Role of CACNA1C variants in Brugada syndrome: clinical aspects and genetic testing strategies

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Background: Inconsistent data support the role of CACNA1C as a disease-causing gene responsible for Brugada syndrome (BrS). As of today, the only gene consistently linked with BrS is SCN5A. Several CACNA1c genetic variants have been reported in association wirh BrS; however, due to the limited evidence, CACNA1C is not suggested for routine genetic screening for BrS.
Purpose: In this study, we carried out a systematic screening of CACNA1C gene, including a functional evaluation of the identified variants, in order to determine the yield of screening in a large series of BrS probands and to address the hypothesis that an appropriate clinical selection of patients would substantially improve the yield of genetic testing.
Methods and results: Overall 564 consecutive patients, referred for BrS genetic testing, were sequenced for CACNA1C gene. Patients were divided in two groups: discovery cohort (n=200 patients) and confirmation cohort (n=363 patients). Furthermore, analysis of the clinical phenotypes of a matched SCN5A positive BrS cohort (n=146) was included for phenotype characterization.
In the discovery cohort we identified 11 different genetic variants of whom 2 (18%) were considered as potentially causative based on ACMG guidelines. However, a large proportion (81%) was classified as variants of unknown significance (VUS). Functional evaluation of the identified variants, including pathogenic and VUS, was assessed by patch-clamp and immunofluorescence studies. Re-evaluation of the variants, including functional studies results, indicated an increase of pathogenic or likely pathogenic variants (81%) getting a yield of screening of 5% in the discovery cohort. Results from the confirmation cohort confirmed a low rate of CACNA1C carriers with a yield of screening of 2.2%.
Analysing the clinical phenotype of all CACNA1C carriers showed a significantly shorter QTc [371 ms ± 16 ms vs. 399±18 ms; p=0.000004]. Furthermore, the prevalence of CACNA1C variants was highest (12.9%) among patients with a QTc in the lowest quartile (QTc <390 ms). ROC curve showed an AUC of 0.91 for QTc a cut-off of 385 ms, suggesting a high predictive accuracy.
Conclusion: We confirmed that CACNA1C variants are not a common cause of BrS, with a yield of screening of 2–5%. However, pathogenic variants are more frequent (12.5%) in patients with a shorter QTc, suggesting a genetic testing strategy in this subgroup of BrS patients. Furthermore, our data highlights the impact of robust functional studies to improve variant classification and reduce uncertainties.