REVIEW

Molecular Pathogenesis of Familial Wolff-Parkinson-White Syndrome. ~Molecular Mechanisms of Cardiac Glycogen Regulation by AMPK~

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Abstract : Familial Wolff-Parkinson-White (WPW) syndrome is an autosomal dominant inherited disease and consists of a small percentage of WPW syndrome which exhibits ventricular pre-excitation by development of accessory atrioventricular pathway. A series of mutations in *PRKAG2* gene encoding gamma2 subunit of 5'AMP-activated protein kinase (AMPK) has been identified as the cause of familial WPW syndrome. AMPK is one of the most important metabolic regulators of carbohydrates and lipids in many types of tissues including cardiac and skeletal muscles. Patients and animals with the mutation in *PRKAG2* gene exhibit aberrant atrioventricular conduction associated with cardiac glycogen overload. Recent studies have revealed "novel" significance of canonical pathways leading to glycogen synthesis and provided us profound insights into molecular mechanism of the regulation of glycogen metabolism by AMPK. This review focuses on the molecular basis of the pathogenesis of cardiac abnormality due to *PRKAG2* mutation and will provide current overviews of the mechanism of glycogen regulation by AMPK. J. Med. Invest. 65 : 1-8, February, 2018

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INTRODUCTION

Wolff-Parkinson-White (WPW) syndrome is the most common cause of ventricular pre-excitation due to rapid conduction through the accessory atrioventricular pathway (1, 2). WPW syndrome, which is characterized by shortened PR interval, delta wave and prolonged QRS in electrocardiography, often leads to ventricular fibrillation and sudden cardiac death. The molecular mechanisms by which accessory bypass are formed have not been clarified well. Although most patients with WPW syndrome are not evidently inherited, a small percentage of WPW syndromes are familial and associated with hypertrophic cardiomyopathy (3-7). The familial WPW syndrome is inherited in an autosomal dominant mode (8).

Since a mutation in *PRKAG2* gene encoding gamma2 subunit of 5'AMP-activated protein kinase (AMPK) was identified as the cause of familial WPW syndrome, a series of mutations in *PRKAG2* gene were found to be associated with familial WPW syndrome. AMPK is a heterotrimeric serine/threonine kinase playing a key role in regulating energy homeostasis. As its name designates, it is activated when intracellular AMP level is increased (Fig. 1). In other words, AMPK acts as an energy fuel sensor responding to ATP consumption (9). AMPK consists of catalytic alpha subunit and two regulatory beta and gamma subunits. There have been two identified isoforms for both alpha and beta subunits and three identified isoforms for gamma subunit in mammals (10-13). The regulatory gamma subunit is assumed to be an AMP/ADP/ATP sensor itself. Recent reports on the crystal structure of mammalian AMPK support this notion (14, 15). Transcripts of *PRKAG2* gene are predominantly expressed in heart, and AMPK gamma3 subunit is abundant in skeletal muscles in contrast (16, 17). AMPK activity is also regulated by phosphorylation of the Thr172 residue of the alpha subunit (18) (Fig. 1). A putative tumor suppressor kinase responsible for Peutz-Jeghers syndrome, LKB1 and Ca2+/calmodulin-dependent protein kinase kinase (CaMKK) beta were identified to be upstream kinases which phosphorylate AMPK (19-23). Recent studies showed dephosphorylation of Thr172 residue by protein phosphatase 2C (PP2C) was also regulated by AMP (24). That is, AMP regulates AMPK activity via allosteric effect and dephosphorylation. In this review, I would like to discuss molecular pathogenesis of familial WPW syndrome by considering molecular mechanisms of glycogen regulation by AMPK.

Genetic Basis of Familial WPW Syndrome.

At least six missense mutations and one insertion in the coding sequence of *PRKAG2* gene encoding AMPK gamma2 subunit were reported to be associated with familial WPW syndrome to date (Table 1). Following the first causal R302Q mutation, a series of mutations in *PRKAG2* gene were found to be associated with familial WPW syndrome such as H383R, N488I or R531G (3, 25-28). Their phenotypes consist of cardiac hypertrophy preexcitation and abnormal conduction, but they exhibit various traits. In families with R302Q mutation in AMPK gamma2, symptomatic onsets of the disease were in late adolescence. On the other hand, a kindred with R531G mutation exhibited severe arrhythmogenic disease as early as age two (3, 27).

A typical hypertrophic cardiomyopathy in adult population occurs due to genetic defects in contractile proteins (reviewed in (29).) In contrast, cardiac hypertrophy dependent on the *PRKAG2* mutations has been thought to occur secondary due to abnormal

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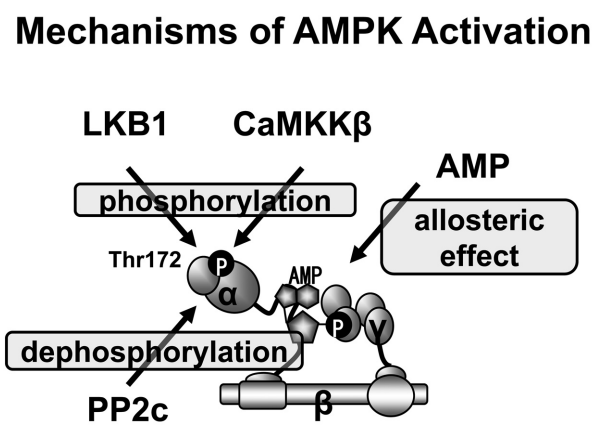

Fig. 1
Molecular mechanisms of AMPK activation.

glycogen accumulation. However, this concept is challenged by a recent finding that genetically manipulated mice harboring mutations both in *PRKAG2* and *GYS* (encoding glycogen synthase) genes exhibited severe cardiac hypertrophy only with moderate glycogen accumulation, in which report the authors suggested involvement of alteration in insulin sensitivity(30). Myofiber disarray, which is a characteristic feature of typical hypertrophic cardiomyopathy, was not detected in samples from patients with N488I or T400N mutation even though myocytes were enlarged, and ventricular preexcitation is likely caused by annulus fibrosis disruption as distinct from the muscular-appearing bypass tract observed in typical WPW syndrome (25, 31, 32). The pathophysiological similarity to other glycogen storage disease such as Pompe disease, which is caused by mutations in the gene encoding for alpha 1,4-glucosidase, has been observed as early as 1970s. Left ventricular hypertrophy and dysfunction associated with WPW syndrome are often found in the patients with Pompe disease (33, 34). Considering cases of glycogen storage disease, glycogen accumulation presumably modulate the electric properties of atrioventricular fibers as accessory pathway and induce ventricular preexcitation (33). That is, glycogen amassment is assumed to enhance conduction from atrial to ventricular muscles through expanding atrio-ventricular muscle remnants. Furthermore, decrease in intracellular pH due to glycogen may also contribute to excitability. Taken together, the mutation in *PRKAG2* gene is supposed to lead to familial WPW syndrome mainly through secondary glycogen accumulation.

There seems no obvious evidence demonstrating accumulation of glycogen specifically located between atrium and ventricle. Therefore, patients with the *PRKAG2* mutations are supposed to exhibit pathological phenotypes of the WPW syndrome only when alterations of electrical properties happen to cause aberrant atrioventricular pathways. There could be inapparent patients conveying the mutations.

Dysregulation of ion channels may play a part in the abnormal electrical conductions. AMPK has been suggested to control a number of cardiac channels including sodium, potassium, and chloride channels. For instance, overexpression of constitutively active AMPK mutant was shown to slow inactivation of cardiac sodium channels, hH1, and prolong action potential duration by using human embryonic TsA201 cells, which could be consistent with QT interval elongation often observed in the WPW patients (35).

AMPK is also associated with another aberrant cardiac glycogen metabolism in human. In addition to familial WPW syndrome, heterozygous R531Q missense mutation in *PRKAG2* gene was found in patients with sporadic fatal congenital heart glycogenosis (36). As there was no mutations found in genes encoding phosphorylase kinases, which are the most common reasons for glycogen metabolism-related disorders, AMPK gamma2 R531Q mutation is supposed to cause the cardiac glycogen storage disease. Patients with the R531Q mutation died of hemodynamic and respiratory failure secondary to hypertrophic nonobstructive cardiomyopathy, but also had WPW-like conduction anomalies. In contrast to other *PRKAG2* missense mutations described above, R531Q mutation gives rise to more severe phenotype, ie. rapid fatal nonlysosomal cardiac glycogenosis of fetal symptomatic onset (36). In addition, another Y487H mutation in *PRKAG2* associated with moderate cardiac hypertrophy and an extremely short PR interval was reported even though its activity and effect on glycogen accumulation were not mentioned (37).

Table 1.
Mutation in human *PRKAG2* gene responsible for familial WPW syndrome and related diseases

mutation	type		location	disease	reference
G100S	missense	point mutation	exon 3	familial WPW	(96)
R302Q	missense	point mutation	exon 7	familial WPW	(3)
H383R	missense	point mutation	exon 11	familial WPW	(26)
T400N	missense	point mutation	exon 11	familial WPW	(25)
N488 I	missense	point mutation	exon 14	familial WPW	(25)
R531G	missense	point mutation	exon 15	familial WPW	(27)
350Leu351	insertion		exon 9	familial WPW	(26)
R384T	missense	point mutation	exon 11	fatal infantile glycogenosis (associated with phosphorylase kinase deficiency)	(97)
K485E	missense	point mutation	exon 14	left ventricular hypertrophy, *de novo* WPW	(98)
Y487H	missense	point mutation	exon 14	moderate cardiac hypertrophy	(37)
E506K	missense	point mutation	exon 14	mild left ventricular hypertrophy	(99)
E506Q	missense	point mutation	exon 14	severe hypertrophic cardiomyopathy	(100)
H530R	missense	point mutation	exon 15	childhood-onset hypertrophic cardiomyopathy	(101)
R531Q	missense	point mutation	exon 15	fatal congenital glycogenosis	(36)
S548P	missense	point mutation	exon 16	hypertrophic cardiomyopathy, mild skeletal muscular glycogenosis	(102)

Therefore, mutation in AMPK gamma2 is closely related to aberrant cardiac glycogen accumulation although the impacts of each mutation on AMPK activity have not been clarified well. Most of mutations related to the cardiac disorders found in the *PRKAG2* gene are located in or between the cystathione beta synthase (CBS) domains, which are recognized as functional domains interacting with AMP, ADP or ATP (Fig. 2). Thus, these mutations are supposed to change the balance of accessibility or affinity for AMP and ATP, which might be one of the reasons for complicated effects on the AMPK activity.

Differentiated induced-pluripotent stem cells (iPS cells) established from patients conveying N488I mutation recapitulates WPW phenotypes including AMPK activation, glycogen accumulation and hypertrophy, which were ameliorated by TALEN-directed genome editing(38). Adeno-associated virus-9-mediated CRISPR/Cas9 gene editing was shown to prevent cardiac disorders in transgenic mice with *PRKAG2* H530R mutation(39). Genome editing-based gene therapy should be a promising way to treat inherited diseases including familial WPW.

It is interesting that many mutations arising naturally in human associated with familial WPW syndrome have been found especially in *PRKAG2* gene. As for human skeletal muscle, AMPK abnormality had not been found until recent report that R225W mutation of human *PRKAG3* gene was associated with increased glycogen content and decreased triglyceride in vastus lateralis muscle (40). R225W mutation caused 2-fold increase in AMPK activity partially purified from the biopsied muscle (40). A screening cohort study which sequenced the *PRKAG3* locus of more than 1000 non-diabetic white population for SNPs found two SNPs (rs 692243, rs6436094), however, which was not associated with pre-diabetic traits such as insulin sensitivity or insulin secretion but with serum LDL cholesterol and apolipoprotein B-100 levels (41). More recently, the rs692243 SNP was suggested to be associated with sporadic WPW in Taiwanese population, instead (42). Similar results were reported as for SNPs in *PRKAA2* gene encoding alpha2 subunit of AMPK in Caucasian female population (43). No single SNP in AMPK components have ever found to be associated with diabetic traits but two Japanese groups reported associated haplotypes (41, 43-46).

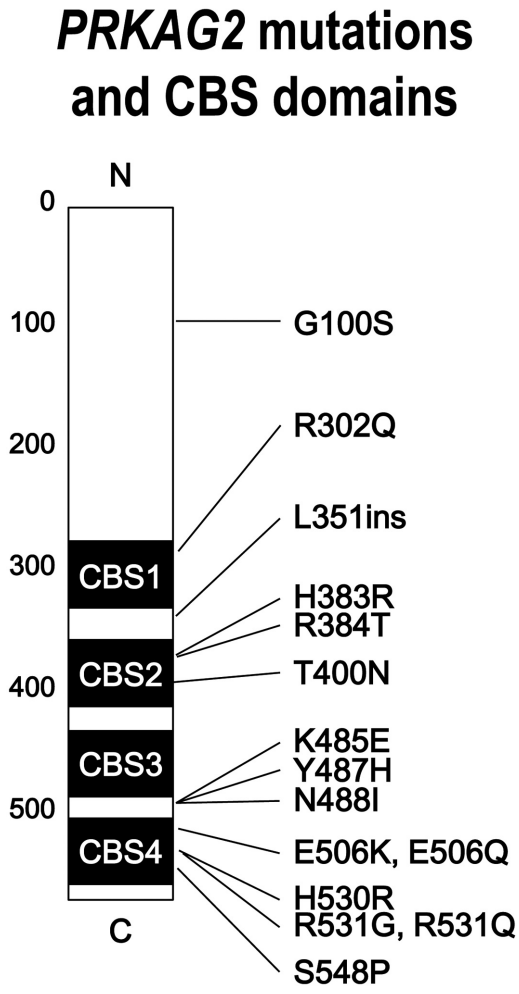

Fig. 2
PRKAG2 mutations identified in the patients of familial WPW and its related diseases.

Significance of Cardiac AMPK

The physiological roles of AMPK have been established over the last two decades. In skeletal muscle, AMPK is prominently activated in response to exercise or electrical stimulation (47-50). AMPK phosphorylates and inactivates acetyl-CoA carboxylase (ACC) in response to muscle contraction (47-52). The consequent reduction in malonyl-CoA facilitates fatty acid oxidation by releasing inhibition of carnitine/palmitoyl-CoA acyl transferase1 (CPT1). Pharmacological activation of AMPK increases GLUT4 translocation and glucose uptake activity similar to the effect of muscle contraction in a wortmannin-insensitive manner (53, 54). Furthermore, the AMPK activation mimics the metabolic effects of muscle contraction metabolome-widely (55, 56).

Interestingly, physical exercise activates AMPK not only in skeletal muscle but also in heart (57). However, AMPK appears to play more important roles during and after ischemia rather than responding to myocardinal contraction in heart, in contrast to skeletal muscle. Cardiac AMPK harbors relatively high basal activity but there is still a room for more enhancement of its activity in spite of the continual contraction. AMPK activity in isolated working hearts were elevated after ischemia followed by aerobic reperfusion in a phosphorylation-dependent manner (58-60). There were no failure in cardiac function, hypertrophy, or fibrosis found in transgenic mice cardiac and skeletal muscle-specifically expressing a kinase dead form of AMPK alpha2 or skeletal muscle specifically expressing another dominant negative form of AMPK alpha2. But these mice showed failure in facilitation of glucose uptake, glycolysis, and fatty acid oxidation after ischemia and postischemic reperfusion with a lower ATP content (61, 62).

In addition, an activator of AMPK, 5-aminoimidazole-4-carboxamide-1-beta-D-ribonucleoside (AICAR, acadesine) was under development in clinical trials for the prevention of ischemia-reperfusion injury. A meta-analysis of five randomized clinical trials of AICAR in patients with coronary artery bypass graft surgery demonstrated 26% reduction in myocardial infarction necessary for left ventricular assistant device and cardiac death (63). AICAR treatment reduced the severity of acute myocardial infarction following to reperfusion and showed 4.2-fold decrease in 2-year mortality (64). AMPK is plausible to play an important protective role in limiting damage associated with ischemia and reperfusion in the heart.

Animal Models of Familial WPW Syndrome with AMPK mutants

A series of mouse models of familial WPW syndrome harboring mutant AMPK gamma2 subunit have been reported. Cardiac-specific transgenic expression of R302Q mutant of *PRKAG2* in mice model has demonstrated the typical phenotype of WPW syndrome such as ventricular preexcitation, development of AV accessory pathway and cardiac hypertrophy (65). AMPK activity in the mutant heart was 2.5-fold decreased and excessive cardiac glycogen

amassment was observed.

Arad *et al.* generated transgenic mice overexpressing the N488I mutant of *PRKAG2* gene product with a cardiac-specific alpha myosin heavy chain promoter. Glycogen was 30-fold accumulated in the hearts of these animals and left ventricular hypertrophy, ventricular preexcitation, sinus node dysfunction and accessory atrioventricular conducting pathways were developed. They observed higher AMPK activity in these mice than in wild type transgenic mice (31). No changes in the activities of such enzymes related to glycogen metabolism as glycogen phosphorylase, phosphorylase kinase, glycogen branching or debranching enzymes were detected in the heart of these transgenic mice (66).

Transgenic mice with specific overexpression of R531G mutant of AMPK gamma2 in heart were also generated and exhibited cardiac hypertrophy, impaired contractile function, electrical conduction abnormalities, and marked glycogen accumulation alike by four weeks of age. At this stage, AMPK activity isolated from hearts of the transgenic mice was abolished but could be restored in the presence of a recombinant upstream kinase, CaMKK beta. Interestingly, at one week of age, there was no detectable evidence of a cardiac phenotype, and cardiac AMPK activity in transgenic mice was comparable to that in control mice. (67)

Molecular Mechanism of Metabolic Regulation of Glycogen by AMPK. ~Lessons from Skeletal Muscles~

Glycogen is a branched polymer of glucose, which serves not only as an energy repository but also as a modulator of the enzyme activity (68-71). The major deposits of glycogen are skeletal muscle and liver in mammals, however, most of other tissues including cardiac and smooth muscle, kidney, brain and adipose tissue can synthesize and accumulate glycogen (72). Recent data have provided a good deal of evidence showing significance of AMPK on glycogen metabolism.

Glycogen synthesis and degradation were regulated by rate-limiting enzymes, glycogen synthase (GS) and glycogen phosphorylase (GP) respectively. An early enzymatic study showed Ser7 residue of GS and Ser1018 and Ser1020 residues of phosphorylase kinase which lies upstream of GP were directly phosphorylated by AMPK in a cell-free assay system (73).

As for glycogenolysis, AICAR stimulation was reported to activate GP in isolated rat soleus muscle (74). However, GP activation by AICAR stimulation in isolated rat myocardium was independent of AMPK activation (75). Furthermore, AICAR stimulation did not alter GP activity nor glycogen content in isolated rat epitroclearis muscle, while a metabolite of AICAR, ZMP was demonstrated to activate GP directly (74, 76). Therefore, AICAR-induced GP activation is supposed to be due to allosteric effect of ZMP, and AMPK does not seem to be active on glycogenolysis.

It has been quite controversial on the relation between AMPK and glycogen synthesis. In skeletal muscles, some earlier studies showed that chronic administration of AICAR on animals resulted in glycogen accumulation (77-79). These phenomena were seemingly good evidence that AMPK also mediates exercise-induced facilitation of glycogen resynthesis. Aschenbach *et al.* demonstrated that acute activation of AMPK alpha2 after AICAR administration in gastrocnemius muscle caused reduction in GS activity in white fibers whereas GS activity in red fibers was conversely increased. They also made a contradictory observation that AICAR stimulation had no effect on GS activity in isolated muscles (80). In contrast, we and others showed that GS inactivation by AICAR treatment consistently with the observation that GS can be directly phosphorylated by AMPK (76, 81, 82).

A natural arising mutation in AMPK was first found in the skeletal muscle of Hampshire Pig (83). R225Q missense mutation in *PRKAG3* gene encoding gamma3 subunit of AMPK was revealed to be the cause of *Rendement Napole* (RN-) phenotype of which skeletal muscle was about 70% more abundant in glycogen. This is also the first direct evidence revealing the close relation between AMPK and glycogen metabolism. AMPK activity in the skeletal muscle of RN- pig was reported as one-third of that of wild type (83). Skeletal muscle-specific transgenic mice overexpressing AMPK gamma3 with R225Q mutation are murine models of RN- of which skeletal muscular glycogen were 1.5- to 2- fold increased (84, 85). In addition, 199V haplotype of porcine *PRKAG3* gene was reported to be associated with higher meat glycogen content than 199I haplotype (86). These earlier findings are contradicting as both of the chronic AICAR administration which should activate AMPK repeatedly and the AMPK mutation whose activity is putatively lower than wild type brought about the same result, muscle glycogen accumulation.

R70Q missense mutation in AMPK gamma1, which is a ubiquitously expressing isoform, corresponds to R302Q of gamma2 and R225Q of gamma3. Specific overexpression of the gamma1 R70Q mutant in skeletal muscle also led to glycogen accumulation (87). AMPK gamma1 R70Q mutant was revealed to be constitutively active by *in vitro* study (16, 88). 2-fold AMPK activation was observed in these mice consistently. In addition, biochemical characterization of the recombinant gamma2 R531Q mutant showed an enhanced basal activity and increased phosphorylation of the alpha subunit with reduction of binding affinities for the AMP and ATP (36). Activity in the AMPK complex containing R225Q mutant of gamma3 was higher than that in WT (84). Taken together, AMPK containing these mutants should be more active than WT in nature. High cellular glycogen content was reported to exert an inhibitory effect on AMPK activity (81, 89). Thus, it is plausible that the decrease in AMPK activities observed in some reports may be secondary due to the glycogen accumulation.

Why active mutants of AMPK induce glycogen accumulation even though AMPK plausibly inactivates GS? One possible reason is vigorous glucose uptake caused by AMPK activation which should supply substrates for glycogen synthesis. A report that glycogen was increased independently of GS or GP activity in transgenic mice whose skeletal muscles overexpressing glucose transporter, GLUT1 supported this notion. These mice resulted in 7- to 8-fold increase in glucose uptake and 10-fold amassment of glycogen in skeletal muscles even though GS activity was lower than that of control mice (90). Besides, transgenic mice overexpressing human GLUT4 in tissues expressing endogenous murine GLUT4 including heart also showed higher glucose uptake activity and induced cardiac glycogen amassment (91, 92). Luptak *et al.* analyzed the carbohydrate metabolism in heart-specific N488I AMPK alpha2 transgenic mice by using [^{13}C]-labeled glucose as a metabolic tracer (93). Isolated N488I mutant expressing hearts time-dependently stored glycogen labeled with [^{13}C] during perfusion of [^{13}C]-glucose within 2 hrs. [^{13}C]-labeled lactate output was also increased. These observations agree with the notion that AMPK activation-derived glucose uptake enhances glycogen accumulation. In addition, after 19 day of age, cardiac expression and activity of UDP-glucose pyrophosphorylase, which catalyses UDP-glucose generation, in the transgenic mice were markedly increased. The progressive decrease in phosphorylation-dependent GS activity was suggested, but total amount of GS protein and glucose-6-phosphate, which is an allosteric activator of GS, were increased at 19 and 49 day of age. These results strongly suggested that chronic AMPK activation increases glycogen storage not only by enhancing glucose influx but also by amplifying glycogen synthesis systems. A series of more recent studies clearly supported this hypothesis. Knock-in mice expressing mutant GS insensitive to glucose-6-phosphate exhibited 80% lower insulin-stimulated glycogen synthesis and reduction in glycogen levels in skeletal muscles, suggesting glucose-6-phosphate dominantly promotes

GS activation (94). Furthermore, AICAR-stimulated glycogen synthesis was completely abolished in these mice (95). The increase in glucose influx by AMPK activation is suggested to stimulate glycogen synthesis by allosteric GS activation mediated by glucose-6-phosphate and enrichment of the substrate (Fig. 3). The causal mutations of familial WPW syndrome are supposed to lead to cardiac glycogen accumulation alike. Furthermore, WPW phenotypes including excessive accumulation of cardiac glycogen, except for hypertrophy as aforementioned, were strikingly ameliorated when mice with *PRKAG2* N488I mutation were crossed with the GS mutant mice insensitive to glucose-6-phosphate, strongly supporting the idea (30).

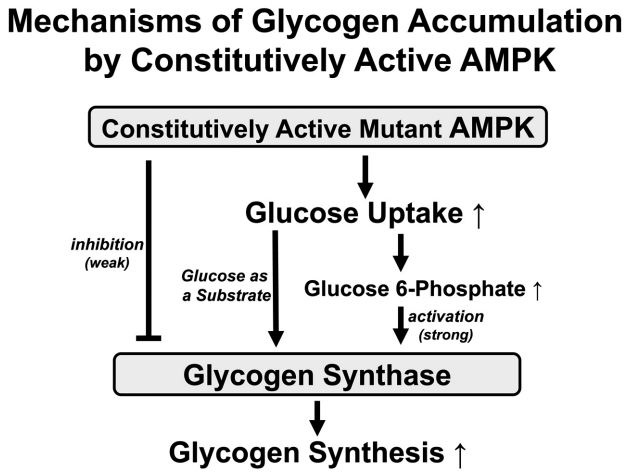

Fig. 3
Possible molecular mechanisms of glycogen accumulation by AMPK mutations.

CONCLUSION

Recent advances of genetic and metabolic investigations on familial WPW syndrome and AMPK have been revealing the molecular mechanism connecting the mutations in *PRKAG2* gene and the cardiac aberrancy. However, little is known what kind of mechanisms is involved in the abnormal atrioventricular conduction caused by glycogen accumulation. Further studies focused on the effects of cardiac AMPK or glycogen accumulation on the regulation of ion channels may provide us more profound understanding. Studies on familial WPW syndrome extended our knowledge about glycogen regulation by AMPK although it is a relatively rare inherited disease. Rapid advance in genome editing technology has been lowering technical hurdles to gene therapy. However, if not to use gene therapy, AMPK and enzymes related to glycogen regulation will be potent therapeutic targets of familial WPW syndrome.

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CONFLICT OF INTERESTS

The author declares no conflicts of interest.

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