

Familial Occurrence of Atrioventricular Nodal Reentrant Tachycardia

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Background—Atrioventricular nodal reentrant tachycardia (AVNRT) is considered a sporadic disease occurring in ≈ 22.5 cases per 10000 in the general population. We define the prevalence and characteristics of familial AVNRT among patients who underwent radiofrequency ablation.

Methods and Results—Ablation reports of all patients with familial AVNRT (at least 2 first-degree family members) who underwent radiofrequency ablation in our institution and in another hospital were reviewed. There were 1587 patients from our institution, of whom 20 had ≥ 1 first-degree relatives with AVNRT. This indicates a familial AVNRT prevalence of 127 cases per 10000 (95% confidence interval, 82–196/10000). First-degree relatives of patients with AVNRT presented a hazard ratio of at least 3.6 for exhibiting AVNRT compared with the general population. After inclusion of 4 families with familial AVNRT who underwent ablation at another hospital our population study comprised a total of 24 families (50 patients) with AVNRT. Patients at ablation were younger in the familial AVNRT group when compared with the sporadic AVNRT group (44.2 ± 19 versus 54.8 ± 18 years old, $P=0.0001$). The male/female ratio was similar, with female predominance. The supraventricular tachycardia mechanism was typical slow/fast reentry in most cases in both groups. The most common familial relationship in our 24 families included a parent and a child in 67% of cases and less often 2 siblings (29%).

Conclusions—Familial AVNRT prevalence is higher than previously believed suggesting that this arrhythmia may have a genetic component. Autosomal dominance with incomplete penetrance is the most likely mode of inheritance. (*Circ Arrhythm Electrophysiol.* 2017;10:e004680. DOI: 10.1161/CIRCEP.116.004680.)

Key Words: child ■ female ■ male ■ parent ■ supraventricular tachycardia

Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common regular type of paroxysmal supraventricular tachycardia (PSVT) in adults.¹ It is considered to be a sporadic disorder that accounts for most cases of PSVT with a prevalence of 22.5/10000 persons and an incidence of 35/100000 person-years.² Nevertheless, there are several reports of AVNRT occurring in twins and members of the same family.^{3–6} To date, the largest report of familial AVNRT includes 14 members from 6 families of whom 13 underwent electrophysiological study (EPS) with ablation in 12. An autosomal-dominant mode of inheritance was suggested.³

However, the sample size out of which these 6 families were taken is unknown rendering the possibility of chance feasible, as sporadic diseases may also occur in 2 first-degree relatives.

In this study, we sought to define the prevalence of familial AVNRT among patients who underwent EPS and radiofrequency ablation at the Tel-Aviv Sourasky Medical Center between years 1992 and 2013. In addition, we assessed

the characteristics of these patients and those collected in another hospital.

Methods

The study was approved by the Tel Aviv Medical Center Institutional Review Board committee.

Patients who underwent AVNRT ablation in our center between years 1992 and 2013 were questioned about the existence of arrhythmias, EPS or RF ablation in other first-degree family members. Efforts were done to gather any documentation of these arrhythmias and procedure reports with a special emphasis on PSVT. Family members who were suspected to have PSVT were invited at our consultation for further work-up. Only cases who underwent diagnostic EPS or radiofrequency ablation and in whom the diagnosis of AVNRT was ascertained were included in the familial AVNRT cohort. Familial AVNRT was defined when at least 2 first-degree relatives had spontaneous clinical episodes of PSVT and AVNRT documented at EPS.

Data of patients from 4 families with at least 2 first-degree relatives with AVNRT who underwent ablation at another hospital (Assuta medical center) by one of the authors (BB) were also included.

The following data were gathered from the familial cohort: (1) patient sex, age at symptoms onset and at ablation; (2) frequency of

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WHAT IS KNOWN

- Atrioventricular nodal reentrant tachycardia (AVNRT) has been considered a sporadic disease occurring in ≈ 22.5 cases per 10000 in the general population.
- Several case reports and small series of AVNRT occurring in members of the same family have been published in the literature. However, whether these case reports truly suggest increased probability of the arrhythmia among family members of patients with AVNRT as well as the prevalence of familial occurrence is unknown.

WHAT THE STUDY ADDS

- The current study found a high familial AVNRT prevalence among a large patient cohort. The prevalence corresponds to 127 cases per 10000 (95% CI of 82–196/10000).
- First-degree relatives of patients with AVNRT presented a hazard ratio of at least 3.6 for exhibiting AVNRT compared with the general population.
- The most common presumed mode of inheritance among the 24 families studied was autosomal dominance with incomplete penetrance.
- The characteristics of patients and the arrhythmias of familial AVNRT patients were not different from nonfamilial AVNRT patients.

AVNRT episodes before ablation; and (3) patient ethnicity. Patients were also contacted to establish a genealogical tree and asked to provide the age, sex, and PSVT arrhythmia status of all first-degree relatives.

Electrophysiological Study

After obtaining patient's informed consent, catheters were inserted and placed at the high right atrium and His area. In some patients, catheters were also placed in the coronary sinus and the right ventricle.⁷

Dual AV node physiology was defined as a ≥ 50 ms increment in AH interval after 10 ms decrement interval during single-atrial extra stimulation or ≥ 50 ms increment in AH interval after shortening pacing cycle length by 10 ms.

Baseline EPS included atrial stimulation (burst or extra stimulus pacing) and ventricular stimulation. If sustained AVNRT (lasting ≥ 30 s) was not induced, the same pacing maneuvers were repeated under isoproterenol infusion and withdrawal as previously described.⁷ AVNRT diagnosis was established according to published criteria and pacing maneuvers as applicable.⁸

Standard definitions of the mechanism of AVNRT were used.⁹

Statistical Analysis

Continuous data were summarized with mean \pm SD and compared using unpaired student *t* test. Categorical data were analyzed using the Fisher exact test. The expected prevalence of AVNRT based on population studies compared with the prevalence of familial AVNRT in the current study was analyzed using a binomial test.

The comparison between the mean ablation ages of familial versus nonfamilial AVNRT was calculated using the mixed linear model, taking into account the families and the intrafamily correlations. The Comprehensive Meta-analysis software was used for calculating the 95% confidence interval of the prevalence of the familial AVNRT, based on the simple Poisson Distribution (<http://www.meta-analysis.com/index.php>), whereas all other analyses were performed using the SPSS software version 21.0 (2012).

Results

Patient Cohort

Overall, 1587 patients (614 males [40%], mean age 55 ± 19 years, 93.7% Jewish) underwent AVNRT ablation at the Tel-Aviv medical center between years 1992 and 2013. Forty-one (2.6%) patients were 9 to 17 years old. Of the total cohort, 1556 did not have first-degree relatives with AVNRT and 31 had (Figure 1). These 31 patients belonged to 20 families including a total of 42 patients (11 of these patients underwent the ablation procedure in another hospital). One of the authors (BB) participated in all outside procedures except for 3. After inclusion of 4 families with familial AVNRT who underwent ablation at another hospital by one of the authors (BB), our population study comprised a total of 24 families (50 patients) with ≥ 2 first-degree relatives with EPS proven AVNRT.

Familial AVNRT Prevalence

Overall, the total AVNRT population at the Tel-Aviv Sourasky Medical Center included a total of 1576 households; 1556 households without familial AVNRT and 20 with familial AVNRT. This corresponds to a prevalence of familial AVNRT of 127/10000 persons (95% confidence interval, 82–196/10000 persons) compared with a known prevalence of PSVT in the general population of 22.5/10000 persons.

The difference between the predicted prevalence of AVNRT according to previous population based studies² and our finding was significant using a binomial test ($P < 0.0001$). Our findings correspond to at least a 3.6 \times higher chance of developing AVNRT among first-degree relatives of patients with AVNRT compared with the general population.

Familial Versus Nonfamilial AVNRT

Patients with familial AVNRT were younger at the age of ablation (Table). When comparing the age at ablation of probands (the first patients in each family who underwent ablation) with nonfamilial patients with AVNRT, an almost significant difference was found (46.5 ± 20.1 versus 54.8 ± 19.0 , $P = 0.052$). Typical AVNRT was more common in both groups occurring in 90% or more of patients, and female predominance was also seen in both groups (Table).

Familial AVNRT Patients' Characteristics

Comparison of the age at which symptoms of palpitations began in families with a parent and a child demonstrated earlier age of symptoms in the second generation compared with the first generation (25.5 ± 17.3 and 45.6 ± 19.9 years, respectively, $P < 0.0001$). However, no difference was found between siblings (18 ± 5.85 versus 24.85 ± 11.8 years, $P = 0.24$) for the first and second siblings, respectively.

All patients with familial AVNRT were Jewish with equal distribution between Ashkenazi and Sephardic Jews (48% Ashkenazi, 46% Sephardic, 3% mixed). None of the patients had evidence for structural heart disease. Finally, most patients ($n = 36$, 73%) reported symptoms frequency before ablation of at least 1 per month, while the rest were either

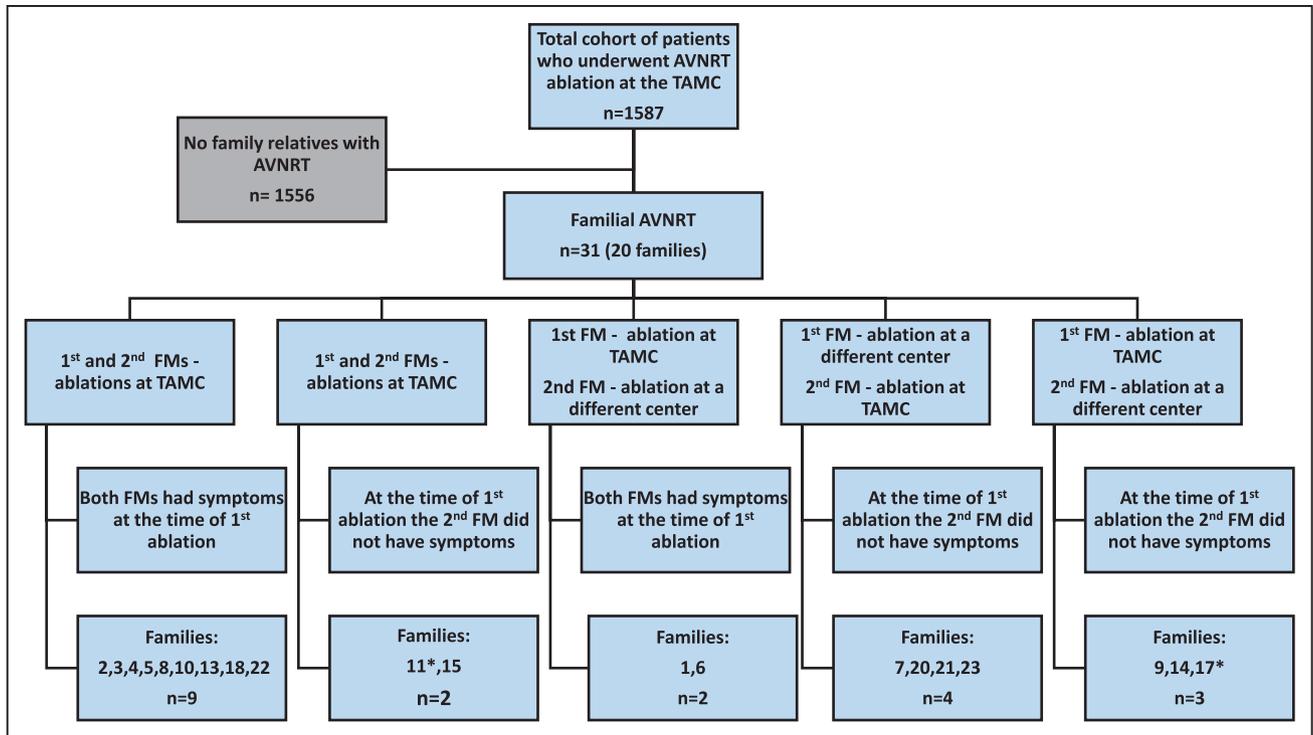


Figure 1. Flow chart describing the study design and how the families with AVNRT were identified. Family’s numbers correspond to those in Figure 2. *Families 11 and 15 had 3 members. The third member in family 11 and the 2 last members in family 15 underwent ablation at a different center. FM indicates family member; and TAMC, Tel-Aviv Medical Center.

ablated shortly after their first AVNRT episode (n=4), had rare episodes occurring every few months to years (n=6) or had variable (n=3) or unknown (n=1) symptom frequency.

Family Pedigrees

Figure 2 shows family trees of the 24 families. In most families only 2 generations are presented as the AVNRT phenotype was not known to be present in other generations. Among the families, 2 included 3 members with AVNRT while the rest had 2 members with this arrhythmia.

Overall, we identified 15 families including a parent and a child, 7 families including 2 siblings, 1 family including a mother and her 2 sons and 1 family including 2 sisters with their grandmother.

Of note, complete family data were not available for family no. 4. Also in 3 families (no. 1, no. 3, and no. 8) in which 2 siblings had EPS-proven AVNRT one of the parents had symptoms suggestive of PSVT without ECG or EPS documentation.

Discussion

Prevalence of Familial AVNRT

Until now, AVNRT was considered to be a sporadic disease with few reports in the literature of familial occurrence.³⁻⁶ However, the prevalence of familial occurrence was unknown. The results of our present study estimate the prevalence of familial AVNRT at 127/10 000 persons (95% confidence interval, 82–196/10 000 persons). These figures are much higher than the reported prevalence of the disease among the general population.² According to our findings, the risk of developing

AVNRT for first-degree relatives of patients with AVNRT is at least 3.6× higher than in the general population.

Familial Versus Sporadic AVNRT

The clinical characteristics of patients with familial AVNRT did not differ from those of patients with sporadic AVNRT. However, we found an earlier age at ablation in patients with familial AVNRT. This difference was almost significant (P=0.052) when comparing only the probands with sporadic AVNRT patients. Moreover, earlier age of disease manifestation was found in the second generation and siblings compared with the first generation, excluding the possibility of a bigger lag between disease manifestation and ablation among the parents. Nevertheless, we cannot rule out that this finding is biased as parental disease may lead to higher and earlier detection rate among offspring. Hayes et al.³ reported 6 families with ≥2 relatives with AVNRT. In one family, all 3 members with AVNRT had evidence for mitral valve prolapse.³ In this study, none of the patients had evidence for structural heart disease.

Table. Patients Baseline Characteristics

	Familial AVNRT (n=42)	Nonfamilial AVNRT (n=1556)	P Value
Age at ablation, y, mean (95 CI)	44.3 (38.9–49.7)	54.8 (53.8–55.7)	<0.001
Females (%)	23 (55)	926 (60)	0.53
Typical AVNRT (%)	37 (88)	1452 (93)	0.2

AVNRT indicates atrioventricular nodal reentrant tachycardia; and CI, confidence interval.

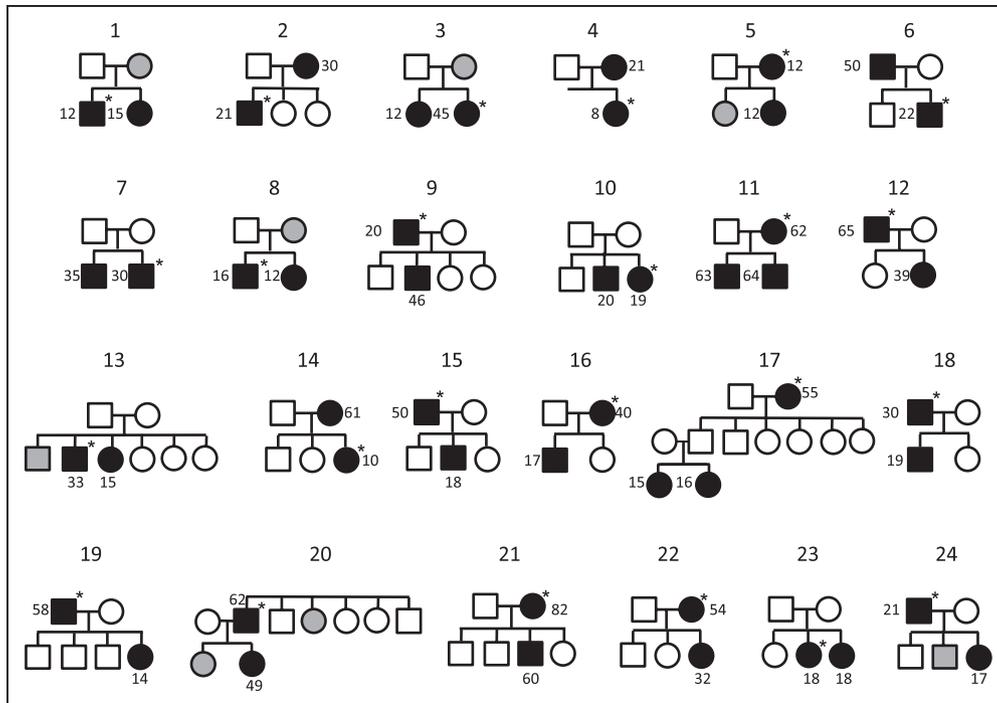


Figure 2. Pedigree trees of the 24 families with familial atrioventricular nodal reentrant tachycardia. Families 12, 16, 19, and 24 did not belong to our center cohort. In black are affected individuals and age of symptoms onset is written beside. In gray (families 1, 3, 5, 8, 13, 20, and 24) individuals with symptoms suggestive of paroxysmal supraventricular tachycardia without documentation. *Marks the first individual who underwent ablation from each family.

Possible Mode of Inheritance

The most common familial relationship in our 24 families included a parent and a child in 67% of cases and less often 2 siblings (29%). Similar familial relationship was reported by others.^{3,4,6} Of note, in 3 families with siblings one of the parents had symptoms suggestive of PSVT. On the basis of these pedigrees, and as the genetic basis of AVNRT is presently unknown (locus heterogeneity is likely), several modes of inheritance are possible. As most families had affected individuals over 2 successive generations, with no sex preference, a dominant inheritance with incomplete penetrance or polygenic inheritance are the most likely patterns. In the remaining families, x-linked and recessive inheritances are possible as well.

Interestingly, in one of our reported families (no. 22) with a mother and a daughter with AVNRT, the son of the daughter had a left lateral accessory pathway that was ablated. An association of dual AV node physiology and left lateral accessory pathway was reported in a pair of identical twins.¹⁰

Genetics

Epidemiological data from patients with Wolff–Parkinson–White syndrome showed that their first-degree relatives have 3× higher chance for preexcitation than the general population.¹¹ Moreover, previous genetic studies in patients with Wolff–Parkinson–White associated mutations in the *PRKAG2* gene and the syndrome.^{12–14} Interestingly, this mutation was associated with the presence of a nodoventricular pathway, a rare type of accessory pathway that shares similar electrophysiological properties with the AV node.¹³ Whether any genetic

involvement of familial AVNRT is related to the *PRKAG2* gene deserves confirmation.

Of note, in contrast to preexcitation that can be usually seen on the surface ECG, dual AV node physiology, the precursor of AVNRT, is rarely observed on the surface ECG. In addition, it is a common finding in patients without AVNRT.¹⁵ Therefore, revealing silent carriers of AVNRT, that is, patients who are prone to develop the arrhythmia in the future is much more difficult compared with Wolff–Parkinson–White syndrome.

It is important to stress that our patient population shares a common genetic background as all patients with familial AVNRT in this study were Jews. Further studies are needed to extrapolate our findings to other populations.

Limitations

Our estimation of the prevalence of AVNRT is based on a population based study from the United States that included all PSVT.² We are unaware of other population-based studies assessing the prevalence of PSVT, and estimations from this study were also used by others.¹ As AVNRT does not account for all cases of PSVT, the actual difference between the prevalence of sporadic AVNRT and familial AVNRT may be even higher. As stated before, our study was confined to a specific ethnic group and validation in other ethnicities is needed. Also, as it is difficult to anticipate on surface ECG who is prone to develop AVNRT, with time, more families with AVNRT may be found. In addition, it is possible that not all patients had full knowledge about relatives with AVNRT. Therefore, our finding may underestimate the true prevalence of familial AVNRT.

Conclusions

Our study is the first to report the prevalence of familial AVNRT using a large patient cohort. We found that the prevalence of familial AVNRT is 127/10000 (95% confidence interval, 82–196/10000 persons). First-degree relatives of patients with AVNRT presented a hazard ratio of at least 3.6 for exhibiting AVNRT compared with the general population. Autosomal dominant with partial penetrance is the most likely mode of inheritance. Further genetic studies are underway to explore the mode of inheritance of this common arrhythmia.

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Disclosures

None.

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