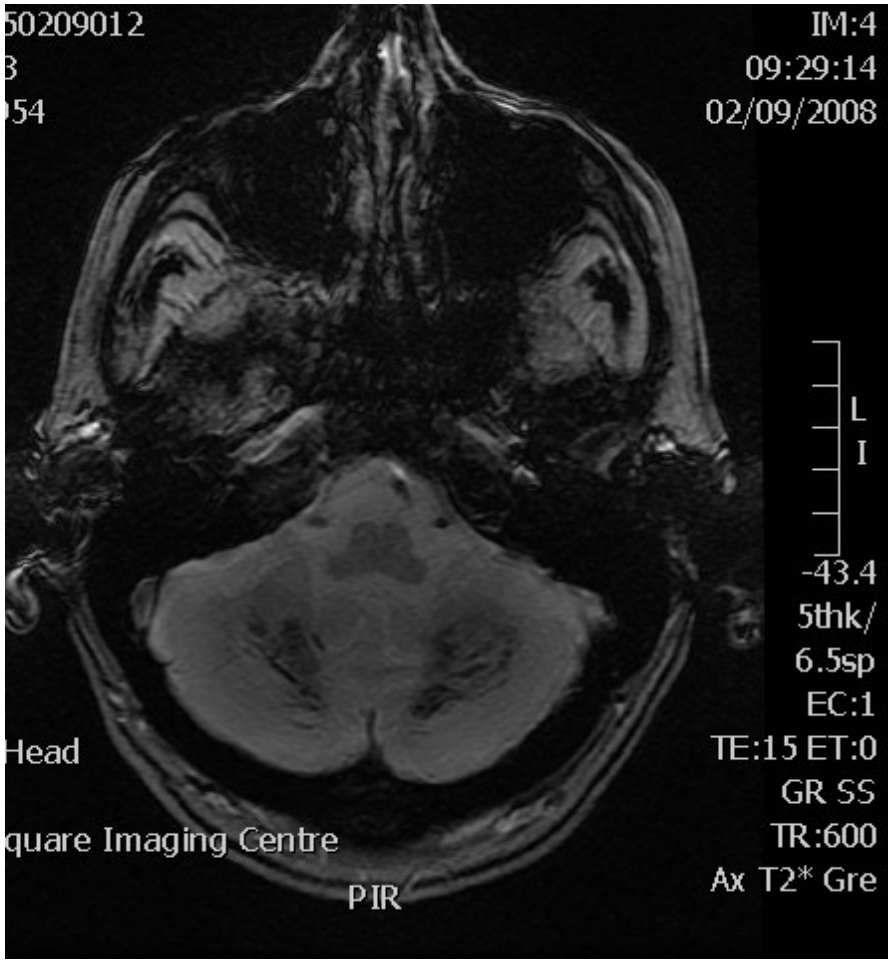
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Head
quare Imaging Centre
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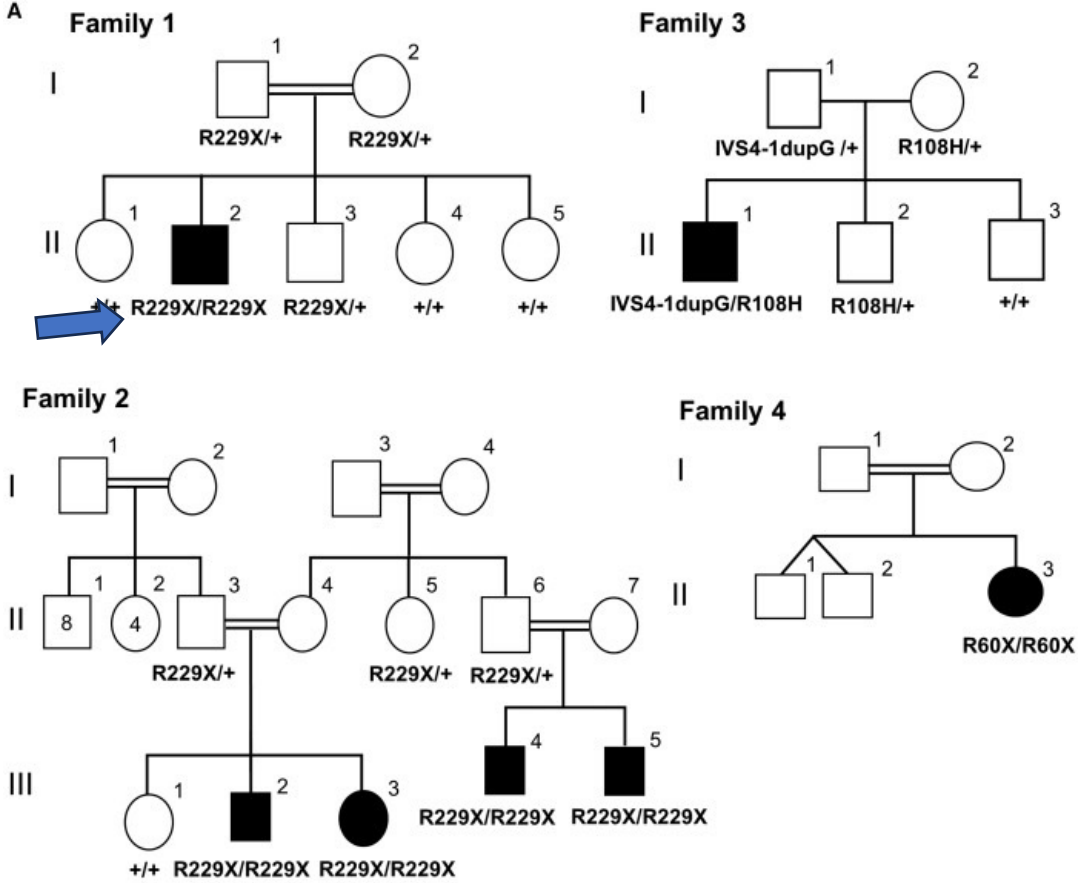
3. Complex movement disorder

A


Family 1
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2
R229X/+
R229X/+
II
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3
4
5
+/+
R229X/R229X
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+/+
+/+
Family 3
I
1
2
IVS4-1dupG /+
R108H/+
II
1
2
3
IVS4-1dupG/R108H
R108H/+
+/+
Family 2
I
1
2
3
4
II
1
2
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4
5
6
7
8
4
R229X/+
R229X/+
R229X/+
III
1
2
3
4
5
+/+
R229X/R229X
R229X/R229X
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Family 4
I
1
2
II
1
2
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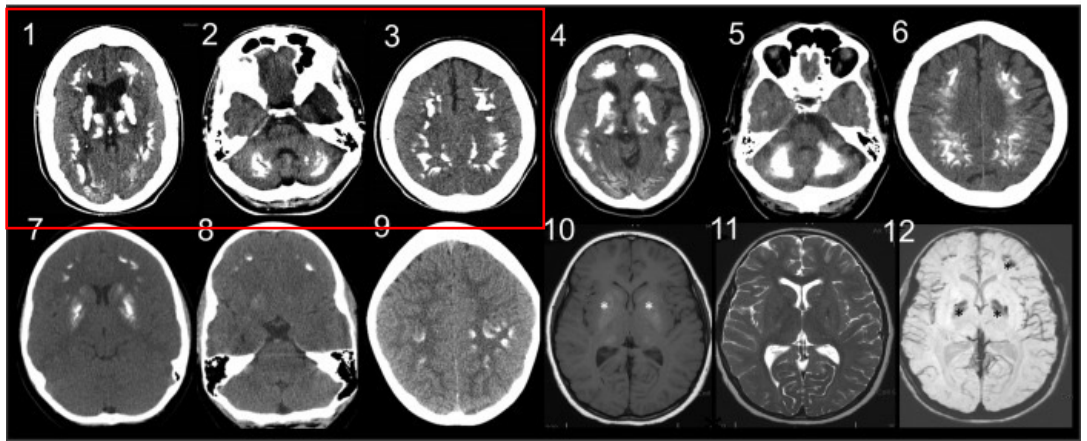
R60X/R60X

B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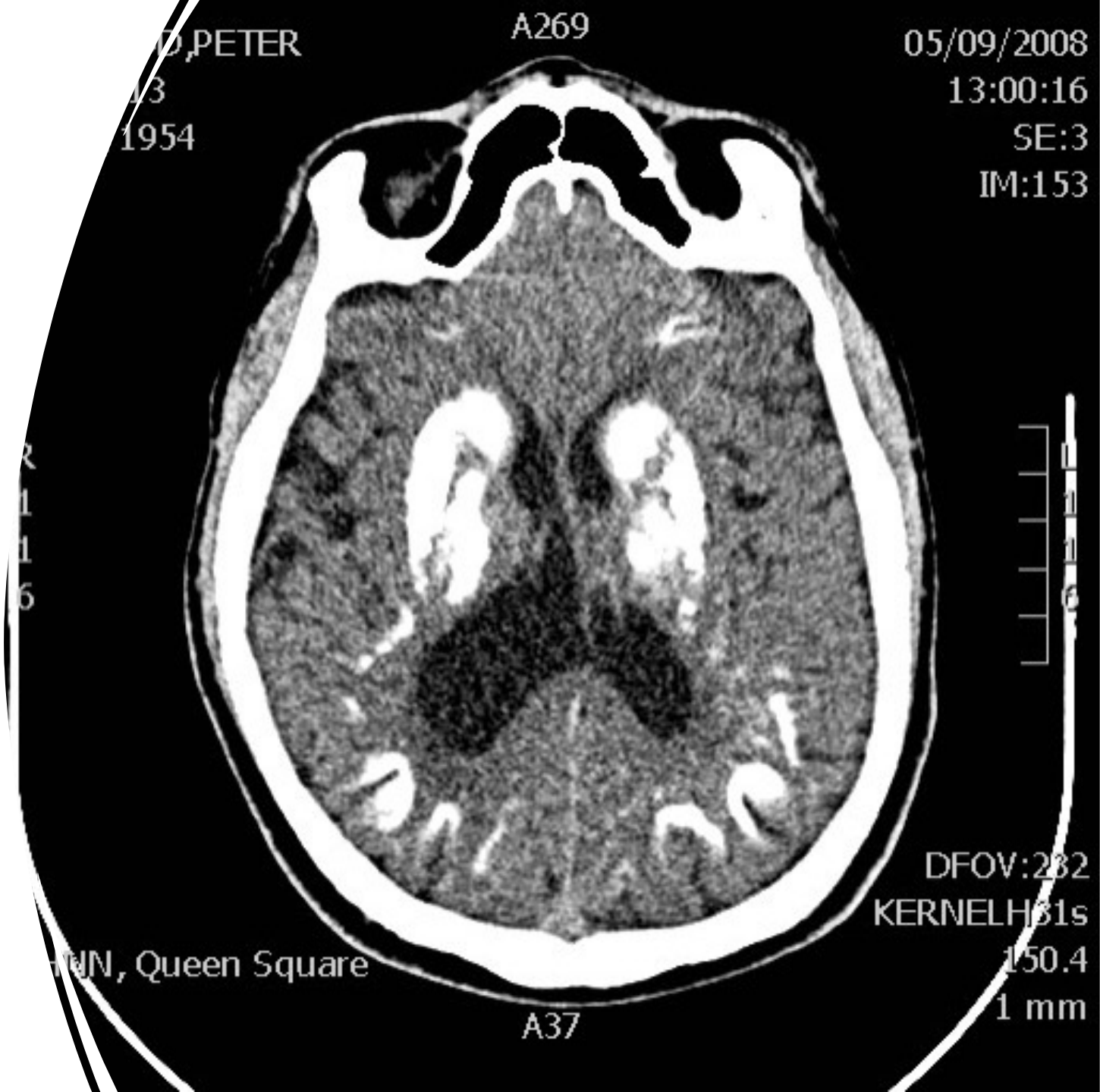
12

When is brain calcification not Fahr's disease?

- Intracranial calcification on brain computed tomography (CT) is a common finding
- Two studies performed in the 1980s examining 7,040 and 6,348 patient scans revealed that 1.02% and 1.1% of patients, respectively, had symmetric intracranial calcification.



Parkinsonism & Related Disorders

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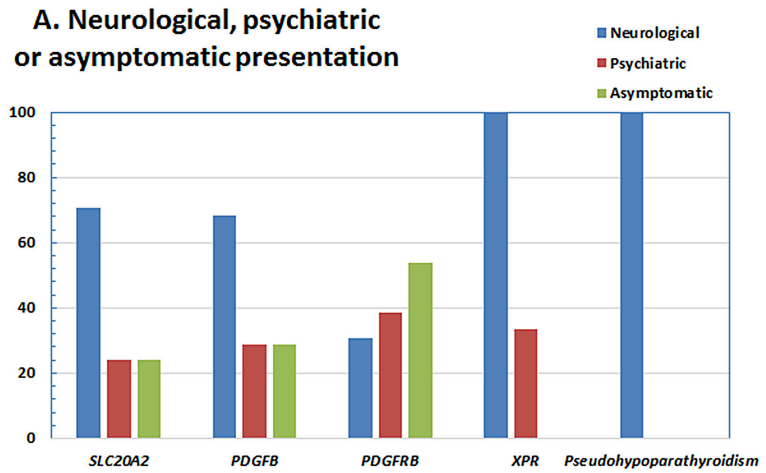
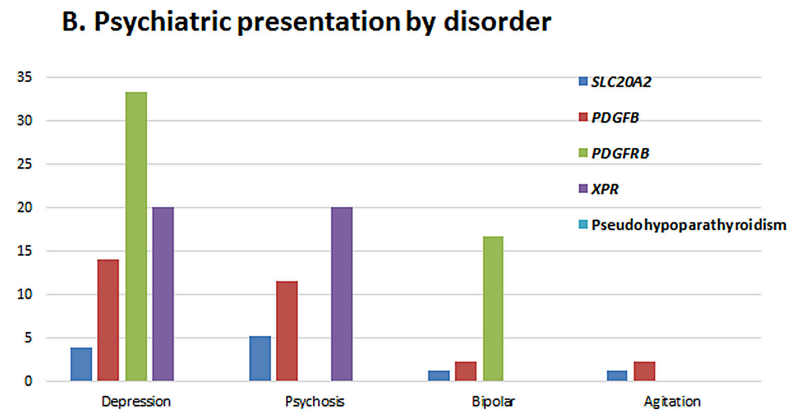
REVIEW ARTICLE | VOLUME 37, P1-10, APRIL 2017 Download Full Issue

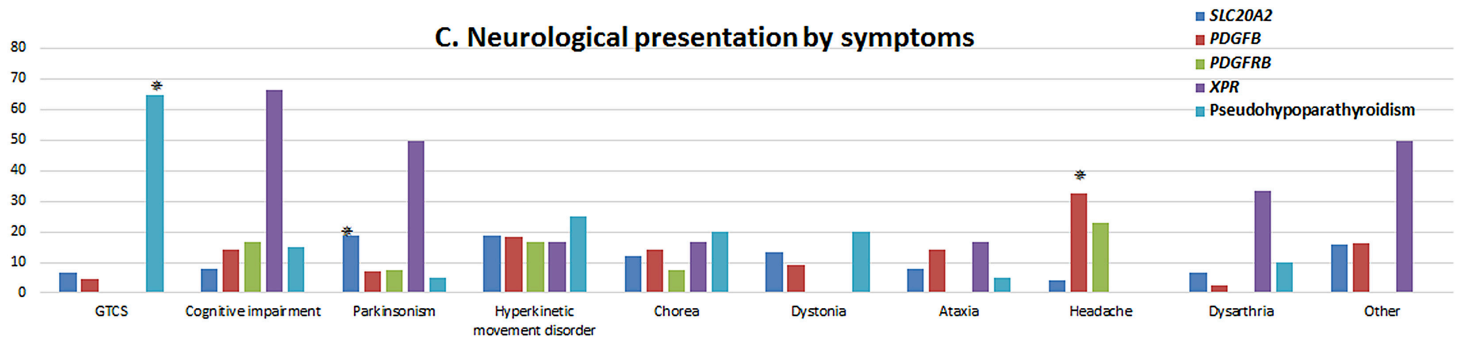
Deconstructing Fahr's disease/syndrome of brain calcification in the era of new genes

Amit Batla • Xin You Tai • Lucia Schottlaender • Robert Erro • Bettina Balint • Kailash P. Bhatia

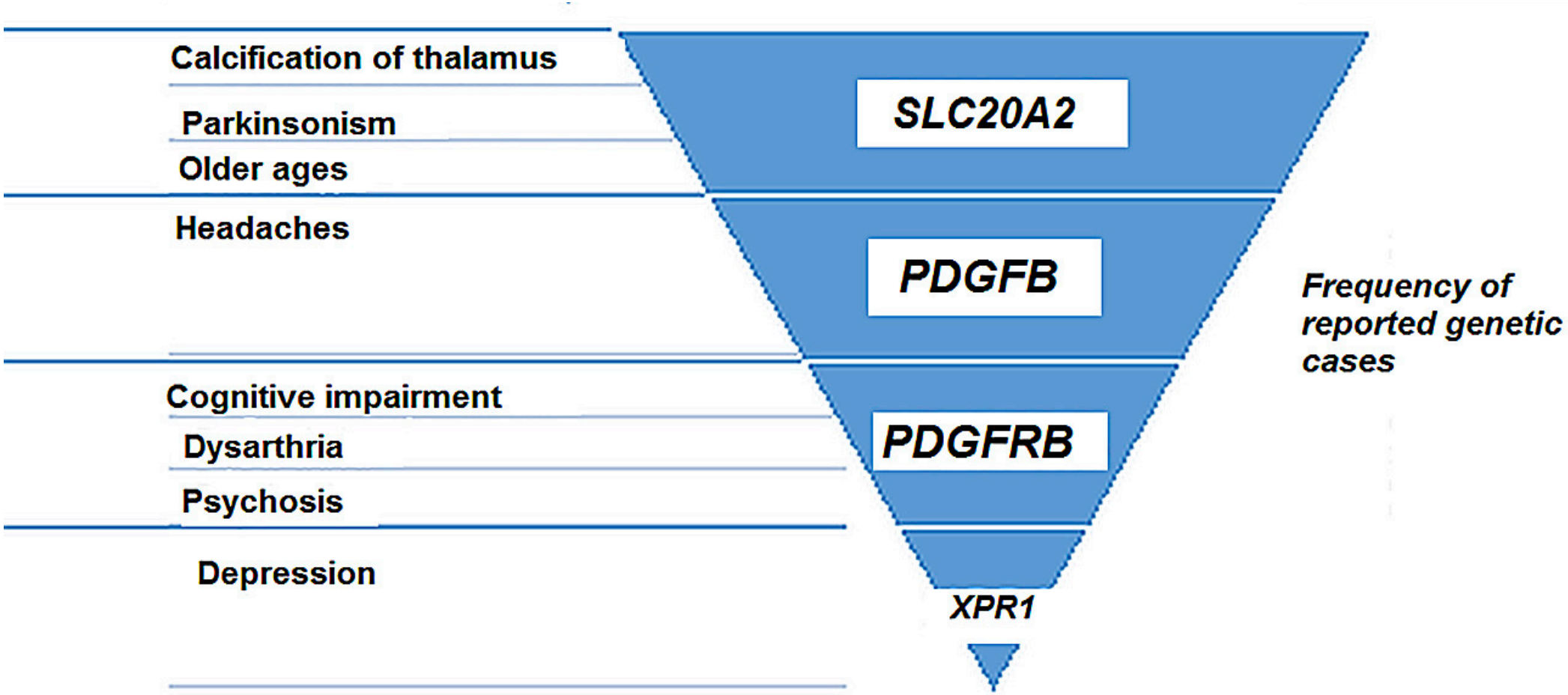
Published: December 27, 2016 • DOI: https://doi.org/10.1016/j.parkreldis.2016.12.024 • Check for updates







Differentiation among genetic IBGC



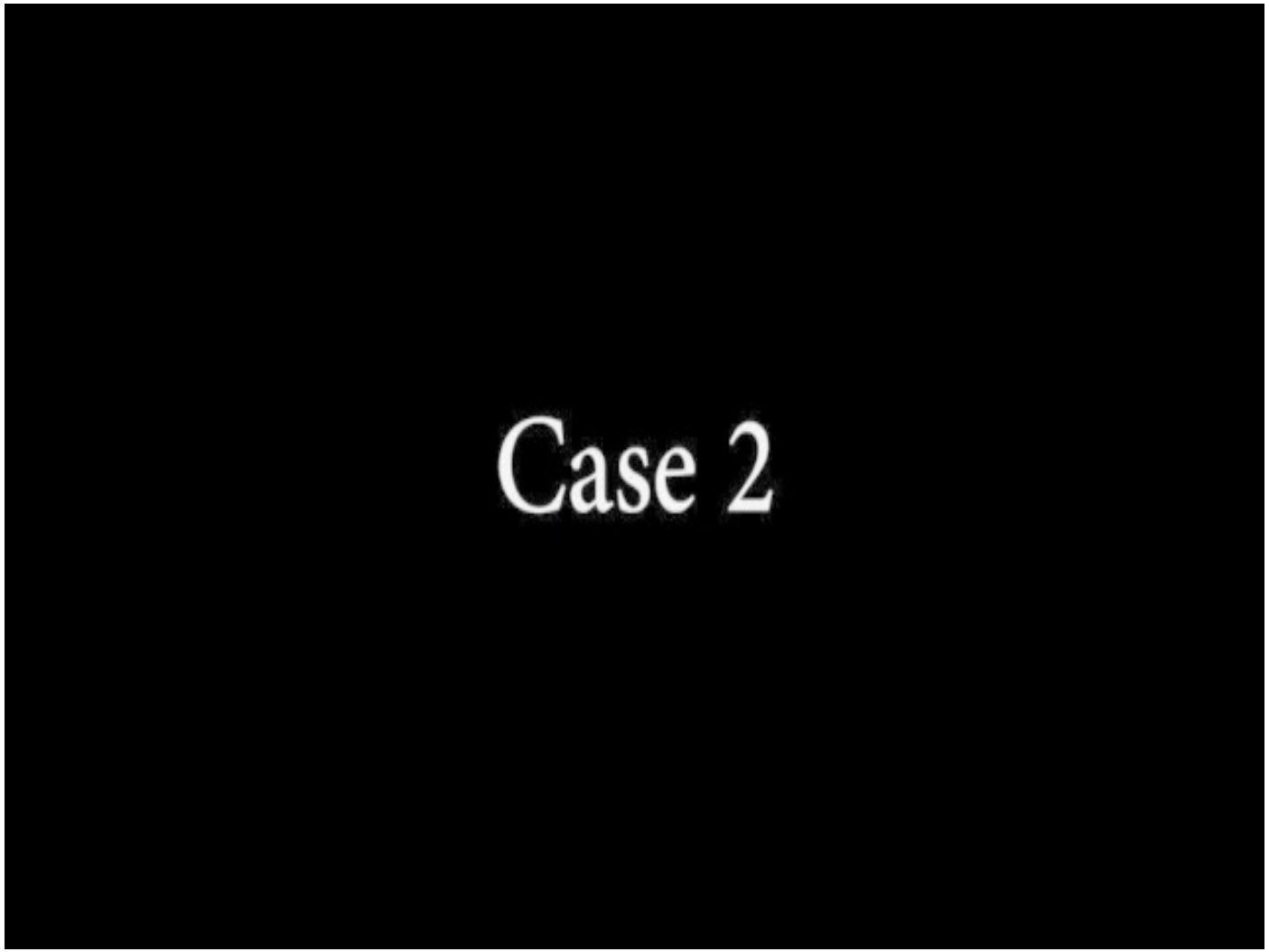
Batla A, Tai XY, Schottlaender L, Erro R, Balint B, Bhatia KP. Deconstructing Fahr's disease/syndrome of brain calcification in the era of new genes. Parkinsonism Relat Disord. 2017 Apr;37:1-10.

	SLC20A2	PDGFB	PDGFRB	XPR1	MYORG	JAM2
Bradykinesia	41 (21.5%)	5 (9.1%)	2 (16.7%)	3 (14.3%)	27 (45.0%)	8 (80%)
Tremor	29 (15.2%)	7 (12.7%)	1 (8.3%)	3 (14.3%)	6 (10.0%)	0 (0%)
Rigidity	32 (16.8%)	4 (6.7%)	1 (8.3%)	2 (9.5%)	14 (23.3%)	6 (60%)
Postural instability	4 (2.1%)	1 (1.8%)	1 (8.3%)	0 (0%)	1 (1.7%)	3 (30%)
Dystonia	26 (13.6%)	5 (9.1%)	0 (0.0%)	1 (4.8%)	4 (6.7%)	5 (50%)
Chorea	7 (3.7%)	7 (12.7%)	0 (0.0%)	0 (0%)	3 (5.0%)	0 (0%)
Speech disturbance	27 (14.1%)	4 (6.7%)	1 (8.3%)	6 (28.6%)	47 (78.3%)	4 (40%)
Ataxia	11 (5.8%)	8 (14.5%)	0 (0.0%)	3 (14.3%)	22 (36.7%)	6 (60%)

Balck, A., et al.(2021), Genotype–Phenotype Relations in Primary Familial Brain Calcification: Systematic MDSGene Review. Mov Disord, 36: 2468-2480.

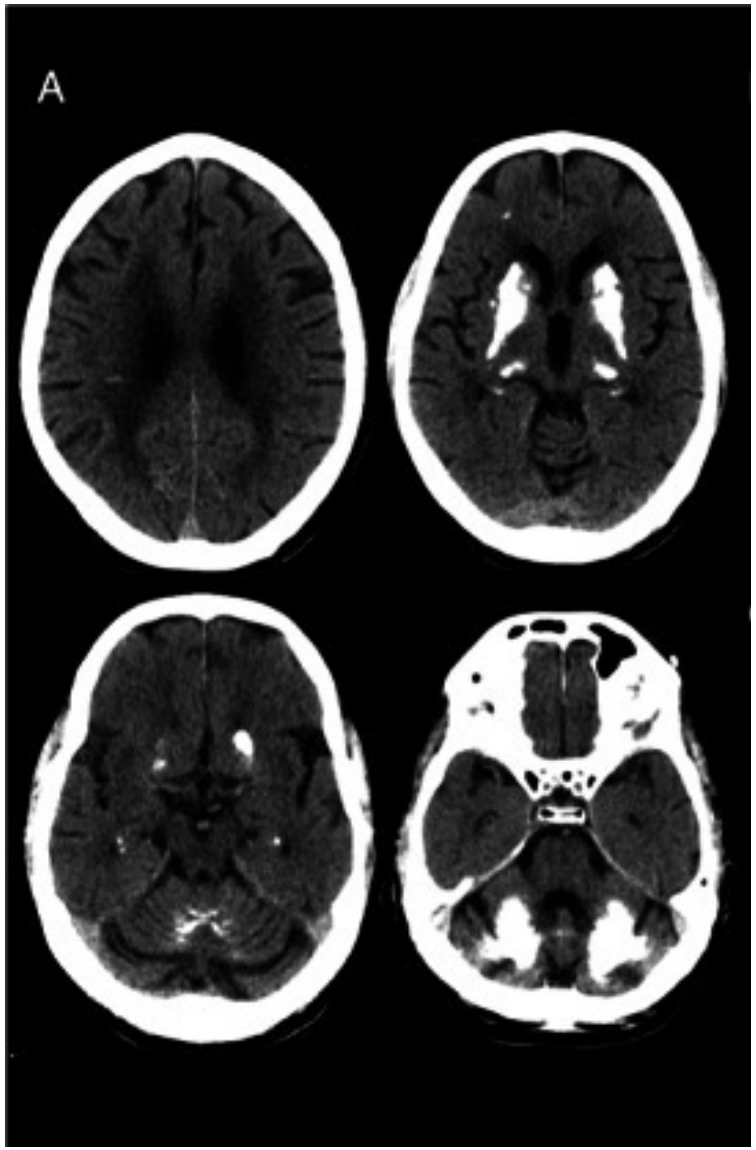
Symptoms

	SLC20A2	PDGFB	PDGFRB	XPR1	MYORG	JAM2
Seizures	9 (4.7%)	4 (6.7%)	1 (8.3%)	2 (9.5%)	2 (3.3%)	3 (30%)
Anxiety	11 (5.8%)	6 (10.9%)	1 (8.3%)	2 (9.5%)	1 (1.7%)	0 (0%)
Psychosis	18 (9.4%)	8 (14.5%)	0 (0.0%)	2 (9.5%)	4 (6.7%)	0 (0%)
Cognitive deficits	58 (30.4%)	19 (34.5%)	3 (25.0%)	8 (38.1%)	26 (43.3%)	5 (50%)
Headache	55 (28.8%)	23 (41.8%)	4 (33.3%)	2 (9.5%)	5 (8.3%)	0 (0%)



Mulroy E, et al. Throat-Clearing Vocalizations in Primary Brain Calcification Syndromes. Mov Disord Clin Pract. 2021 Mar 13;8(4):627-630

CT



Mulroy E, et al. Throat-Clearing Vocalizations in Primary Brain Calcification Syndromes. Mov Disord Clin Pract. 2021 Mar 13;8(4):627-630

Survey

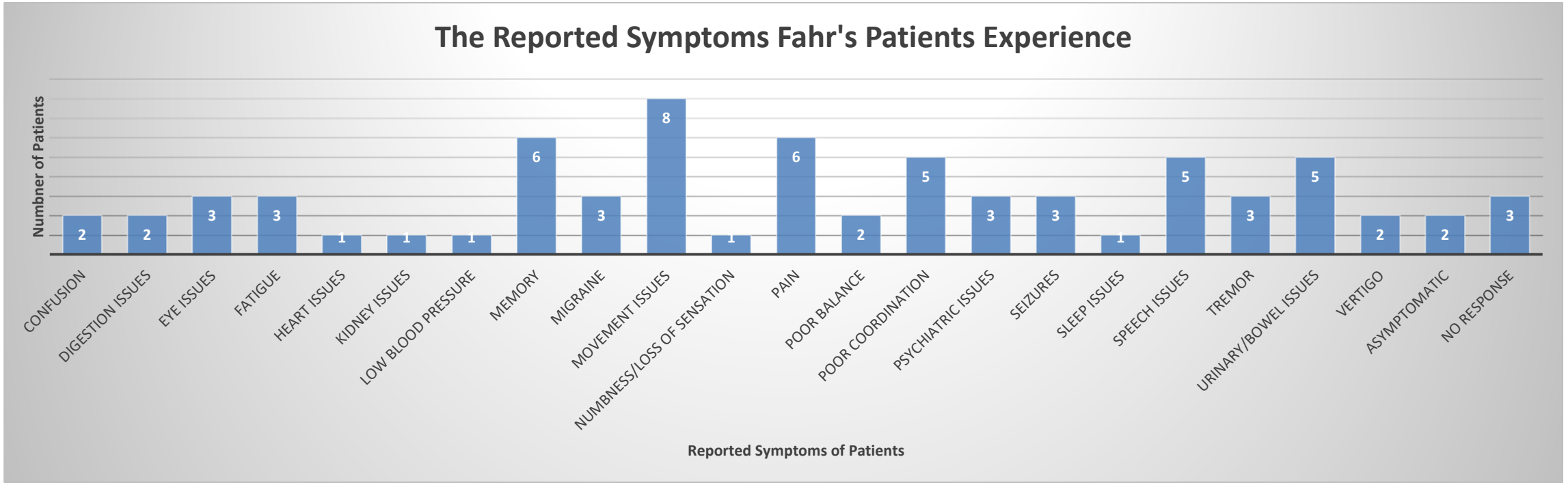
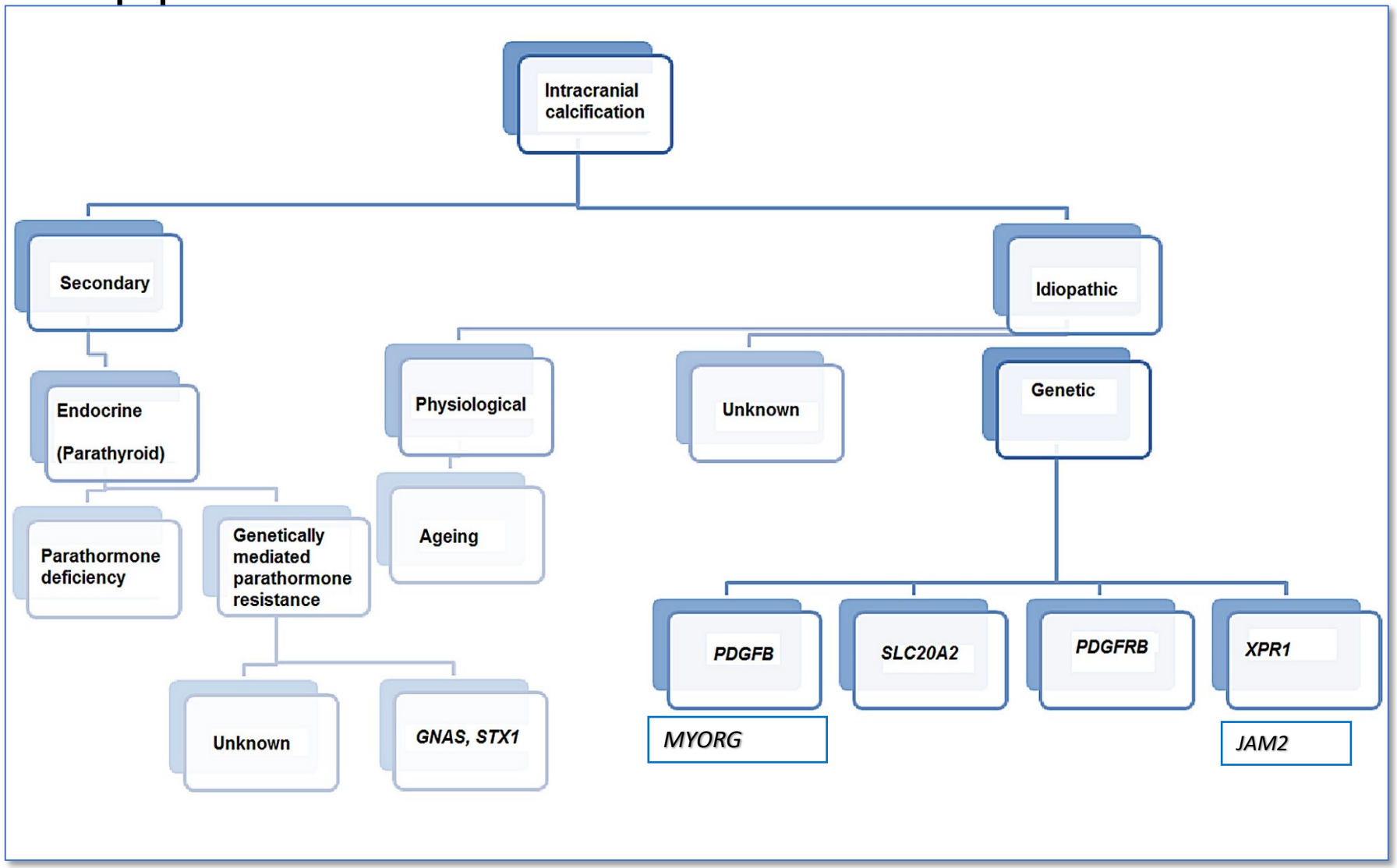


Figure 2: Response to questions on the reported symptoms of Fahr’s patients, data has been analysed and presented in 23 broad categories
Source Fahr Beyond

Approach to Management

Approach



Disorders of *GNAS* Inactivation-
pseudohypoparathyroidism Ia, Ib, and Ic (PHP-Ia, -Ib, -Ic)
pseudopseudohypoparathyroidism (PPHP)
progressive osseous heteroplasia (POH)
osteoma cutis (OC).

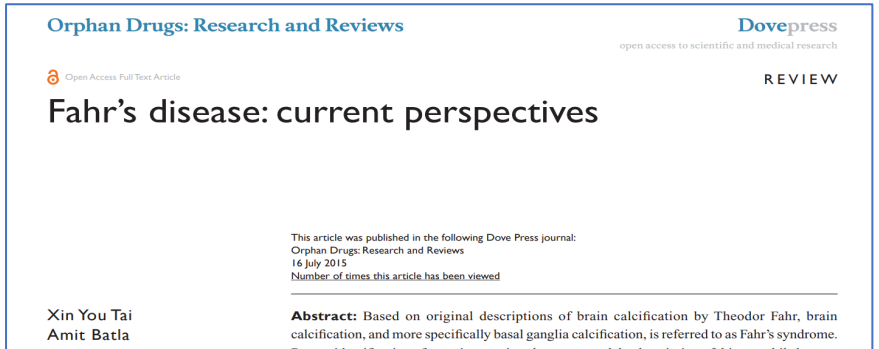
Batla A, Tai XY, Schottlaender L, Erro R, Balint B, Bhatia KP. Deconstructing Fahr's disease/syndrome of brain calcification in the era of new genes. Parkinsonism Relat Disord. 2017 Apr;37:1-10.

Imaging

Radiological CT findings	*SLC20A2*		*PDGFB*		*PDGF-RB*		*XPR1*		Pseudohypoparathyroidism	
Basal Ganglia	64	(100)	36	(94.7)	13	(100)	5	(100)	19	(95.0)
Thalamus	37	(57.8)	6	(17.6)	1	(7.7)	4	(80.0)	7	(35.0)
Cerebellum	31	(48.4)	13	(34.2)	9	(69.2)	5	(100)	11	(55.0)
(of which Dentate nucleus specifically)	28	(43.8)	4	(10.5)	3	(23.1)	0	(0)	10	(50.0)
Sub-cortical grey matter/ grey-white junction	25	(39.1)	17	(44.7)	5	(38.5)	3	(60.0)	7	(35.0)
Cortical areas	11	(17.2)	1	(2.6)	0	(0)	3	(60.0)	2	(10.0)

Calcium and Parathyroid

Condition		Calcium	Phosphate	PTH levels	Calcitriol
Hypoparathyroidism		Low	High	Low	Low
Pseudohypoparathyroidism	**Type 1A**	Low	High	Low	High
	Type 1B	Low	High	Low	High
	Type 2	Low	High	Low	High
Pseudopseudohypoparathyroidism		Normal	Normal	Normal	Normal



Orphan Drugs: Research and Reviews

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REVIEW

Fahr's disease: current perspectives

This article was published in the following Dove Press journal:
Orphan Drugs: Research and Reviews
16 July 2015
Number of times this article has been viewed

Xin You Tai
Amit Batla

Abstract: Based on original descriptions of brain calcification by Theodor Fahr, brain calcification, and more specifically basal ganglia calcification, is referred to as Fahr's syndrome.

Symptomatic treatment

- Dopamine- Parkinsonism
- Anticholinergic- Dystonia
- Tetrabenazine- Chorea

- Botox- for dystonia, spasticity

- DBS- STN/ GPI

DBS in brain calcifications due to Fahr’s?

ELSEVIER

Parkinsonism & Related Disorders

Volume 96, March 2022, Pages 88-90

Correspondence

Deep brain stimulation in a Parkinson's disease patient with calcifications and a mutation in the SLC20A2 gene

Nina Asheim Birkeland [1], Viel Nyborg Carlsen [1], Sasha Gulati, Emil K. Gustavsson, Jan O. Aasly

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https://doi.org/10.1016/j.parkreldis.2022.01.019 ↗

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Highlights

- A patient with levodopa responsive early-onset Parkinson's disease.
- Successful deep brain stimulation surgery on patient with large brain calcifications.

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Case Report

Bilateral deep brain stimulation of the subthalamic nucleus effectively relieves dystonia secondary to Fahr's disease: a case report

Yu Ma, Ming Ge, Fangang Meng, Kai Zhang & **Jianguo Zhang**

Pages 582-586 | Received 14 Nov 2012, Accepted 29 Jan 2013, Accepted author version posted online: 05 Feb 2013, Published online: 28 Feb 2013

Download citation https://doi.org/10.3109/00207454.2013.772611

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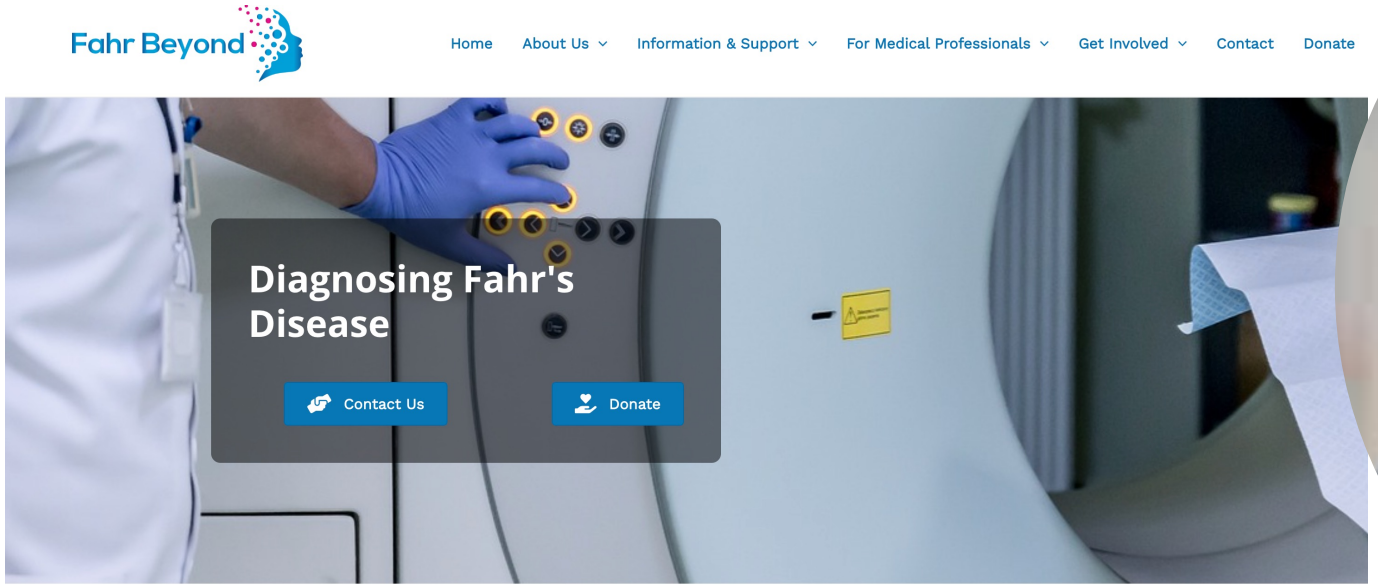
Abstract

Fahr's disease (FD) is a rare movement disorder characterized by bilateral intracranial calcifications that is refractory to most treatments. We present the case of a 26-year-old male with FD who was unable to walk independently and could not eat solid food because of poor swallowing capability and severe cervical dystonia. Injections of botulin toxin into the neck muscles, as well as biperiden, tiapride, amantadine, L-dopa and clonazepam were ineffective. Deep brain stimulation (DBS) was performed with two permanent electrodes containing four contact sites implanted bilaterally into the subthalamic nucleus (STN). The antidystonic effect was evident immediately after STN stimulation, and it was sustained during a 24-month

Management- Multidisciplinary team input

Physiotherapy and occupational therapy to optimize joint mobility, minimize contractures, maintain posture, and maximize motor function
Adaptive aids for ambulation and mobility (walkers and wheelchairs)
Speech and language therapy (for dysarthria) and communication devices
Swallow assessment for safety of swallow
Dietetic input to maintain adequate caloric requirements and prevent malnutrition
Treatment of constipation and gastroesophageal reflux
Prompt PEG referral (as needed) to support any feeding difficulties
Vision support
Appropriate educational setting (and statementing of needs as appropriate)
Dental extraction or bite blocking if orolingual dystonia leads to recurrent tongue biting
Prompt recognition and treatment of painful factors that may exacerbate the movement disorder, such as occult GI bleeding, urinary tract infections, pressure sores from immobility, and bone fractures.


Fahr Beyond
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Diagnosing Fahr's Disease
Contact Us
Donate
Fahr Beyond is privileged to have as medical leads Professor Bhatia and Dr Batla both based at the National Hospital for Neurology and Neurosurgery in London, UK. Furthermore, we have communication with other leading Neurologists and Neurosurgeons in four different National Health Service Trusts across the UK.
Not only that we stay up to date with the current medical and academic literature on Fahr's and Fahr's like conditions.
Fahr's usually is only evident on a Computerised Tomography scan, it has been noted that Magnetic Resonance Imaging scans can

Fahr Beyond

CALCIFADE (ClinicalTrials.gov Identifier: NCT05662111

Arm	Intervention/treatment
Active Comparator: EtidronateEtidronate 20 mg/kg for two weeks on and ten weeks off during 12 months	Drug: EtidronateThe dosage of etidronate is 20 mg/kg for twee weeks and ten weeks off. Etidronate is given in capsules of 200 mg. Etidronate capsules are administered orally. During the study, participants will receive etidronate in four periods of two weeks during the twelve months of follow-up. Other Name: Etidronate disodium
Placebo Comparator: PlaceboPlacebo for two weeks on and ten weeks off during 12 months	Drug: PlaceboPlacebo is given in capsules and are administered orally. During the study, participants will receive placebo in four periods of two weeks during the twelve months of follow-up. Other Name: Etidronate disodium

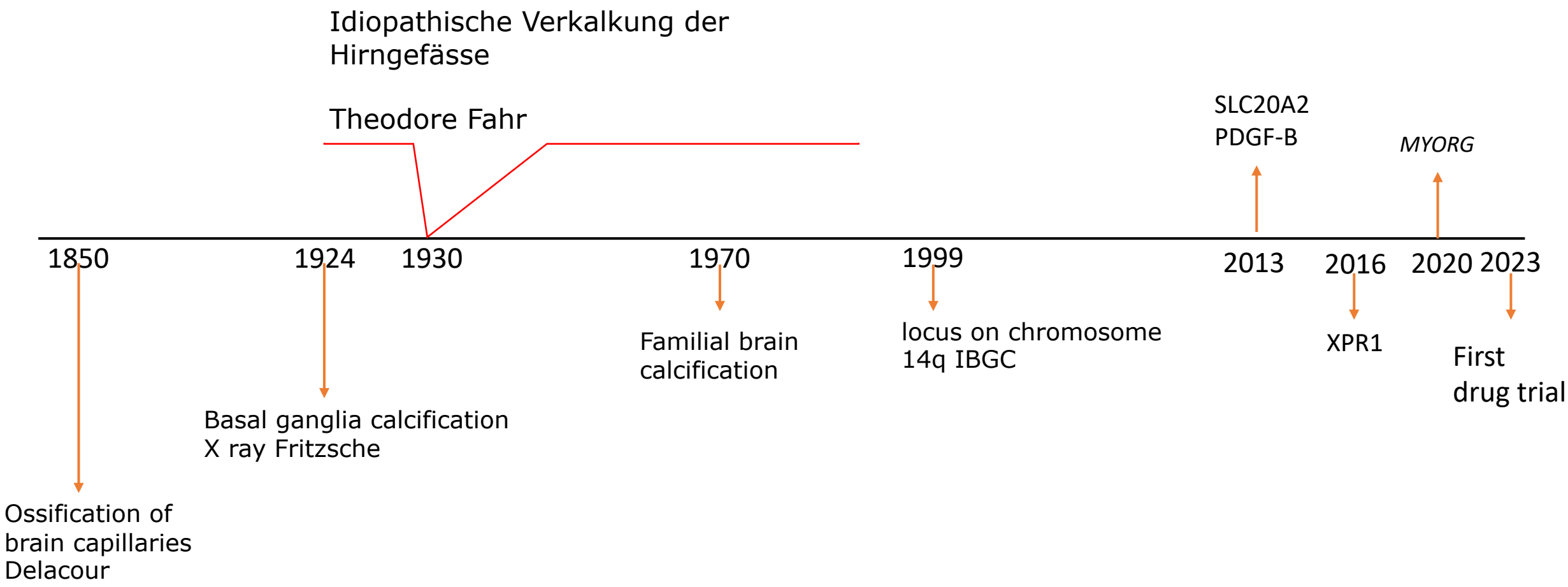
Primary Outcome Measures

Overall cognitive functioning, Memory, attention

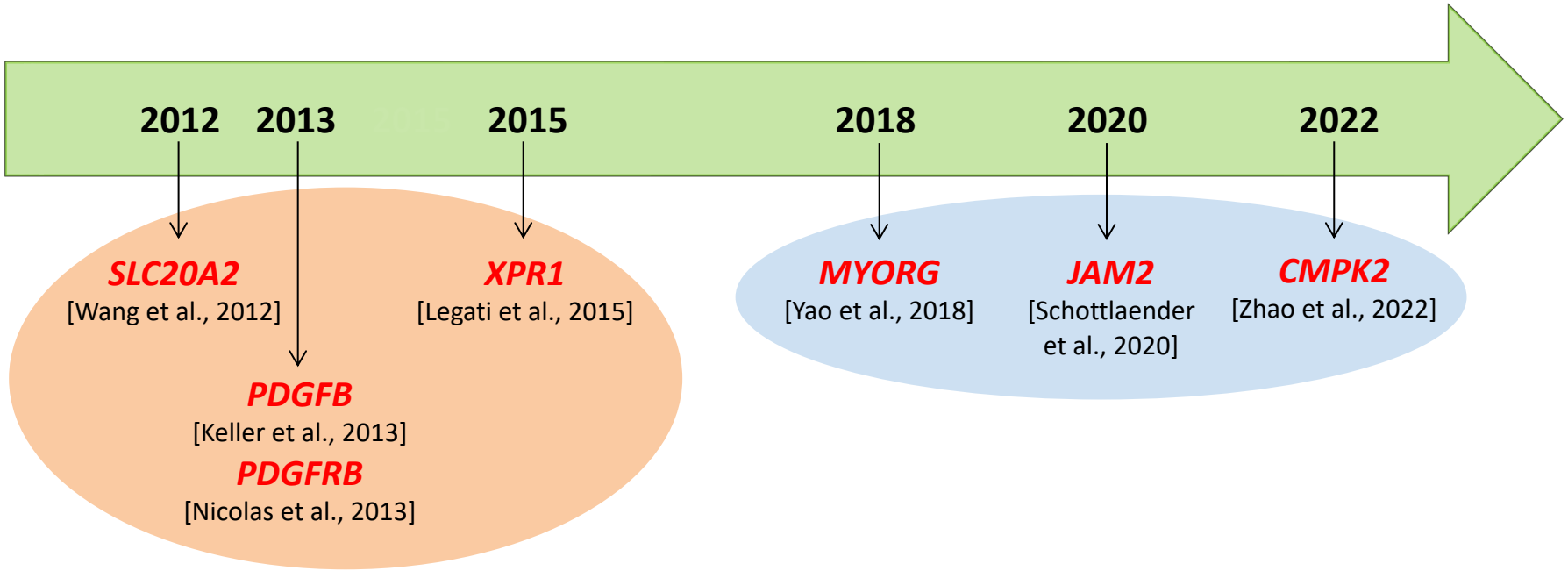
Secondary outcome measures

Mobility, Neuropsychiatric symptoms , Activities of daily living , Quality of life, Brain calcification volume

How Fahr have we come

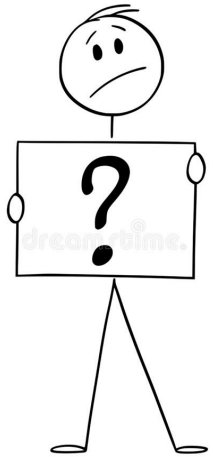


Genetics of Fahr's Disease



Gene	Inheritance	Frequency
SLC20A2	AD	~40%
PDGFB	AD	~11%
PDGFRB	AD	~2%
XPR1	AD	~2%
MYORG	AR	~12%
JAM2	AR	N.A.
CMPK2	AR	N.A.

~55%

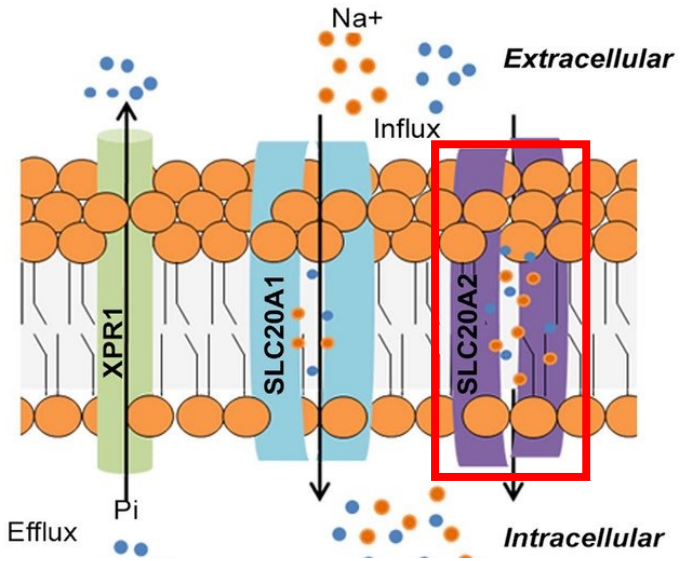


~1/3 cases

SLC20A2

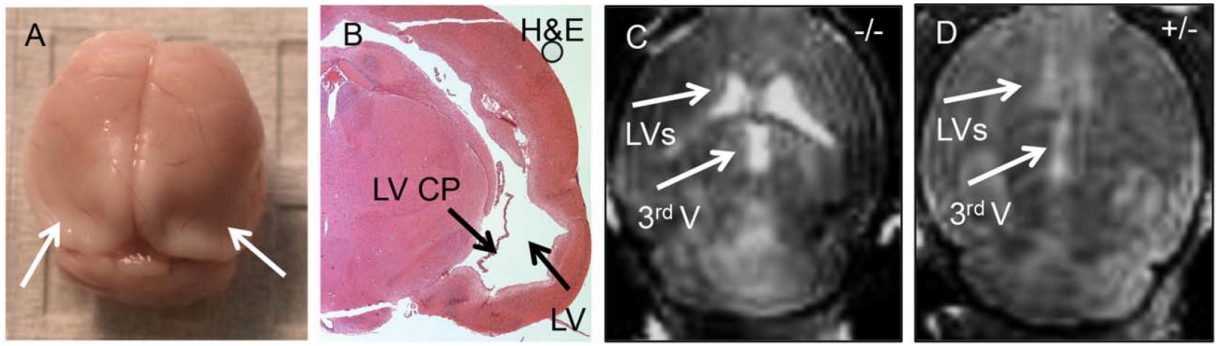
[Chr 8p11.21]

- Encodes the type III Na^+-dependent inorganic phosphate (Pi) transporter 2 (**PiT2**)
- PiT2 is a transmembrane **Na^+/Pi cotransporter**
- **Loss of function** is the most probable causal mechanism



Neurons, astrocytes and endothelial cells

SLC20A2 -/- *SLC20A2 +/-*



Mouse model

› Brain Pathol. 2017 Jan;27(1):64-76.

PDGFB

[Chr 22q13.1]

- Encodes a ligand for PDGFRB (platelet derived growth factor beta – PDGFB)
- Mutations are predicted to impair PDGFB secretion

PDGFRB

[Chr 5q32]

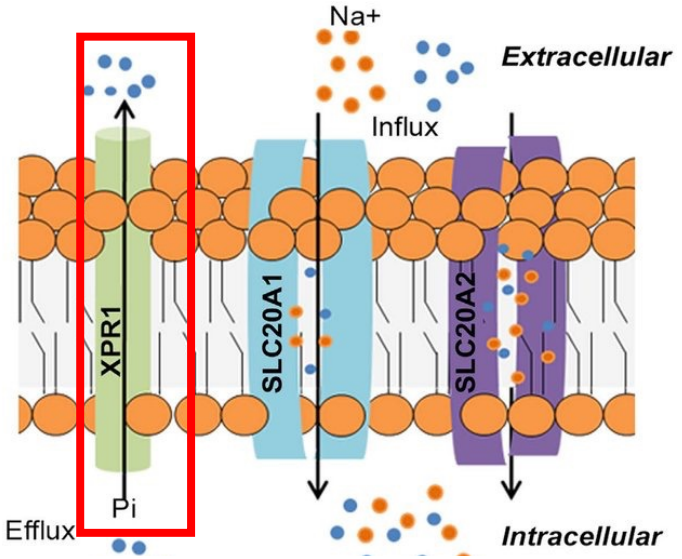
- Encodes the platelet derived growth factor receptor beta (PDGFB)
- Mutations are predicted to impair PDGFB signalling

- Signalling axis is essential during embryonic development and early post-natal life in regulating pericyte formation and recruitment along newly forming vessels.
- Animal models lacking PDGFB/PDGFRB expression show reduced pericyte coverage of blood vessels.
- During adult life, pericytes exert several functions in the regulation of the BBB at the NVU, including blood flow regulation, possible formation of endothelial junctions, and astrocytic end-foot polarization.

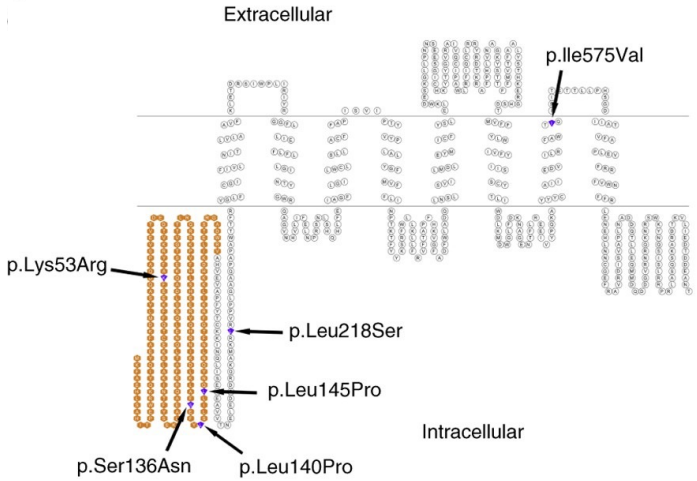
XPR1

[Chr 1q25.3]

- Encodes a cell surface multipass membrane protein initially identified as the mammalian receptor for xenotropic murine leukemia viruses
- Mediates phosphate export



Neurons, astrocytes and endothelial cells



MYORG

[Chr 9p13.13]

- Encodes a **transmembrane glycosidase localized to endoplasmic reticulum**
- Expressed in astrocytes localized to the endoplasmic reticulum and playing a role as glycosyl hydrolase.
- Function unknown

JAM2

[Chr 1q25]

- Encodes **junctional adhesion molecule 2**, which is highly expressed in neurovascular unit-related cell types (endothelial cells and astrocytes) and predominantly localizes on the plasma membrane.
- Junctional adhesion molecules play an important role in the regulation of cell polarity, endothelium permeability, and leukocyte migration and the BBB function.
- *JAM2* disease-causing variants may result in impaired cell-to-cell adhesion function and altered integrity of the NVU ultimately leads to BBB dysfunction and brain calcification at this level.

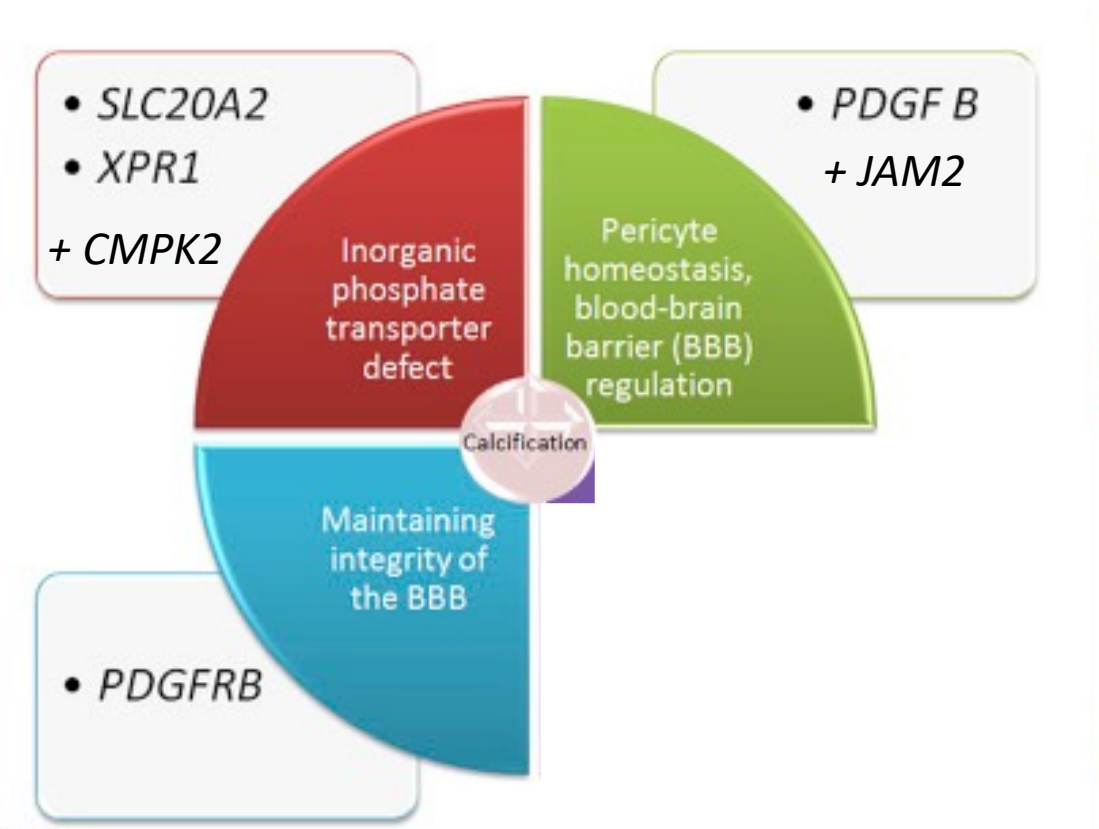
CMPK2

[Chr 2p25.2]

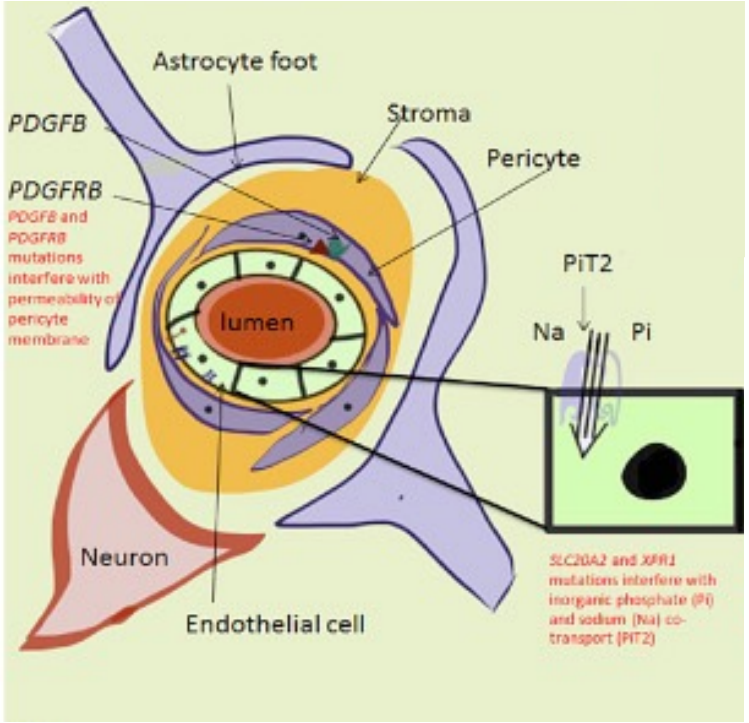
- *CMPK2* is highly expressed in neurons and endothelial vascular cells.

- Its reduced expression in a mutant animal knock-out mouse model has been shown to lead to a reduced number of mitochondrial DNA copies, down-regulated mitochondrial proteins, reduced ATP production, and elevated intracellular inorganic phosphate (Pi) level, causing progressive intracranial calcification.

What mechanism(s) cause(s) Fahr's Disease



The hallmarks of Fahr's disease are hydroxyapatite deposits in the basal ganglia and other brain regions



1) Calcium-Phosphate homeostasis

2) Maintaining the integrity of the blood brain barrier

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Quiz 1

Which of these structures is not affected by calcium deposition in Fahr's disease?

A. Basal ganglia

B. Thalamus

C. Subcortical white matter

D. Cerebellum

E. Optic nerve

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Quiz 2

Which of these is not a cause of brain calcifications?

A. PTH deficiency

B. CNS tuberculosis

C. Hypermanganesemia

D. Carbon monoxide poisoning

E. Cockayne syndrome

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Quiz 3

Which of these Fahr's disease-related genes are associated with autosomal recessive mode of inheritance?

A. *SLC20A2*, *PDGFB*

B. *SLC20A2*, *XPR1*

C. *SLC20A2*, *PDGFRB*

D. *JAM2*, *MYORG*

E. *XPR1*, *JAM2*

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Key conclusions

- Fahr's Disease is a rare **genetic neuropsychiatric disorder** characterised by **bilateral, symmetrical, progressive** calcifications in the brain (mainly basal ganglia, thalamus, cerebellum and subcortical white matter)

- The hallmarks of Fahr's disease are hydroxyapatite deposits in the basal ganglia and other brain regions

- Genes associated with Fahr's disease with AD mode of inheritance are *SLC20A2*, *PDGFB*, *PDGFRB*, *XPR1*. Genes associated with Fahr's disease with AR mode of inheritance are *MYORG*, *JAM2*, *CMPK2*.

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Thanks for your attention

Questions or interest in research studies?

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