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Parental Electrocardiographic Screening Identifies a High Degree of Inheritance for Congenital and Childhood Nonimmune Isolated Atrioventricular Block

Alban-Elouen Baruteau, MD; Albin Behaghel, MD; Swanny Fouchard, PhD; Philippe Mabo, MD; Jean-Jacques Schott, PhD; Christian Dina, MS; Stéphanie Chatel, PhD; Elisabeth Villain, MD; Jean-Benoit Thambo, MD, PhD; François Marçon, MD; Véronique Gournay, MD, PhD; Francis Rouault, MD; Alain Chantepie, MD; Sophie Guillaumont, MD; François Godart, MD, PhD; Raphaël P. Martins, MD; Béatrice Delasalle, MS; Caroline Bonnet, MD; Alain Fraisse, MD, PhD; Jean-Marc Schleich, MD, PhD; Jean-René Lusson, MD; Yves Dulac, MD; Jean-Claude Daubert, MD; Hervé Le Marec, MD, PhD; Vincent Probst, MD, PhD

Background—The origin of congenital or childhood nonimmune isolated atrioventricular (AV) block remains unknown. We hypothesized that this conduction abnormality in the young may be a heritable disease.

Methods and Results—A multicenter retrospective study (13 French referral centers, from 1980–2009) included 141 children with AV block diagnosed in utero, at birth, or before 15 years of age without structural heart abnormalities and without maternal antibodies. Parents and matched control subjects were investigated for family history and for ECG screening. In parents, a family history of sudden death or progressive cardiac conduction defect was found in 1.4% and 11.1%, respectively. Screening ECGs from 130 parents (mean age 42.0±6.8 years, 57 couples) were compared with those of 130 matched healthy control subjects. All parents were asymptomatic and in sinus rhythm, except for 1 with undetected complete AV block. Conduction abnormalities were more frequent in parents than in control subjects, found in 50.8% versus 4.6%, respectively ($P<0.001$). A long PR interval was found in 18.5% of the parents but never in control subjects ($P<0.0001$). Complete or incomplete right bundle-branch block was observed in 39.2% of the parents and 1.5% of the control subjects ($P<0.0001$). Complete or incomplete left bundle-branch block was found in 15.4% of the parents and 3.1% of the control subjects ($P<0.0006$). Estimated heritability for isolated conduction disturbances was 91% (95% confidence interval, 80%–100%). *SCN5A* mutation screening identified 2 mutations in 2 patients among 97 children.

Conclusions—ECG screening in parents of children affected by idiopathic AV block revealed a high prevalence of conduction abnormalities. These results support the hypothesis of an inheritable trait in congenital and childhood nonimmune isolated AV block. (***Circulation*. 2012;126:1469-1477.**)

Key Words: atrioventricular block ■ conduction ■ ECG screening ■ genetics ■ pediatrics

Atrioventricular (AV) block is a rare electrocardiographic finding in neonates and children who are at risk of sudden death in the absence of cardiac pacing. It can be caused by various conditions such as transplacental passage of maternal anti-Ro/SSA or anti-La/SSB antibodies, structural congenital heart disease, postoperative complications, myocarditis, neuromuscular disorder, or metabolic disease. However, in some cases, no obvious cause of AV conduction disorder can be identified. Familial clustering of progressive cardiac conduction defect (PCCD) of unknown cause, including congenital AV block, has been reported. Published pedigrees have shown an autosomal dominant inheritance with incomplete penetrance and variable expressivity.[1–3] Given that a limited number of genes have been found to be responsible for hereditary PCCD in

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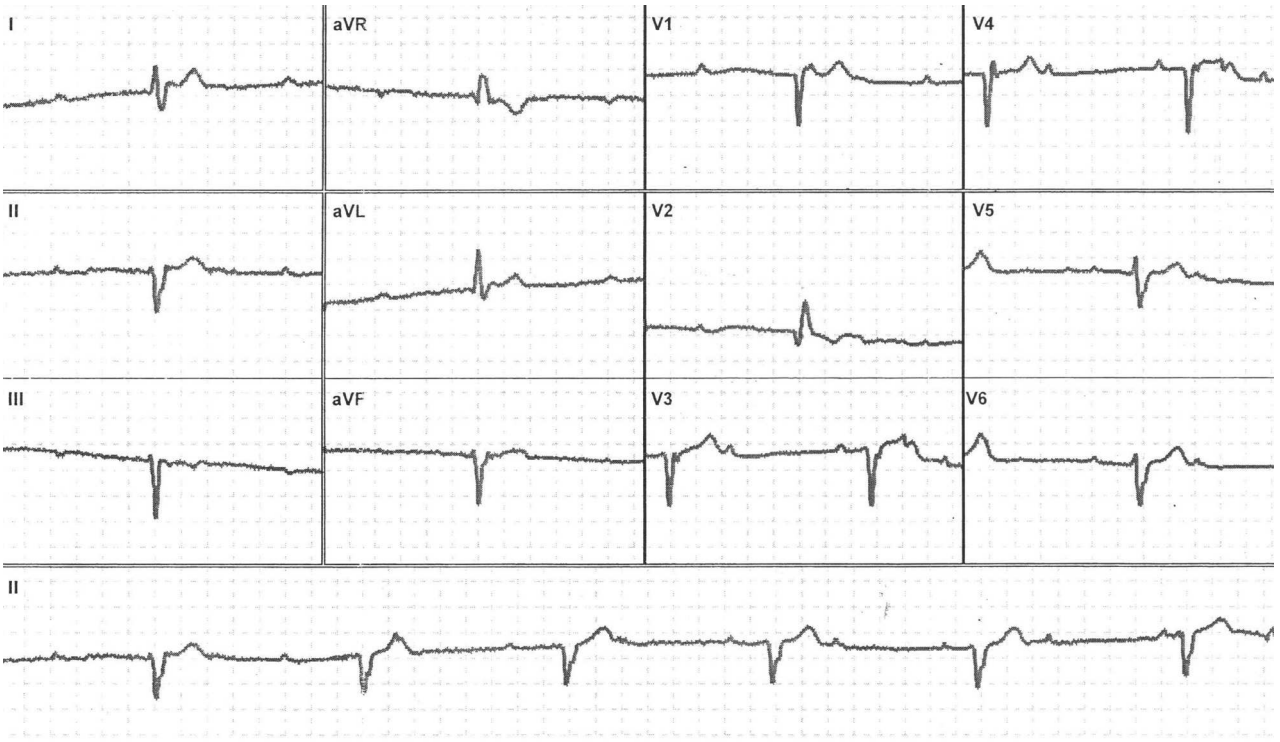


Figure 1. Screening ECG of a 56-year-old father showing third-degree atrioventricular block and a wide QRS complex escape rhythm.

adults[4–6] and that it has been recently shown that several common variants modulate heart rate, PR interval, and QRS complex durations,[7–9] we hypothesized that idiopathic AV block in the young may be a heritable disease.

Editorial see p 1434
Clinical Perspective on p 1477

This hypothesis was tested in a nationwide (France) retrospective cohort of children with idiopathic pediatric AV block, with examination of family histories of conduction disorders or sudden death and the electrocardiographic characteristics of apparently healthy parents.

Methods

Clinical Investigation

A retrospective study conducted from 1980 to 2009 at 13 French tertiary hospitals provided the basis for a clinical database of 141 children presenting with nonimmune isolated AV block diagnosed in utero or in early childhood. Because 9% of mothers who are seronegative at the time of fetal diagnosis later become seropositive,[10] and once they are detected, the antibodies permanently remain in the maternal serum, the mothers of all patients included in the present study systematically underwent, on inclusion, a screening for antibodies to soluble nuclear antigens 48-kd SSB/La, 52-kd SSA/Ro, and 60-kd SSA/Ro by use of previously described high-sensitivity, quantitative radioligand assays.[11] AV block was classified as congenital if it was diagnosed in utero, at birth, or during the first month of life and as childhood AV block if diagnosed between the first month and the fifteenth year of life.[12] The methodology and available data on the clinical characteristics of these patients have been reported previously.[10] The parents of the 141 children studied were contacted by the genetic research unit of l'Institut du Thorax, Nantes, France, and informed about the possibility of parental screening for asymptomatic cardiac conduction disorders. Relatives were asked about family histories of sudden death, PCCD, or heart block at a young age and invited to consult a cardiologist to undergo physical examination and a screening 12-lead ECG. Healthy control subjects from the general population, matched for age and sex, were also enrolled at l'Institut du Thorax and subjected to review of family history, physical examination, and a screening 12-lead ECG. The study was conducted according to the French guidelines for genetic research and was approved by the Ethics Committee of Nantes University Hospital. All participants gave their informed written consent.

ECGs were centralized at l'Institut du Thorax and analyzed by 3 medical investigators. ECG readers were blinded between control subjects and family members. The 3 ECG readers all analyzed each ECG, and measurements were then averaged. Paper speed was 25 mm/s. Heart rate, P-wave duration, PR interval, QRS-complex duration, QRS axis, and QT interval were measured at rest with DatInf Measure dedicated software (DatInf GmbH). All included values were averaged from 3 to 5 interval measurements. QT interval was measured in the lead that showed the longest QT, usually V_2 or V_3, and QT rate correction was performed with Bazett's formula, as recommended.[13] The mean frontal plane electric axis, determined by the vector of the maximal QRS deflection, was considered to be normal within $-30°$ and $+90°$. Left-axis deviation was defined as $-30°$ and beyond and right-axis deviation as $+90°$ and beyond. Complete or incomplete right bundle-branch block (RBBB) and left bundle-branch block (LBBB) and left anterior or posterior fascicular block were defined according to American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations.[14,15] PR-interval duration <200 ms was considered normal. First-, second-, and third-degree AV blocks were classified according to consensual definition.[16] Sinus bradycardia was defined as a sinus rhythm <60 bpm.

Statistical Analysis

Analyses were performed with PASW Statistics 18 software (SPSS Inc). Categorical variables were expressed as numbers and percentages. Continuous variables with normal distribution were expressed as mean$\pm$SD. Time variables were presented with median (25th–75th percentiles) or median (minimum-maximum). Parents and control subjects were matched 1-to-1 for sex and age on ECG

recording. Nonparametric tests for paired data were used to compare the 2 groups. The McNemar test was performed for categorical variables and Wilcoxon signed rank tests for continuous variables. The Kaplan-Meier method was used to estimate time to complete block and pacemaker implantation.

To compare children's data from groups with 0, 1, or 2 affected parents, a 1-way ANOVA was performed for continuous variables with a Tukey post hoc test if needed, and a Pearson χ^2 test was used for categorical variables. To compare continuous variables with nonnormal distribution, a Kruskal-Wallis test was performed. A 2-sided P value <0.05 was considered statistically significant.

Genetic Analysis

For 141 children, 97 parents gave their written consent for a blood sample from their child. Genomic DNA was extracted from peripheral blood lymphocytes by use of standard protocols. Mutation screening of *SCN5A* was performed by high-resolution melting assay on the Light Cycler 480 System (Roche) followed by bidirectional sequencing of abnormal profiles or directly by sequencing (ABI PRISM 3730 DNA Sequencer, Applied Biosystems).

Heritability Estimate

To estimate heritability, we used the biometric model, assuming a quantitative liability normalized (mean 0 and variance 1) trait L and a threshold T above which an individual is declared affected (Falconer). The variance of L is divided into polygenic G (variance s^2_p) and environmental E (variance s^2_e) components. This classic model was modified slightly to allow 2 different thresholds, *Tp* and *To*, which reflect the different severity of status in parents and offspring: $L=G+E$. Both components follow a normal distribution, $L\sim N(0, s^2g)+N(0, s^2e)$, with $s^2g+s^2e=1$. Because of independence of the 2 components $L\ N(0, s^2g+s^2e)$ heritability is the proportion of genetic variance: $h^2=s^2g/(s^2g+s^2e)=s^2g$.

We simulated trios (1 child and 2 parents) for a grid of heritability values i and retained trios in which the children were affected ($L>To$) to estimate mean L_i in parents (μ_p), conditioned on the children being severely affected. The likelihood of observing 66 affected children of 130 given children polygenic value was estimated for each heritability value i as follows: $Li(A/pg)=66\times\log_e(\pi)+64\times\log_e(1-\pi)$. $\pi=\Phi^{-1}(Tp, \mu=\mu_p, \sigma^2=1)$.

Results

A total of 130 parents, including 57 couples and 16 isolated parents, and 130 matched control subjects were analyzed. Sex ratio was 0.88 in the 2 groups, and mean age at the time of ECG recording was 42.0±6.8 and 42.0±6.6 years, respectively.

Characteristics of Nonimmune Isolated AV Block in Children

A cohort of 141 white children affected by a nonimmune isolated AV block was compiled. Their characteristics and long-term outcomes have been published elsewhere.[10] Briefly, AV block was asymptomatic in 119 patients (84.4%) and complete in 100 (70.9%). Incomplete AV block progressed to complete in 29 patients (70.7%) with incomplete block. At 10 years' time, the proportion of children with incomplete block was 81.1%±3.6%. Narrow QRS complexes were present in 18 (69.2%) of 26 patients with congenital AV block and 106 (92.2%) of 115 with childhood AV block. Pacemakers were implanted in 112 children (79.4%), during the first year of life in 18 (16.1%) and before 10 years of age in 90 (80.4%). The median (25th–75th percentile) time to pacemaker implantation was 2.0 (0–8.5) years. The pacing indication was prophylactic in 70 children (62.5%). During a median (25th–75th percentile) follow-up of 11 (6–16.5) years, no patient died or developed dilated cardiomyopathy. At the time of last follow-up, children's median (minimum-maximum) age was 15 (2–34) years. No complications occurred during long-term follow-up in 127 children (90.1%).

Table 1. Characteristics of ECG Parameters in Parents and Matched Control Subjects

	Parents (n=130)	Control Subjects (n=130)	*P* Value
Male/female sex ratio	0.88	0.88	
Age at ECG, y			
Mean±SD	42.0±7	42.0±7	
Median (minimum-maximum)	41 (24–65)	40 (25–62)	
Heart rate, bpm			0.69
Mean±SD	69±12.0	68±10.0	
Median (minimum-maximum)	69 (48–100)	65 (47–92)	
P wave, ms			<0.001
Mean±SD	98.2±22.3	88.6±12.8	
Median (minimum-maximum)	98 (47–188)	87 (56–125)	
PR interval, ms			0.33
Mean±SD	165±39	156±19	
Median (minimum-maximum)	157 (97–313)	160 (110–200)	
QRS complex, ms			<0.001
Mean±SD	109±29	73±13	
Median (minimum-maximum)	105 (55–247)	74 (41–110)	
QRS axis, °			0.15
Mean±SD	38±47	46±29	
Median (minimum-maximum)	60 (−140 to 140)	60 (−60 to 100)	
QT interval, ms			<0.001
Mean±SD	408±69	372±30	
Median (minimum-maximum)	392 (245–587)	370 (317–451)	
Corrected QT interval, ms			0.002
Mean±SD	423±36	408±25	
Median (minimum-maximum)	417 (350–549)	405 (360–462)	

All conduction intervals were significantly longer in parents than in control subjects. No difference appeared when heart rates in the 2 groups were compared.

Family History

None of the parents or control subjects had a personal history of unexplained syncope, known conduction disorders, or pacemaker implantation. A family history of sudden death was found in 1 parent (1.4%) and no control subjects ($P=1.0$). PCCD history was found in 8 parents (11.1%) and no control subjects ($P=0.01$). No family history of congenital or childhood AV block was found in the 2 groups. No consanguineous marriages were known in the families of affected children.

Screening ECG Analysis

All parents and control subjects were asymptomatic and in sinus rhythm except for 1 asymptomatic parent in whom previously

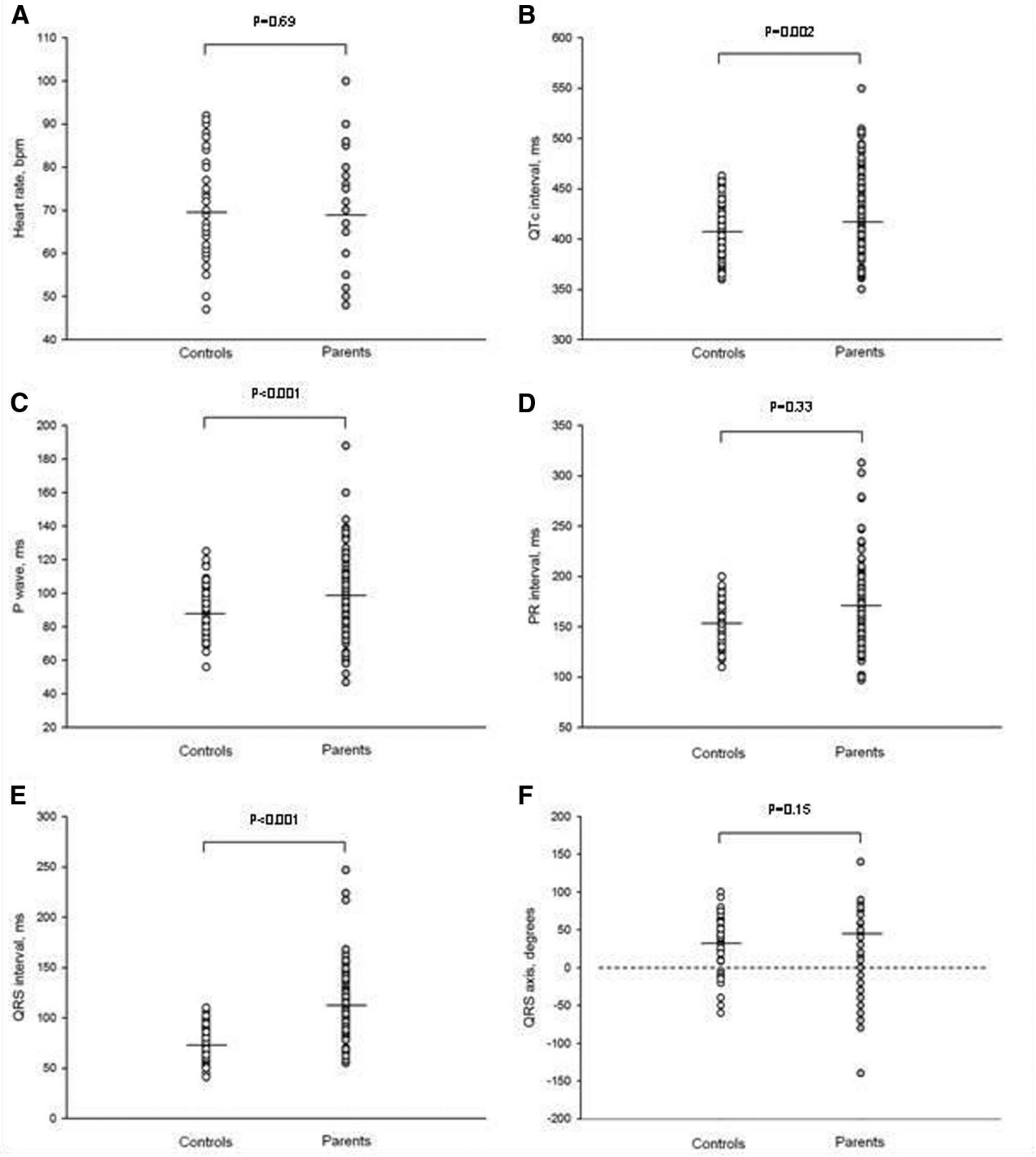


Figure 2. Comparison of heart rate (**A**), QRS axis (**F**), and different conduction intervals between parents and matched control subjects. P wave (**C**), PR interval (**D**), QRS complex (**E**), corrected QT interval (QTc) (**B**) durations were longer in parents than in control subjects. No differences appeared when heart rate and QRS axis were compared in the 2 groups.

undetected permanent complete AV block with broad QRS complex escape rhythm was found (Figure 1). ECG characteristics are presented in Table 1 and Figure 2. P wave, QRS complex, QT interval, and corrected QT-interval durations were significantly longer in parents than in control subjects. No significant difference was found when we compared heart rate, PR interval, and QRS axis in the 2 groups. Conduction abnormalities were more frequent in parents than in control subjects (Table 2), respectively found in 66 (50.8%) and 6 (4.6%) individuals ($P<0.001$). PR interval was prolonged in 24 parents (18.5%) but in no control subjects ($P<0.0001$). Complete or incomplete RBBB was observed in 51 parents (39.2%) and 2 control subjects (1.5%; $P<0.0001$). Incomplete RBBB was significantly more frequent in parents than in control subjects, found in 16 (12.3%) versus 2 (1.5%) cases, respectively ($P<0.001$). Complete or incomplete LBBB was found in 20 parents (15.4%) and 4 control subjects (3.1%; $P<0.0006$). Intraventricular conduction defect of any type (RBBB, LBBB,

Table 2. Subclinical Characterized Conduction Disturbances in Parents and Matched Control Subjects

	Parents, n (%)	Control Subjects, n (%)	*P* Value
Sinus bradycardia	14 (10.7)	12 (9.2)	0.67
Normal AV and intraventricular conduction	64 (49.3)	124 (95.4)	<0.001
Isolated incomplete RBBB	13 (10.0)	2 (1.5)	0.004
Incomplete RBBB+LAFB	2 (1.5)	0 (0)	0.16
Isolated complete RBBB	16 (12.3)	0 (0)	<0.0001
Complete RBBB+LAFB	4 (3.1)	0 (0)	0.05
Isolated LAFB	5 (3.8)	4 (3.1)	0.74
Isolated LPFB	0 (0.0)	0 (0)	
Isolated incomplete LBBB	2 (1.5)	0 (0)	0.16
Isolated complete LBBB	0 (0.0)	0 (0)	
Isolated first-degree AVB	7 (5.4)	0 (0)	0.008
First-degree AVB+incomplete RBBB	1 (0.8)	0 (0)	0.32
First-degree AVB+complete RBBB	7 (5.4)	0 (0)	0.008
First-degree AVB+complete RBBB+LAFB	5 (3.8)	0 (0)	0.02
First-degree AVB+LAFB	3 (2.3)	0 (0)	0.08
Third-degree AVB	1 (0.8)	0 (0)	0.32
PR prolongation	24 (18.5)	0 (0)	<0.0001
Impaired conduction in the RBBB	51 (39.2)	2 (1.5)	<0.0001
Impaired conduction in the LBBB	20 (15.4)	4 (3.1)	<0.0006

AV indicates atrioventricular; RBBB, right bundle-branch block; LBBB, left bundle-branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; and AVB, atrioventricular block.

left-axis deviation, right-axis deviation) was observed in 59 parents (45.4%) and 6 control subjects (4.6%; $P<0.0001$). Sinus bradycardia was not found in a statistically different proportion in the 2 groups (Figure 3). Among the 57 trios (made up of a child and his or her 2 parents) with available ECGs, cardiac conduction impairment was found in at least 1 parent of 39 children (68.4%) and in both parents of 17 children (29.8%).

Heritability Estimate

The heritability estimate for isolated conduction disturbances was very high, calculated at $h^2=91\%$ (95% confidence interval, 80%–100%). Individuals with at least 1 parent presenting with asymptomatic conduction impairment had a 6-fold increased relative risk of presenting with isolated nonimmune AV block.

Phenotype of Children According to Parents

Children were classified in 3 groups, respectively, of having 0, 1, or 2 parents presenting with subclinical conduction abnormalities (Table 3). No difference was found to be significant when the 3 groups were compared one to each other. Severity of conduction disorders in children, evaluated by age at diagnosis, time of progression from incomplete to complete heart block, baseline heart rate, presence of block-related symptoms, and age at cardiac pacing, did not differ significantly in these groups.

Genetic Study in Children

SCN5A gene screening was performed in 97 children and led to the identification of 2 different mutations in 2 children (p.Thr1806SerfsX27 and p.Arg367His). The p.Thr1806SerfsX27 mutation carrier was diagnosed at 7 years of age with first-degree AV block; the mutation was also found in her father, who was affected by a cardiac conduction defect (first-degree AV block, complete RBBB, and left anterior hemiblock). For the second mutation, the child was diagnosed at 12 months with a 2/1 AV block. The mutation was inherited from his mother, who did not present with any conduction block; however, pacemakers had been implanted in his maternal aunt and grandmother (no ECG or DNA available). This mutant p.Arg367His has been described in Brugada syndrome and early repolarization syndrome cases and failed to generate any current.[17–19]

Discussion

The aim of the present study was to evaluate the hypothesis that idiopathic AV block in the young may be a heritable disease. Parental ECG screening performed in a large cohort of children with pediatric idiopathic heart block provided strong evidence for a genetic origin in congenital and childhood nonimmune isolated AV block.

ECG screening in asymptomatic parents of children affected by idiopathic AV block revealed a high prevalence of impaired cardiac conduction characterized by a long P wave and prolonged PR and QRS intervals, indicative of intra-atrial, AV, and intraventricular conduction abnormalities. Moreover, well-characterized conduction disturbances were more frequent in parents than control subjects, mainly consisting of first-degree AV block, complete or incomplete RBBB, and left-axis deviation. The very low rate of conduction abnormalities observed in control subjects was comparable with that of historical studies reporting ECG findings in the general population. In a series of 122 043 asymptomatic adults, the prevalence of first-degree AV block, complete RBBB, and complete LBBB was reported to be 6.5, 1.8, and 0.13 per 1000, respectively, in this age group.[16,20,21] In addition, we found that congenital and childhood isolated nonimmune AV block is a highly heritable trait, because almost 95% of variation in the presence of the trait was attributed to heritable factors.

A genetic contribution has been suggested for a long time by reports of familial clusters of isolated heart block segregation, which included some rare pediatric cases.[1,3,4,22,23] Similarly, some affected children have been described in large families in whom *SCN5A* and *TRPM4* have been identified as the genes causing the conduction defect, but their ECG phenotype differed from the propositus cases in the present study because they presented with intraventricular conduction impairment.

This is the first relatively large-scale study looking for heritability in a cohort with pediatric idiopathic heart block. The present findings demonstrate a high degree of inheritance and a strong genetic contribution in the pathogenesis of congenital and childhood nonimmune isolated AV block.

A family history of sudden death or conduction disturbances was not relevant to determine whether an isolated pediatric heart block may be inherited or not, because the vast majority of index cases had no known family history. To date,

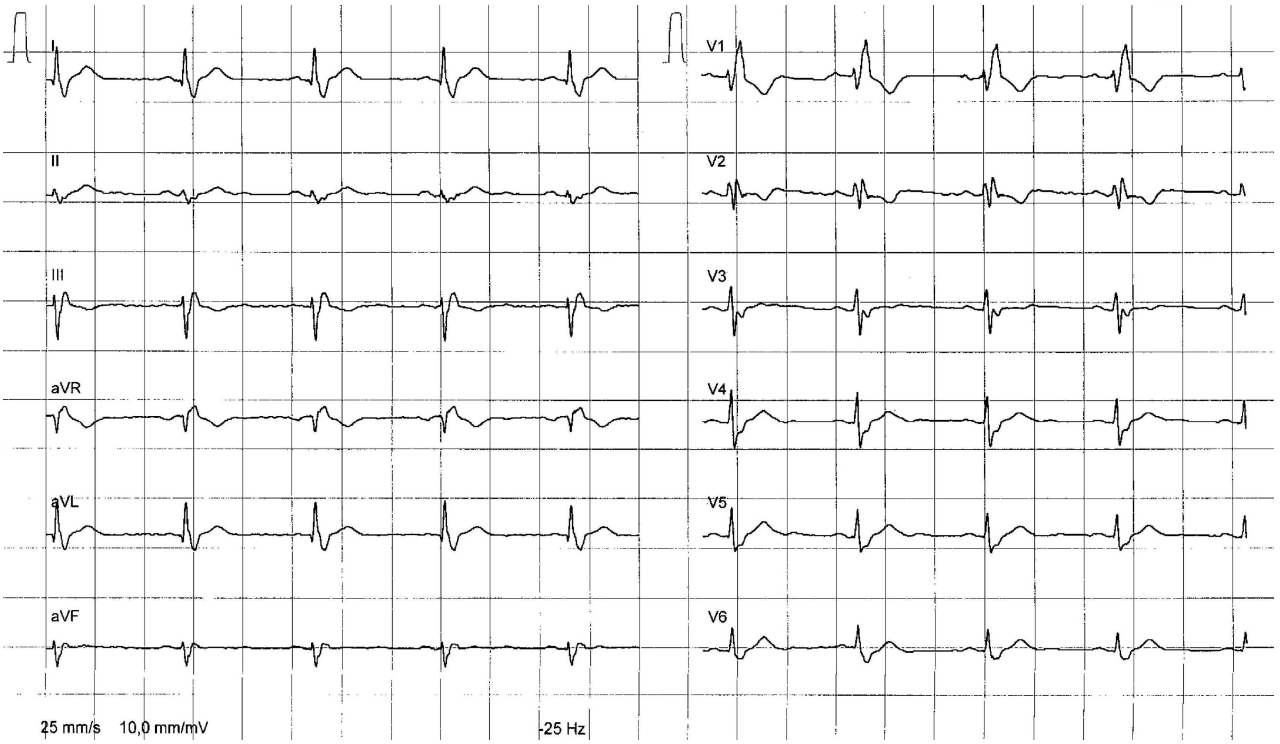


Figure 3. Screening ECG of a 48-year-old father showing sinus rhythm, complete right bundle-branch block, and left-axis deviation.

all published cases of inherited congenital or childhood isolated heart block have revealed an autosomal dominant inheritance in familial pedigrees, which suggests a major effect of the causative mutation.[2–6,22–25] Our findings from parental screening make this transmission mode less probable here. The phenotype of our propositus associates complete heart block with a narrow QRS complex, which differs from that reported to date in large affected families. These former data suggest that pediatric isolated AV block may have a distinct genetic background. The role of consanguinity has been discussed because this condition has been reported in some families with AV conduction defect, but no evidence of consanguineous marriages in families was found.[26] However, both parents were found to have subclinical conduction abnormalities in nearly 30% of the cases. Nonaffected parents may also be carriers of a variant with an incomplete penetrance. Parental phenotype appeared less severe than that of the children, mainly with diffuse conduction impairment but without complete heart block, except in 1 case. We hypothesize that parents may carry 1 or more allelic variant with a mild effect, which would explain the less severe phenotype. Once inherited from both parents, variants may cause more severe cardiac conduction disturbances in their progeny. This kind of transmission should correspond to a polygenic model of inheritance.

Surprisingly, we found different ECG phenotypes in children and their parents. Children were mainly diagnosed with permanent, complete AV block and narrow QRS escape rhythm. Those initially presenting with incomplete AV block progressed to a permanent, complete block in a short mean time and also had a narrow QRS complex. Only 17 (12.0%) of the 141 children were diagnosed with intraventricular conduction abnormalities. In contrast, parental ECG screening revealed mainly bundle-branch defects, particularly RBBB and left-axis deviation, possibly associated with first-degree AV block. An isolated PR-interval prolongation without evidence of infrahisian conduction impairment was found in only 5% of the parents.

In 1901, Morquio first called attention to a familial segregation of cardiac conduction disorders.[26] Since then, several cases of familial heart block segregation have been reported in the literature. They can be classified into 3 distinct clinical entities: (1) PCCD or hereditary Lenègre disease, also designated by some authors as progressive familial heart block type I or hereditary bundle-branch defect[2,4,22]; (2) progressive familial heart block type II[2]; and (3) hereditary progressive atrioventricular conduction defect.[1] Both a genetic background and congenital cases have been published for PCCD and progressive familial heart block type II.

PCCD is an autosomal dominant inherited disorder with incomplete penetrance, which phenotype associates RBBB possibly with right- or left-axis deviation or a prolonged PR interval.[27] Progression to complete heart block with a wide QRS escape rhythm can lead to syncope or sudden death. PCCD is an isolated conduction disorder, but some cases of dilated cardiomyopathy have been described in overlapping syndromes.[28] This is the most frequently reported type of hereditary heart block. To date, linkage analysis of large affected families has led to the identification of several causal mutations in 3 main genes[4–6,23,28–34]: *SCN5A*, the gene encoding the α-subunit of the cardiac sodium channel; *SCN1B*, the gene encoding the function-modifying sodium channel β1-subunit; and *TRPM4*, the gene encoding the transient receptor potential subfamily M member 4, a

Table 3. Comparison of Children's Characteristics in Groups With 0, 1, or 2 Affected Parents

	No Affected Parent (n=18)	1 Affected Parent (n=22)	2 Affected Parents (n=17)	*P* Value
Male/female sex ratio	1.57	0.57	0.7	0.27
Family history, n				
PCCD	1	3	3	0.46
Congenital AV block	0	0	0	1.0
Childhood AV block	0	0	0	1.0
Sudden death	0	1	0	0.45
At diagnosis				
Age at diagnosis, y				
Mean±SD	3.8±4.7	3.7±3.5	3.8±4.9	0.99
Median (minimum-maximum)	2.5 (0–19.0)	3.0 (0–12.0)	1.3 (0–15.0)	0.71
Congenital AV block, n (%)	4 (22.2)	3 (13.6)	3 (17.6)	0.78
Childhood AV block, n (%)	14 (77.8)	19 (86.4)	14 (82.4)	0.78
Complete AV block, n (%)	14 (77.8)	14 (63.6)	10 (58.8)	0.29
Wide QRS complex, n (%)	4 (22.2)	2 (9.1)	3 (17.6)	0.51
Heart rate, bpm, mean±SD	56±15	55±16	62±24	0.68
P wave, ms, mean±SD	96±66	70±18	80±19	0.37
QRS complex, ms, mean±SD	82±23	81±36	89±35	0.78
cQT interval, ms, mean±SD	456±100	450±47	403±64	0.25
At last follow-up				
Follow-up time, y	11.6±6.7	10.8±8.6	11.1±6.9	0.95
PM implantation, n (%)	13 (72.2)	16 (72.7)	12 (70.6)	0.99
Time,* mo				
Median (minimum-maximum)	6 (0–132)	0 (0–300)	13 (0–122)	0.53
Age at first PM, y				
Mean±SD	5.4±6.4	6.0±6.1	5.4±4.9	0.96
Median (minimum-maximum)	4 (0–22)	5 (0–25)	3 (0–15)	0.34
Mortality, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.0

PCCD indicates progressive cardiac conduction defect; AV, atrioventricular; cQT, corrected QT; and PM, pacemaker.
*Time between AV block diagnosis and first pacemaker implantation.

calcium-activated nonselective cation channel. The *NKX2.5* gene, which encodes a homeobox transcription factor, has also been identified in isolated pediatric AV blocks, but a conduction defect is most often associated with a secundum atrial septal defect or tetralogy of Fallot.[32,33]

Progressive familial heart block type II has been described in a South African family of European descent as an autosomal dominant cardiac disorder of adult onset. The pattern may present with associated isolated conduction disturbances, isolated dilated cardiomyopathy, or both.[34] Conduction impairment is characterized by sinus bradycardia and AV block with a narrow QRS complex. No gene has been identified yet, but a locus has been mapped to chromosome 1q32.2-q32.3.[35]

Hereditary progressive atrioventricular conduction defect is a rare condition, transmitted in an autosomal dominant manner with incomplete penetrance. It has been described in a limited number of families, including congenital cases of AV block.[1,36–38] ECG features were characterized by a progressive increase in AV conduction delay, from first-degree to complete AV block, with no associated intraventricular conduction defect.[1]

In the present study, the ECG phenotype of affected parents was close to that described in PCCD with RBBB, possibly associated with PR prolongation or left- or right-axis deviation, as in the historical descriptions of the idiopathic Lev-Lenègre disease.[39,40] Interestingly, the ECG phenotype of their children was similar to that described in hereditary progressive atrioventricular conduction defect. No differences appeared when we compared children from 0, 1, or 2 affected parents. The mixing of these 2 distinct phenotypes in the same family is highly unusual, although we found it in 39 of 57 trios made up of an affected child and his or her 2 parents. Why the ECG phenotype differs between a child and his or her parents remains to be clearly elucidated. We have previously shown that the pathophysiology of the *SCN5A*-related hereditary Lenègre disease results from haploinsufficiency of the cardiac Na^+ channel gene, which exacerbates physiological age-related progressive conduction slowing caused by fibrosis or an alternative process.[30] We hypothesize that children, despite the strong effect of inherited variants, may have a high safety factor that leads to sufficient impulse propagation for almost normal conduction in the His bundle and its branches. The hypothesis that the heart in the young human does not need all of the Na^+ channels for proper impulse propagation has been proposed.[30] Compensatory mechanisms of an unknown nature could also explain the difference in the phenotype between a child and his or her parents. ECG follow-up of these children until adulthood would be of interest

to determine whether intraventricular conduction impairment would subsequently appear with aging.

Study Limitations

We did not initially perform cardiological screening of siblings and second-degree relatives. At the time we designed the present study, we believed that we could not clinically or ethically justify offering ECG screening to these families, because the chances of identifying clinically relevant findings seemed smaller than the possible side effects (such as psychological stress, unforeseen diagnostic findings outside this context, and health insurance refusal or complaint) that could arise from such screening. Given our results, we are now aware that an isolated AV block in the young, despite apparently being sporadic with no known family history, may also reveal familial transmission of conduction disturbances.

Another limitation is that only 57 trios (including a child and his or her 2 parents) were constituted. Analysis of more familial clusters should lead to the ability to find differences when children from 0, 1, or 2 affected parents are compared.

Conclusions

ECG screening in parents of children affected by idiopathic AV block revealed diffuse subclinical impairment of cardiac conduction, which provides strong evidence for a genetic origin in congenital and childhood nonimmune isolated AV block. The heritability estimate confirmed the high contribution of genetic factors. Extensive investigations are now needed to assess family pedigrees and to determine the mode of transmission, which would open the field to further molecular studies.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The origin of congenital or childhood nonimmune isolated atrioventricular (AV) block remains unknown. Because familial clustering of progressive cardiac conduction defects of unknown causes, including congenital AV block, has been reported, we hypothesized that idiopathic AV block in the young may be a heritable disease. This hypothesis was tested in a nationwide (France) retrospective cohort of 141 idiopathic pediatric AV blocks. Screening ECGs from 130 parents (mean age 42.0±6.8 years, 57 couples) were compared with 130 matched healthy control subjects. Although a family history of sudden death or progressive cardiac conduction defect, respectively, was found in only 1.4% and 11.1% of parents, conduction abnormalities were more frequent in parents than in control subjects, found in 50.8% versus 4.6%, respectively ($P<0.001$), and estimated heritability for isolated conduction disturbances was 91% (standard error, 1.019; $P=2.10^{-16}$). *SCN5A* mutation screening identified 2 mutations in 2 patients among 97 children. Thus, ECG screening in parents of children affected by idiopathic AV block revealed diffuse subclinical impairment of cardiac conduction, which provides strong evidence for a genetic origin in congenital and childhood nonimmune isolated AV block. Such an ECG screening may be helpful in clinical practice if other obvious causes have been ruled out. Heritability estimate confirmed a high contribution of genetic factors, which opens the field to further molecular studies.