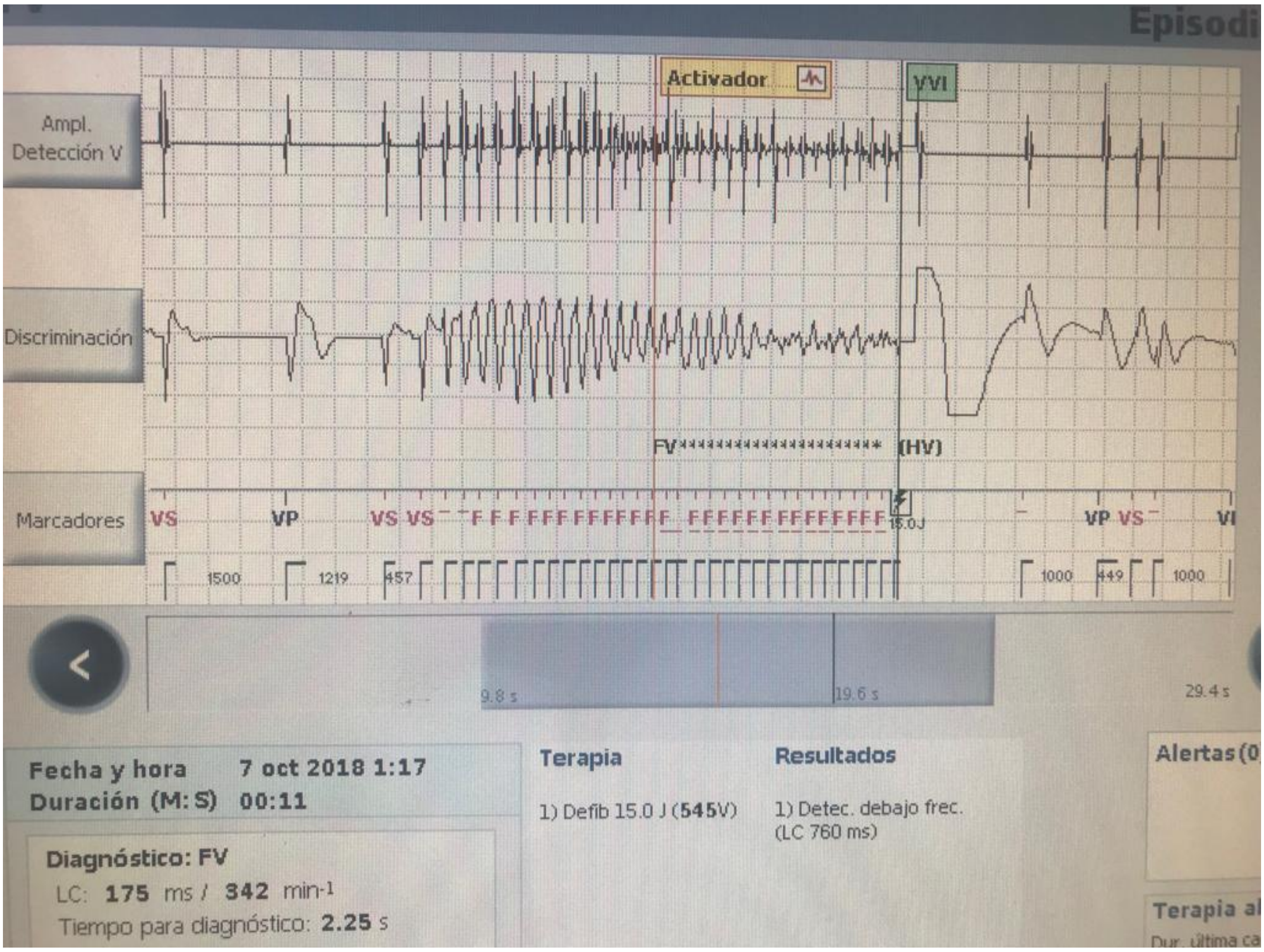
Paciente de 30 años con superposición de Síndrome de Brugada y DAVD con descarga de CDI – 2018

Dr. Alejandro Ventura

Estimados amigos de Cardiolatina
Quisiera compartir con ustedes un evento médico, que si bien no generará controversias, por su contundencia y espectacularidad, me llama a homenajear a través de él a la ciencia médica toda:

Mi paciente Santiago G. tiene 30 años, es de La Escondida (Provincia del Chaco) y acaba de nacer de nuevo.
Se murió mientras dormía el día 7/10/18 a la 1:17 hs y volvió a nacer esa misma noche.
Tiene un Síndrome de Brugada y CDI.
El año que viene festejará su nuevo cumpleaños junto a su mujer y sus 3 hijitos, gracias a los Dres. Brugada y el Dr. Michel Mirowski y otros tantos que permitieron que esto sea posible.
Les adjunto el trazado del CDI.
Gracias

Alejandro Ventura


Ampl. Detección V
Activador
VVI
Discriminación
FV (HV)
Marcadores
VS VP VS VS F F F FFF FFFFFFF F FFFFFF FFFFFFFF
15.0J
VP VS
1500
1219
457
1000
449
1000
9.8 s
19.6 s
29.4 s
Fecha y hora 7 oct 2018 1:17
Duración (M:S) 00:11
Diagnóstico: FV
LC: 175 ms / 342 min-1
Tiempo para diagnóstico: 2.25 s
Terapia
1) Defib 15.0 J (545V)
Resultados
1) Detec. debajo frec. (LC 760 ms)

OPINIONES DE COLEGAS

¿Tal vez agregarle quinidina, como sugieren Sami y el Prof Belhassenn?

Un abrazo

Edgardo Schapachnik

Buenas tardes! Nítida e instructiva imagen de un trazado de un CDI en acción para los que no estamos acostumbrados a trabajar con dispositivos.

Adhiero a la propuesta del Dr Edgardo, incluso plantearía también ARF (ablación) de sustrato para disminuir la posibilidad de TV-FV y con ello las descargas del Dispositivo.

Cordialmente

Juan Carlos Manzzardo

Muchas gracias por compartir el caso.

Sería interesante saber un poco de la historia clínica del paciente y ver el ECG.

Saludos,

Mario D. Gonzalez

Les envío un resumen de la historia clínica del paciente. Además las imágenes de los ECG y de ventriculograma derecho.

El caso es una asociación de Brugada+DAVD.

Paciente de 29 años sexo masculino

Antecedentes:.

***Heredo-F**: Tía (hna. del padre) fallecida MS a los 40 años

Abuela paterna MS a los 35 años

10 hnos. sin antec.

*Marzo/2008: Episodio sincopal

*30/06/2008: Muerte súbita reanimada

Examen físico normal

Ecocardiograma Normal

Laboratorio normal, Chagas neg.

*El 21/07/2008 se realiza implante de CDI VVI.

Evolución:

*Asintomático hasta 2009

*Octubre 2009: Internación por 3 choques,

Interrogación CDI:

Descargas apropiadas por TV rápida posiblemente polimorfa en zona de FV

*ECOCARDIOGRAMA 28/10/09:

Diámetros y función sistólica ventricular izquierda normal.

Dilatación leve de VD (36 mm en 4 cámaras) a predominio del TSVD

(41 mm). Con Hipoq. leve de cara anterior y apical VD.

*Ante la imposibilidad de realizar RNM se realiza un estudio hemodinámico:

Coronarias sin lesiones angiograficas.

Ventriculograma derecho: Zonas de aquinesia segmentaria en los segmentos infundibular y apical. Signos de hipertrofia septal (pilas de monedas) compatible con DAVD.

*Estudio Genético: Dr Ramón Brugada:

Dr. Alejandro Ventura,

La muestra ha sido analizada por el Servicio Genético CGC. Este servicio identifica variantes genéticas en genes asociados con la muerte súbita cardiaca. A partir de su solicitud, hemos realizado el análisisdel panel**CGC Global***(55 genes; ACTC1, ACTN2, ANK2, CACNA1C, CACNB2, CASQ2, CAV3, CRYAB, CSRP3, DES, DMD, DSC2, DSG2, DSP, EMD, FBN1, GLA, GPD1L, HCN4, JPH2, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, PDLIM3, PKP2, PLN, PRKAG2, RYR2, SCN4B, SCN5A, SGCA, SGCB, SGCD, TAZ, TCAP, TGFB3, TGFBR2, TNNC1, TNNI3, TNNT2, TPM1, TTN, VCL)*

Sospecha Clínica/Diagnóstico de Referencia

Síndrome de Brugada /Cardiomiopatía arritmogénica de ventrículo derecho

Resultados GenéticosTipo 2: Variante genética desconocida en el caso índice

Se ha identificado una variante en este individuo en un gen no relacionado con la sospecha clínica.

La variante V55I no ha sido previamente descrita en la literatura científica como patogénica pero se ha encontrado en la población sana en baja frecuencia (12/12992 cromosomas, 0.1%). Análisis computacionales que calculan la funcionalidad de la variante en la proteína la describen como posiblemente benigna. A pesar de estas observaciones, para ayudarnos a definir la patogenicidad de esta variante se necesitarían más estudios familiares y moleculares.

El gen LDB3 está asociado a Cardiomiopatía Hipertrófica, Dilatada, Cardiomiopatía no compactada y Miopatía Miofibrilar. El significado de esta variante en un contexto de Síndrome de Brugada/Cardiomiopatía arritmogénica de ventrículo derecho, se desconoce por el momento.

Es importante correlacionar la información clínica y genética.

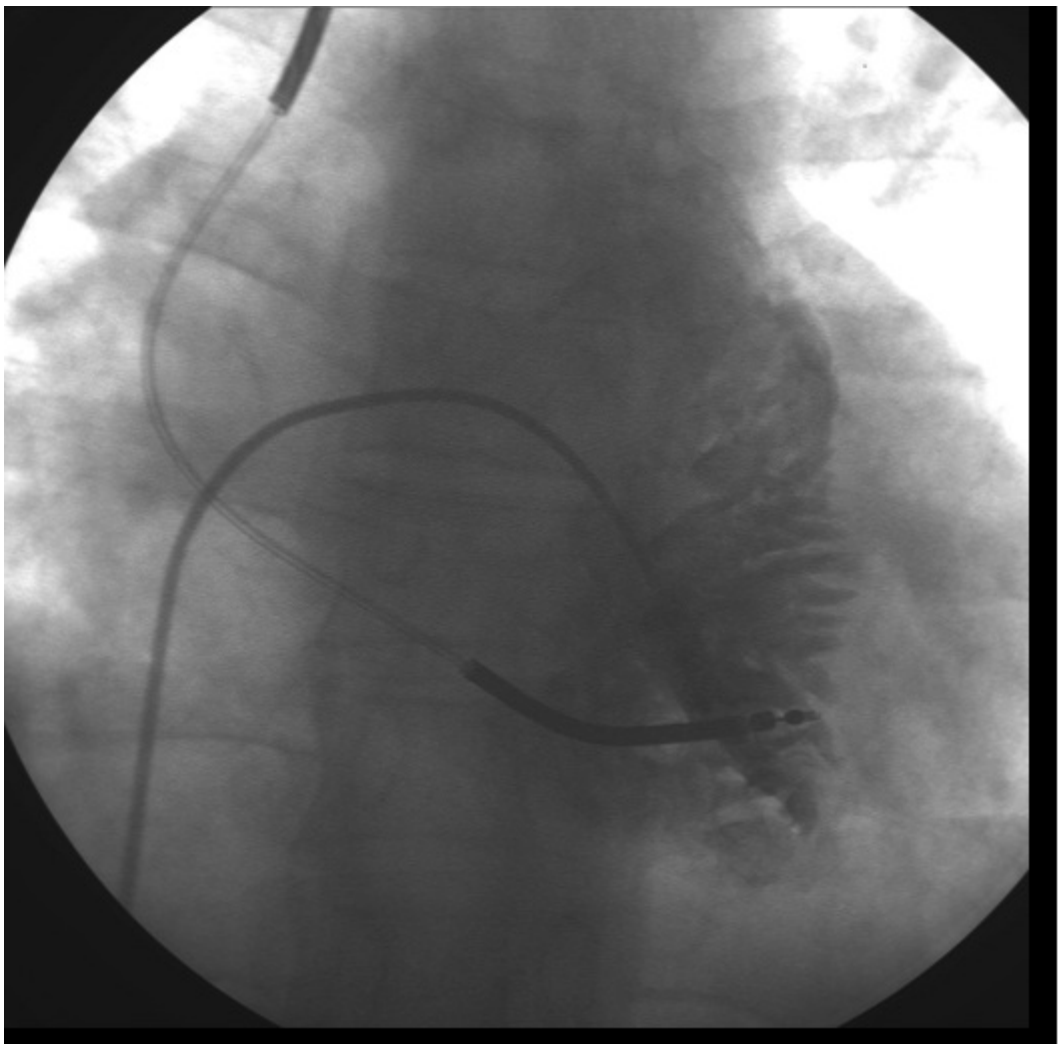
Gen	Secuencia de referencia	Cambio de nucleòtido	Cambio de aminoàcido	Tipo de variante
LDB3	NM_001080116	c.163G>A	p.V55I	Missense

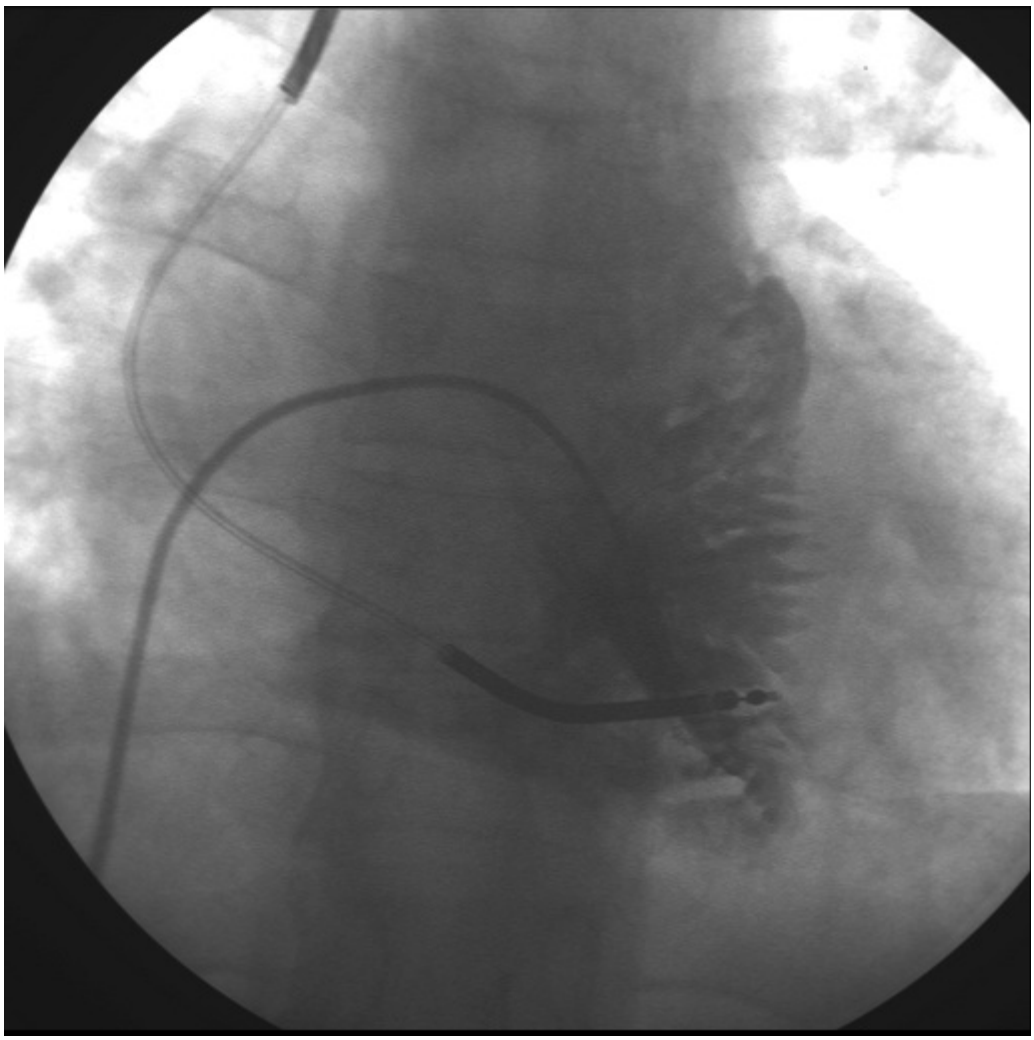
Desde entonces no tuvo más síntomas ni terapias hasta el 7/10/18 a la madrugada.

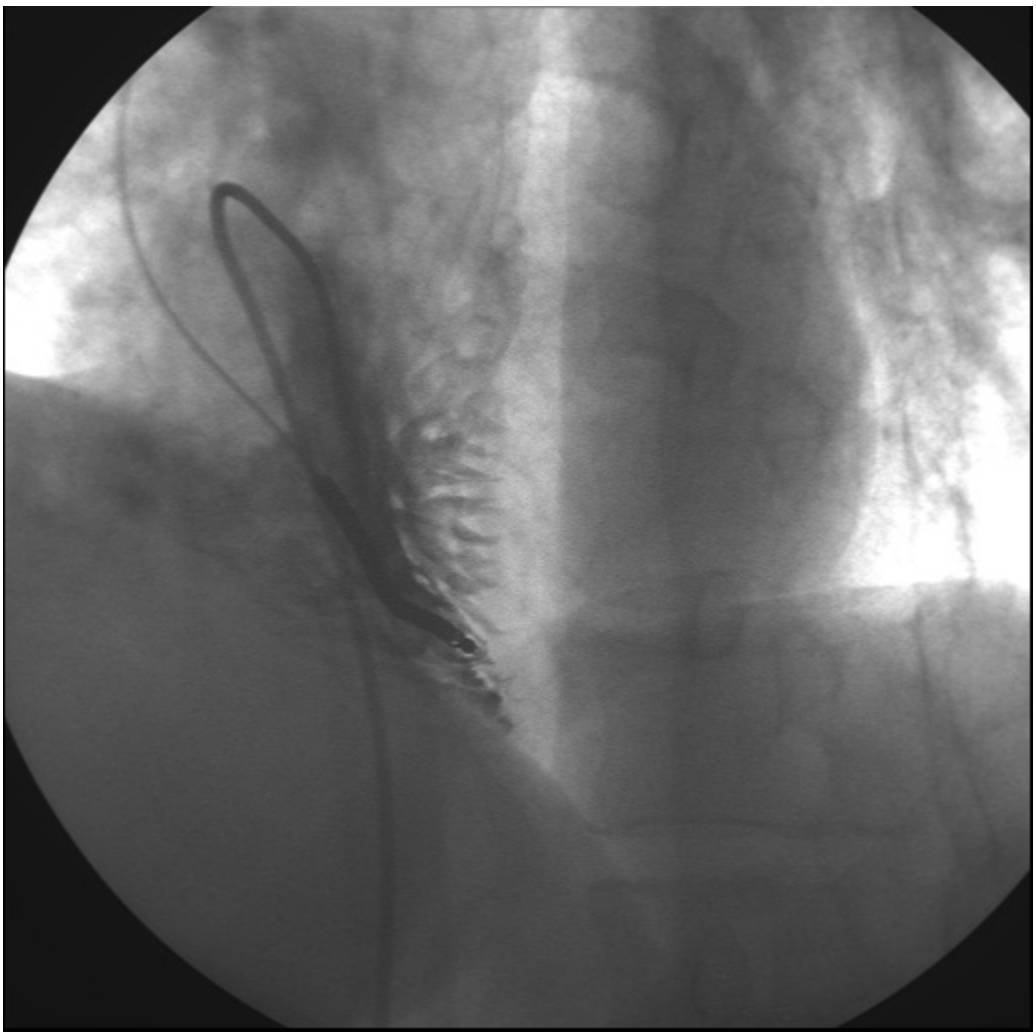
Le hicimos ECG a los hijos y hermanos, todos normales.

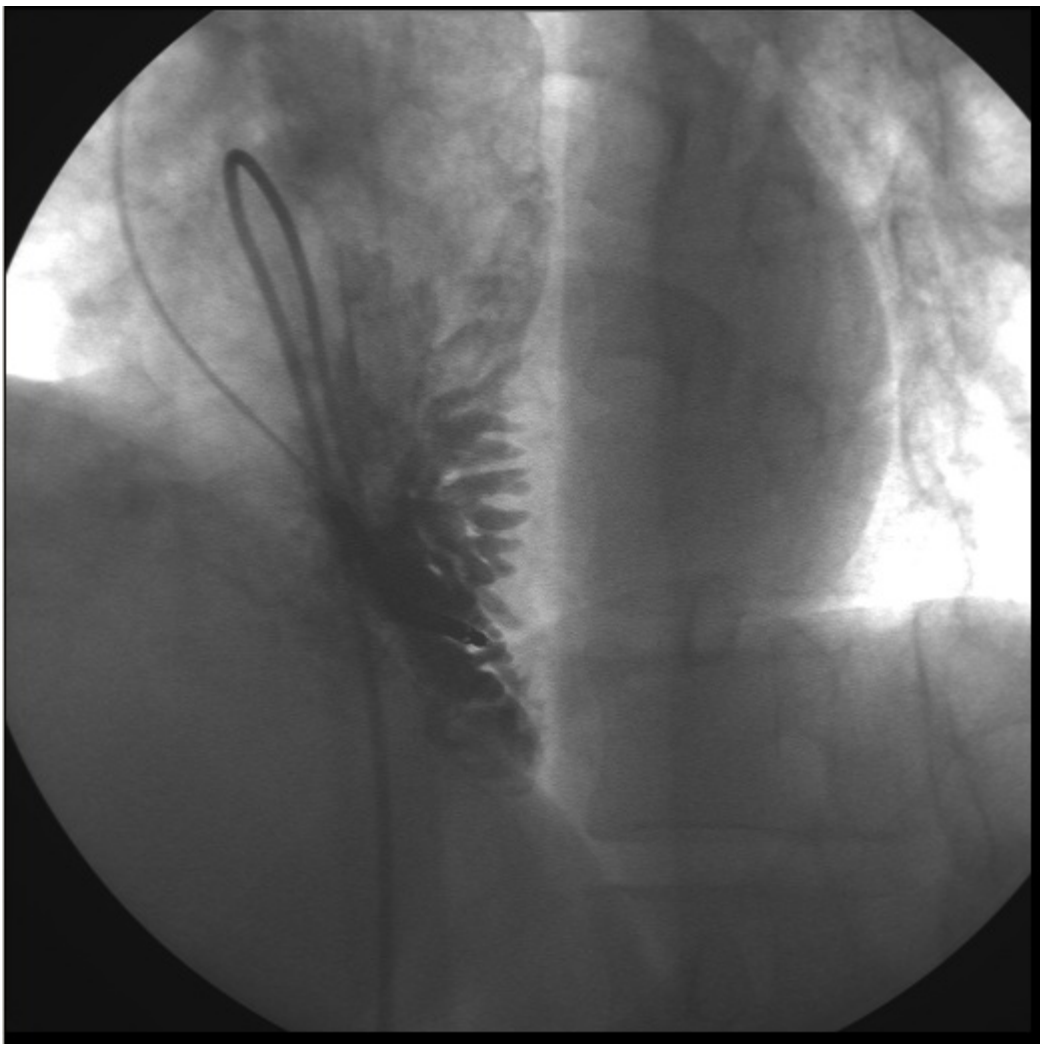
Saludos

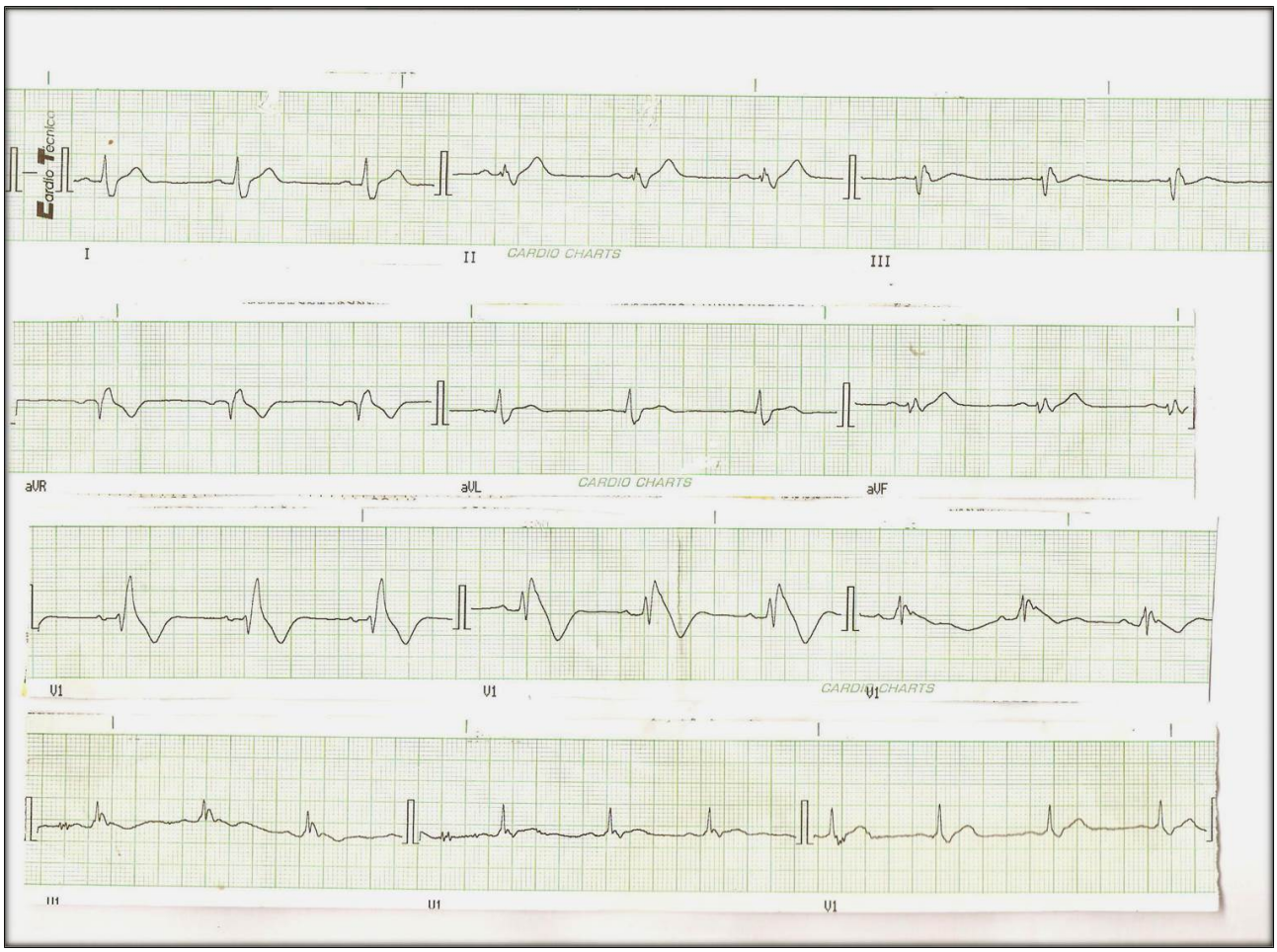
Alejandro Ventura











Excelentes logros... nada más ni nada menos que una vida.

Celeste Damico

Estimado Alejandro: La mutación encontradaen el gen LDB3 como tu bien lo comentas está asociada a cardiomiopatía hipertrófica, dilatada, no compactada y miopatía miofibrilar y te diria que .muy probablemente nada tiene a ver con el fenotipo encontrado *"overlappying Brugada syndrome/ARVC/D*.

Este gen LDB3 que Ramón há encontrado tiene por tarea proporcionar instrucciones para crear una proteína llamada enlace de dominio LIM 3 (LDB3).

La proteína LDB3 se encuentra en el miocárdio y en el músculo esquelético. Las proteínas LDB3 se encuentran dentro del sarcómero (unidad funcional de la contracción y relajación del músculo cardiaco),. Esta proteína se une a otras proteínas participando del mantenimiento de la estabilidad de los discos Z que forman el límite de la unidad contráctil. Los discos Z unen a los sarcómeros vecinos para formar miofibrilas de actina (finas) y de miosina (gruesas), interdigitadas forman la unidad básica de las fibras musculares.

La unión de los sarcómeros y la formación de miofibrillas proporcionan la fuerza de contracción y relajación muscular mecanismo conocido como translapación y destraslapación. Varias versiones diferentes (isoformas) de la proteína LDB3 se producen a partir del gen LDB3. Mutaciones em este gen causan las 4 entidades que mencionaste, y la ubicación citogenética de este gen se encuentra en el brazo largo del cromossoma 10 (10q23.2) en la posición 23.2. El gen LBD3 há recebido várias otras denominaciones: **LDB3Z1, ZASP, LDBEZ4, y LDB3Z4.**

Deberias proponerle a Ramón tentar uma publicación haciendo los test necessários para ver si existe alguna relación con el fenotipo encontrado. No se si seria posible.

El tema es tan nuevo que hasta la fecha apenas se han publicado 40 artículos em el Pubmed acerca de este gen (Casi todos em 2016, 2017 y 2018. Apenas 1 em 2015):

Referencias

1. Levitas A, Konstantino Y, Muhammad E, Afawi Z, Marc Weinstein J, Amit G, Etzion Y, Parvari R. D117N in Cypher/ZASP may not be a causative mutation for dilated cardiomyopathy and ventricular arrhythmias. Eur J Hum Genet. 2016 May;24(5):666-71. doi: 10.1038/ejhg.2015.195.

2. Lim WF, Burdach J, Funnell AP, Pearson RC, Quinlan KG, Crossley M. Directing an artificial zinc finger protein to new targets by fusion to a non-DNA-binding domain.Nucleic Acids Res. 2016 Apr 20;44(7):3118-30. doi: 10.1093/nar/gkv1380

3. Simonik EA, Cai Y, Kimmelshue KN, Brantley-Sieders DM, Loomans HA, Andl CD, Westlake GM, Youngblood VM, Chen J, Yarbrough WG, Brown BT, Nagarajan L, Brandt SJ. LIM-Only Protein 4 (LMO4) and LIM Domain Binding Protein 1 (LDB1) Promote Growth and Metastasis of Human Head and Neck Cancer (LMO4 and LDB1 in Head and

Neck Cancer). PLoS One. 2016 Oct 25;11(10):e0164804. doi: 10.1371/journal.pone.0164804

4. Shao Z, Cai Y, Xu L, Yao X, Shi J, Zhang F, Luo Y, Zheng K, Liu J, Deng F, Li R, Zhang L, Wang H, Li M, Ding Y, Zhao L. Loss of the 14-3-3σis essential for LASP1-mediated colorectal cancer progression via activating PI3K/AKT signaling pathway.Sci Rep. 2016 May 9;6:25631. doi: 10.1038/srep25631

5. Batonnet-Pichon S, Behin A, Cabet E, Delort F, Vicart P, Lilienbaum A.Myofibrillar Myopathies: New Perspectives from Animal Models to Potential Therapeutic Approaches. J Neuromuscul Dis. 2017;4(1):1-15. doi: 10.3233/JND-160203. Review.

6. Wright JD, An SW, Xie J, Yoon J, Nischan N, Kohler JJ, Oliver N, Lim C, Huang CL. Modeled structural basis for the recognition ofα2-3-sialyllactose by soluble Klotho.FASEB J. 2017 Aug;31(8):3574-3586. doi: 10.1096/fj.201700043R.

7. Hoang T, Lambert JA, Martin R. SCL/TAL1 in Hematopoiesis and Cellular Reprogramming. Curr Top Dev Biol. 2016;118:163-204. doi: 10.1016/bs.ctdb.2016.01.004. Epub 2016 Feb 18. Review.

8. Vincent AE, Grady JP, Rocha MC, Alston CL, Rygiel KA, Barresi R, Taylor RW, Turnbull DM.Mitochondrial dysfunction in myofibrillar myopathy. Neuromuscul Disord. 2016 Oct;26(10):691-701. doi: 10.1016/j.nmd.2016.08.004

9. Godamudunage MP, Foster A, Warren D, Lyons BA. Grb7 protein RA domain oligomerization. J Mol Recognit. 2017 Aug;30(8). doi: 10.1002/jmr.2620

10. Rahman S, Magnussen M, León TE, Farah N, Li Z, Abraham BJ, Alapi KZ, Mitchell RJ, Naughton T, Fielding AK, Pizzey A, Bustraan S, Allen C, Popa T, Pike-Overzet K, Garcia-Perez L, Gale RE, Linch DC, Staal FJT, Young RA, Look AT, Mansour MR. Activation of the LMO2 oncogene through a somatically acquired neomorphic promoter in T-cell acute lymphoblastic leukemia. Blood. 2017 Jun 15;129(24):3221-3226. doi: 10.1182/blood-2016-09-742148

11. Endres M, Kneitz S, Orth MF, Perera RK, Zernecke A, Butt E. Regulation of matrix metalloproteinases (MMPs) expression and secretion in MDA-MB-231 breast cancer cells by LIM and SH3 protein 1 (LASP1). Oncotarget. 2016 Sep 27;7(39):64244-64259. doi: 10.18632/oncotarget.11720

12. Watts NR, Zhuang X, Kaufman JD, Palmer IW, Dearborn AD, Coscia S, Blech-Hermoni Y, Alfano C, Pastore A, Mankodi A, Wingfield PT. Expression and Purification of ZASP Subdomains and Clinically Important Isoforms: High-Affinity Binding to G-Actin. Biochemistry. 2017 Apr 11;56(14):2061-2070. doi: 10.1021/acs.biochem.7b00067

13. Kim AY, Lim B, Choi J, Kim J.The TFG-TEC oncoprotein induces transcriptional activation of the humanβ-enolase gene via chromatin modification of the promoter region. Mol Carcinog. 2016 Oct;55(10):1411-23. doi: 10.1002/mc.22384

14. Guo Y, Liang Z, Hou X, Zhang Z. Diverse gene expression patterns in response to anticancer drugs between human and mouse cell lines revealed by a comparative

transcriptomic analysis. Mol Med Rep. 2017 Oct;16(4):4469-4474. doi: 10.3892/mmr.2017.7176. Epub 2017 Aug 4. PMID: 28791417 Free PMC Article

15. Kley RA, Olivé M, Schröder R. New aspects of myofibrillar myopathies. Curr Opin Neurol. 2016 Oct;29(5):628-34. doi: 10.1097/WCO.0000000000000357. Review.

16. Wyles SP, Li X, Hrstka SC, Reyes S, Oommen S, Beraldi R, Edwards J, Terzic A, Olson TM, Nelson TJ. Modeling structural and functional deficiencies of RBM20 familial dilated cardiomyopathy using human induced pluripotent stem cells. Hum Mol Genet. 2016 Jan 15;25(2):254-65. doi: 10.1093/hmg/ddv468

17. Rot I, Baguma-Nibasheka M, Costain WJ, Hong P, Tafra R, Mardesic-Brakus S, Mrduljas-Djujic N, Saraga-Babic M, Kablar B. Role of skeletal muscle in ear development. Histol Histopathol. 2017 Oct;32(10):987-1000. doi: 10.14670/HH-11-886Review.

18. Ansseau E, Eidahl JO, Lancelot C, Tassin A, Matteotti C, Yip C, Liu J, Leroy B, Hubeau C, Gerbaux C, Cloet S, Wauters A, Zorbo S, Meyer P, Pirson I, Laoudj-Chenivesse D, Wattiez R, Harper SQ, Belayew A, Coppée F. Homologous Transcription Factors DUX4 and DUX4c Associate with Cytoplasmic Proteins during Muscle Differentiation. PLoS One. 2016 Jan 27;11(1):e0146893. doi: 10.1371/journal.pone.0146893

19. Hata Y, Yoshida K, Kinoshita K, Nishida N. Epilepsy-related sudden unexpected death: targeted molecular analysis of inherited heart disease genes using next-generation DNA sequencing. Brain Pathol. 2017 May;27(3):292-304. doi: 10.1111/bpa.12390

20. Fang M, Du H, Han B, Xia G, Shi X, Zhang F, Fu Q, Zhang T. Hypoxia-inducible microRNA-218 inhibits trophoblast invasion by targeting LASP1: Implications for preeclampsia development. Int J Biochem Cell Biol. 2017 Jun;87:95-103. doi: 10.1016/j.biocel.2017.04.005

21. Ntusi NA, Shaboodien G, Badri M, Gumedze F, Mayosi BM. Clinical features, spectrum of causal genetic mutations and outcome of hypertrophic cardiomyopathy in South Africans. Cardiovasc J Afr. 2016 May/Jun;27(3):152-158. doi: 10.5830/CVJA-2015-075

22. Segerer SE, Bartmann C, Kaspar S, Müller N, Kapp M, Butt E, Kämmerer U. The cytoskeletal protein LASP-1 differentially regulates migratory activities of choriocarcinoma cells.Arch Gynecol Obstet. 2016 Feb;293(2):407-14. doi: 10.1007/s00404-015-3830-y

23. Wu H, Zhou J, Mei S, Wu D, Mu Z, Chen B, Xie Y, Ye Y, Liu J. Circulating exosomal microRNA-96 promotes cell proliferation, migration and drug resistance by targeting LMO7.J Cell Mol Med. 2017 Jun;21(6):1228-1236. doi: 10.1111/jcmm.13056

24. Chiang CH, Grauffel C, Wu LS, Kuo PH, Doudeva LG, Lim C, Shen CK, Yuan HS.Structural analysis of disease-related TDP-43 D169G mutation: linking enhanced stability and caspase cleavage efficiency to protein accumulation. Sci Rep. 2016 Feb 17;6:21581. doi: 10.1038/srep21581

25. Chen X, Long F, Cai B, Chen X, Chen G.A novel relationship for schizophrenia, bipolar and major depressive disorder Part 3: Evidence from chromosome 3 high density association screen. J Comp Neurol. 2018 Jan 1;526(1):59-79. doi: 10.1002/cne.2431

26. Celestino-Soper PB, Doytchinova A, Steiner HA, Uradu A, Lynnes TC, Groh WJ, Miller JM, Lin H, Gao H, Wang Z, Liu Y, Chen PS, Vatta M. Evaluation of the Genetic Basis of Familial Aggregation of Pacemaker Implantation by a Large Next Generation Sequencing Panel. PLoS One. 2015 Dec 4;10(12):e0143588. doi: 10.1371/journal.pone.0143588. eCollection 2015. Erratum in: PLoS One. 2016;11(1):e0147455

27. Al-Absi B, Razif MFM, Noor SM, Saif-Ali R, Aqlan M, Salem SD, Ahmed RH, Muniandy S.Contributions of IKZF1, DDC, CDKN2A, CEBPE, and LMO1 Gene Polymorphisms to Acute Lymphoblastic Leukemia in a Yemeni Population.Genet Test Mol Biomarkers. 2017 Oct;21(10):592-599. doi: 10.1089/gtmb.2017.0084

28. Youn YC, Lim YK, Han SH, Giau VV, Lee MK, Park KY, Kim S, Bagyinszky E, An SSA, Kim HR. Apolipoprotein ε7 allele in memory complaints: insights through protein structure prediction. Clin Interv Aging. 2017 Jul 11;12:1095-1102. doi: 10.2147/CIA.S131172

29. Avila-Smirnow D, Gueneau L, Batonnet-Pichon S, Delort F, Bécane HM, Claeys K, Beuvin M, Goudeau B, Jais JP, Nelson I, Richard P, Ben Yaou R, Romero NB, Wahbi K, Mathis S, Voit T, Furst D, van der Ven P, Gil R, Vicart P, Fardeau M, Bonne G, Behin A. Cardiac arrhythmia and late-onset muscle weakness caused by a myofibrillar myopathy with unusual histopathological features due to a novel missense mutation in FLNC. Rev Neurol (Paris). 2016 Oct;172(10):594-606. doi: 10.1016/j.neurol.2016.07.017

30. Zheng J, Chen S, Chen Y, Zhu M, Hong D. A novel mutation in the PDZ-like motif of ZASP causes distal ZASP-related myofibrillar myopathy.Neuropathology. 2017 Feb;37(1):45-51. doi: 10.1111/neup.12328. Epub 2016 Aug 21.

31. Fichna JP, Maruszak A, Żekanowski C. Myofibrillar myopathy in the genomic context. J Appl Genet. 2018 Nov;59(4):431-439. doi: 10.1007/s13353-018-0463-4Review.

32. Han CY, Lim SW, Koo JH, Kim W, Kim SG.PHLDA3 overexpression in hepatocytes by endoplasmic reticulum stress via IRE1-Xbp1s pathway expedites liver injury. Gut. 2016 Aug;65(8):1377-88. doi: 10.1136/gutjnl-2014-308506.

33. Shan S, He X, He L, Wang M, Liu C. Coexistence of congenital left ventricular aneurysm and prominent left ventricular trabeculation in a patient with LDB3 mutation: a case report. J Med Case Rep. 2017 Aug 19;11(1):229. doi: 10.1186/s13256-017-1405-1

34. Tønne E, Holdhus R, Stansberg C, Stray-Pedersen A, Petersen K, Brunner HG, Gilissen C, Hoischen A, Prescott T, Steen VM, Fiskerstrand T.Syndromic X-linked intellectual disability segregating with a missense variant in RLIM. Eur J Hum Genet.2015 Dec;23(12):1652-6. doi: 10.1038/ejhg.2015.30

35. Lim L, Wei Y, Lu Y, Song J.ALS-Causing Mutations Significantly Perturb the Self-Assembly and Interaction with Nucleic Acid of the Intrinsically Disordered Prion-Like Domain of TDP-43. PLoS Biol. 2016 Jan 6;14(1):e1002338. doi: 10.1371/journal.pbio.1002338

36. Jin H, Lee K, Kim YH, Oh HK, Maeng YI, Kim TH, Suh DS, Bae J. Scaffold protein FHL2 facilitates MDM2-mediated degradation of IER3 to regulate proliferation of cervical cancer cells.Oncogene. 2016 Sep 29;35(39):5106-18. doi: 10.1038/onc.2016.54

37. Yang JZ, Ma SR, Rong XL, Zhu MJ, Ji QY, Meng LJ, Gao YY, Yang YD, Wang Y.Characterization of multidrug-resistant osteosarcoma sublines and the molecular mechanisms of resistance. Mol Med Rep. 2016 Oct;14(4):3269-76. doi: 10.3892/mmr.2016.5590

38. Datta D, Arion D, Corradi JP, Lewis DA Altered expression of CDC42 signaling pathway components in cortical layer 3 pyramidal cells in schizophrenia. Biol Psychiatry. 2015 Dec 1;78(11):775-85. doi: 10.1016/j.biopsych.2015.03.030. Epub 2015 Apr 11.

39. Carvalho AAS, Lacene E, Brochier G, Labasse C, Madelaine A, Silva VGD, Corazzini R, Papadopoulos K, Behin A, Laforêt P, Stojkovic T, Eymard B, Fardeau M, Romero N. Genetic Mutations and Demographic, Clinical, and Morphological Aspects of Myofibrillar Myopathy in a French Cohort. Genet Test Mol Biomarkers. 2018 Jun;22(6):374-383. doi: 10.1089/gtmb.2018.0004

40. Ramzan K, Bin-Abbas B, Al-Jomaa L, Allam R, Al-Owain M, Imtiaz F.Two novel LHX3 mutations in patients with combined pituitary hormone deficiency including cervical rigidity and sensorineural hearing loss. BMC Endocr Disord. 2017 Mar 16;17(1):17. doi: 10.1186/s12902-017-0164-8

Abdrés R. Pérez Riera

Mañana te escribiré lo que sabemos del overlapying Brugada syndrome/ARVC/D

Andrés

Este caso de Brugada es un poco “atípico” porque está asociado con una cardiopatía orgánica (DAVD) y además habrás visto que en el ECG hay un BRD geniuno. ¿Qué opinas de esto último?

Alejandro Ventira

Ya te comentare en detalle lo que pienso Estoy en este momento de partida para nuestro litoral Al regreso te explico en detalle lo que pienso Por ahora les mando un manuscrito no presentado porque estoy esperando las siempre inteligentes opiniones de Nikus.

Me gustaria saber lo que piensa Ramón que es el más grande geneticista en relación a Brugada en todo el mundo. Talvez el discorde con algunas cosas que está aquié< Puede ser que lo convidemos para que lo deje mejor al texto.

Leelo detalladamnete

El lunes o domingo a la noche seguimos la charla Estou sintiendo la bocina del motorista

Buen fin de semana para todos

lean sobretodo lo referente a que la única mutation con valor de evidencia es la SCN5A

Andrés R. Pérez Riera

Estimado Alejandro: muy interesante el caso y muchas gracias por subirlo al foro. Tengo varias inquietudes que formularle desde mi ignorancia:
El Gen LDB3, para complicarnos la vida a los cardiólogos que desconocemos de genética, en la cual me incluyo, es denominado de muchas formas MFM4; ZASP; CMD1C; CMH24; CMPD3; LVNC3; CYPHER; LDB3Z1; LDB3Z4; ORACLE; PDLIM6.
La displasia arritmogénica del VD consiste en una distrofia genéticamente determinada del miocardio ventricular derecho, con una sustitución de las células musculares por células fibroadiposas.
Los genes implicados: ACTN2, DSC2, DSG2, DSP, JUP, TMEM43, LDB3(1), PKP2, RYR2, TGFB3 codifican para proteínas de unión celular y de remodelación de los discos intercalares (placoglobina, placofilina, desmogleina, desmocolina, desmoplaquina).
También se describió transmisión familiar autosómica dominante y penetrancia variable; y recesiva, asociadas a queratodermia palmoplantar y síndrome del pelo lanoso.

1: Clin Genet. 2015 Aug;88(2):172-6. doi: 10.1111/cge.12458. Epub 2014 Sep 8.
A mutation in the Z-line Cypher/ZASP protein is associated with arrhythmogenic right ventricular cardiomyopathy.
Lopez-Ayala JM1, Ortiz-Genga M2, Gomez-Milanes I3, Lopez-Cuenca D1, Ruiz-Espejo F3, Sanchez-Munoz JJ1, Oliva-Sandoval MJ1, Monserrat L2, Gimeno JR1.

El ECG muestra un BRD con un patrón tipo I de Brugada, y ondas epsilón bien visibles desde V3; estás características electrocardiográficas están descriptas en la displasia arritmogénica. No entiendo por qué si tenemos una patología del VD se habla de síndrome de Brugada en este caso?
Por otra parte el tratamiento antiarrítmico es diferente en ambas patologías.
Como mujer curiosa me gustaría, si es posible, ver un poco más del trazado previo a la arritmia y el posterior.

Muchas gracias por todo.

Afectuosamente

Isabel Konopka

Este abstract adjunto está publicado en nuestra revista. (Yo soy editor ejecutivo de ella) estamos peleando su inclusión en el Pubmed. Pueden abrir tranquilos que no tiene copy. Considero que este articulo algo que me orgulla. Tanto que desde su publicación está en primer lugar de accesos. Este articulo es fundamental para que se entienda el gen principal del Brugada syndrome.

Esta revista tiene por editor Jefe al Dr Luiz Carlos de Abreu PhD Trabajo junto a él hace 2 años formando Mestres y Doctores en el laboratorio de pesquiza y escrita cientifica. Tenemos alumnos de otros Paises por determinacion de nuestra escuela de manera que

quien desee pleitear el maestardo o doctorado que me escirba y veremos si tiene condiciones.

La revista se llama Journal of Human Growth and Development (JHGD)

Los trabajos de Abreu sobre variabilidad del RR tuvieron tanta repercusión que recientemente fue convidado y pasó 3 meses en Harvard. Tiene mas de 200 manuscritos sobre el tema. Este investigador me ha dado la oportunidad de desarrollar en pleno nuestra potencialidad.

Andrés R. Pérez Riera

Cardiac sodium channel, its mutations and their spectrum of arrhythmia phenotypes

Andrés Ricardo Pérez-Riera1, Rodrigo Daminello Raimundo1,2, Rodrigo Akira Watanabe3, José Luiz Figueiredo1, Luiz Carlos de Abreu1,4

Doi: http://dx.doi.org/10.7322/jhgd.122759

Abstract:

The mechanisms of cellular excitability and propagation of electrical signals in the cardiac muscle are very important functionally and pathologically. The heart is constituted by three types of muscle: atrial, ventricu- lar, and specialized excitatory and conducting fibers. From a physiological and pathophysiological point of view, the conformational states of the sodium channel during heart function constitute a significant aspect for the diagnosis and treatment of heart diseases. Functional states of the sodium channel (closed, open, and inactivated) and their structure help to understand the cardiac regulation processes. There are areas in the cardiac muscle with anatomical and functional differentiation that present automatism, thus subjecting the rest of the fibers to their own rhythm. The rate of these (pacemaker) areas could be altered by modifications in ions, temperature and especially, the autonomic system. Excitability is a property of the myocardium to react when stimulated. Another electrical property is conductivity, which is characterized by a conduction and activation process, where the action potential, by the all-or-nothing law, travels throughout the heart. Heart relaxation also stands out as an active process, dependent on the energetic output and on specific ion and enzymatic actions, with the role of sodium channel being outstanding in the functional process. In the gene mutation aspects that encode the rapid sodium channel (SCN5A gene), this channel is responsible for sev- eral phenotypes, such as Brugada syndrome, idiopathic ventricular fibrillation, dilated cardiomyopathy, early repolarization syndrome, familial atrial fibrillation, variant 3 of long QT syndrome, multifocal ectopic ventricular contractions originating in Purkinje arborizations, progressive cardiac conduction defect (Lenègre disease), sudden infant death syndrome, sick sinus syndrome, sudden unexplained nocturnal death syndrome,

among other sodium channel alterations with clinical overlapping. Finally, it seems appropriate to consider the “so- dium channel syndrome” (mutations in the gene of the α subunit of the sodium channel, SCN5A gene) as a single clinical entity that may manifest in a wide range of phenotypes, to thus have a better insight on these cardiac syndromes and potential outcomes for their clinical treatment.

Keywords: arrhythmia syndromes, action potential, depolarization, cardiac conduction

---

Estimado Alejandro: sospecho que el diagnóstico de DAVD lo realizaron por RNM cardiaca.

¿Cómo ha evolucionado la función del CD a la largo de estos años?

Concuerdo que no es en ECG de un Brugada típico.

¿En qué circunstancias se presentaban las arritmias que revirtió el CDI. Nocturnas, con Sme febril o en la actividad?

Un abrazo

Martin Ibarrola

Martin

El diagnóstico de DAVD se hizo por Eco, Ventriculograma derecho y RMN.

En el último Eco el VD está dilatado con hipoquinesia en pared lateral y apical.

Todos los choques ocurrieron en reposo durante la noche, sin síndrome febril.

Alejandro Ventura

Muchas gracias Alejandro.

Será cuestión por parte de Brugada si el gen encontrado es una variante de Brugada.mas DAVD.

Mi interrogante es si la displasía puede afectar el TSVD.

Que las arritmias sean en la descanso nocturno habla a favor de un Brugada asociado.

Gracias por compartir tu caso!

Un abrazo

Martin Ibarrola

Interesante que en el trazado se ve como sale con choque de solo 15 J... nosotros casi siempre programamos a 35 y 45 J

José Enrique Ortiz Barreno

Brugada syndrome versus ARVC/D

Increasing evidence suggests the presence of structural changes affecting the right ventricular outflow tract (RVOT) in patients withBrugadaSyndrome (BrS). Patients with BrS frequently exhibit structural abnormalities localized to the RVOT and these changes may be age- and gene-dependent. The BrS may represent a heterogeneous group of disorders with a unifying ECG abnormality (**Gray B, Semsarian C, Sy RW.Brugada syndrome: a heterogeneous disease with a common ECG phenotype?J Cardiovasc Electrophysiol. 2014;25(4):450–6**.). Mutations or loss of expression of plakophilin-2; (PKP2) leads to reduced sodium current (INa), the PKP2-INa^{+}relation could be partly consequent to the fact that PKP2 facilitates proper trafficking of proteins to the intercalated disc, and additionally, PKP2 mutations can be present in patients diagnosed withBrS (BrS type 12)(**Ishikawa T, Sato A, Marcou CA, Tester DJ, Ackerman MJ, Crotti L, et al. A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5. Circulation Arrhythmia and electrophysiology. 2012;5(6):1098-107**)., thus supporting the previously proposed notion that ARVC and BrS are not two completely separate entities, but "bookends" in a continuum of variable Na^{+}current deficiency and structural disease. An overlapping disease state of BrS12 andARVCcan change phenotypically during its clinical course. Therefore, careful examination and attentive follow-up are required for patients with BrS orARVC.

Gray et al. demonstrated a high incidence of RVOT morphologic abnormalities in BrS as well as important relations between such abnormalities and clinical, genetic and electrical manifestations of disease. It confirmed that BrS is indeed a heterogeneous disorder covering the spectrum of channelopathy and “cardiomyopathy” with the abnormalities anatomically localized to the RVOT in many cases such as Alejandro case. Additionally, Increased RVOT volume and abnormal RVOT function related healthy cohort. Global RV dilatation or dysfunction however Absence ofglobal RV dilatation or dysfunction. Spontaneous type 1 ECG patternorlate potentials is associated with lower RVEF (**Gray B, Gnanappa GK, Bagnall RD, et al.Relations between right ventricular morphology and clinical, electrical and genetic parameters in Brugada Syndrome.PLoS One. 2018;13(4):e0195594**.). (**Doesch C, Michaely H, Haghi D, Schoenberg SO, Borggrefe M, Papavassiliu T.How to measure the right ventricular outflow tract with cardiovascular magnetic resonance imaging: a head-to-head comparison of methods.Hellenic J Cardiol. 2014;55(2):107–18**.). BrS andARVC/D clinical features can coexist in a single patient, and EPS might be useful for determining the phenotype of overlapping disease (e.g., BrS-like orARVC/D-like) (**Kataoka S, Serizawa N, Kitamura K, et al. An overlap of Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia. J Arrhythm. 2016;32(1):70-3.**). An overlapping disease state of BrS andACcan change phenotypically during its clinical course. Therefore, careful examination and attentive follow-up are required for patients with BrS orAC. There are few studies that have systematically explored the association between structural abnormalities and the electrical and genetic profile of patients with BrS (**van Hoorn F, Campian ME, Spijkerboer A, Blom MT, Planken RN, van Rossum AC, et al.SCN5A mutations in Brugada syndrome are associated with increased cardiac dimensions and reduced contractility.Bastiaenen R, Cox AT, Castelletti S, Wijeyeratne YD, Colbeck N, Pakroo N, et al.Late gadolinium enhancement in Brugada syndrome: A marker for subtle underlying cardiomyopathy?Heart Rhythm. 2017;14(4):583–9.**)

BrS 12has the following characteristics: **Cytogenetic Location:**3p21.2-2-p14.3;**OMIM:**602701;**Gene:**SLMAP Sarcolemma-Associated Protein.Immunohistochemical localization of SLAP in cardiac muscle revealed that SLAPassociatedwith the sarcolemma and also displayed a reticular pattern of staining that resembled the transverse tubules and the sarcoplasmic reticulum. The SLAPs define afamilyof tail-anchoredmembraneproteinsthat exhibit tissue specificexpressionand are uniquely situated to serve a variety of roles through their coiled-coil motifs.(**Wigle JT, Demchyshyn L, Pratt MA, Staines WA, Salih M, Tuana BS. Molecular cloning, expression, and chromosomal assignment of sarcolemmal-associated proteins. A family of acidic amphipathic alpha-helical proteins associated with the membrane J Biol Chem. 1997;272(51):32384-94)**.).;**Ion channel and effect:**INa^+loss-of-function;**Protein:**Sarcolemma membrane-associated protein, a component of T-tubes and the sarcoplasmic reticulum – influences trafficking of Nav1.5;**% Probands:**Rare.;**HGNC ID:**16643.

Cerrone et al mentioned that the patients with BrS diagnostic could represent a rather heterogenic group comprising of individuals with mutations of desmosomal genes in as

much as 3% of cases(**Cerrone M, Lin X, Zhang M, Agullo-Pascual E, Pfenniger A, Chkourko Gusky H, Novelli V, Kim C, Tirasawadichai T, Judge DP, Rothenberg E, Chen HS, Napolitano C, Priori SG, Delmar M. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. Circulation. 2014; 129:1092–1103. doi: 10.1161/ CIRCULATIONAHA.113.003077**)1 They suggests that mutations of PKP2 gene present in patients diagnosed with BrS and consecutive loss of desmosomal integrity could lead to reduced Na^+current and hereby arrhythmogenic state through delayed depolarization**Forkmann M, Tomala J, Huo Y, Mayer J, Christoph M, Wunderlich C, Salmas J, Gaspar T, Piorkowski C Epicardial Ventricular Tachycardia Ablation in a Patient With Brugada ECG Pattern and Mutation of PKP2 and DSP Genes. Circ Arrhythm Electrophysiol. 2015 Apr;8(2):505-7. doi: 10.1161/CIRCEP.114.002342.**

The relation between PKP2 and I_{Na}described in the paragraphs above led Cerrone et al. to speculate that, if a PKP2 mutation primarily impacts I_{Na}function (rather than desmosomal structure), its presence would manifest in a manner clinically similar to BrS. Interestingly, after the initial description of BrS, Corrado et al suggested that this condition could share several clinical features with ARVC, implying that these were not completely distinct clinical entities(**Corrado D, Basso C, Buja G, Nava A, Rossi L, Thiene G. Right bundle branch block, right precordial stsegment elevation, and sudden death in young people.Circulation.2001;103:710–717**.)(**Corrado D, Buja G, Basso C, Nava A, Thiene G. What is the Brugada syndrome?Cardiology in review.1999;7:191–195**). Cerrone et al screened by direct sequencing a cohort of 200 patients with clinical diagnosis of BrS and no mutations on the most prevalent genes. They discovered five single amino acid substitutions in five unrelated patients(**Cerrone M, Lin X, Zhang M, et al. Missense Mutations in Plakophilin-2 Cause Sodium Current Deficit and Associate with a Brugada Syndrome Phenotype.Circulation.2014 Mar 11;129(10):1092-103. doi: 10.1161/CIRCULATIONAHA.113.003077**). In order to assess if these missense variants in PKP2 could affect the cardiac I_{Na}, they used an HL-1 cell line, stably silenced for the endogenous PKP2. In the absence of PKP2, these cells showed a decrease in endogenous INa. Cells transiently transfected with each one of the PKP2 mutants associated with the BrS phenotype showed significantly decreased I_{Na}, when compared with cells transfected with wild type PKP2. Similar results were obtained when these authors used a line of human iPSC-derived cardiomyocytes from a patient lacking PKP2 at the cell membrane(**Awad MM, Dalal D, Tichnell C, et al. Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2.Human mutation.2006;27:1157**)(Kim C, Wong J, Wen J, et al. Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs.Nature.2013;494:105–110.). In these cells, I_{Na}increased upon transfection with wild type PKP2. Transfection with one of the PKP2 mutants associated with BrS was not able to restore normal I_{Na}. These data represent the first evidence that missense mutations in PKP2 can cause a decrease in cardiac I_{Na}. When combined with other factors (such as decreased electrical coupling

and/or fibrosis), a reduction in I_{Na}could facilitate the development of arrhythmias, even in the absence of a structural cardiomyopathy. Cerrone et al. propose that PKP2 mutations provide at least part of the molecular substrate of BrS. The inclusion of PKP2 as part of routine BrS genetic testing remains premature; yet, the possibility that some patients showing signs of disease may harbor PKP2 variants should be considered when the genotype is negative for other genes associated with BrS.

Campuzano et al have performed a genetic revision of allPKP2genetic variants currently associated withBrS. In all variants the authors identified a lack of solid evidences in order to establish a definite genotype-phenotype association. Hence, despite they believe thatPKP2analysis should be considered as a part of molecular genetic testing inBrSpatients, comprehensive clinical and molecular studies should be performed before establishing pathogenic association. Therefore,PKP2variants inBrScases should be interpreted carefully and additional studies including family segregation should be performed before translation into clinical practice.(**Campuzano O, Fernández-Falgueras A, Iglesias A, Brugada R. Brugada Syndrome and PKP2: Evidences and uncertainties.Int J Cardiol. 2016 Jul 1;214:403-5. doi: 10.1016/j.ijcard.2016.03.194).**

Summary of Differential Diagnosis Between ARVC/D and Brugada Syndrome

I)Age at presentation

Ø**ARVC/D:**The mean age at diagnosis is 31 years (±13; range: 4-64 years).

Ø**BrS:**presenting typically in the fourth or fifth decade of life.(35–40 years of age)over the last several years, there has been growing evidence in the literature of onset of the disease during childhood.

II)Sex, male/female ratio. Women with BrS typically show more benign clinical features with a lower percentage of type 1 BrP ECG and a lower prevalence of symptoms (**Benito B, Sarkozy A, Mont L, et al. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol 2008;52:1567–73**.). Males have a 5.5-fold increased risk of sudden cardiac death, and mean age for development of ventricular fibrillation is 41± 15 years (**Mizusawa Y, Wilde A. Brugada syndrome. Circ Arrhythm Electrophysiol 2012; 5: 606-616**.).

Ø**ARVC/D:**

Ø**BrS:**. The male/female ratio is 8/1 -10/1 (**Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–1963**.). Male predominance is significant in Asian countries (90%– 96%), but only 60%–70% of the patients were males in European studies (**Milman A, Gourraud JB, Andorin A, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;XX:XX–XXX**). The clinical characteristics and risk markers of BrS depend on the characteristics of male patients. Females have lower

incidences of symptoms and spontaneous type 1 ECG pattern than males(**Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P, Brugada J. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol 2008; 52:1567–1573**). Ventricular fibrillation (VF) induced by programmed electrical stimulation (PES) was less frequent in females than in males. Females had better prognosis (cardiac events ratio 0.56%/y) than did males (2.4%/y). They failed to identify a risk factor for VF in females because of the low event ratio, but found significant prolongation of PR and HV intervals in females in whom cardiac events occurred. Females had less frequent spontaneous type 1 ECG, less frequent PES-induced VF, and a lower incidence of arrhythmic events (0.7%) than males (**Sieira J, Conte G, Ciconte G, et al. Clinical characterisation and long-term prognosis of women with Brugada syndrome. Heart 2016;102:452–458**.). The multicenter international Survey on Arrhythmic Events in BrS included 59 females with BrS. The survey showed that the percentage of females was higher in Caucasians than in Asians. A history of VF, spontaneous type 1 ECG, and PES-induced VF were less frequent in females than in males. After excluding pediatric patients, the age at the onset of VF was older in females (49.5 years) than in males (43 years). An SCN5A mutation was found more frequently in females than in males. These gender differences became unclear in pediatric patients (age ,16 years) and elderly patients (age .60 years)**Milman A, Gourraud JB, Andorin A, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;XX:XX–XXX**.. Berthome et al included 494 female patients. The study showed that the frequencies of symptoms, spontaneous type 1 ECG, and PES-induced VF were lower in females than in males. Females had a long-corrected QT interval and narrow QRS interval. Age at the time of cardiac events was older in females (48.6 years) than in males (43 years). The incidence of events during follow-up was not high in females (0.4%/y), especially in asymptomatic females (0.2%/y), and gender was significantly associated with cardiac events. Multivariable analysis showed that index patients, previous SCD, syncope, fQRS, and broad QRS interval(l≥.120 ms) were independent predictors of cardiac events(**Berthome P, Tixier R, Briand I, et al. Clinical presentation and follow-up of women affected by Brugada syndrome. Heart Rhythm 2018;15:XX–XXX.**.. Common observations in those studies were that a history of VF, spontaneous type 1 ECG, and PES-induced VF were not frequent in females and that females had good prognosis. A history of aborted cardiac arrest is a powerful predictor of prognosis. ECG risk markers including prolongation of PR and QRS intervals, sinus node dysfunction, and fQRS were not coincident risk markers in those studies, but these markers were associated with conduction disturbance. The occurrence of any conduction abnormality might indicate that female patients are at a high risk of VF. According to the repolarization theory of BrS, the mechanism is epicardial action potential change caused by increased outward currents or decreased inward currents, which are the opposite directions males and females have different ion channel distributions, and moreover, sex hormones modulate ion currents (**Odening KE, Koren G. How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity. Heart Rhythm 2014;11:2107–2115**.). Females have

larger calcium currents (ICa-L) and smaller potassium currents, including transient outward current (Ito), delayed rectifier potassium current (IK: IKr and IKs) and inward rectifier potassium current (IK1) than do males. Estrogen prolongs the QT interval in females with LQTS by decreasing Ito, IK, and IK1 and increasing ICa-L. Testosterone increases outward currents (Ito, IK1, and IKs), decreases ICa-L, and shortens the QT interval in male patients after puberty. Increase in Ito and decrease in ICa-L have a pivotal role in action potential changes, causing repolarization heterogeneity and phase 2 reentry in BrS (**Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, Scornik FS, Antzelevitch C. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. Circulation 2002;106:2004–2011**). Estrogen relieves but testosterone enhances arrhythmogenic action potential change in BrS. Patients with BrS had a high level of testosterone (**Shimizu W, Matsuo K, Kokubo Y, et al. Sex hormone and gender difference— role of testosterone on male predominance in Brugada syndrome. J Cardiovasc Electrophysiol 2007;18:415–421**) Additionally, reduction of testosterone by castration masked Brugada ECG(**Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. Pacing Clin Electrophysiol 2003; 26:1551–1553**.)Low concentrations of sex hormones in children and elderly patients would be a reason why there are no gender differences in such periods. Protective effects of estrogen on arrhythmogenicity in BrS can explain the male predominance during adulthood. The mechanism of BrS has been debated, but the explanation of gender differences by hormonal changes indicates that repolarization changes are also important for arrhythmogenicity in BrS.

III)Race

Ø**ARVC/D:**Caucasian predominance

Ø**BrS:**Asian predominance

IV)Geographic distribution worldwide

Ø**ARVC/D:**Endemic in Veneto area, and Greek Naxos island

Ø**BrS:**Endemic in Thailand,Philippines, JapanSudden unexplained nocturnal death syndrome (SUNDS) has been reported worldwide. SUNDS is endemic in Southeast Asia and is colloquially known as Bangungut in the Philippines, Lai Tai in Thailand, and Pokkuri in Japan. Although SUNDS in Thailand and Japan have been determined to be phenotypically, genetically and functionally identical to the Brugada syndrome, the relationship between Bangungut/SUNDS in the Philippines and the Brugada syndrome has not been clarified. Bangungut/SUNDS and the Brugada syndrome appear closely related. Pathophysiological mechanisms of the BrS may explain the enigma of Bangungut/SUND. Whether Bangungut/SUNDS is phenotypically, genetically and functionally an allele of the BrS remains inconclusive due to lack of research data..

V)Prevalence

Ø**ARVC/D:**The estimated prevalence of ARVC/D in the general population is approximately 1:5000, affecting men more frequently than women with a ratio of 3:1, (**Corrado D, Thiene G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: clinical impact of molecular genetic studies****Circulation.2006;113(13):1634–7**.) ARVC/D accounts for 11%–22% of cases of SCD in the young athlete patient population, accounting for ap .proximately 22% of cases in athletes in northern Italy (**Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people.N Engl J Med.1988;318(3):129–33**)and about 17% of SCD in young people in the United States (**Dalal D, Nasir K, Bomma C, et al. Arrhythmogenic right ventricular dysplasia: a United States experience.Circulation.2005;112(25):3823–32**.).

Ø**BrS:**The BrS prevalence varies among regions and ethnicities, affecting mostly males.In the pediatric population is low (0.0098%) compared with the adult population (0.14–0.7%). Nevertheless, in recent years, there has been growing evidence in the literature of earlier onset of the disease (**Hermida JS, Lemoine JL, Aoun FB, Jarry G, Ray JL, Quiet JC. Prevalence of the Brugada syndrome in an apparently healthy population. Am J Cardiol 2000; 86: 91–94.**). The estimated worldwide prevalence of Brugada pattern ECG changes is 0.23%, and they are most commonly seen in people of Asian descent, followed by people in Europe and the United States.

VI)Incidence

Ø**ARVC/D:**Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare (1:2000–1:5000) inherited cardiac condition (**Pilichou K, Thiene G, Bauce B, Rigato I, Lazzarini E, Migliore F, Perazzolo Marra M, Rizzo S, Zorzi A, Daliento L, Corrado D, Basso C (2016) Arrhythmogenic cardiomyopathy.Orphanet J Rare Dis 11:33**

Ø**BrS:**The incidence of BrS is about 9 times more frequent in males than females (**Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10:1932–63**).

VII)Inheritance pattern

Ø**ARVC/D:**

Ø**BrS:**autosomal dominant inheritance with incomplete penetrance or sporadic (**Mizusawa Y, Wilde A. Brugada syndrome. Circ Arrhythm Electrophysiol 2012; 5: 606-616**.).

VIII)Genetic variants

Ø**ARVC/D:**

Currently 60% of patients meeting Task Force Criteria (TFC) have an identifiable mutation in one of the desmosomal genes.Pathogenicmutationsin genes encoding the cardiac desmosome can be found in approximately 60% of index patients, leading to our current perception ofARVCas a desmosomal disease.Bhonsale A, Groeneweg JA, James CA,

etal.Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy−associated mutation carriers.Eur Heart J. 2015;36:847–855

In a cohort with o137 individualsMurray et a. describe that a small but significant percentage (4.3%) of individuals with ARVC may have putative likely pathogenic/pathogenic variants reported in the sarcomere genes. meeting 2010 TFC for a diagnosis of ARVC, negative for pathogenic desmosomal variants,TMEM43,SCN5A, andPLNwere screened for variants in the sarcomere genesACTC1,MYBPC3,MYH7,MYL2,MYL3,TNNC1,TNNI3,TNNT2, andTPM1) through either clinical or research genetic testing. A similar yield has recently also been reported by Medeiros et al. (**Medeiros−Domingo A, Saguner A, Magyar I, etal.Arrhythmogenic right ventricular cardiomyopathy: Implications of next−generation sequencing in appropriate diagnosis.Europace. 2016;9:1063–1069**.)**Murray B1, Hoorntje ET2,3, Te Riele ASJM3,4, Tichnell C1, van der Heijden JF4, Tandri H1, van den Berg MP5, Jongbloed JDH2, Wilde AAM6, Hauer RNW3,4, Calkins H1, Judge DP1, James CA1, van Tintelen JP3,7, Dooijes D8.Identification of sarcomeric variants in probands with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). J Cardiovasc Electrophysiol. 2018 Jul;29(7):1004-1009. doi: 10.1111/jce.13621. Epub 2018 May 21**. The ARVC/D Genetic Variants Database is a freely available collection of variants associated with ARVC and can be accessed via the linkhttp://www.arvcdatabase.info/

Reduced $Na_V1.5$ at the ID in samples from patients with desmosomal mutations(**Noorman M, Hakim S, Kessler E, Groeneweg J, Gpj Cox M, Asimaki A, van Rijen HV, van Stuijvenberg L, Chkourko H, van der Heyden MA, Vos MA, de Jonge N, van der Smagt JJ, Dooijes D, Vink A, de Weger RA, Varro A, de Bakker JM, Saffitz JE, Hund TJ, Mohler PJ, Delmar M, Hauer RN, van Veen TA. Remodeling of the cardiac sodium channel, connexin43 and plakoglobin at the intercalated disk in patients with arrhythmogenic cardiomyopathy.Heart rhythm.2012;10:412–419**).Experimental models have shown correlation between loss of PKP2 expression, and reduced I_{Na}**Sato PY, Coombs W, Lin X, Nekrasova O, Green KJ, Isom LL, Taffet SM, Delmar M. Interactions between ankyrin-g, plakophilin-2, and connexin43 at the cardiac intercalated disc.Circ res.2011;109:193–201.)(Sato PY, Musa H, Coombs W, Guerrero-Serna G, Patino GA, Taffet SM, Isom LL, Delmar M. Loss of plakophilin-2 expression leads to decreased sodium current and slower conduction velocity in cultured cardiac myocytes.Circ res.2009;105:523–526**.)(Cerrone M, Noorman M, Lin X, Chkourko H, Liang FX, van der Nagel R, Hund T, Birchmeier W, Mohler P, van Veen TA, van Rijen HV, Delmar M. Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency.Cardiovasc res.2012;95:460–468.) the co-existence of clinical sodium channelopathy (BrS) and genetic variation in PKP2. not only loss of PKP2, but also single amino acid mutations, can interfere with I_{Na}In some cases, mutations in PKP2 can be part of the BrS molecular substrate.

Andrés R. Pérez Riera.