



## Review

## Genetics and molecular biology of brain calcification

Hao Deng<sup>a,b,\*</sup>, Wen Zheng<sup>a,b,1</sup>, Joseph Jankovic<sup>c</sup><sup>a</sup> Department of Neurology, Third Xiangya Hospital, Central South University, Changsha, China<sup>b</sup> Center for Experimental Medicine, Third Xiangya Hospital, Central South University, Changsha, China<sup>c</sup> Department of Neurology, Baylor College of Medicine, Houston, TX, USA

## ARTICLE INFO

## Article history:

Received 18 November 2014

Received in revised form 14 April 2015

Accepted 15 April 2015

Available online 20 April 2015

## Keywords:

Brain calcification

Fahr's disease

Hypoparathyroidism

Genetics

Molecular biology

## ABSTRACT

Brain calcification is a common neuroimaging finding in patients with neurological, metabolic, or developmental disorders, mitochondrial diseases, infectious diseases, traumatic or toxic history, as well as in otherwise normal older people. Patients with brain calcification may exhibit movement disorders, seizures, cognitive impairment, and a variety of other neurologic and psychiatric symptoms. Brain calcification may also present as a single, isolated neuroimaging finding. When no specific cause is evident, a genetic etiology should be considered. The aim of the review is to highlight clinical disorders associated with brain calcification and provide summary of current knowledge of diagnosis, genetics, and pathogenesis of brain calcification.

© 2015 Elsevier B.V. All rights reserved.

## Contents

|  |    |
|--|----|
| 1. Introduction .....  | 21 |
| 2. Primary familial brain calcification.....                                   | 22 |
| 2.1. 8p11.21 and the <i>SLC20A2</i> gene.....                                  | 22 |
| 2.2. 22q13.1 and the <i>PDGFRB</i> gene, 5q32 and the <i>PDGFRB</i> gene ..... | 22 |
| 3. Hypoparathyroidism .....  | 23 |
| 3.1. 11p15.2 and the <i>PTH</i> gene .....                                     | 23 |
| 3.2. 3q21.1 and the <i>CASR</i> gene.....                                      | 24 |
| 3.3. 19p13.3 and the <i>GNA11</i> gene .....                                   | 24 |
| 3.4. 6p24.2 and the <i>GCM2</i> gene.....                                      | 24 |
| 4. Pseudohypoparathyroidism.....   | 24 |
| 4.1. 20q13.32 and the <i>GNAS</i> gene .....                                   | 25 |
| 5. Mitochondrial encephalomyopathies .....                                     | 25 |
| 6. DiGeorge syndrome .....   | 25 |
| 6.1. 22q11.21 and the <i>TBX1</i> gene.....                                    | 25 |
| 7. Hypoparathyroidism, sensorineural deafness, and renal anomaly syndrome..... | 26 |
| 7.1. 10p14 and the <i>GATA3</i> gene .....                                     | 26 |
| 8. Kenny–Caffey syndrome.....  | 26 |
| 8.1. 1q42.3 and the <i>TBCE</i> gene.....                                      | 26 |
| 8.2. 11q12.1 and the <i>FAM111A</i> gene .....                                 | 26 |
| 9. Band-like calcification with simplified gyration and polymicrogyria .....   | 26 |
| 9.1. 5q13.2 and the <i>OCNL</i> gene .....                                     | 27 |
| 10. Proliferative vasculopathy and hydranencephaly–hydrocephaly syndrome ..... | 27 |

\* Corresponding author. Present address: Center for Experimental Medicine, Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Changsha, Hunan 410013 China. Tel.: +86 731 88618372; fax: +86 731 88618339.

E-mail address: [hdeng008@yahoo.com](mailto:hdeng008@yahoo.com) (H. Deng).

<sup>1</sup> Hao Deng and Wen Zheng contributed equally to this work.

|       |  |    |
|-------|--|----|
| 10.1. | 14q24.3 and the <i>FLVCR2</i> gene .....                                   | 27 |
| 11.   | Aicardi–Goutieres syndrome .....   | 27 |
| 11.1. | 3p21.31 and the <i>TREX1</i> gene .....                                    | 27 |
| 11.2. | 13q14.3 and the <i>RNASEH2B</i> gene .....                                 | 27 |
| 11.3. | 11q13.1 and the <i>RNASEH2C</i> gene .....                                 | 28 |
| 11.4. | 19p13.2 and the <i>RNASEH2A</i> gene .....                                 | 28 |
| 11.5. | 20q11.23 and the <i>SAMHD1</i> gene .....                                  | 28 |
| 11.6. | 1q21 and the <i>ADAR</i> gene .....  | 28 |
| 11.7. | 2q24.2 and the <i>IFIH1</i> gene .....                                     | 28 |
| 12.   | Coats plus syndrome .....  | 28 |
| 12.1. | 17p13.1 and the <i>CTC1</i> gene .....                                     | 28 |
| 13.   | Labrune syndrome .....   | 28 |
| 14.   | Nasu–Hakola disease .....  | 28 |
| 14.1. | 6p21.1 and the <i>TREM2</i> gene .....                                     | 29 |
| 14.2. | 19q13.12 and the <i>TYROBP</i> gene .....                                  | 29 |
| 15.   | Autoinflammation, lipodystrophy, and dermatosis syndrome .....             | 29 |
| 15.1. | 6p21.32 and the <i>PSMB8</i> gene .....                                    | 29 |
| 16.   | Carbonic anhydrase 2 deficiency .....                                      | 29 |
| 16.1. | 8q21.2 and the <i>CA2</i> gene .....                                       | 29 |
| 17.   | Cockayne syndrome .....  | 29 |
| 17.1. | 10q11.23 and the <i>ERCC6</i> gene, 5q12.1 and the <i>ERCC8</i> gene ..... | 30 |
| 18.   | Down syndrome .....  | 30 |
| 19.   | Biotinidase deficiency .....   | 30 |
| 19.1. | 3p25.1 and the <i>BTD</i> gene .....                                       | 30 |
| 20.   | Dihydropteridine reductase deficiency .....                                | 30 |
| 20.1. | 4p15.32 and the <i>QDPR</i> gene .....                                     | 30 |
| 21.   | Diffuse Neurofibrillary Tangles with Calcification .....                   | 30 |
| 22.   | Leukodystrophies .....   | 30 |
| 23.   | Additional gene mutations associate with brain calcification .....         | 32 |
| 24.   | Conclusions .....  | 32 |
|       | Review criteria .....  | 32 |
|       | Competing interests .....  | 33 |
|       | Acknowledgments .....  | 33 |
|       | References .....   | 33 |

## 1. Introduction

Brain calcification may be encountered as an incidental neuroimaging finding in otherwise normal individuals or may be seen in patients with a variety of neurological or metabolic disorders including secondary hypoparathyroidism and mitochondrial diseases, numerous hereditary and non-hereditary syndromes, and other acquired conditions including brain infection, trauma, and toxicity related to manganese, iron, lead, and carbon monoxide (Bekiesinska-Figatowska et al., 2013; Jankovic, 2005; Nicolas et al., 2013a). The prevalence of brain calcification ranges from 1% in young subjects to over 20% in the elderly (Forstl et al., 1992; Yamada et al., 2013), but only a minority of brain calcifications can be attributed to genetic etiology (Sobrido et al., 1993; Taglia et al., 2014). Brain calcification usually occurs bilaterally, and is often detected in basal ganglia, dentate nucleus, thalamus, and centrum semiovale (Kiroglu et al., 2010). Although the epidemiology of brain calcification has not been well studied, it has been reported to occur in 0.36% of 12,000 unselected consecutive patients, with two-thirds of the cases older than 60 years (Brannan et al., 1980). Based on examinations of computed tomography (CT) scans of the head, the frequency of brain calcification in the elderly is approximately 20%, typically seen as punctuate lesions, but in 1–2% calcium deposits present as patchy lesions (Yamada et al., 2013). In autopsy cases, the frequency of brain calcification was reported to range from 40% to 72%, and microscopic calcifications were even more frequent (Manyam, 2005). Patients with brain calcification may exhibit neurological and/or psychiatric symptoms with diverse ages at onset and varying severity, whereas other individuals with brain calcification remain asymptomatic throughout life (Manyam, 2005; Yamada and Hayashi, 2000). The clinical manifestations include

movement disorders such as parkinsonism, tremor, chorea, thetosis, hyperkinetic mutism, and ataxia. Other neurological disorders associated with brain calcifications include seizures or stroke like events, and a variety of cognitive and psychiatric symptoms such as dementia, psychosis, mood and other behavioral disorders (Calabro et al., 2013; Chen et al., 2013; Inbody and Jankovic, 1986; Mehanna and Jankovic, 2013).

The brain calcification deposits usually contain calcium hydroxylapatite ( $\text{Ca}_{10}[\text{PO}_4]_6[\text{OH}]_2$ ) as a major component; other components may include zinc, iron, and magnesium (Beall et al., 1989; Duckett et al., 1977). The mechanism underlying calcification and the reasons for the selective vulnerability of the basal ganglia to calcium deposition are not well understood. It is also not known why intracellular calcium and calcium-binding proteins, such as calbindin- $\text{D}_{28\text{K}}$ , are involved in selective neurodegeneration involving primarily the substantia nigra of patients with Parkinson's disease, the striatum of patients with Huntington's disease, and the nucleus basalis of patients with Alzheimer's disease (Damier et al., 1999a,b; Surmeier, 2007). It is possible, however, that damage to the media and intima of cerebral vessels including small arteries, veins, and endothelial cells of capillaries and arterioles leads to increased vascular permeability which leads to leakage of plasma proteins into the extravascular space. Deposits of electron-dense calcium bodies in the capillary walls and the parenchyma result in calcification (Tsuchiya et al., 2011; Yamada et al., 2013). Indeed, brain calcifications have been noted in patients with vascular parkinsonism and other vascular brain disorders (Mehanna and Jankovic, 2013; Ramonet et al., 2006).

Imaging studies are critical in the diagnosis of disorders associated with brain calcifications. Although significant clinical differences exist between all these differential diagnoses, calci-

Download English Version:

<https://daneshyari.com/en/article/1902182>

Download Persian Version:

<https://daneshyari.com/article/1902182>

[Daneshyari.com](https://daneshyari.com)