

Patient with a *PRKAG2* mutation who developed Immunoglobulin A nephropathy: a case report

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Background

PRKAG2 syndrome (PS) is a rare, early-onset autosomal dominant inherited disease caused by mutations in *PRKAG2*, the gene encoding the regulatory $\gamma 2$ subunit of adenosine monophosphate-activated protein kinase. *PRKAG2* syndrome is associated with many cardiac manifestations, including pre-excitation, arrhythmias, left ventricular hypertrophy, and chronotropic incompetence frequently leading to early pacemaker placement. A meta-analysis of genome-wide association data in subjects with chronic kidney disease (CKD) identified a susceptibility locus in an intron of *PRKAG2*, which has been replicated in other studies. However, CKD has not been reported in patients with PS or mutations in *PRKAG2*.

Case summary

We report a case of a woman diagnosed at age 27 with PS when she presented with atrial fibrillation and pre-excitation on electrocardiogram. By age 35, she had developed mild renal insufficiency and a biopsy demonstrated IgA nephropathy (IGAN).

Discussion

This is the first reported case of IGAN in a patient with PS. We discuss both PS and IGAN and the potential mechanisms by which they could be related.

Keywords

IgA nephropathy • *PRKAG2* • Pre-excitation • Case report

Learning points

- *PRKAG2* syndrome (PS) is a rare, early-onset autosomal dominant inherited disease caused by mutations in *PRKAG2*, the gene encoding the regulatory $\gamma 2$ subunit of adenosine monophosphate-activated protein kinase (AMPK).
- *PRKAG2* syndrome is associated with many cardiac manifestations, including pre-excitation, supraventricular and ventricular arrhythmias, left ventricular hypertrophy, and chronotropic incompetence frequently leading to early pacemaker placement.
- While chronic kidney disease has not been directly linked to PS, there are potential mechanisms by which AMPK activation could result in injury to B cells or glomerular cells. Our patient had PS and developed biopsy-proven immunoglobulin A nephropathy.

Background

PRKAG2 syndrome (PS) is a rare, early-onset autosomal dominant inherited disease caused by mutations in *PRKAG2*, the gene encoding the regulatory $\gamma 2$ subunit of adenosine monophosphate-activated protein kinase (AMPK). *PRKAG2* syndrome is associated with many cardiac manifestations, including pre-excitation, supraventricular and ventricular arrhythmias, left ventricular hypertrophy, and chronotropic incompetence frequently leading to early pacemaker placement.¹ The left ventricular hypertrophy is secondary to abnormal glycogen storage² and activation of hypertrophic signalling pathways.^{3,4}

Interestingly, a meta-analysis of genome-wide association data in subjects with chronic kidney disease (CKD) identified a susceptibility locus in an intron of *PRKAG2*,⁵ which has been replicated in other studies.^{6,7} However, CKD has not been reported in patients with PS

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or mutations in *PRKAG2*. We present a case of PS with immunoglobulin A (IgA) nephropathy (IGAN).

Timeline

Age 27	Presented with atrial fibrillation with a rapid ventricular response. On conversion she was noted to have pre-excitation on electrocardiogram.
Age 28	Discovered her mother had WPW and <i>PRKAG2</i> mutation. Patient received genetic testing demonstrating <i>PRKAG2</i> .
Ages 28–35	Maintained on Bisoprolol 1.25 mg daily and prn Flecainide.
Age 31	Routine laboratory work notable for mildly increased creatinine and borderline glomerular filtration rate (GFR).
Age 35	Creatinine up to 151 $\mu\text{mol/L}$ and GFR 51 mL/min/1.73 m^2 and protein was noted in urine. Biopsy performed demonstrating immunoglobulin A nephropathy. Started on Ramipril 2.5 mg daily for hypertension and proteinuria.
Age 38	She remains stable 10 years and 4 months since her initial diagnosis from both cardiac and renal perspectives.

Case presentation

A 36-year-old woman was noted in her 20s to have occasional episodes of palpitations and breathlessness. She presented at the age of 27 years in atrial fibrillation with a ventricular response of 204 b.p.m. She was given intravenous amiodarone and converted to sinus rhythm. A repeat electrocardiogram (ECG) showed a short PR interval with a delta wave consistent with Wolff-Parkinson-White syndrome (Figure 1). A transthoracic echocardiogram showed normal biventricular function and no significant valvular disease. She was prescribed flecainide 200 mg as needed.

At a follow-up evaluation by her cardiologist, she denied palpitations, syncope, or falls. Her pulse was 70 b.p.m., and her blood pressure was 115/84 mmHg. Her jugular venous pressure was normal, and her exam revealed normal heart sounds. Her ECG was consistent with a left anteroseptal accessory pathway.

The following year, it was discovered that the patient's Mother also suffered from Wolff-Parkinson-White syndrome and had a *PRKAG2* mutation. In addition, her maternal grandfather reportedly had a history of 'hypertrophic cardiomyopathy', atrial fibrillation, and complete heart block requiring permanent pacemaker implantation. Upon evaluation by a cardiac geneticist, the patient was confirmed to have inherited the *PRKAG2* mutation. It was recommended that she continue to receive long-term cardiology surveillance with serial echocardiograms, treadmill exercise stress tests, and ECGs.

Over the next 8 years, the patient was maintained on daily bisoprolol 1.25 mg with flecainide 200 mg as needed. Periodic Holter monitors were performed demonstrating heart rates in the 40s at times without symptoms. Routine blood tests at the age of 31 years demonstrated borderline abnormal renal function with a serum creatinine of 92 $\mu\text{mol/L}$ (normal range 44–80 $\mu\text{mol/L}$) and an estimated glomerular filtration rate (GFR) of 61 mL/min/1.73 m^2 (normal eGFR >60 mL/min/1.73 m^2).

By the age of 35 years, her creatinine had risen to 107 $\mu\text{mol/L}$, her blood urea nitrogen (BUN) was 7.3 mmol/L (normal range 2.1–87.1 mmol/L), and her estimated GFR was 61 mL/min/1.73 m^2 . A urinalysis showed 2+ proteins and 3+ glucose. On follow-up evaluation by a nephrologist a few months later, her laboratories were notable for a creatinine of 151 $\mu\text{mol/L}$, BUN 10.5 mmol/L, and GFR 51 mL/min/1.73 m^2 . Her urine protein/creatinine ratio was 75. Her parathyroid hormone was reportedly 75 pg/mL (normal range 15–65 pg/mL). Her C3 and C4 levels were normal. An abdominal ultrasound showed normal kidneys bilaterally. A renal biopsy established a diagnosis of IGAN (Figures 2–5), with mild-to-moderate mesangio-proliferative activity and evidence of some chronicity. Focal, global, and segmental glomerulosclerosis, and focal interstitial fibrosis/tubular atrophy was present. Also noted in the renal parenchyma were vacuolated tubular cells and interstitial foam cells, which have been associated with subsets of genetic abnormalities including glycogen storage diseases, but are not usually found in IGAN. Additionally, her blood pressure was 143/83 mmHg. She was started on ramipril 2.5 mg daily for both her hypertension and proteinuria.

She remains stable 10 years and 4 months since her initial diagnosis from both cardiac and renal perspectives.

Discussion

Since its discovery and first report in 2001,⁸ most of the attention in patients with PS has focused on the cardiac manifestations described above. Genome-wide association studies have identified that the rs7805747 SNP in an intron of *PRKAG2* is associated with CKD and decreased GFR. Furthermore, differential methylation of *PRKAG2* in DNA from blood was noted in CKD subjects.⁹ Other hereditary glycogen storage diseases are associated with renal disease, such as renal tubular dysfunction.¹⁰ Gene-targeted knock-in mice with the Arg531Gly mutation in *Prkag2* exposed to a high fat diet showed severe kidney injury characterized by glycogen accumulation, inflammation, apoptosis, cyst formation, and impaired renal function.¹¹

Immunoglobulin A nephropathy is characterized by deposits of IgA₁ in the glomeruli. This process may be the consequence of deposition of circulating immune complexes or the formation of immune complexes *in situ* in the glomeruli.¹² These complexes involve a reaction between abnormally glycosylated IgA₁ and an auto-antibody that recognizes carbohydrate side chains of IgA₁ that are deficient in galactose.

The mechanisms by which mutations in *PRKAG2* may lead to IGAN or CKD are unclear. Mutations in *PRKAG2* generally lead to inappropriate activation of AMPK. Recent studies suggest that AMPK may contribute to renal disease. AMPK appears to activate fibroblasts and could induce renal fibrosis in obstructive or ischaemia-reperfusion injury.¹³ AMPK inhibits Akt and activates the FOXO3a

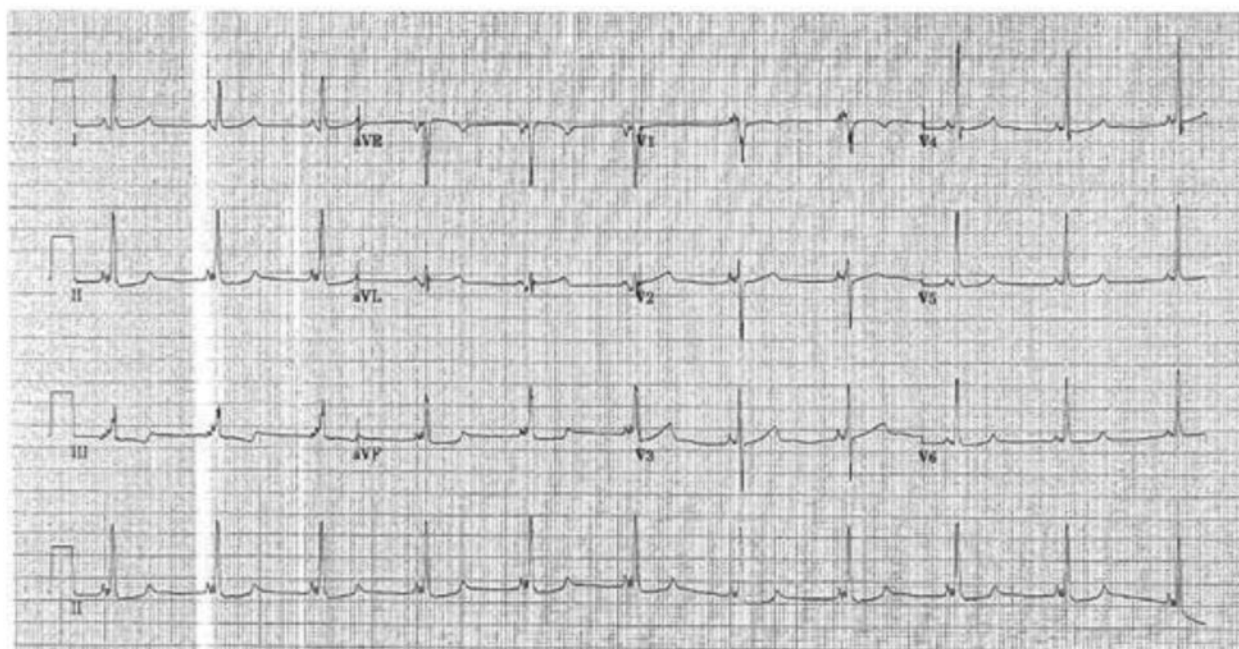


Figure 1 Electrocardiogram with short PR interval and delta wave.

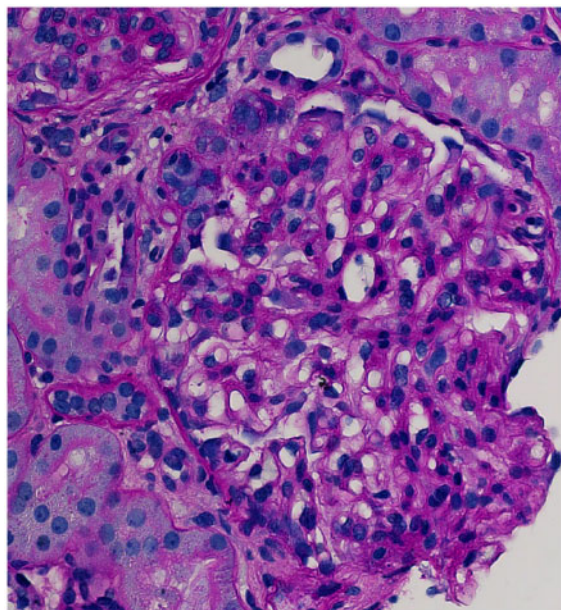


Figure 2 PAS stain (Glomerulus): Mesangioproliferative glomerulonephritis with increased cellularity within the mesangial areas PAS, Periodic acid-Schiff.

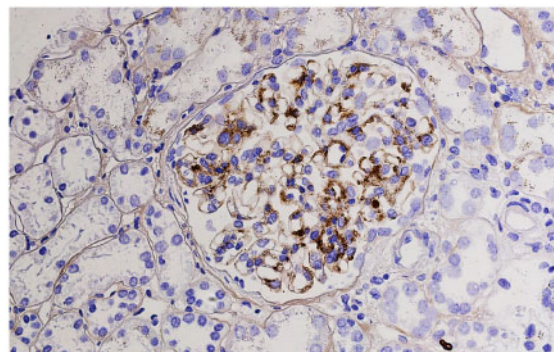


Figure 3 Immunoglobulin A immunohistochemical stain (Glomerulus): Positive (brown/tan) staining within mesangial and paramesangial capillary areas.

transcription factor in cervical cancer cells,¹⁴ leading to oxidative stress, inflammation, and apoptosis. We have shown that the *PRKAG2* Thr400Asn mutation leads to up-regulation of the sodium-dependent

glucose transporter SGLT1 in cardiomyocytes,^{15,16} which is also known to be expressed in renal epithelial cells. Furthermore, our unpublished data suggest that SGLT1 mediates oxidative stress in cardiomyocytes. Inappropriate AMPK activation secondary to *PRKAG2* mutations leads to inappropriate glucose uptake in cardiomyocytes, possibly mediated by SGLT1 and other glucose transporters. It is possible that this excess glucose in other cells, such as B cells or glomerular cells, leads to abnormalities in glycosylation of IgA₁ that is critical to the pathogenesis of IGAN. It is important to note that physiological activation of AMPK may actually be salutary in kidney

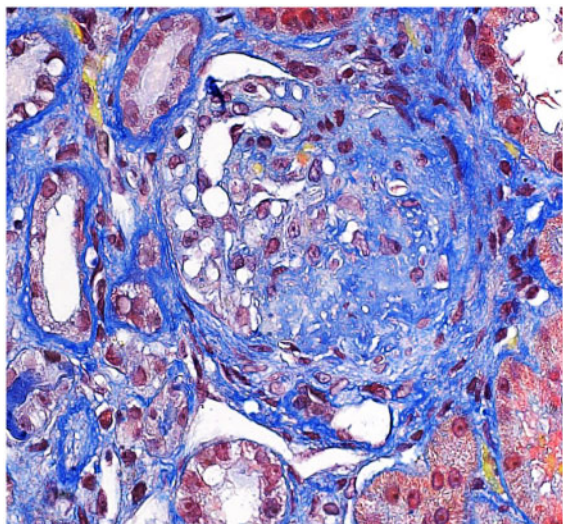


Figure 4 Masson trichrome stain (Glomerulus): segmental sclerosis. Compare the cellular portion on the left half of the glomerulus with the blue acellular portion on the right, with adhesions to the glomerular capsule causing obscuring of the urinary space.

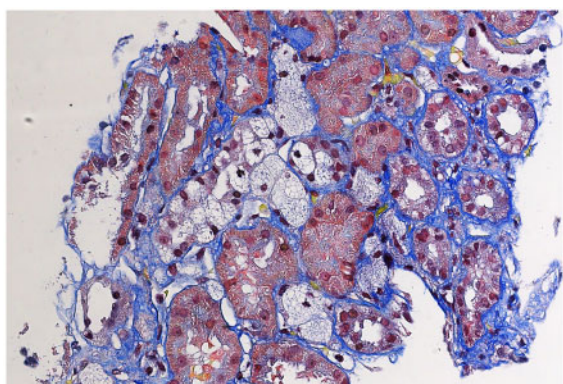


Figure 5 Masson trichrome stain (Tubulointerstitium): vacuolated tubular epithelial cells and interstitial foam cells. These changes are not typically found with IGAN but have been described in of glycogen storage diseases.

disease.¹⁷ However, inappropriate activation of AMPK secondary to *PRKAG2* mutations may be deleterious.

The presence of vacuolated tubular cells and interstitial foam cells on renal biopsy suggests that AMPK activation was directly contributing to the nephropathy, since similar vacuolation is seen in cardiomyocytes in the setting of *PRKAG2* mutations.¹⁸ However, renal impairment seemed to lag behind the cardiac manifestations in this patient. We speculate that kidneys have a greater physiological reserve than the heart, so that significant renal impairment must occur before changes in serum creatinine are evident.

Although the mechanisms leading from *PRKAG2* mutations to IGAN remain speculative, the presence of two fairly rare diseases in a young woman suggests a possible link that warrants further investigation.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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