

**Cerebral aneurysms and cerebrovascular abnormalities  
reported in four patients with Floating-Harbor syndrome;  
implications for clinical care.**

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## **ABSTRACT**

Floating-Harbor syndrome (FHS) is a rare multi-systemic heritable disorder caused by variants in the *SRCAP* gene. Most individuals with FHS have characteristic facial features, short stature with delayed bone age, and speech and language impairment. Although FHS has been likely under-diagnosed due to a combination of lack of recognition of the clinical phenotype and limited access to genomic testing, it is a rare condition with around 100 individuals reported in the medical literature. Case series have been biased towards younger individuals (vast majority <20 years of age) meaning that it has been challenging to provide appropriate and accurate medical advice for affected individuals in adulthood.

We report two young adults with FHS who presented with intracerebral haemorrhage likely secondary to ruptured cerebrovascular aneurysms, with devastating consequences, making a total of four FHS patients reported with significant cerebrovascular abnormalities. Three of these four patients had hypertension in adulthood, at least one in conjunction with normal renal structure and function. We explore the possible relationships between hypertension, renal pathology and aneurysms in the context of FHS, and consider mechanisms through which disruption of the *SRCAP* protein may lead to vascular pathology.

We recommend that clinicians should have a particularly low threshold to investigate symptoms suggestive of cerebrovascular disease in FHS. We advise that patients with FHS should have regular blood pressure monitoring, renal ultrasound at diagnosis with a repeat in adulthood and timely investigation of symptoms that may be neurological in origin. For patients with FHS, particularly those who are known to have hypertension in adulthood, we advise that clinicians should consider undertaking at least one MRA (Magnetic Resonance Imaging with Angiography) to check for cerebral aneurysms.

**KEYWORDS:** Floating-Harbor syndrome; cerebral aneurysm; subarachnoid haemorrhage; cerebrovascular disease; hypertension; neuroradiological screening

## INTRODUCTION

### ***Floating-Harbor syndrome***

Floating-Harbor syndrome (FHS) is a rare neurodevelopmental genetic condition associated with mutations in the *SRCAP* gene which encodes the SNF2-related chromatin-remodelling ATPase (*SRCAP*) protein (2, 3). Inheritance is autosomal dominant, though the vast majority of reported cases involve *de novo* mutations. *SRCAP* is thought have widespread effects on cell growth and division, affecting transcription, repair and replication of DNA via a role in chromatin remodelling (4). Most individuals with FHS have the typical features, described in **Box 1** (1) . Medical conditions previously associated with the condition have previously been summarised by Reschen *et al.*, and include renal pathology such as polycystic disease and hydronephrosis, growth hormone deficiency, precocious puberty, middle ear and ocular abnormalities (5).

Two single patients with FHS have been previously reported with cerebrovascular aneurysms (6, 7); here we present a further two patients with similar findings and consider what impact these data have on clinical management of patients with FHS.

#### **Box 1: The Floating-Harbor Phenotype**

- Characteristic facial features **are the most distinctive features of the syndrome**; triangular facies, a broad-based long nose with narrow bridge and overhanging tip, deep set eyes, low set ears and short philtrum
- Persistent short stature (final adult height typically 140-155cm), **though this may be dependent on whether growth hormone treatment was given.**
- Speech development **is usually** delayed, typically expressive>receptive, dysarthria and verbal dyspraxia, hypernasality and a high-pitched voice **often observed.**
- Low birth weight with a normal head circumference **is commonly observed**
- Early feeding difficulties and poor postnatal growth are often seen
- Bone age **is often** significantly delayed in early childhood but tends to normalise between the ages of 6-12 years.
- Skeletal abnormalities **are variable but** include brachydactyly, clinodactyly, prominent joints and swelling of fingertips (that appear clubbed), and short broad thumbs.
- Intellectual impairment is invariably present but typically ranges from mild to moderate. Gross and fine motor development usually normal.
- Challenging behaviour can be a feature with ADHD spectrum disorders, and sometimes aggressive and violent episodes that can be difficult to manage.

**For detailed phenotyping data for FHS, see the analysis of 52 patients with FHS by Nikel *et al.*, (1)**

## **CLINICAL REPORT**

We present two young adults with FHS with intracerebral haemorrhage in adulthood likely secondary to cerebral aneurysm. In addition, we performed a literature review and summarise two previously published reports, each of a single patient with FHS and cerebrovascular aneurysm presenting in young adulthood. Our patients are described below, and the available data from all four patients is summarised in **Table 1**.

**Patient 1:** A female diagnosed with FHS in childhood, with typical features of the condition (**Table 1**). She was diagnosed with hypertension as a young adult; this was controlled with ramipril. She had no known renal problems but did not undergo renal ultrasound. At 35 years she presented to medical services with a suspected first seizure (a sudden onset rigid and unresponsive episode) and unconsciousness, requiring ventilatory support. Computer Tomography (CT) scans showed a large intracerebral haemorrhage suspected to be secondary to a left middle cerebral artery aneurysm (**Figure 1A-C**). After discussion with the family regarding the catastrophic impact of this, it was agreed that further medical treatment would not be of benefit and the patient later died. A post mortem was not conducted.

**Patient 2:** A male diagnosed with FHS in childhood, with typical features of the condition (**Table 1**). He had a normal renal ultrasound at 21 years of age and normal renal function. As a young adult he developed hypertension; this was controlled with ramipril. At 34 years he was found unresponsive following collapse, after previously being seen 12 hours earlier. Head CT scans showed right temporal subarachnoid and intracerebral haemorrhage without hydrocephalus that was secondary to a right middle cerebral artery aneurysm. Treatment was with embolisation (coiling) of the aneurysm together with craniotomy for evacuation of the hematoma (**Figure 1D-F**). Post-operatively there was temporary left-sided weakness and visual neglect with a post-operative right frontal lobe infarction; these clinical deficits subsequently resolved following rehabilitation. Nine months later the patient presented with a generalised tonic-clonic seizure and was commenced on long term anti-epileptic medication.

Figure 1: Neuroimaging findings (CT scans) from Patient 1 and 2

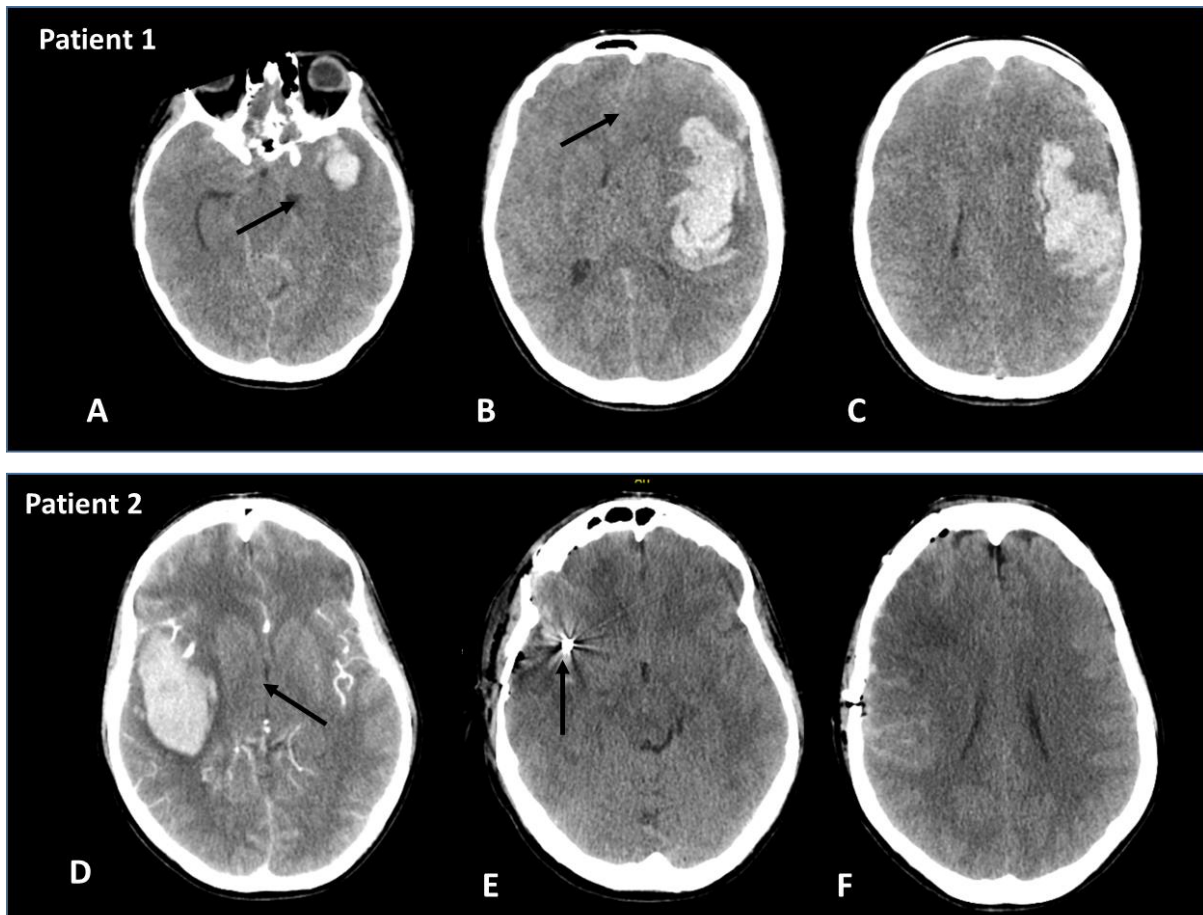


Figure 1: Upper row, axial unenhanced CT images of the brain in Patient 1, showing a large acute hematoma involving left anterior-temporal, insular and frontal lobes, with mass effect and associated uncal and subfalcine herniation (arrows in A and B respectively). On review of the unenhanced CT images by a specialist neuroradiologist (FD), an aneurysmal bleed from the left middle cerebral artery was suspected given the location of blood; a structural vascular lesion could not be identified prior to death.

Lower row, axial enhanced CT images (D) and unenhanced CT images (E and F) of the brain in Patient 2, demonstrating large right fronto-insular hematoma (D) with mass effect on the midline and compression of the third ventricle (arrow in D). The hematoma was surgically evacuated (E and F) and found to be caused by an aneurysm of the middle cerebral artery that was subsequently coiled (arrow in E).

**Table 1: Comparison of our two patients with two previously published patient reports**

|  | <b>Patient 1<br/>(35y female - deceased)</b>  | <b>Patient 2<br/>(34y male)</b>   | <b>Patient 3<br/>(22y female)</b>   | <b>Patient 4<br/>(35y female)</b>  |
|--|---|---|---|--|
| <b>Previously reported?</b>            | No  | No  | Yes<br><b>(Paluzzi et al 2008) (7)</b>  | Yes<br><b>(Coughlin et al 2017) (6)</b>  |
| <b>Pregnancy</b>                       | Nil noted. Born at term   | Nil noted. Born at term   | Nil noted. Born at term   |  |
| <b>Birth weight</b>                    | 2.95kg z = -1.1   | 2.72kg z = -1.9   | 3.01kg z = -0.98  |  |
| <b>Feeding</b>                         | Poor feeding in first year of life  |   |   |  |
| <b>Facial features</b>                 | Triangular facies, broad prominent nose, short philtrum, small posteriorly rotated ears, thin lips, deep set eyes, crowded dentition                          | Triangular facies, broad prominent nose, short philtrum, low set posteriorly rotated ears.  | Prominent nose, broad nares, short philtrum, wide mouth, small chin, deep set eyes.   | Reported to be consistent with Floating-Harbor syndrome  |
| <b>Limb features</b>                   | Broad thumbs and halluces, spindle-shaped fingers, prominent interphalangeal joints   | Small hands, BL 5 <sup>th</sup> finger clinodactyly, fingers appeared clubbed, congenital hip dysplasia   | Leg length discrepancy 1cm with intermittent limp. BL clinodactyly in hands.  |  |
| <b>Growth</b>                          | At 15y: Height 139.8cm, z= -3.6, weight 30kg, z= -4.2, OFC 51.8cm, z= -2.4  | Adult: Height 154.5cm, z= -3.3, weight 54.4kg, z= -2.0, OFC 58cm, z= 0.6.   |   |  |
| <b>Development and learning</b>        | Mild learning difficulties, speech delay, expressive more than receptive  | Speech delay, expressive more than receptive language. Normal motor development. Attended special educational needs school  | Delayed speech and language, expressive more than receptive. Normal motor development   |  |
| <b>Behaviour</b>                       | Unpredictable volatile episodes   |   |   |  |
| <b>Skeletal findings</b>               | Delayed bone age of 1y at 2 y chronological age. 1 <sup>st</sup> and 2 <sup>nd</sup> phalanges short.   | Bone age 2y6m at 6y6m chronological age   | Bone age of 1y at 2y chronological age.   |  |
| <b>Hypertension and renal findings</b> | Adult-onset hypertension, controlled with ramipril daily dose. Renal USS not performed prior to death.  | Adult-onset hypertension controlled with ramipril daily dose. Renal USS aged 21y – normal. Repeat advised in light of cerebrovascular disease.                                  | Unknown   | Hypertension documented, additional details unknown  |
| <b>Additional findings</b>             | Osteoporosis. Strabismus, coeliac disease. Growth hormone measures within normal limits   | Mild hearing loss. Treated with growth hormone from 10-12 years   | Absence seizures confirmed on EEG at 4y old. Treated with growth hormone from 6y. Avascular necrosis L femoral epiphysis at 15 years  | Hyperlipidaemia, allergic rhinitis   |
| <b>Cerebrovascular findings</b>        | Large intracerebral haemorrhage suspected to be secondary to rupture of left middle cerebral artery aneurysm. Evidence of uncus herniation and midline shift. | Right temporal subarachnoid and intracerebral haemorrhage without hydrocephalus secondary to rupture of right middle cerebral artery aneurysm. Treated with coiling of aneurysm | Blood seen in the occipital horn of the left lateral ventricle suggestive of subarachnoid haemorrhage, secondary to left internal carotid artery aneurysm rupture. Treated with embolization. | MoyaMoya appearance and basilar apex aneurysm. Treated with coiling for aneurysm prior to rupture. |
| <b>Genetic testing</b>                 | NM_006662.3: SRCAP: c.7275_7276delAC;p.(Pro2426Thrfs*16)  | NM_006662.3: SRCAP: c.7303C>T; p.(Arg2435*)   | Karyotype 46XX. No documented gene sequencing   | NM-006662.3: SRCAP: c.7273dupA; p.(Thr2425Asnfs*18)  |

Abbreviations: OFC – orbitofrontal circumference, BL – bilateral, y –year, m - month

## DISCUSSION

Four adult patients have now been reported with cerebrovascular disease co-existing with FHS; this has involved identification of intracerebral haemorrhage or cerebral aneurysms in all cases and an additional concern regarding a MoyaMoya phenotype in one case. Three of four patients were known to have hypertension requiring treatment in adulthood. None were found to have renal pathology though full clinical details are not available for the previously published two cases. Cerebrovascular aneurysms are rare in young adults and have a high mortality. Given that aneurysms are amenable to detection and intervention prior to rupture and that this improves outcome, we discuss appropriate recommendations for clinical care of patients with FHS.

### ***SRCAP and cerebrovascular disease***

Genome and exome sequencing of FHS patients has identified dominant negative mutations of the *SRCAP* gene as the predominant cause of the syndrome (8). The SRCAP protein is part of a chromatin remodelling complex that is highly conserved across species. Such complexes are capable of altering chromatin organisation through nucleosome displacement which then alters interaction between histones and DNA and alters the accessibility of nucleosomal DNA to DNA-binding proteins that have a role in transcription, repair and replication of DNA (9). Missense variants likely exert pleiotropic effects via an impact on chromatin and nucleosome organisation in addition to transcription and downstream signalling pathways.

Several recurrent mutations have been reported in *SRCAP*, such as those in exon 34 of the gene, including the mutation we describe in patient two, and these are thought to lead to protein truncation, leading to loss of terminal AT-hook DNA-binding motif domains (8). The AT-hook motif is found in many DNA-binding proteins that have a key role in chromatin



organisation and gene expression, and disruption of this motif is predicted to alter protein function (10) although the mechanism of this is not yet known.

Independently to chromatin organisation, *SRCAP* is also thought to also exert impact as a transcriptional regulator through its activation of the cAMP response-element-binding protein (CREBBP) which in turn activates a number of transcription factors and mediates widespread gene expression (11). *SRCAP* is therefore able to influence multiple signalling pathways, such as the Notch signalling pathway and steroid-receptor mediated transcription pathways, in addition to its role in chromatin remodelling(12, 13). There is considerable evidence that Notch signalling is critical to vascular development and has a role in vessel homeostasis in adults, including vascular repair (14). Disruption of Notch signalling has already been implicated in the aetiology of intracranial aneurysms and arteriopathy, for example in Alagille syndrome (15).

Rubenstein-Taybi syndrome is a rare condition caused by mutations in the *CREBBP* gene which is closely-related to *SRCAP*, and shares considerable phenotypic overlap with FHS. Of note, both renal tract malformations and vascular pathology such as cerebral aneurysms have previously been reported in Rubenstein-Taybi syndrome, providing further evidence for a link between *SRCAP*, *CREBBP* and vasculopathy (16).

In summary, *SRCAP* is well-placed to have diverse effects on cell growth including vascular development and homeostasis via its role in chromatin remodelling. In addition, there are other plausible mechanisms by which disruption of *SRCAP* function may lead to vascular pathology, through transcription activation via CREBBP or downstream effects on Notch signalling pathways. Additional functional studies are needed to explore these hypotheses further, for example by measuring the impact of the presence of the truncated *SRCAP* protein on signalling pathways in cell lines derived from patients with FHS.

## **The role of hypertension in cerebrovascular disease**

Three of the four described FHS patients with cerebrovascular disease were known to have hypertension in adulthood and this was sufficient to require pharmacological treatment in our two patients. Renal pathology that may account for hypertension has previously been reported in some patients with FHS, for example polycystic kidney disease (5). However, the aetiology of hypertension was not known for our patients – patient one had not undergone renal investigations prior to death, whereas patient two had a normal renal ultrasound in adulthood and has normal renal function.

The relationship between hypertension and cerebrovascular aneurysms is complex and may be different for individuals with FHS compared with the general population. Data assessing the aetiology and consequences of hypertension in patients with FHS with hypertension is minimal. However, of note recent large meta-analyses have indicated that in the general population, hypertension is not a risk factor for *development* and *growth* of cerebral aneurysms but that it is a risk factor for aneurysmal *rupture* and intracerebral haemorrhage (17).

### **Cerebrovascular aneurysms**

Although intracranial aneurysms are an occasional incidental finding in post-mortem studies of the older population, they are very rare in children and young adults (18). Rupture of cerebral aneurysms typically results in subarachnoid and intracerebral haemorrhage, often with resulting raised intracranial pressure and associated mortality. Prior to rupture, a significant proportion (>50% in one case series) of cerebral aneurysms are completely asymptomatic (19), providing support for the use of screening neuroimaging, however the exact role of serial neuroimaging is not yet well-defined.

The risk posed by un-ruptured cerebral aneurysms has been widely debated; recent studies suggest that the risk is higher for posterior versus anterior circulation aneurysms, and that the five year cumulative rupture rate increases with aneurysm size, more rapidly above 7mm

diameter to as much as 40% for aneurysms over 25mm (20). Critical review of the literature indicates that aneurysms larger than 5mm in patients under 60 years of age should be seriously considered for treatment, whereas small aneurysms under 5mm can be managed conservatively, typically with anti-hypertensives and smoking cessation where relevant (21).

### ***Cerebrovascular disease, short stature and growth hormone***

Cerebral aneurysms and cerebrovascular disorders such as MoyaMoya syndrome have been previously reported in other syndromes that also involve short stature and growth disturbance as occurs in FHS, for example in microcephalic osteodysplastic primordial dwarfism type 2 (MOPD II) (22).

This has often been attributed to shared genetic effects on both cell growth and vascular development in developmental disorders. MOPD II involves biallelic mutations in the gene *PCNT*, which encodes pericentrin, a centrosomal protein important for cell cycle progression. Similar to the Notch signalling proteins, pericentrin is also thought to be involved in vascular homeostasis, particularly with regard to inflammatory and infection-related environmental insults (23), which may explain the link with cerebrovascular aneurysms in both FHS and MOPDII.

However, it is also worth noting that many patients with short stature such as occurs in both FHS and MOPDII are treated with growth hormone. An association has been suggested between cerebral aneurysms and hypersecretion of growth hormone from pituitary adenomas, via growth hormone-induced changes in collagen in cerebral vessels (24), suggesting that there could be secondary effects of growth hormone therapy on vascular structure. However, only two of the patients presented herein received growth hormone therapy for short stature, suggesting this is not a consistent association.

### ***Implications for screening in FHS***

The data described above regarding the presence of both renal and cerebrovascular pathology in FHS, though not necessarily co-existing within an individual, provide strong evidence to suggest that regular blood pressure monitoring and a renal ultrasound scan at diagnosis and repeated in adulthood should be part of routine clinical care for FHS patients.

In addition, identification and treatment of asymptomatic unruptured aneurysms with neuroimaging screening may benefit this group of patients, particularly if hypertension has been identified since it is a known risk factor for aneurysm rupture. We recommend that as a minimum, clinicians should request neuroimaging investigation of patients with FHS who develop any signs suggestive of cerebrovascular disease, such as headache, visual disturbance, seizures and focal neurological deficits. A high level of patient awareness is required to permit individuals to seek appropriately urgent medical attention in such circumstances; for patients with intellectual disability and speech impairments, accurate and timely communication of symptoms to a medical professional may be difficult.

The associated costs and impact of regular neuroimaging need to be considered; this is challenging for rare disorders like FHS where little data exists to assist. As a comparison, it has recently been recommended that patients with MOPD II, the short stature syndrome described above, should be offered neuroimaging surveillance for cerebrovascular disease, with magnetic resonance imaging every two years in adulthood (25). MRI with magnetic resonance angiography (MRA) would be in general favoured for screening over CT angiography. This avoids repeated radiation exposure and the use of contrast necessary for CT angiography. MRA is considered an appropriate method for detection of asymptomatic arteriopathy and the cost of MRA screening is at least partially offset by the high treatment costs associated with the high morbidity that results from untreated cerebrovascular disease.

We advise that serious consideration be given to MRA serial screening for adults with FHS, particularly in patients with co-existing hypertension, and recommend that at least one MRA scan be undertaken in adult FHS patients with hypertension. More long term observational data are required to determine whether serial MRA screening is indeed beneficial and to determine optimal intervals between scans, as normal vasculature at one time point does not exclude subsequent development of aneurysms.

### **Conclusions**

We report two further patients with FHS and cerebrovascular bleeds making a total of four published patients with FHS co-existing with cerebrovascular abnormalities. While three of these four patients were reported to have hypertension requiring medical treatment, none were known to have renal pathology although limited data was available for some patients. Obtaining adequately-powered prospective case control data regarding associated medical conditions is difficult for rare disorders. There is currently insufficient evidence in the literature to understand the exact relationship between hypertension, renal pathology and cerebrovascular aneurysms in FHS. However, the existing data suggests that these are important associations with FHS.

We recommend that clinicians and patients should have raised awareness of symptoms such as sudden onset headache, visual disturbance, seizures or focal neurological deficits with a low threshold to investigate such symptoms promptly with neuroimaging. This requires both patient and clinician awareness to ensure this occurs in the required rapid timeframe. In addition, given that renal pathology and hypertension are frequently asymptomatic, we continue to advise blood pressure monitoring at least annually and a baseline renal ultrasound at diagnosis, repeated in adulthood. Following the reported cases of cerebral aneurysm in patients with FHS, and that aneurysms are usually asymptomatic prior to rupture we suggest that additional neuroimaging screening could benefit this cohort of

patients, particularly if there is evidence of hypertension. We advise that at least one MRA scan is undertaken in patients with FHS and co-existing hypertension.

A specific link between *SRCAP* mutations and vascular pathology has not yet been confirmed. Further studies are required to identify how truncated proteins interact with wild-type *SRCAP* protein to disrupt its binding to DNA and chromatin targets, and to understand the further downstream effects on transcription activation and signalling pathways such as Notch. Additional *in vitro* functional studies of *SRCAP* alongside long-term observational follow up of patients with FHS will help to expand our understanding of the relationship between hypertension, cerebrovascular disease and renal pathology in this patient group.

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