# Cardiac valve involvement in ADAR -related type I interferonopathy

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SHORT REPORT

# Cardiac valve involvement in *ADAR*-related type I interferonopathy

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## ABSTRACT

**Background** Adenosine deaminases acting on RNA (*ADAR*) mutations cause a spectrum of neurological phenotypes ranging from severe encephalopathy (Aicardi-Goutières syndrome) to isolated spastic paraplegia and are associated with enhanced type I interferon signalling. In children, non-neurological involvement in the type I interferonopathies includes autoimmune and rheumatological phenomena, with calcifying cardiac valve disease only previously reported in the context of MDA5 gain-of-function.

**Results** We describe three patients with biallelic *ADAR* mutations who developed calcifying cardiac valvular disease in late childhood (9.5–14 years). Echocardiography revealed progressive calcification of the valvular leaflets resulting in valvular stenosis and incompetence. Two patients became symptomatic with biventricular failure after 5–6.5 years. In one case, disease progressed to severe cardiac failure despite maximal medical management, with death occurring at 17 years. Another child received mechanical mitral and aortic valve replacement at 16 years with good postoperative outcome. Histological examination of the affected valves showed fibrosis and calcification.

**Conclusions** Type I interferonopathies of differing genetic aetiology demonstrate an overlapping phenotypic spectrum which includes calcifying cardiac valvular disease. Individuals with *ADAR*-related type I interferonopathy may develop childhood-onset multivalvular stenosis and incompetence which can progress insidiously to symptomatic, and ultimately fatal, cardiac failure. Regular surveillance echocardiograms are recommended to detect valvular disease early.

## INTRODUCTION

Adenosine deaminases acting on RNA (ADAR) catalyse the hydrolytic deamination of adenosine to inosine in double-stranded RNA (dsRNA). Failure of this editing activity results in upregulation of interferon production, likely induced by unmodified endogenous nucleic acids signalling through the cytoplasmic dsRNA sensor MDA5.[1] Both loss-of-function mutations in *ADAR* and gain-of-function mutations in *IFIH1* encoding MDA5 have been classified within the type I interferonopathy grouping, proposed to represent a novel set of inborn errors of immunity where an upregulation of type I interferon signalling is central to disease pathogenesis.[2] Such mutations are associated with a variety of phenotypes, ranging from the severe early onset encephalopathy Aicardi-Goutières syndrome, through isolated spastic paraparesis to complete non-penetrance.[3]

Non-neurological features have also been recorded in the type I interferonopathy context, most frequently vasculitic chilblain-like lesions, glaucoma and a predisposition to autoimmune phenomena.[4] Of note, heterozygous mutations in *IFIH1* can cause Singleton-Merten syndrome (SMS), characterised by deforming arthropathy, abnormal tooth development and aortic and cardiac valve calcification frequently leading to death.[5] Although previously considered to represent a distinct phenotype, recent studies have indicated that SMS constitutes part of the type I interferonopathy disease spectrum.[6 7] Here we report, for the first time, three children with biallelic *ADAR* mutations presenting with calcifying cardiac valve disease, further emphasising the phenotypic overlap across the type I interferonopathies.

## CASE REPORTS

### Patient 1

The oldest child of healthy unrelated Polish parents, patient 1 was born after a normal pregnancy and delivery. The neonatal period and infancy were unremarkable, and he started to walk independently by 10 months. At 1 year of age, he developed convulsions and ataxia after a febrile illness. An initial MRI brain was normal. Following the acute illness, he experienced a regression of motor skills and stopped walking for 3 months. By age 7 years, he was mostly wheelchair dependent, although he could still take a few steps with a trolley at the age of 10 years. Other problems included feeding difficulties, gastro-oesophageal reflux, faltering growth, hypermetropia and hypothyroidism.

Examination at age 9 years revealed freckles on his face and hands. He had a very soft systolic murmur, but cardiovascular examination was otherwise normal. There was no ptosis and there was a full range of eye movements without nystagmus. He had dysarthric speech. He had hypotonic arms with good muscle strength but symmetrically hypertonic legs with fixed flexion contractures at the knees. Reflexes were generally brisk, especially in the legs.



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Early blood investigations demonstrated intermittently elevated lactates with significant hyperalaninaemia, but at age 9 years blood lactate was repeatedly normal (1.1–1.3 mmol/L) with normal plasma amino acid profile, including normal alanine. Cerebrospinal fluid (CSF) investigations revealed normal glucose, protein, neurotransmitters and 5-methyltetrahydrofolate. Total CSF neopterin and dihydrobiopterin were elevated at 108 nmol/L (normal 7–65) and 23.3 nmol/L (0.4–13.9), respectively, with normal tetrahydrobiopterin at 33 nmol/L (9–39).

MRI brain demonstrated symmetrically increased signal in the lenticular nuclei and posterior limbs of the internal capsules. Nerve conduction studies showed a demyelinating sensorimotor axonal neuropathy. The clinical features and MRI appearances led to suspicion of Leigh syndrome spectrum,[8] which was further investigated by muscle biopsy at 9 years of age. Muscle histology showed mild myopathic features with excess lipid, but no ragged-red fibres or cytochrome oxidase-negative fibres. Muscle respiratory chain enzyme assays demonstrated an isolated deficiency of complex IV (0.007, reference 0.014–0.034) with normal activities of complex I, complexes II+III and coenzyme $Q_{10}$. Exome sequencing revealed compound heterozygous pathogenic *ADAR* variants c.577C>G;p.Pro193Ala (paternally derived) and c.3202+1G>A (maternally derived), as previously reported.[9] The p.Pro193Ala substitution represents the most frequent pathogenic variant in *ADAR* so far identified,[10] while the canonical splice-site variant is not recorded in control databases (https://gnomad.broadinstitute.org/).

Echocardiography at age 9.5 years demonstrated normal chamber dimensions, normal biventricular function but mild aortic valve calcification causing mild aortic valvular regurgitation without aortic stenosis. This appeared to be static over several years. At 11 years of age, he had bilateral femoral osteotomies with plate removal 3 years later in the absence of any perioperative problems. Aged 14 years, echocardiography showed normal chamber dimensions and ventricular function but mild aortic and mitral valve disease with trivial aortic and mild mitral regurgitation. At 16.4 years of age, his left atrium and ventricle appeared dilated (left ventricular end-diastolic dimension (LVEDd) 51.2 mm, z-score +4.39). He had normal ventricular function but worsening valvular disease with an echobright anterior mitral valve leaflet, restricted movement of the mitral valve leaflets, moderate mitral stenosis (mean inflow gradient 8.9 mm Hg, heart rate (HR) 87), mild-to-moderate mitral regurgitation and mild-to-moderate aortic regurgitation (peak velocity 3.1 m/s).

At 17 years of age, he presented with a 2-month history of increasing cough especially at night, chest pain and pedal oedema. On examination he was tachypnoeic, especially when supine. He had low volume pulses and cardiac auscultation revealed a loud second heart sound, an ejection systolic murmur at the upper left sternal edge, pansystolic and diastolic murmurs at the apex. He had decreased air entry bibasally and 3–4 cm hepatomegaly. Echocardiography showed large bilateral pleural effusions measuring about 10 cm in size and a small pericardial effusion around the left ventricle and right atrium. The inferior vena cava and hepatic veins were significantly dilated with no respiratory variation. There was severe left atrial (z-score +19) and right atrial (z-score +6.6) dilatation. There was no ventricular hypertrophy, but the left ventricle was dilated (LVEDd 56.8 mm, z-score +7), with good ventricular systolic function (EF 65%). The most striking feature was the progression of the mitral and aortic valve calcification with extremely echobright appearances of the mitral and aortic annuli (figure 1A–D). There was severe mitral valve stenosis (mean pressure gradient 19 mm Hg, HR 105) with severe mitral regurgitation, and moderate tricuspid regurgitation (peak velocity 4 m/s) without tricuspid valve stenosis. There was moderate aortic stenosis with maximal aortic valve velocity of 3.9 m/s, but no obvious aortic regurgitation. He received maximal medical management for heart failure and pulmonary hypertension and chest drains for the pleural effusions. Extensive multidisciplinary discussion concluded that there were no curative therapeutic options, and he received palliative care at home. He died a month later.

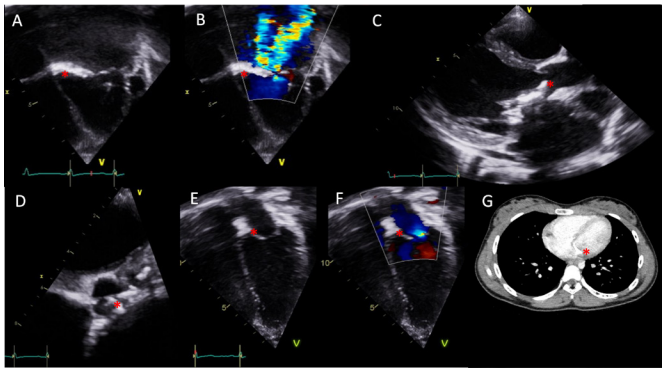


**Figure 1** Echocardiogram and CT imaging. Images are annotated with a red asterisk to indicate the position of calcifications. (A) Four-chamber view demonstrating mitral valve calcification in patient 1. (B) Doppler echocardiogram demonstrating severe mitral regurgitation in patient 1. (C) Long axis view demonstrating aortic valve calcification in patient 1. (D) Short axis view demonstrating calcification of non-coronary and left coronary cusps of the aortic valve in patient 1. (E) Four-chamber view demonstrating mitral valve calcification in patient 2. (F) Doppler echocardiogram demonstrating mild mitral regurgitation in patient 2. (G) CT imaging demonstrating mitral valve calcification in patient 3.

## Patient 2

Patient 2, the younger sister of patient 1, had a normal birth and developed normally until age 9 months when she experienced an acute encephalopathy following a febrile illness, associated with cerebellar ataxia, dystonia, seizures and global developmental delay. Investigations revealed hyperalaninaemia, demyelinating sensorimotor neuropathy and bilateral basal ganglia signal hyperintensity consistent with Leigh syndrome on brain MRI.

Examination at age 5.5 years revealed microcephaly, freckling of her hands and face, generalised hypertonia, proximal lower limb muscle weakness and brisk reflexes. Worsening neurodisability led to wheelchair dependence by 7 years of age. Exome sequencing revealed the same compound heterozygous pathogenic *ADAR* variants observed in her brother.

At 14 years, she began to develop mild posture-dependent pedal oedema. Echocardiogram at 15 years of age showed normal chamber dimensions and normal ventricular function but mild focal calcification of the non-coronary cusp of the aortic valve with no other valvular abnormalities. Currently at 16 years of age, her echocardiogram continues to show normal chamber dimensions and ventricular function but with calcification of the mitral valve, mild mitral regurgitation (figure 1E,F) and mild thickening of the non-coronary cusp of the aortic valve.

## Patient 3

This female child was born to unrelated parents of Caribbean origin after a normal pregnancy and delivery. The neonatal period and infancy were unremarkable, developing normally until age 2 years when she began to demonstrate progressive

walking difficulties with lower limb spasticity, ataxia, dysarthria and nystagmus. T2 axial brain MRI revealed periventricular white matter high signal. At age 11 years, she complained of myalgia and arthralgia. Two years later, a mild systolic murmur was noted and echocardiography demonstrated moderate aortic and mitral valve calcifications with mild mitral stenosis and mild mitral regurgitation.

Examination at age 16 years revealed moderate psychomotor retardation, spastic tetraparesis and mitral and aortic valve murmurs. Echocardiography showed LVEDd of 40 mm, wall thickness 8–9 mm (z-score +2.3) and good systolic function (EF 65%). The mitral and aortic valves were severely calcified with severe mitral stenosis (mean pressure gradient 11–12 mm Hg, HR 82) and moderate mitral regurgitation. The aortic stenosis was severe (mean pressure gradient 65 mm Hg) with mild aortic regurgitation. CT of the heart confirmed mitral valve calcification (figure 1G) and aortic leaflet and annular calcifications. T2 axial brain MRI brain demonstrated periventricular white matter high signal, and calcifications were seen in the basal ganglia, dentate nuclei, thalami and right caudate on brain CT. Nerve conduction studies revealed a progressive sensorimotor axonal neuropathy involving large and small fibres. Normal investigations included full blood count, renal and liver function, creatine kinase, erythrocyte sedimentation rate and C reactive protein. Immunological studies showed positive antinuclear antibody (ANA) (1:200) without anti-DNA antibodies. There was an upregulation of interferon-stimulated gene transcripts in blood (interferon score=7.4; normal <2.4), and serum interferon-alpha, measured using digital ELISA technology, ranged from normal (10 fg/mL; normal <10 fg/mL) to moderately elevated levels (35 fg/mL). CSF interferon-alpha protein was elevated (103 fg/mL). Sequencing of genes related to known type I interferonopathies identified two *ADAR* variants, c.518A>G;p.Asn173Ser and c.1552dup;p.Thr518Asnfs*31. The p.Asn173Ser substitution, although present in gnomAD (144 of 282 856 alleles) was previously observed in another child with ADAR-related disease,[11] while the second (novel) variant results in a frameshift and truncated protein. Parental testing confirmed biallelic inheritance. Owing to the severity of heart disease, the patient underwent mechanical mitral and aortic valve replacements. Pathological studies of the aortic valve demonstrated fibrosis and calcification (figure 2A–C). Echocardiography 6 months after surgery showed no left ventricular hypertrophy, good left ventricular function (EF 65%) and prosthetic valves working well.

## DISCUSSION

The type I interferonopathies are grouped on the premise of shared pathogenic upregulation of type I interferon signalling. One argument in favour of the type I interferon hypothesis is an overlap of clinical features across genotypes, with intracranial calcification, vasculitic skin lesions and glaucoma being particularly frequent associations. However, genotype-specific differences have also been noted, including cerebral vasculopathy in SAMHD1 disease, and bilateral striatal necrosis with ADAR dysfunction.[4] SMS was previously considered a distinct disorder, but the recent clarification of its molecular basis has revealed that this phenotype represents part of a broader spectrum associated with MDA5 gain-of-function. A specific heterozygous mutation in *ADAR* (c.3019G>A;p.Gly1007Arg), acting as a dominant-negative, can variably cause both skin lesions consistent with dyschromatosis symmetrica hereditaria and a neurological phenotype. Significant dystonia was reported in one such pedigree, which included an adult male who died at age 38 years of cardiac failure due to aortic valve calcification and stenosis.[12] Here, we provide further evidence of clinical overlap across the interferonopathy genotypes, demonstrating that life-threatening cardiac valve dysfunction with calcification can occur in the context of both *IFIH1* and *ADAR* mutations.

The clinical and MRI features observed in patients 1 and 2 initially led to suspicion of a mitochondrial disorder in the Leigh syndrome spectrum. Although *ADAR* mutations are a recognised cause of Leigh syndrome, there are now >89 different monogenic causes of this syndrome,[13] and a specific genetic diagnosis is frequently only made after genome-wide next-generation sequencing.[14] The presence of skin freckles and cardiac valve calcification may facilitate clinical recognition of ADAR deficiency in a child with suspected Leigh syndrome. Cardiac valvular disease is extremely uncommon in primary mitochondrial disorders and the few reported cases include two siblings with defective biosynthesis of coenzyme $Q_{10}$ caused by biallelic mutations in *PDSS1*.[15]

Together with a recent description of lethal pulmonary hypertension with *IFIH1* and *TREX1* mutations,[16] our findings highlight the need to monitor cardiopulmonary status with regular echocardiograms to detect valvular disease early in the type I interferonopathy context, and further emphasise a likely shared pathogenesis. The favourable postoperative course in patient 3 suggests that surgical intervention with cardiac valve replacement may be indicated where medical management has failed in interferonopathy-related valvular cardiac disease. Other potential therapeutic options that might be considered include JAK 1/2 blockade using ruxolitinib, which has shown beneficial effects in patients with MDA5 gain-of-function mutations.[17 18] However, further studies are needed to test the hypothesis that valvular disease is a direct effect of an interferon-driven inflammatory process, and therefore determine whether anti-interferon therapies might be an effective disease-modifying treatment.

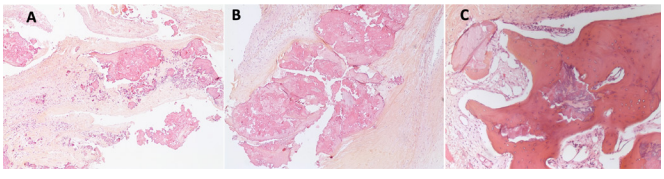


**Figure 2** Histological findings of explanted mitral valve from patient 3. (A, B) Fibrosis and calcification of the valvular tissue remodelled by the presence of fibrous nodules and areas of microcalcifications. (C) Ossification of the valve.

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