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Atypical case of ulnar-mammary syndrome with ventricular tachycardia and lack of TBX3 mutation

Authors:
A Zlotina¹, A Kiselev¹, A Kostareva¹, ¹Almazov National Medical Research Centre, Institute of Molecular Biology and Genetics - Saint-Petersburg - Russian Federation,

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Introduction: Congenital heart malformation can represent an isolated disorder or be a part of complex syndromic phenotypes characterized by significant clinical and genetic heterogeneity. An example of such rare and complex clinical conditions is a group of so-called "heart-hand" congenital syndromes, where a patient along with a severe cardiac pathology presents various abnormalities of limb skeleton and additional dysmorphia. At present, the molecular basis of heart-hand syndromes and phenotypically similar conditions is only partly described.

Purpose: A 30-year-old woman with a complex phenotypic picture typical for the rare inherited ulnar-mammary syndrome (MIM 181450) was hospitalized due to the frequent episodes of non-sustained ventricular tachycardia. In addition, phenotypic features involved the pathology of 4th-5th digits and ulna hypoplasia, hypoplasia of the mammary glands, abnormalities of the teeth with mandibular dysplasia, delay in sexual development. Here we aimed to determine the genetic basis of the described phenotype to extend knowledge on causative genes and molecular mechanisms of the complex congenital malformation.

Methods: The genomic screening was carried out by whole-exome sequencing (WES) approach as well as by oligonucleotide array-based comparative genome hybridization (array-CGH). Bidirectional sequencing by the Sanger method was done to validate the high-throughput sequencing data.

Results: To date, the only gene associated with the ulnar-mammary syndrome is TBX3 (locus 12q24.21) that encodes a transcription factor belonging to the evolutionary-conserved T-box family. Nevertheless, in the present clinical case we did not reveal any genetic defects in TBX3 as well as in other genes currently known to be responsible for «heart-hand» conditions either by WES and the Sanger sequencing or CGH-array. On the results of WES data analysis, we identified a novel missense variant in SYNM gene (exon 1, p.A58V), encoding an intermediate filament protein synemin. Synemin was shown to be abundant in all muscle cells types but is also expressed in other cell types, including the mammary glands and adipose tissue. As regards the pathological conditions, it was previously shown that mice lacking SYNM demonstrate myopathic and osteopenic phenotypes, while a spectrum of SYNM mutations and their clinical impact have not been yet characterized.

Conclusions: Here we present a nontypical clinical case of ulnar-mammary syndrome with no association with TBX3 mutation. We suggest that the genetic variant in SYNM gene could contribute to the complex phenotype. Further comprehensive functional studies are required to evaluate the possible role of SYNM mutations in development of ulnar-mammary syndrome and ventricular arrhythmias.