Familial Brugada Syndrome Associated With a Complete Deletion of the *SCN5A* and *SCN10A* Genes

Síndrome de Brugada familiar asociado con una deleción completa de los genes SCN5A *y* SCN10A

To the Editor,

Brugada syndrome (BS) is a channelopathy with an associated risk of malignant ventricular arrhythmias and sudden death. The diagnosis is established based on the patient's electrocardiography (ECG) pattern and clinical characteristics. The main treatment for BS is defibrillator implantation, although promising ablation techniques have been developed recently.[1] In a large percentage of patients, the baseline ECG findings are normal or inconclusive, and a drug challenge is required to confirm the condition. This may also occur with members of the patients' families, who can inherit the disease. Genetic study can identify the cause, confirm the diagnosis, and avoid unnecessary tests and follow-up in patients and their family members.

The main gene implicated in BS is the sodium channel gene, *SNC5A*, but other genes may make a smaller contribution. For a genetic study to be considered complete, in addition to examining all these genes, copy number variations (CNV), such as large deletions or duplications, should be ruled out, as a small percentage of BS cases may be due to these variants. We present the case of a family with BS, whose genetic study by massive next-generation sequencing (NGS) enabled identification of the etiology.

The proband, a 13-year-old boy, was hospitalized for palpitations after intense exercise. He had experienced no previous symptoms and was not receiving drug therapy. Before this event, he had undergone monitoring by the arrhythmia unit with yearly ECG testing because his father had been diagnosed with BS (showing a spontaneous type 1 ECG pattern and induced fibrillation on electrophysiology study) and was treated with defibrillator implantation. On admission, ECG testing showed an atrial flutter associated with a Brugada type 1 pattern (Figure A). The flutter remitted spontaneously, and a nodal rhythm with the same type 1 pattern was recorded later (Figure B). The patient was discharged in sinus rhythm, without the need for medication. He underwent an outpatient electrophysiology study, in which no ventricular arrhythmias were induced. Holter ECG testing showed sinus bradycardia, sinus pauses, and frequent atrial extrasystoles, findings considered to indicate probable sinus node dysfunction.

The boy's father had never experienced shocks from the device, and had shown no signs of sinus dysfunction or atrial arrhythmias. Genetic study of the *SCN5A* gene had been performed previously by Sanger sequencing, with negative results. The proband's 11-year-old brother was asymptomatic and showed a Brugada type 2 pattern on the baseline ECG. When the proband was hospitalized, drug challenge had not been performed in the 2 boys. The father had no brothers. The mother was healthy/asymptomatic and her ECG was normal. There were no other known cases in the family (Figure C).

Genetic study of the boy using an NGS panel identified complete deletion of the *SCN5A* and *SCN10A* genes (Figure D). Confirmation using another, more specific molecular technique for CNV study (SNP-array) enabled characterization of the deletion (Figure E), which included 8 genes. Only 3 of these genes have been associated with the disease: *SCN5A* and *SCN10A* (BS), and *ACVR2B* (complex congenital heart defects). Genetic study of the family (by SNP-array, low-cost and accurate) identified the same deletion in the affected father and asymptomatic brother.

The deletion had not been described previously. A similar deletion is recorded in the DECIPHER database, but only 3 of the genes identified are involved (*EXOG, SCN5A* and *SCN10A*); it is considered pathogenic and was found in a male without a described phenotype. Several studies have reported large partial deletions in the *SCN5A* gene in BS patients.[2–5] In all these cases, multiplex ligation-dependent probe amplification (MLPA) was used after a previous genetic study had yielded negative results (Table). Lastly, we mention the coexistence of atrial flutter and BS in the proband. *SCN5A* has an important pathophysiological role in sinus node automatism, and the mutations that generate hypofunction of this canal have been associated with both sinus dysfunction (with atrial arrhythmias) and BS.[6]

In conclusion, this is the first reported example of complete deletion of the *SCN5A* and *SCN10A* genes causing familial BS. It provides a clear illustration of the usefulness of NGS in the diagnosis of these diseases. It is now possible to carry out a complete genetic study using this technique, which enables identification of point variants and CNV in the genes of interest, avoids false-negative results, and provides adequate family screening. The development of this technology is leading to the identification of new molecular mechanisms and broadening our knowledge of the etiology of these diseases.

Table
BS Patients With a Previously Negative or Inconclusive Genetic Study, Later Found to Have a Deletion in the *SCN5A* Gene

Patient	Age, y	ECG: BS pattern	Family history	Previous genetic study	CNV identified in *SCN5A*	Reference
1	13	Yes	Yes. Father with BS on ECG	Sanger sequencing negative in his affected father	3p22.2 deletion (includes complete deletion of the *SCN5A* gene by NGS)	Present study
1	16	Sudden cardiac death, autopsy shows no cardiac abnormalities	No	Variant of uncertain pathogenicity in *SCN5A* (Glu1053Lys)	Deletion of the *SCN5A* gene promotor region (by MLPA)	Jenewein et al.[4]
1	38	Yes	Possiblye affected son	Sanger sequencing negative at 27 years	Deletion of exon 23 (by MLPA)	Hertz et al.[5] Broendberg et al.[2]
1	14	Yes	Sudden cardiac death in maternal uncle	Sanger sequencing negative	Deletion of exons 9 and 10 (by MLPA)	Eastaugh et al.[3]

BS, Brugada syndrome; CNV, copy number variations; ECG, electrocardiogram; MLPA, multiplex ligation-dependent probe amplification; NGS, next-generation sequencing.

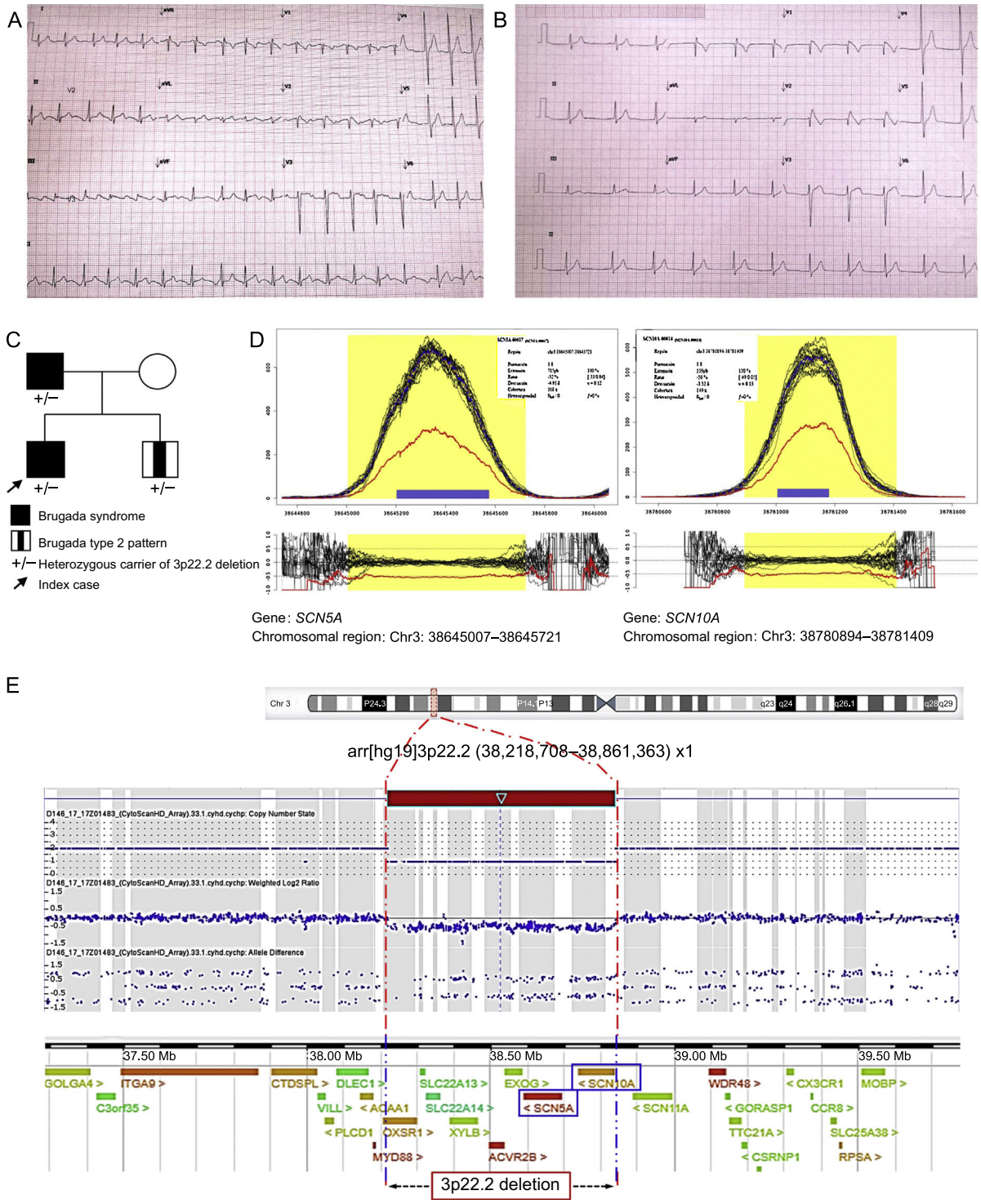

Figure. Familial Brugada syndrome. A. Electrocardiogram of the index case in atrial flutter. B. Posterior Brugada type 1 pattern. C. Family pedigree; familial genetic study (SNP-array). D. Analysis of NGS coverage shows a deletion in heterozygosis; abscissa axis, genomic region; ordinate axis, sequence coverage (number of reads); each black line represents 1 single case; the blue line, the median of all cases, and the red line, the index case. E. 3p22.2 deletion, characterized by SNP-array; the graph shows a signal decrease in this region. NGS, massive next-generation sequencing. This figure is shown in color only in the online version of the article.

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CONFLICTS OF INTEREST

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Outcomes After Surgical Treatment of Severe Tricuspid Regurgitation in a Contemporary Series

Resultados del tratamiento quirúrgico de la insuficiencia tricuspídea grave en una serie contemporánea

To the Editor,

Tricuspid regurgitation (TR) has received little attention from clinicians and researchers, and in Spain few centers have published their experience with this process.[1] In 2013, our group reported the outcomes of surgical treatment of severe TR in a series of 119 consecutive patients who underwent surgery between April 1996 and February 2010, and high perioperative and long-term mortality was found.[2] Today, this series should be considered historic, and the outcomes cannot serve as a guide for predicting those that would currently be obtained after surgery for TR. The objective of the present study was to analyze the clinical and echocardiographic outcomes of a recent sample of patients with severe TR who underwent surgery.

This retrospective study included 87 consecutive patients with severe TR who underwent tricuspid surgery in our hospital between March 2010 and December 2013. The indication for tricuspid surgery was established by the presence of a symptomatic and severe tricuspid lesion according to the echocardiographic definition described in our previous study.[2] Treatment was decided by consensus among cardiologists, cardiac surgeons, and the patient. Repair was always the preferred option if technically feasible, essentially in cases with absence of significant organ damage. As an exception, valve replacement was considered, according to the judgement of the surgeon, in cases with functional damage and prior cardiac surgery. Perioperative and long-term morbidity and mortality were analyzed, as well as onset of new severe TR. Predictive factors were studied.

In the period analyzed, ring-free annuloplasty according to the De Vega technique was performed in 4 patients while ring annuloplasty was done in 60; 23 patients received biologic prostheses while none received mechanical prostheses. The Table summarizes the patients' baseline characteristics, complications after surgery, and perioperative mortality. Overall, 74.7% of the patients were women (mean age, 64.64 [10.08] years). The etiology was organic in 60.9% of tricuspid replacements and functional in 85.9% of repairs. In the group with repaired valves, the patients were older (40.6% vs 17.4% > 70 years; P = .044), had higher preoperative pulmonary pressures (pulmonary artery systolic pressure, 55.67 [14.85] vs 39.65 [14.06] mmHg; P<.001), and a lower proportion of tricuspid surgery alone (7.8% vs 52.2%; P<.001). In 47.1% of the patients, a complication arose during the postoperative period, and perioperative mortality was 8%.

A multivariate analysis was performed to identify predictors of perioperative mortality. The analysis included left ventricular ejection fraction < 45%, the only variable significantly associated with the event in the univariate analysis (Table of the supplementary material), as well as the variables identified as predictors in our previous study (age, duration of extracorporeal circulation).[2] The only predictor of perioperative mortality was left ventricular ejection fraction < 45% (odds ratio, 10.531; 95% confidence interval [CI], 1.262-87.905; P = .030).

After discharge following the operation, changes in TR were assessed in 66 of the 80 survivors (82.5%) in echocardiographic follow-up (median, 30 [interquartile range, 20-44] months). Severe TR occurred in 4 patients, all belonging to the group of ring-free annuloplasty (7.1% of patients with follow-up in this group). Predictors of the onset of severe TR during follow-up were not assessed, given its low incidence.

Mortality was assessed after a follow-up that included all survivors of the perioperative period (median, 38 [30.25-48] months).

Mortality during overall follow-up was 18.8% among patients alive on discharge from hospital and the overall mortality (perioperative and during overall follow-up) was 25.3%. A univariate analysis of overall mortality was performed (Table, Supplementary material) and multivariate analysis of the variables with a significant association was performed. The only predictor of overall mortality was the duration of extracorporeal circulation (hazard ratio, 1.012; 95% CI, 1.003-1.021; P=.009). The Figure shows the survival curve during follow-up of the cohort of patients in the study.

In the present study, perioperative mortality was 8%, comparable to that found in other extensive studies in Spain,[3] but somewhat lower than 18.5%, the mortality rate obtained in our previous study.[2] The reasons for the improved perioperative mortality in our study cannot be inferred from this study because of its design. One possibility would be that the indication for surgery is increasingly made in earlier stages of the disease, in line with studies that have shown higher mortality in patients with