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CLINICAL LETTER

Lamin A/C Missense Mutation R216C Pinpoints Overlapping Features Between Brugada Syndrome and Laminopathies

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A 31-year-old man experienced at-rest cardiac arrest. After successful resuscitation, the baseline ECG demonstrated sinus rhythm with concave ST segment elevation in right precordial leads (V1–V3) followed by a negative and symmetrical T-wave. Neither coronary artery disease nor electrolytes' imbalances were detected. In the following days, ECG showed a spontaneous type 1 Brugada ECG pattern (Figure [A1]), more evident with right precordial leads in II and III intercostal spaces. Transthoracic echocardiography (Figure [A2]) failed to show any cardiomyopathy. Cardiac MRI showed normal chambers dimension, wall thickness, volume, and function (left ventricular end diastolic volume, 67.7 mL/m^2; IVS, 1 cm; left ventricular end fraction, 59.7%). Late gadolinium enhancement sequences were negative; adipose and fibrous tissue infiltration were excluded.

The patient was implanted with a transvenous single chamber cardioverter defibrillator (Medtronic). Several appropriate ICD interventions on VT and ventricular fibrillation were recorded in the following years.

Family history (Figure [B]) was positive for sudden cardiac death: the maternal grandfather died at age 45 years, a II degree maternal cousin died during sleep at age 40 years. The proband's mother showed a first degree atrioventricular block (PR interval=280 ms) and right bundle branch block (Figure [A3]). A neurological examination in the index case and his mother was negative and creatine phosphokinase levels were normal in both.

Informed written consent was obtained from all family members. Study was approved by the Local Ethics Committee (152/2013/O/Oss, June 1, 2013). Molecular genetic analysis was performed by next generation sequencing using PED MASTR Plus assay comprising 52 cardiac electrical disorders related genes, SCN5A included (www.agilent.com).

The c.646C>T variation in exon 4 of Lamin A/C (p.R216C) was identified. The minor allele frequency in gnomAD is 0.000007080 (https://gnomad.broadinstitute.org/). MLPA analysis of SCN5A was negative.

The nonconservative amino acid substitution p.R216C is located in the coiled 1B domain, critical for lamin assembly (Figure [C]). In silico prediction tools describe it as possibly pathogenic. The variant has been reported in three patients with AV-block and atrial fibrillation/VF[1,2] and in 36 subjects belonging to a large white kindred, associated to low penetrance and a mild phenotype.[3] Same-site variants have been reported (R216H, R216L) with very low population frequency (<0.00003) and classified as of uncertain significance. Missense variants in nearby residues (L215P, L215V, K219N, K219T, R220C, R220G) have been described in association with cardiac or neuromuscular phenotypes (https://www.ncbi.nlm.nih.gov/clinvar). Cascade genetic analysis identified the p.R216C variant in proband's mother and in proband's uncle (III2) associated with first degree atrioventricular block and left anterior hemiblock at ECG. His 41 years old son (IV3), also carrier of the mutation, showed intermittent second degree type 1 atrio-ventricular block and Brugada type 2 ECG (Figure [A4]).

To our knowledge, this is the first time in which Brugada Syndrome (BrS) is described associated to a LMNA gene mutation.

Key Words: Brugada syndrome ■ Lamin A/C ■ translational medical research

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Nonstandard Abbreviations and Acronyms

BrS	Brugada Syndrome

In our patient, the clinical picture of BrS is not linked to a SCN5A mutation. On the other hand, he had no evidence of a cardiac conduction system disease, therefore, had no markers of a LMNA-related disease. On the contrary, all other family members who carried the p.R216C LMNA mutation showed, although mild, signs of conduction disturbances supporting a functional effect of the mutation.

Recently published papers have documented INa currents alterations in cells carrying LMNA gene mutations; in particular, Salvarani and co-workers demonstrated a direct interaction between Lamin A/C protein and SCN5A gene promoter in induced pluripotent stem cell K219T LMNA-mutated derived cardiomyocytes. A considerable reduction in SCN5A expression in cardiac cells due to epigenetic inhibition was shown.[4] Notably, SCN5A is the strongest BrS gene and the sodium current perturbation is considered as the main pathogenic mechanism. In this context, our case represents a first phenotypic proof of concept of the direct LMNA-SCN5A interaction. As counterpart, the possible occurrence of structural alteration of the right ventricular outflow tract in BrS is emerging. Nademanee et al[5] reported fibro-fatty replacement of the right ventricular outflow tract in both autoptic and in vivo collected cardiac samples from BrS patients. However, any cardiac abnormality was evident at ecocardiography and/or cardiac magnetic resonance imaging on the same patients suggesting that BrS pattern could be a very early sign of a structural disease.

Mutations in desmosomal genes, associated to arrhythmogenic cardiomyopathy, have also been described in BrS patients, underlining the overlapping of the 2 diseases.[6] Notably, LMNA gene mutations have been associated to arrhythmogenic cardiomyopathy. The identification of a known pathogenic LMNA gene mutation in a classic BrS phenotype, as in our patient, further reinforces the idea that BrS could be caused by or could masquerade an occult cardiomyopathy.

Although extensive gene panel analysis has been performed the possibility of the coexistence in our case of another mutation related to Brugada pattern susceptibility could not be definitively ruled out.

In conclusion, we propose BrS as part of the laminopathies spectrum, and we suggest LMNA gene screening in BrS patients to gain further evidence supporting this view.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Liu N, Zheng M, Li S, Bai H, Liu Z, Hou CH, Zhang S, Pu J. Genetic mechanisms contribute to the development of heart failure in patients with atrioventricular block and right ventricular apical pacing. *Sci Rep.* 2017;7:10676. doi: 10.1038/s41598-017-11211-2
2. Nishiuchi S, Makiyama T, Aiba T, Nakajima K, Hirose S, Kohjitani H, Yamamoto Y, Harita T, Hayano M, Wuriyanghai Y, et al. Gene-based risk stratification for cardiac disorders in LMNA mutation carriers. *Circ Cardiovasc Genet.* 2017;10:pii: e001603. doi: 10.1161/CIRCGENETICS.116.001603.
3. Al-Saaidi RA, Rasmussen TB, Birkler RID, Palmfeldt J, Beqqali A, Pinto YM, Nissen PH, Baandrup U, Mølgaard H, Hey TM, et al. The clinical outcome of LMNA missense mutations can be associated with the amount of mutated protein in the nuclear envelope. *Eur J Heart Fail.* 2018;20:1404–1412. doi: 10.1002/ejhf.1241
4. Salvarani N, Crasto S, Miragoli M, Bertero A, Paulis M, Kunderfranco P, Serio S, Forni A, Lucarelli C, Dal Ferro M, et al. The K219T-Lamin mutation induces conduction defects through epigenetic inhibition of SCN5A in human cardiac laminopathy. *Nat Commun.* 2019;10:2267. doi: 10.1038/s41467-019-09929-w
5. Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, Makita N, Kowase S, Boonmee N, Vitayakritsirikul V, et al. Fibrosis, connexin-43, and conduction abnormalities in the brugada syndrome. *J Am Coll Cardiol.* 2015;66:1976–1986. doi: 10.1016/j.jacc.2015.08.862
6. Moncayo-Arlandi J, Brugada R. Unmasking the molecular link between arrhythmogenic cardiomyopathy and brugada syndrome. *Nat Rev Cardiol.* 2017;14:744–756. doi: 10.1038/nrcardio.2017.103

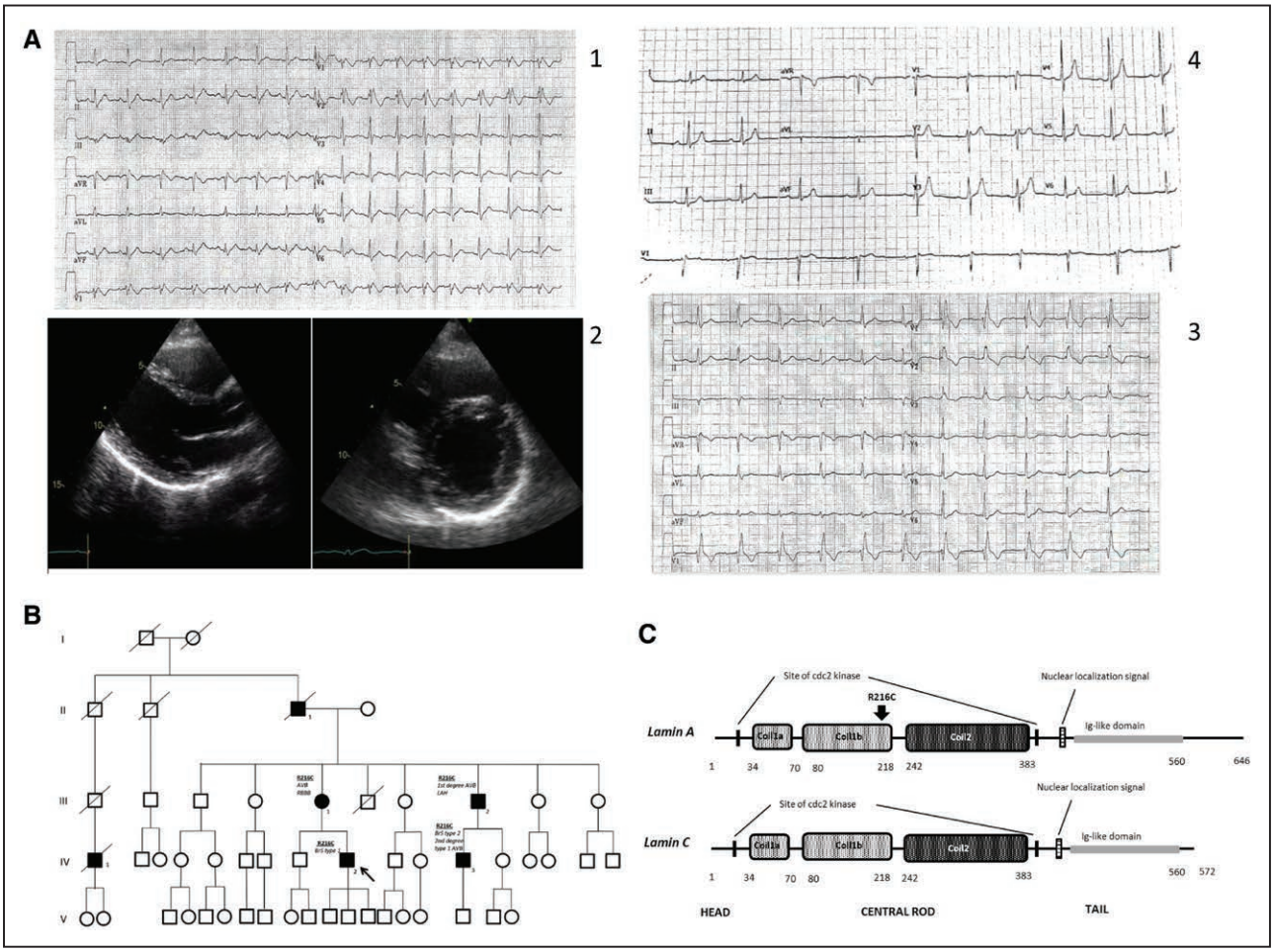

Figure. ECGs of the proband and his affected relatives (mother and a cousin), proband's echocardiographic images and family tree, and the schematic representation of LMNA/C protein structure with R216C mutation position.
A1, Proband's ECG showing a slightly prolonged PR interval and a typical type 1 Brugada pattern in lead V1 and V2.**A**2, Bidimensional long-axis (left) and short-axis (right) parasternal echocardiographic images showing normal biventricular dimension. **A**3, Proband's mother ECG showing a AVB-I with a PR interval of 280 ms and a right bundle branch block with a QRS of 150 ms. **A**4, Proband's cousin ECG showing type 2 Brugada pattern, first degree AVB (PR=240 ms). **B**, Family tree: II1: Proband's grandfather, †SCD 45 y; III1: proband's mother, AVB+RBBB; III2: proband's uncle, first degree AVB+LAH; IV1: proband's cousin, †SCD 40 y; IV2: proband, CA 31 y, Brugada type 1 ECG pattern; IV3: proband's first cousin, second degree type 1 AVB, Brugada type 2 ECG pattern. **C**, Schematic representation of Lamin A and C proteins. R216C location in the coil1B domain (arrow). AVB indicates atrioventricular block; CA, cardiac arrest; LAH, left anterior hemiblock; LBBB, left bundle branch; and SCD, sudden cardiac death.