

IDENTIFICATION OF A GENE RESPONSIBLE FOR FAMILIAL WOLFF-PARKINSON-WHITE SYNDROME

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ABSTRACT

Background The Wolff-Parkinson-White syndrome, with a prevalence in Western countries of 1.5 to 3.1 per 1000 persons, causes considerable morbidity and may cause sudden death. We identified two families in which the Wolff-Parkinson-White syndrome segregated as an autosomal dominant disorder.

Methods We studied 70 members of the two families (57 in Family 1 and 13 in Family 2). The subjects underwent 12-lead electrocardiography and two-dimensional echocardiography. Genotyping mapped the gene responsible to 7q34-q36, a locus previously identified to be responsible for an inherited form of Wolff-Parkinson-White syndrome. Candidate genes were identified, sequenced, and analyzed in normal and affected family members to identify the disease-causing gene.

Results A total of 31 members (23 from Family 1 and 8 from Family 2) had the Wolff-Parkinson-White syndrome. Affected members of both families had ventricular preexcitation with conduction abnormalities and cardiac hypertrophy. The maximal combined two-point lod score was 9.82 at a distance of 5 cM from marker D7S636, which confirmed the linkage of the gene in both families to 7q34-q36. Haplotype analysis indicated that there were no alleles in common in the two families at this locus, suggesting that the two families do not have a common founder. We identified a missense mutation in the gene that encodes the $\gamma 2$ regulatory subunit of AMP-activated protein kinase (*PRKAG2*). The mutation results in the substitution of glutamine for arginine at residue 302 in the protein.

Conclusions The identification of this genetic defect has important implications for elucidating the pathogenesis of ventricular preexcitation. Further understanding of how this molecular defect leads to supraventricular arrhythmias could influence the development of specific therapies for other forms of supraventricular arrhythmia. (N Engl J Med 2001;344:1823-31.)

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THE Wolff-Parkinson-White syndrome is the second most common cause of paroxysmal supraventricular tachycardia in most parts of the world and is the most common cause in China, being responsible for more than 70 percent of cases.¹ In Western countries, the prevalence of the Wolff-Parkinson-White syndrome is 1.5 to 3.1 per 1000 persons.²⁻⁴ Tachycardias associated with the syndrome are usually paroxysmal and may

produce symptoms of presyncope, syncope, and shortness of breath and cause sudden death. Conduction through an accessory pathway and the association of the Wolff-Parkinson-White syndrome with supraventricular tachycardia have led to the creation of an in vivo reentry model for arrhythmias.⁵ Research on the Wolff-Parkinson-White syndrome has appropriately focused on the atrioventricular pathways, which led to ablation as an effective therapy.⁶ We evaluated two families with familial Wolff-Parkinson-White syndrome in which the probands presented with syncope and the electrocardiographic features of the syndrome. A clinical evaluation of members of both families was followed by linkage analysis to identify the chromosomal location of the causative gene.

METHODS**Clinical Evaluation**

Written informed consent was obtained from all participants according to the guidelines of Baylor College of Medicine; the National Heart, Lung, and Blood Institute of the National Institutes of Health; and the University of Ottawa Heart Institute. Subjects were evaluated by means of a detailed analysis of their medical history, a physical examination, 12-lead electrocardiography, and two-dimensional echocardiography. A total of 57 members of Family 1 and 13 members of Family 2 were examined. Two subjects in Family 1 and six subjects in Family 2 underwent invasive electrophysiologic study.

Ventricular preexcitation was diagnosed on the basis of the presence of a short PR interval (<120 msec) with a widened QRS complex (>110 msec) or an abnormal initial QRS vector (a delta wave). In the case of subjects who had a pacemaker, base-line 12-lead electrocardiograms were obtained from their medical records, when possible. Sinoatrial abnormalities and conduction disease were diagnosed if chronotropic incompetence or high-grade sinoatrial or atrioventricular block was present on the electrocardiogram. Left ventricular hypertrophy was diagnosed if the thickness of the septal wall or the left ventricular free wall was at least 13 mm.

Chromosomal Mapping and Identification of Candidate Genes

Peripheral blood was obtained from each family member we evaluated. DNA was extracted from white cells, and lymphocytes

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were isolated for the development of transformed cell lines.⁷ Genotyping was carried out with short tandem-repeat polymorphisms from the 7q34–q36 region. We examined a total of 12 markers from the Genethon linkage map, and 2 additional polymorphic repeats were identified from the published sequence of P1-derived artificial chromosomes in the region. An autosomal dominant pattern of inheritance was assumed, and penetrance was estimated to be 99 percent on the basis of the observed pattern of inheritance. The frequencies of the disease allele and the normal allele were assumed to be 0.0001 and 0.9999, respectively. The allele frequencies in the case of markers were calculated to be $1/n$, where n is the number of alleles observed in the two pedigrees. Two-point linkage analysis was performed with version 5.2 of the linkage program.⁸ Once the disease-causing locus was identified, we used a candidate-gene approach to identify the responsible gene.

We identified sequences of P1-derived artificial chromosomes from the Human Genome Project by searching draft sequences containing Genethon markers mapped to the region. We identified two additional informative polymorphic markers from these sequences to narrow the critical region. We then entered each sequence into the National Center for Biotechnology Information BLAST search program (<http://www.ncbi.nlm.nih.gov/BLAST/>) to identify candidate genes, one of which was the gene that encodes the $\gamma 2$ subunit of AMP-activated protein kinase (*PRKAG2*).

Identification of the Mutation in the *PRKAG2* Gene

Exon–intron boundaries for protein-encoding sequences of *PRKAG2* (GenBank accession number, AJ249976) complementary DNA (cDNA) were identified in the GenBank data base with use of the BLAST search program within the following P1-derived artificial chromosome clones: RP11-79612 (cDNA bp 1 to 205; GenBank accession number, AC074257), RP5-1127D14 (bp 557 to 843; GenBank accession number, AC006358), and RP4-563H24 (bp 844 to 1800; GenBank accession number, AC006966). Intronic primers were derived on the basis of these sequences. Primer sequences are available with the full text of this article at <http://www.nejm.org> and at <http://www.bcmcardiofellows.org>. Fragments of genomic DNA were amplified by the polymerase chain reaction (PCR), and the products were purified with use of the QIAquick PCR purification kit (Qiagen, Valencia, Calif.). In the case of protein-encoding sequences (bp 206 to 556) that were not identified in the GenBank data base, RNA was isolated from lymphoblastoid cells with a random primer and reverse-transcribed with use of the Prostar system (Stratagene, Cedar Creek, Tex.). Direct sequencing reactions were performed in both the sense and antisense directions on an automated sequencer (Prism 377, Perkin–Elmer Applied Biosystems, Foster City, Calif.) with use of a technique involving dye-labeled terminators.⁹

RESULTS

Clinical Evaluation

Analysis of Families 1 and 2 (Fig. 1) showed that the mode of transmission of the Wolff–Parkinson–White syndrome was consistent with an autosomal dominant pattern of inheritance. Transmission occurred with high penetrance but with a variable degree of expression. Initial clinical presentations included reports of palpitations, presyncope, and syncope. The onset of clinical symptoms typically occurred in

late adolescence or the third decade of life. All 24 subjects (16 from Family 1 and 8 from Family 2) for whom base-line 12-lead electrocardiograms were available had evidence of ventricular preexcitation. Paroxysmal atrial fibrillation or flutter occurred in association with the Wolff–Parkinson–White syndrome in 44 percent of the subjects in Family 1 and 38 percent of the subjects in Family 2. Twelve members of Family 1 had had recurrent syncope. A total of eight subjects underwent invasive electrophysiologic studies, and a total of 10 anomalous conduction pathways were identified. Two of the eight (Subjects III-5 and IV-1 in Family 2) had two accessory connections, or tracts. Typical accessory pathways, including two right-sided pathways and one posterolateral pathway, were identified. Five of the eight family members who were studied had evidence of preexcitation with decremental conduction properties.

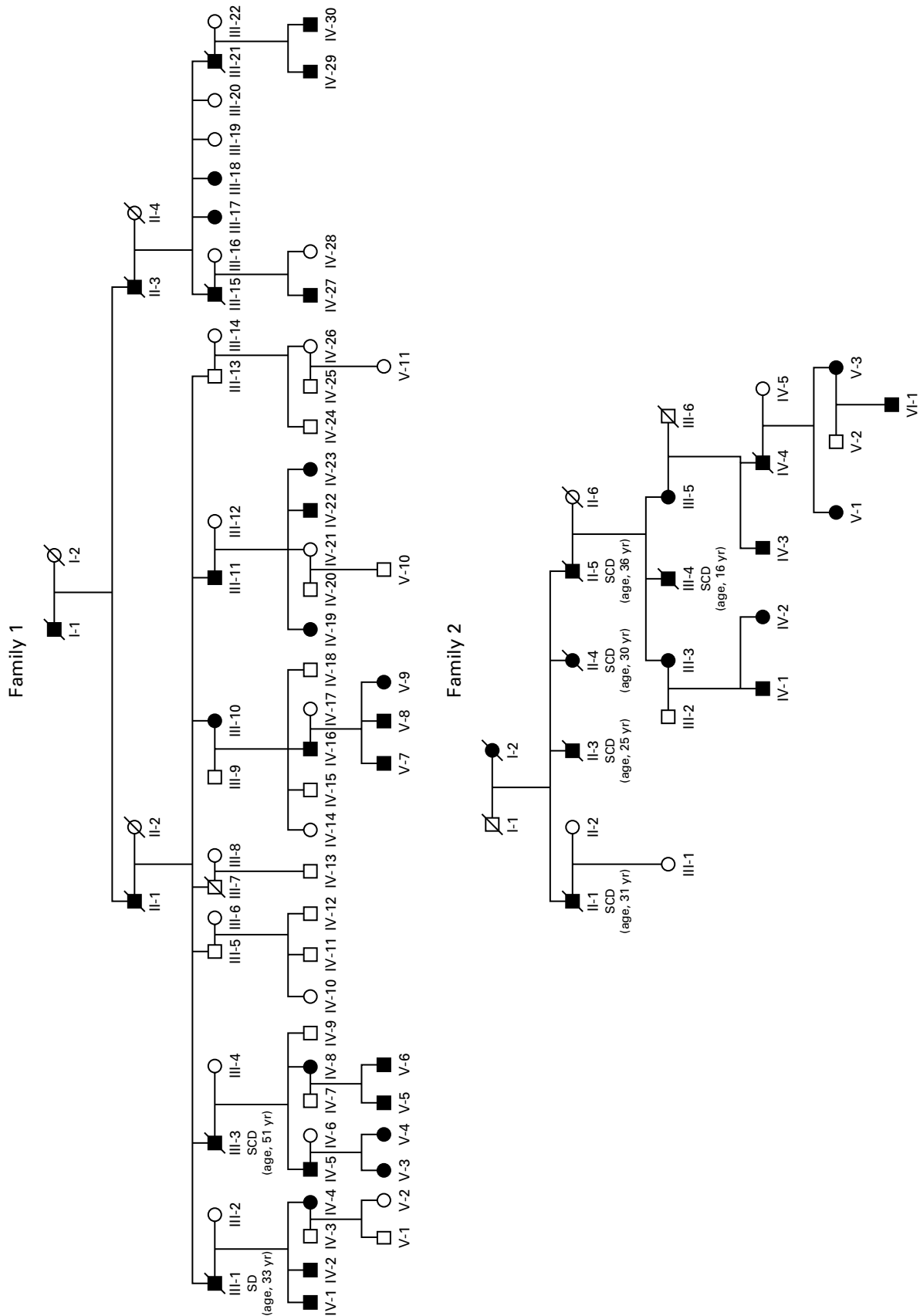
In addition to preexcitation, other forms of conduction disease were seen. Three young women (Subjects V-3 and V-4 in Family 1 and Subject V-1 in Family 2) had resting heart rates of less than 50 beats per minute and an inadequate heart-rate response to exercise. Progression to high-grade sinoatrial or atrioventricular block requiring the implantation of a pacemaker occurred in 76 percent of the affected members of both families who were older than 30 years of age. Cardiac hypertrophy was identified in 8 of 31 affected subjects (26 percent) who were evaluated. In two members of Family 1 (Subjects IV-1 and IV-16) hypertrophy progressed to left ventricular dysfunction (ejection fraction, <40 percent). In one member of Family 2 who had left ventricular hypertrophy (Subject IV-4) severe left ventricular dysfunction developed that required cardiac transplantation at the age of 42 years. Six patients died before the age of 40 years, but whether they had the Wolff–Parkinson–White syndrome or other features of the phenotype is unknown, since neither medical records nor postmortem findings were available.

Chromosomal Location and Haplotype Analysis

In determining the chromosomal location of the gene responsible for familial Wolff–Parkinson–White syndrome in Family 1, we first assessed whether there was linkage to 7q34–q36, a locus previously identified as the site of a gene responsible for a familial form of hypertrophic cardiomyopathy and the Wolff–Parkinson–White syndrome.¹⁰ The maximal two-point lod score was 9.82 for marker D7S636 at a distance of 0 cM. The maximal two-point lod score was 1.64

Figure 1 (facing page). Pedigrees of Two Families with Familial Wolff–Parkinson–White Syndrome.

The members of each family who died suddenly of an undetermined cause (SD) or from cardiac causes (SCD) and the age at death are shown. Solid symbols denote affected family members, circles female family members, squares male family members, and symbols with a slash deceased family members.



for marker D7S2439 in the analysis involving Family 2. The maximal combined lod score for both families was 9.82 at a distance of 5 cM from marker D7S636. Combined haplotype analysis indicated a shared region among affected members flanked by markers D7S2461 and D7S483 corresponding to a

genetic distance of less than 2.6 cM. Haplotype analysis with the use of a total of 10 polymorphic-repeat markers and 1 single-nucleotide polymorphism for Family 1 and Family 2 indicated that there were no alleles in common segregating at this locus, suggesting the two families do not share a recent common

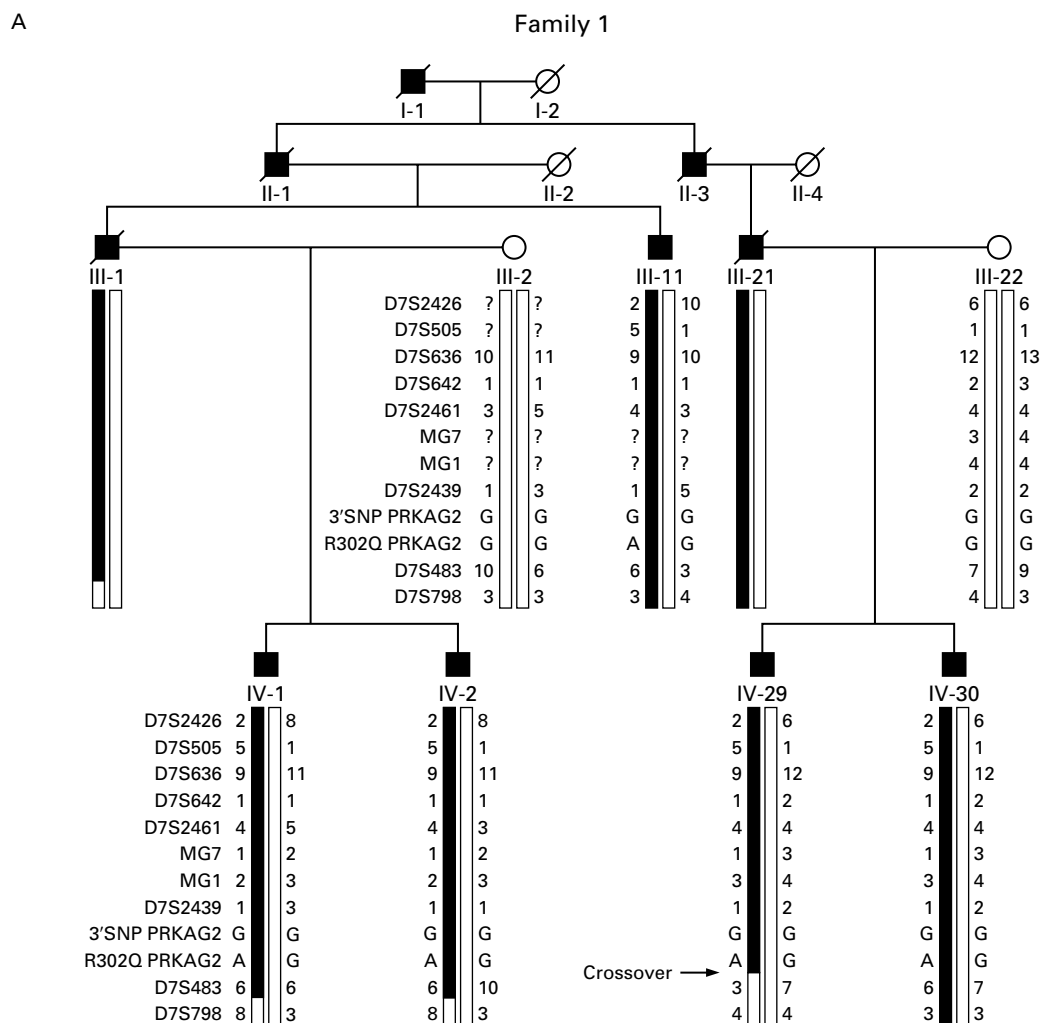
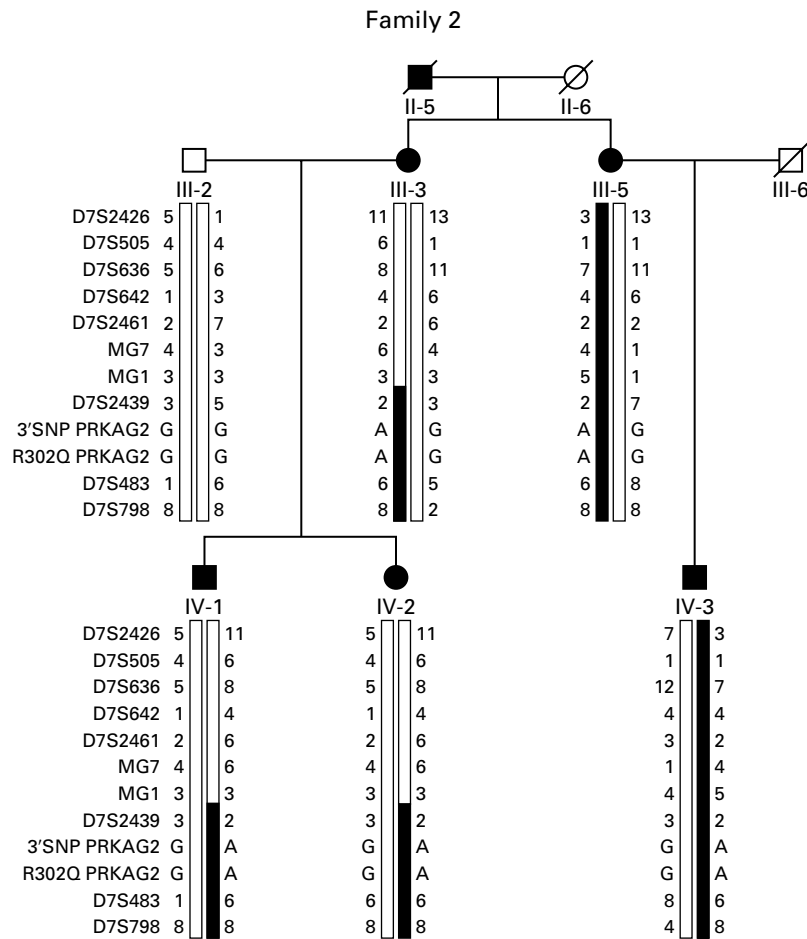


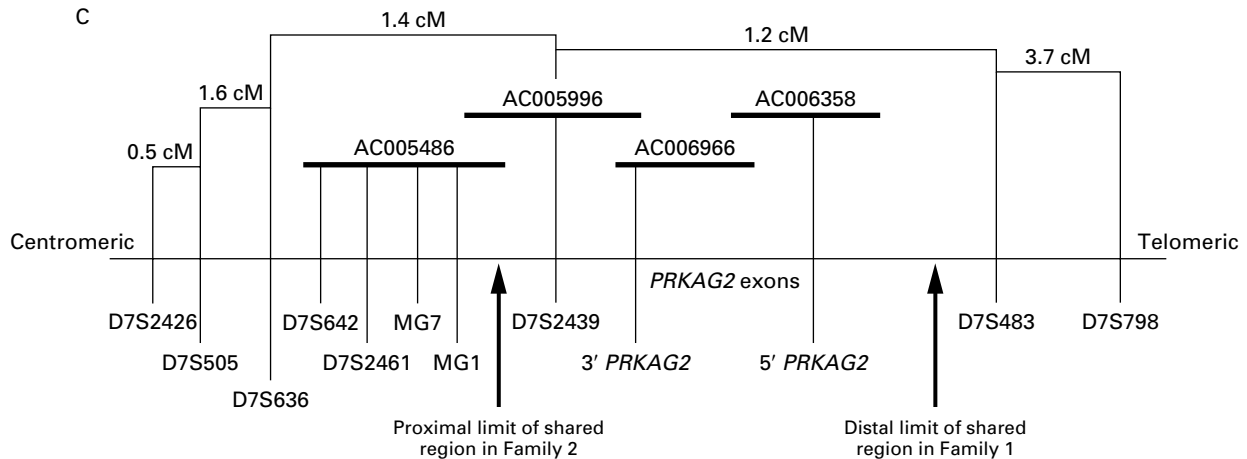
Figure 2. Haplotypes, Recombination, and Genetic Map of the *PRKAG2* Genomic Region in Family 1 and Family 2.

Panel A shows the results of haplotype analysis of nine members of Family 1 involving numerous polymorphic-repeat markers and one single-nucleotide polymorphism in the 3' untranslated region (3' SNP) of *PRKAG2*. MG7 and MG1 are novel markers identified on the basis of the sequence of P1-derived artificial chromosomes. In Subject IV-29, a crossover occurred between D7S2439 and D7S483, marking the distal limit of the shared region in this family. In Panel B, the results of haplotype analysis of six members of Family 2 involving the same polymorphic markers indicate that a crossover occurred between D7S2439 and MG1 in Subject III-3, marking the proximal limit of the shared region in this family. All affected members of Family 2 had a mutation (the substitution of adenine for guanine) at bp 1912 in the 3' untranslated region of *PRKAG2*. All affected members of Family 1 had the R302Q mutation in *PRKAG2*. All affected members of Family 2 had a mutation (the substitution of adenine for guanine) at bp 1912 in the 3' untranslated region of *PRKAG2*, whereas none of the affected members of Family 1 had this mutation. Panel C shows the distance (in centimorgans) of each marker shown in Panels A and B from the region of interest. Black bars in Panels A and B show the region shared by all the affected members of both families. In Panel C, an integrated map of the *PRKAG2* genomic region shows the genetic distances in centimorgans derived from the Genethon linkage map and the approximate positions of the crossovers (arrows). The drawing is not to scale. The accession numbers of the sequenced P1-derived artificial chromosomes are shown above the bold lines.

B



C



founder. The distinct haplotype of affected members in each family is shown in Figure 2.

Identification of the Mutation in the PRKAG2 Gene

After we determined that PRKAG2 was in the critical genomic region, we amplified and sequenced from

genomic DNA affected and unaffected family members. A sequence variation (the substitution of adenine for guanine) was identified that corresponded to bp 995 of the PRKAG2 cDNA sequence in all affected members in Family 1. This change results in a change in the amino acid at residue 302 from ar-

guanine to glutamine (R302Q). The identical sequence variation was subsequently found in all affected members of Family 2. Unaffected relatives in both families had no evidence of this sequence variation. The same PCR product from genomic DNA was sequenced in 300 chromosomes from control subjects selected from the general population, which showed no evidence of sequence variation. The existence of the R302Q mutation was independently confirmed by analysis of the results of restriction-enzyme digestion (Fig. 3). Taken together, the findings indicate that this mutation in *PRKAG2* is likely to cause familial Wolff–Parkinson–White syndrome. An additional sequence variation (the substitution of adenine for guanine) was identified at bp 1912 in the 3' untranslated region of *PRKAG2* that was present in all affected members of Family 2, but not Family 1. This finding further confirms that these two families are unrelated. We have analyzed the protein-encoding sequence of *PRKAG2* in genomic DNA from five patients with sporadic cases of the Wolff–Parkinson–White syndrome and did not detect any mutations.

DISCUSSION

We studied two families in which the probands presented with the Wolff–Parkinson–White syndrome. Of the total of 70 family members whom we

examined, 31 were affected in five generations. The trait is inherited in an autosomal dominant pattern with complete penetrance and variable degrees of expression. All affected subjects had electrocardiographic evidence of preexcitation. Certain features occurred more commonly in our subjects than in those with sporadic Wolff–Parkinson–White syndrome. Paroxysmal atrial fibrillation and flutter were present in 44 percent of the subjects in Family 1 and 38 percent of the subjects in Family 2, an incidence that is significantly higher than the incidence of 15 to 20 percent that has been reported for sporadic Wolff–Parkinson–White syndrome.^{11,12} In addition, conduction abnormalities and cardiac hypertrophy are uncommonly associated with sporadic Wolff–Parkinson–White syndrome but were commonly seen in the two families that we studied.¹³ Electrophysiological studies showed a higher than expected incidence of preexcitation with decremental conduction properties.^{14,15} Six subjects died suddenly from cardiac causes before the age of 40 years. Although definitive diagnoses could not be confirmed in these obligate gene carriers, this finding suggests that the risk of sudden death is higher in patients with familial Wolff–Parkinson–White syndrome than in patients with sporadic cases. Nevertheless, the Wolff–Parkinson–White syndrome is a well-recognized cause of sudden death,

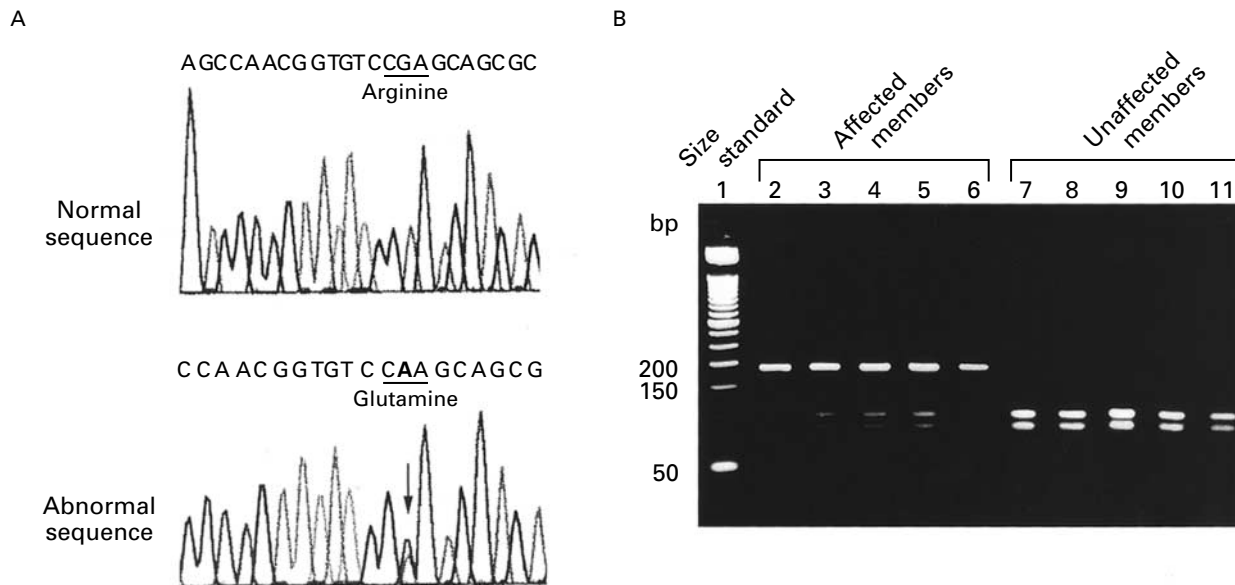


Figure 3. Sequence Analysis and Secondary Confirmation of the *PRKAG2* Mutation.

Sequence analysis of the sense strand of genomic DNA from an affected member of Family 1 indicates the substitution of adenine (A) for guanine (G) at bp 995 of *PRKAG2* complementary DNA. This results in the substitution of glutamine for arginine (R302Q) in the *PRKAG2* protein (arrow in Panel A). The mutation contained within a 190-bp amplicon abolishes an *Hpy188I* restriction-enzyme site, resulting in the persistence of this fragment in affected members after restriction-enzyme digestion (Panel B).

and in studies of young survivors of sudden cardiac arrest who did not have gross structural heart disease, the syndrome was present in up to 33 percent of patients.^{16,17}

In both families the gene responsible mapped to 7q34-q36, which had been previously documented to be the locus responsible for disease in a family with combined hypertrophic cardiomyopathy and the Wolff-Parkinson-White syndrome.¹⁰ Using the candidate-gene approach, we identified the gene *PRKAG2*,

which encodes the $\gamma 2$ regulatory subunit of AMP-activated protein kinase. The genetic defect is a point mutation resulting in the substitution of glutamine for arginine (R302Q). That the mutation was responsible for the phenotype in these families was confirmed by the following findings: the mutation was present in all affected members of two unrelated families, the mutation was absent in all unaffected members of both families as well as in 300 chromosomes from control subjects, and the substituted ar-

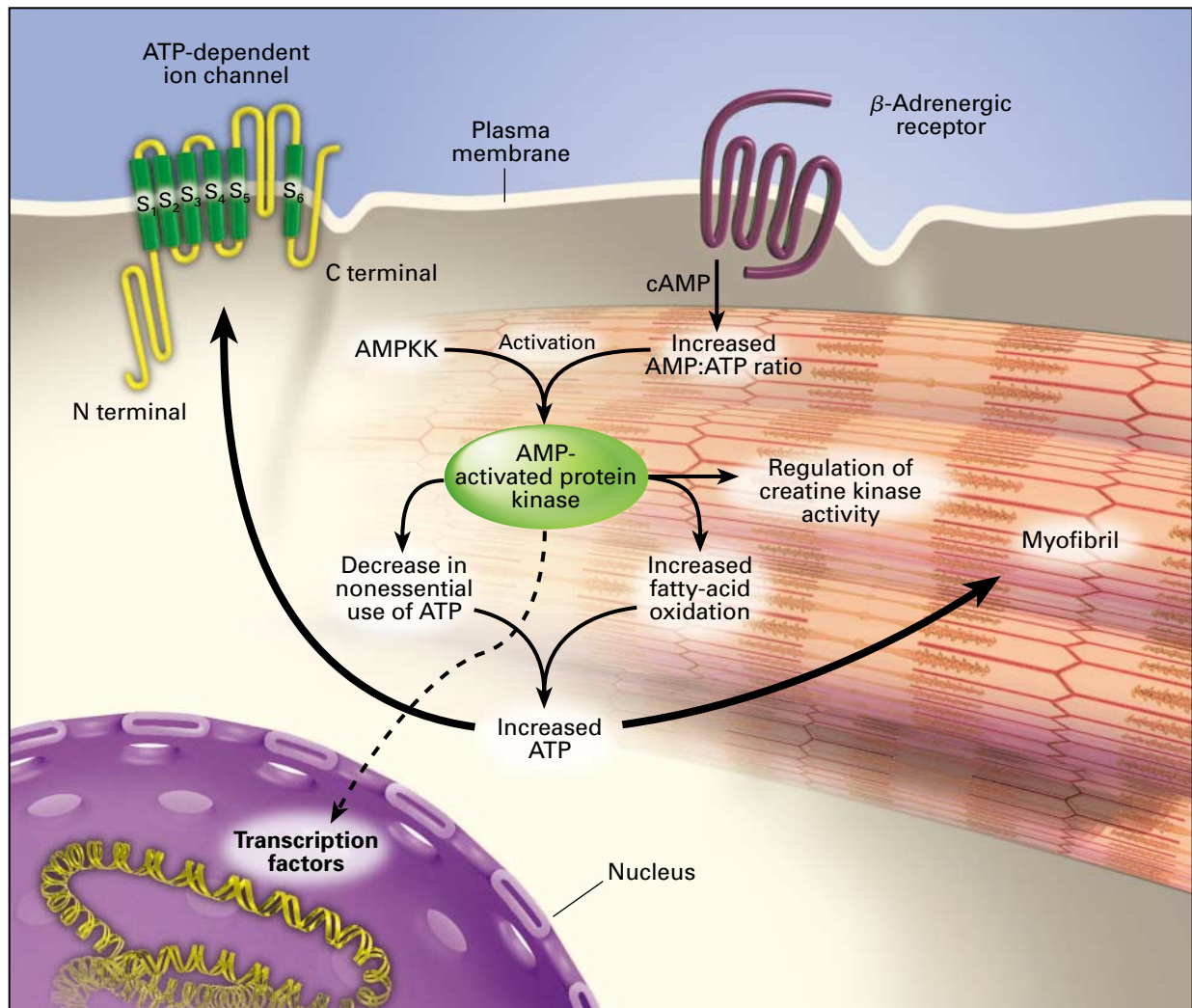


Figure 4. Regulation and Function of AMP-Activated Protein Kinase.

In response to an elevated ratio of AMP to ATP, AMP-activated protein kinase is activated by both direct AMP binding and phosphorylation by AMP-activated protein kinase kinase (AMPKK). AMP-activated protein kinase may also be activated in response to the increase in cyclic AMP (cAMP) and resultant increase in the AMP:ATP ratio induced by β -adrenergic stimulation. The diverse functions of AMP-activated protein kinase include the inactivation of nonessential ATP-consuming pathways, the regulation of the activity of creatine kinase, and the restoration of ATP levels through increased fatty-acid oxidation to meet vital cellular needs such as ion-channel activity and sarcomeric contraction. In addition, AMP-activated protein kinase may migrate to the nucleus and regulate gene transcription.

ginine is highly conserved across several species, reflecting the functional biologic importance of this amino acid.

The same mutation occurred in the two families despite the absence of a common founder. The absence of a common founder is based on the following evidence: the two families were not known to be related, they did not share alleles segregating in the vicinity of the *PRKAG2* gene, and the single-nucleotide polymorphism identified at bp 1912 of *PRKAG2* was present in all affected members of Family 2, but not Family 1. Nucleotide substitutions tend not to occur at random. Substitutions of adenine for guanine, as occurred in the mutation identified in the two families we studied, are 10 to 40 times as frequent as other base substitutions.¹⁸ The substitution in *PRKAG2* occurred at a CG doublet, and these doublets are often referred to as "hot spots" for mutation.¹⁹

The *PRKAG2* gene consists of 569 amino acids with a calculated molecular mass of 63 kd.²⁰ The γ subunit of the AMP-activated protein kinase heterotrimer functions as the AMP-binding site, thus regulating the activity of the protein. However, it is not possible to determine whether the R302Q mutation directly affects AMP binding, since the sequence of the AMP-binding site is not known.²¹

AMP-activated protein kinase functions as a metabolic sensor in cells, responding to cellular energy demands by regulating diverse ATP-using pathways and ATP-generating pathways.²² In the presence of an elevated ratio of AMP to ATP, AMP-activated protein kinase is activated by the direct binding of AMP, which exposes a threonine of the catalytic unit. The threonine is then phosphorylated by an upstream kinase (AMP-activated protein kinase kinase).²⁰ Activation decreases the use of ATP for nonessential functions and stimulates ATP-generating pathways, conserving ATP for more vital cellular requirements (Fig. 4). The *PRKAG2* isoform has a high level of expression in cardiac tissue, and it is also present in skeletal muscle, the brain, the placenta, the liver, the kidneys, and the pancreas.²⁰

The Wolff-Parkinson-White syndrome is thought to be due to accessory pathways derived from muscle fibers that provided direct continuity between atrial and ventricular myocardium during cardiogenesis.²³ The molecular defect that we found may in some way inhibit the normal regression of muscle fibers during atrioventricular septation. Although the propensity for arrhythmias in patients with familial Wolff-Parkinson-White syndrome is well known, the mechanism that triggers these episodes at the molecular level is not understood. The activation of AMP-activated protein kinase in response to β -adrenergic stimulation could account for the development of tachyarrhythmias during exercise or metabolic stress.^{24,25}

It is unclear whether the R302Q mutation acts as

an activating or inactivating mutation. However, the mutation probably leads to an alteration in the phosphorylation of downstream substrates within the heart. Potential targets are likely to include enzymes involved in energy metabolism and ion-channel proteins. An important task will be to identify the proteins whose phosphorylation is affected by this mutation. Although AMP-activated protein kinase affects gene expression,^{26,27} its role during cardiac development is unknown. The identification of this genetic defect has important implications for the diagnosis and treatment of the Wolff-Parkinson-White syndrome. The relation between the role of AMP-activated protein kinase in cardiac electrophysiology and the management of supraventricular arrhythmias and conduction disease remains to be elucidated.

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REFERENCES

1. Wan Q, Wu N, Fan W, Tang YY, Jin L, Fang Q. Clinical manifestations and prevalence of different types of supraventricular tachycardia among Chinese. *Chin Med J (Engl)* 1992;105:284-8.
2. Packard JM, Graettinger JS, Graybiel A. Analysis of the electrocardiograms obtained from 1000 young healthy aviators: ten year follow-up. *Circulation* 1954;10:384-400.
3. Hejtmancik MR, Hermann GR. The electrocardiographic syndrome of short P-R interval and broad QRS complexes: a clinical study of 80 cases. *Am Heart J* 1957;54:708-21.
4. Guize L, Soria R, Chaouat JC, Chrétien JM, Houe D, Le Heuzey JY. Prévalence et évolution du syndrome de Wolff-Parkinson-White dans une population de 138 048 sujets. *Ann Med Interne* 1985;136:474-8.
5. Kastor JA, Goldreyer BN, Moore EN, Spear JF. Re-entry — an important mechanism of cardiac arrhythmias. *Cardiovasc Clin* 1974;6:111-35.
6. Jackman WM, Wang X, Friday KJ, et al. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. *N Engl J Med* 1991;324:1605-11.
7. Neitzel H. A routine method for the establishment of permanent growing lymphoblastoid cell lines. *Hum Genet* 1986;73:320-6.
8. Ott J. Analysis of human genetic linkage. Rev. ed. Baltimore: Johns Hopkins University Press, 1991.
9. Rosenblum BB, Lee LG, Spurgeon SL, et al. New dye-labeled terminators for improved DNA sequencing patterns. *Nucleic Acids Res* 1997;25:4500-4.
10. MacRae CA, Ghaisas N, Kass S, et al. Familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome maps to a locus on chromosome 7q3. *J Clin Invest* 1995;96:1216-20.
11. Campbell RW, Smith RA, Gallagher JJ, Pritchett EL, Wallace AG. Atrial fibrillation in the preexcitation syndrome. *Am J Cardiol* 1977;40:514-20.
12. Bauernfeind RA, Wyndham CR, Swiryn SP, et al. Paroxysmal atrial fibrillation in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1981;47:562-9.
13. Al-Khatib SM, Pritchett EL. Clinical features of Wolff-Parkinson-White syndrome. *Am Heart J* 1999;138:403-13.
14. Klein GJ, Guiraudon GM, Kerr CR, et al. "Nodoventricular" accessory pathway: evidence for a distinct accessory atrioventricular pathway with atrioventricular node-like properties. *J Am Coll Cardiol* 1988;11:1035-40.
15. Aliot E, de Chillou C, Revault d'Allones G, Mabo P, Sadoul N. Mahaim tachycardias. *Eur Heart J* 1998;19:Suppl E:E25-E31, E52-E53.
16. Benson DW Jr, Benditt DG, Anderson RW, et al. Cardiac arrest in young, ostensibly healthy patients: clinical, hemodynamic, and electrophysiologic findings. *Am J Cardiol* 1983;52:65-9.

17. Topaz O, Perin E, Cox M, Mallon SM, Castellanos A, Myerburg RJ. Young adult survivors of sudden cardiac arrest: analysis of invasive evaluation of 22 subjects. *Am Heart J* 1989;118:281-7.
18. Cooper DN, Krawczak M. The mutational spectrum of single base-pair substitutions causing human genetic disease: patterns and predictions. *Hum Genet* 1990;85:55-74.
19. Thompson MW, McInnes RR, Willard HF. Thompson & Thompson genetics in medicine. 5th ed. Philadelphia: W.B. Saunders, 1991.
20. Cheung PC, Salt IP, Davies SP, Hardie DG, Carling D. Characterization of AMP-activated protein kinase gamma-subunit isoforms and their role in AMP binding. *Biochem J* 2000;346:659-69.
21. Woods A, Cheung PCF, Smith FC, et al. Characterization of AMP-activated protein kinase beta and gamma subunits: assembly of the heterotrimeric complex in vitro. *J Biol Chem* 1996;271:10282-90.
22. Crute BE, Seefeld K, Gamble J, Kemp BE, Witters LA. Functional domains of the alpha catalytic subunit of the AMP-activated protein kinase. *J Biol Chem* 1998;273:35347-54.
23. Dunnigan A. Developmental aspects and natural history of preexcitation syndromes. In: Benditt DG, Benson DW Jr, eds. Cardiac preexcitation syndromes: origins, evaluation, and treatment. Boston: Martinus Nijhoff Publishing, 1986:21-9.
24. Furlanello F, Bertoldi A, Bettini R, Dallago M, Vergara G. Life-threatening tachyarrhythmias in athletes. *Pacing Clin Electrophysiol* 1992;15:1403-11.
25. Moule SK, Denton RM. The activation of p38 MAPK by the beta-adrenergic agonist isoproterenol in rat epididymal fat cells. *FEBS Lett* 1998;438:287-90.
26. Leclerc I, Kahn A, Doiron B. The 5'-AMP-activated protein kinase inhibits the transcriptional stimulation by glucose in liver cells, acting through the glucose response complex. *FEBS Lett* 1998;431:180-4.
27. Winder WW, Holmes BF, Rubink DS, Jensen EB, Chen M, Holloszy JO. Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. *J Appl Physiol* 2000;88:2219-26.

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CORRECTION

**Identification of a Gene Responsible for Familial
Wolff–Parkinson–White Syndrome**

Identification of a Gene Responsible for Familial Wolff–Parkinson–White Syndrome . On page 1823, in the list of authors, “Al-Sayegh Hassan” should have read, “Ali Hassan Al Sayegh.”

CORRECTION

Identification of a Gene Responsible for Familial Wolff–Parkinson–White Syndrome

Identification of a Gene Responsible for Familial Wolff–Parkinson–White Syndrome . On page 1823, the first sentences under the heading “Clinical Evaluation” should have read, “Written informed consent was obtained from all participants according to the guidelines of the University of Ottawa Heart Institute and the Inherited Heart Disease Section, National Heart, Lung, and Blood Institute, National Institutes of Health. The DNA analysis was performed at Baylor College of Medicine without the submission of a protocol to the Baylor College of Medicine institutional review board as required by federal regulations.”