World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:17, No:10, 2023

Previously Undescribed Cardiac Abnormalities in Two Unrelated Autistic Males with Causative Variants in CHD8

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Abstract : Introduction: Autism is the most common neurodevelopmental disorder. Autism is characterized by difficulties in social interaction and adherence to stereotypic behavioral patterns and frequently co-occurs with epilepsy, intellectual disabilities, connective tissue disorders, and other conditions. CHD8 codes for chromodomain-helicase-DNA-binding protein 8 - a chromatin remodeler that regulates cellular proliferation and neurodevelopment in embryogenesis. CHD8 is one of the genes most frequently involved in autism. Patients and methods: 2 unrelated male patients, P3 and P12, aged 3 and 12 years old, underwent whole genome sequencing, which determined that they both had different likely pathogenic variants, both previously undescribed in literature. Sanger sequencing later determined that P12 inherited the variant from his affected mother. Results: P3 and P12 presented with autism, a developmental delay, ataxia, sleep disorders, overgrowth, and macrocephaly, as well as other clinical features typically present in patients with causative variants in CHD8. The mother of P12 also has autistic traits, as well as ataxia, hypotonia, sleep disorders, and other symptoms. However, P3 and P12 also have different cardiac abnormalities. P3 had signs of a repolarization disorder: a flattened T wave in the III and aVF derivations and a negative T wave in the V1-V2 derivations. He also had structural valve anomalies with associated regurgitation, local contractility impairment of the left ventricular, and diastolic dysfunction of the right ventricle. Meanwhile, P12 had Wolff-Parkinson-White syndrome and underwent radiofrequency ablation at the age of 2 years. At the time of observation, P12 had mild sinus arrhythmia and an incomplete right bundle branch block, as well as arterial hypertension. Discussion: Cardiac abnormalities were not previously reported in patients with causative variants in CHD8. The underlying mechanism for the formation of those abnormalities is currently unknown. However, the two hypotheses are either a disordered interaction with CHD7 – another chromodomain remodeler known to be directly involved in the cardiophenotype of CHARGE syndrome – a rare condition characterized by coloboma, heart defects and growth abnormalities, or the disrupted functioning of CHD8 as an A-Kinase Anchoring Protein, which are known to modulate cardiac function. Conclusion: We observed 2 unrelated autistic males with likely pathogenic variants in CHD8 that presented with typical symptoms of CHD8-related neurodevelopmental disorder, as well as cardiac abnormalities. Cardiac abnormalities have, until now, been considered uncharacteristic for patients with causative variants in CHD8. Further accumulation of data, including experimental evidence of the involvement of CHD8 in heart formation, will elucidate the mechanism underlying the cardiophenotype of those patients. Acknowledgements: Molecular genetic testing of the patients was made possible by the Charity Fund for medical and social genetic aid projects «Life Genome.»

Keywords : autism spectrum disorders, chromodomain-helicase-DNA-binding protein 8, neurodevelopmental disorder, cardio phenotype
Conference Title : ICA 2023 : International Conference on Autism
Conference Location : Barcelona, Spain
Conference Dates : October 23-24, 2023