AMP-activated protein kinase and familial Wolff–Parkinson–White syndrome: new perspectives on heart development and arrhythmogenesis

The study of families with inherited cardiac arrhythmias has established the genetic basis of primary arrhythmogenic disorders. Culprit genes have been identified for familial causes of ventricular arrhythmias, including the long QT syndrome, Brugada syndrome, and polymorphic ventricular tachycardia[1–3]. Thus far, the genetic defects leading to these disorders have been shown to affect ion channel proteins ('channelopathies') or in the case of polymorphic ventricular tachycardia, the cardiac ryanodine receptor which is known to be involved in intracellular calcium handling. Recently, we identified genetic mutations in the gene encoding for the gamma 2 regulatory subunit (PRKAG2) of AMP-activated protein kinase as responsible for the familial syndrome of ventricular preexcitation, atrial fibrillation, and conduction defects[4–6]. The novel association of this protein with abnormal atrioventricular connections and supraventricular arrhythmias offers a new perspective on heart development and arrhythmogenesis.

The clinical syndrome

Following our initial description of two unrelated families with this genetic disease, we have subsequently identified two additional families and have assessed in total 47 affected patients. Inheritance of this arrhythmic syndrome occurs with a high degree of penetrance, with virtually all genetic carriers showing discernible electrocardiographic abnormalities prior to symptomatic presentation. The predominant clinical feature is that of electrocardiographic evidence of ventricular preexcitation in youth. The vast majority of patients have received a diagnosis of the Wolff–Parkinson–White syndrome due to the frequent recurrence of reciprocating tachycardias, pre-excited atrial fibrillation and atrial flutter. Clinical presentations of syncope of palpitations typically occur in late adolescence or the third decade of life, although childhood presentation has been observed. Electrophysiological studies in some patients have demonstrated typical accessory pathways, consistent with the findings in a previously reported kindred[7]. In addition, variant atrioventricular connections consistent with fasciculo-ventricular pathways appear to be the substrate of ventricular pre-excitation in other patients. Progression from frequent tachyarrhythmias to severe sinus bradycardia requiring permanent pacemaker implantation commonly occurs by the fourth decade of life. Loss of pre-excitation in association with high-grade atrioventricular block is seen in some patients. The development of chronic atrial fibrillation occurs in over 80% of patients >50 years. This high incidence of atrial fibrillation and conduction disease is present at a much greater frequency than is seen in sporadic Wolff–Parkinson–White, suggesting the development of these rhythm disturbances is as a result of the genetic defect rather than the presence of accessory atrioventricular connections.

Cardiac hypertrophy has been detected by echocardiography in one-third of affected patients and has not been observed in the absence of rhythm disturbances. A retrospective review of patients from two pedigrees indicates a higher than expected prevalence of systemic hypertension requiring medical therapy by age 50. Premature sudden death (age <40 years) has occurred in 10% of patients and is probably secondary either to degeneration of rapid supraventricular arrhythmias or brady-asystolic rhythms.

Genetic linkage and the candidate gene approach

In 1995, MacRae et al. identified a genetic locus on chromosome 7 (7q3) in a family with inherited Wolff–Parkinson–White syndrome and hypertrophic cardiomyopathy[8]. We identified a large, French–Canadian family with a similar clinical phenotype, and mapped the disease-causing gene to this region. Genetic analysis of a second, unrelated family with the identical clinical phenotype provided data that reduced the shared region of DNA among all affected individuals to a region of 2 cM. The complex clinical phenotype of this syndrome suggested the causative gene should have diverse cellular functions. The ideal candidate gene must provide a...
mechanistic basis for the structural defect of Wolff–Parkinson–White, namely congenital accessory atrioventricular connections, the higher than expected prevalence of atrial arrhythmias/conduction defects, and the presence of cardiac hypertrophy in some patients. Using the approach of identifying a causative gene based on the entire clinical spectrum, PRKAG2 emerged as a leading candidate for the following reasons. Firstly, it is evident that AMP-activated protein kinase functions at the level of transcriptional gene regulation\[9,10\]. Mutations in regulators of gene expression are known causes of congenital heart defects\[11,12\]. Second, the function of AMP-activated protein kinase and similar kinases in the regulation of ion channel gating through phosphorylation is well-recognized and provides a mechanism for the high prevalence of atrial fibrillation and conduction defects observed in this syndrome\[13,14\]. Lastly, the significant role of AMP-activated protein kinase in metabolic pathways, including glucose metabolism\[15,16\], is suggestive of a metabolic cause of cardiac hypertrophy.

Novel insights into disease pathogenesis and potential implications

The AMP-activated protein kinase (AMPK) is a heterotrimer, with the gamma subunit involved in regulating the activity of the protein\[17\]. Our understanding of AMPK in the heart is still evolving. The identification of the PRKAG2 genetic defect should lead to an understanding of the pathogenesis of accessory atrioventricular connections in the developing heart. Presumably, this molecular defect in some way inhibits the complete regression of the muscular continuity between the atria and ventricles present prior to atrioventricular septation. Although the propensity for arrhythmias is well known in Wolff–Parkinson–White, the molecular trigger for these events is not understood. The known activation of AMPK in response to beta-adrenergic stimulation may account for episodes of tachyarrhythmias observed in response to exercise or metabolic stress\[18\].

The high prevalence of paroxysmal and chronic atrial fibrillation in this syndrome suggests a primary role of AMPK in the regulation of cardiac ion channels. The identification of the cardiac ion channel(s) serving as substrate for AMPK should provide insights into the molecular basis of this common arrhythmia and may serve as targets for the development of more specific therapy. This is particularly relevant considering the molecular mechanism for atrial fibrillation from any cause remains elusive.

The role of AMPK in glucose metabolism in the heart implies the cardiac hypertrophy seen in some patients is probably secondary to abnormal glycogen content in cardiac muscle. This concept is supported by the finding that a mutation in the porcine homologue of the gamma 3 regulatory subunit of AMPK in the Hampshire pig results in a phenotype of excess glycogen content in skeletal muscle\[19\]. Thus, the cardiac hypertrophy observed in this familial syndrome is more likely analogous to that observed in the metabolic cardiomyopathies of childhood. The pathogenesis, therefore, is probably distinct from that of cardiac hypertrophy resulting from mutations in sarcomeric proteins\[20\].

The prevalence of early onset systemic hypertension in a significant number of patients is intriguing. AMPK regulates endothelial nitric oxide synthase (eNOS), a key regulator of blood pressure homeostasis\[21\]. The eNOS mouse knockout model exhibits a phenotype of systemic hypertension and left ventricular hypertrophy\[22\]. Thus, impaired regulation of eNOS may predispose to hypertension and further contribute to cardiac hypertrophy.

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References


