Brugada Syndrome and related cardiac conduction disorders: A strategy to understand the etiology of Sudden Cardiac Death among patients with Schizophrenia and Psychotic Bipolar Disorder

Gupta R[1], Bigdeli TB[1], Fanous AH[1]

Department of Psychiatry, SUNY Downstate Health Sciences University, Brooklyn, New York (1)

BACKGROUND

Brugada Syndrome (BrS), a complex arrhythmogenic disorder, is one of the chief causes of sudden cardiac death (SCD) in patients without structural heart disease.

It is an oligogenic disorder, with low penetrance

The most typical presentation of BrS is syncope or resuscitated cardiac arrest in the third or fourth decade of life due to polymorphic ventricular tachycardia or ventricular fibrillation.

More than 80% of adult patients with BrS are men, but there is an equal gender ratio in children.

BrS is known to affect 1 in 2000 people.

Two ECG patterns for BrS are: **Type 1** (coved-type) represents the **only diagnostic** pattern for BrS, marked by a prominent **coved** ST-segment elevation >2 mm or 0.2 mV, while non-Type 1 ECG is defined as one of the following: Type 2 ECG, Type 3 ECG, and ECG displaying coved or saddleback ST-elevation with J-wave amplitude ≥1 mm and <2 mm.

Sudden Cardiac Death (SCD) in turn, is one of the leading causes of mortality among patients with schizophrenia. It is defined by the WHO as death within 1 h of symptom onset (witnessed) or within 24 h of being observed alive and symptom free (unwitnessed).

It affects more than 3 million people annually worldwide, and accounts for 200,000 to 450,000 deaths annually in the USA, which equates to 15 to 20 % of all deaths and 50 % of overall cardiac mortality.

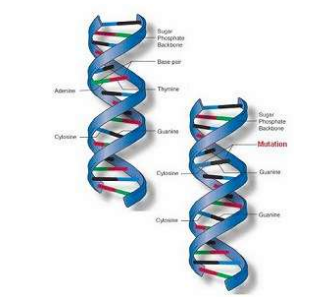
SCD is 2-4 times more common among patients with schizophrenia when compared to general population.

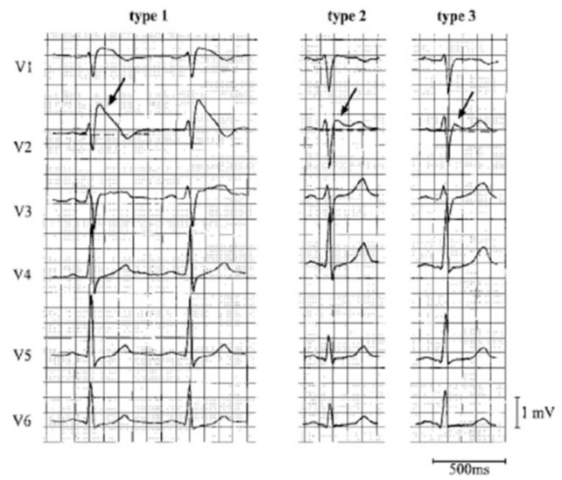
Although SCD is associated with number of clinical factors commonly seen in patients with schizophrenia, including, unhealthy lifestyle, psychotropic drugs, substance use, and metabolic syndrome, however, there is also a role for inherited conduction disorders, like BrS.

BrS is estimated to be ~10 times more common among patients with schizophrenia.

RESULTS

Among the **27** known BrS associated genes, **5** were found to be nominally significant in the SCHEMA study – ***HCN4*** ($P<10^{-5}$) ***CACNA2D1*** ($P<0.001$), ***ANK2*** and ***CACNA1C*** ($P<0.01$), and ***ABCC9*** ($P<0.05$)
In addition to a replicated association with common variants in ***CACNA1C*** ($P<10^{-16}$), the landmark Psychiatric Genomic Consortium (PGC) genome-wide association study (GWAS) detected subthreshold associations in or near ***ANK2*** ($P<10^{-4}$), and ***HCN4*** and ***CACNA2D1*** ($P<0.001$).





Brugada-pattern EKG

AIMS

To evaluate the evidence for shared genetic etiology of Schizophrenia and BrS

METHODS

We postulated that there is a partially shared genetic basis of schizophrenia and BrS.
We reviewed the available evidence in support of this hypothesis, including results from the Schizophrenia Exome Sequencing Meta-analysis (SCHEMA) consortium (24, 248 cases and 97, 322 controls) and Psychiatric Genomic Consortium (PGC) with 34,000 cases and 45,000 controls.
SCHEMA consortium is a large multi-site collaboration dedicated to generating, and analyzing sequencing data of patients with schizophrenia aimed to improve understanding of its genetic architecture and speed up gene discovery.
The PGC is one of the largest experiments in the history of psychiatry. It's key goal is to utilize global collaboration to advance genetic discovery of biologically, clinically, and therapeutically meaningful insights into various psychiatric disorders, including schizophrenia; it mainly conducts very large genome-wide association studies (GWAS) and rare copy number variation studies.

DISCUSSION

This study indicates that there is an overlap between the Schizophrenia and BrS genetics. This should not come as a surprise or an anomaly, because genes underlying complex medical conditions have been found to have pleiotropic effects in recent discoveries. It is well known that pathophysiology of schizophrenia involves abnormalities of **ion channels**, synaptic machinery, neuronal migration and growth, etc.
BrS pathophysiology is relatively simpler than that of schizophrenia, but yet to be elucidated fully. It's mainly a channelopathy, but some structural gene mutations have also been described.
CACNA2D1 and ***CACNA1C*** code for α2δ subunit and α subunit of voltage-gated calcium channel ($Ca_V1.2$). Former is a binding site for gabapentinoids, for example, Gabapentin; a drug with some mood-stabilizing properties; while the latter is responsible for prolonged action potential in cardiomyocytes, dendrites and dendritic spines of cortical neurons. ***ABCC9*** codes ATP binding cassette transporter of K_{ATP} channel (ATP-sensitive Potassium channel). Alternate splicing of this gene codes for sulfonylurea receptors, expressed in cardiomyocytes and neurons. ***HCN4*** codes for hyperpolarization-activated cyclic nucleotide-gated channel 4; channels expressed in the pacemaker region in the heart. ***ANK2*** codes for Ankyrin-2 or Ankyrin-B protein; it plays an essential role in the localization and membrane stabilization of ion transporters and ion channels in cardiomyocytes, and also in vertebrate long-range axonal transport by coupling the dynein-dynactin motor complex to organelle cargoes such as synaptic vesicles and mitochondria. However, there haven't been any studies on the role of ANK2 in mammalian brain. We need to validate these results in larger and different data sets. We also need more basic science studies to look at the exact role of these putative genes in the biology of BrS among patients with Schizophrenia and how it may play a role in causing SCD among them.

CONCLUSIONS

Leveraging publicly available large genomic data repositories, we evaluated the evidence regarding possible shared genetic basis of schizophrenia with BrS.
We found evidence supporting genetic association between schizophrenia and BrS.
Based on these preliminary findings, we recommend a need for future studies with more robust methodology, involving large samples, and adjusting for different treatment variables as confounders to replicate these initial results.

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