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SYSTEMATIC- REVIEW

Cardiac Phenotypes and Endophenotypes in Schizophrenia : A systematic Review

Phenotypes et endophenotypes cardiaques dans la schizophrénie: Une Revue systématique

Amine Larnaout[1], Zeynab Jebberi[2], Mohamed Salah Hamdi[3], Rania Lansari[1], Mohamed Sami Mourali[2], Wahid Melki[1]

1. University of Tunis El Manar, Faculty of Medicine of Tunis, 1002, Razi Hospital, Department of Psychiatry D. Research Laboratory LR18SP03 : Maladies Neurodégénératives et Troubles Psychiatriques, 2010, Manouba, Tunisia
2. University of Tunis El Manar, Faculty of Medicine of Tunis, 1002, La Rabta University Hospital, Cardiology Department
3. University of Tunis El Manar, Faculty of Medicine of Tunis, 1002, Charles Nicolle University Hospital, Internal Medicine Department

Abstract

Background: Schizophrenia is increasingly recognized as a multisystemic disorder. Cardiac anomalies, including autonomic, electrophysiological, and structural heart abnormalities, are frequently reported in patients with schizophrenia. However, the distinction between phenotypes and endophenotypes remains unclear.

Methods: In this review, we synthesized clinical, neurobiological, and genetic evidence to assess cardiac alterations in schizophrenia and evaluate their potential as endophenotypes.

Results: Autonomic dysfunction, especially reduced heart rate variability (HRV) and impaired parasympathetic regulation, emerged as the most consistent cardiac phenotype, and the only one that fulfills the criteria for an endophenotype. In contrast, electrophysiological anomalies such as QT/QTc prolongation, T-wave changes, and some structural heart anomalies show genetic associations with schizophrenia but lack sufficient heritability and longitudinal data to be classified as endophenotypes.

Conclusion: Among all cardiac anomalies reported in schizophrenia, autonomic dysfunction, particularly HRV impairment, was the only one that fulfilled the endophenotype criteria. However, most of the reviewed studies were observational, which limits the robustness of our conclusions. Future heritability and multi-omic studies are needed to understand the complex pathogenomic interlink between mental and heart diseases.

Keywords: Schizophrenia, heart, anomalies, phenotypes, endophenotypes

Résumé

Introduction: La schizophrénie est de plus en plus reconnue comme un trouble multisystémique. Les anomalies cardiaques, incluant les dysfonctionnements autonomes, les anomalies électrophysiologiques et structurelles du cœur, sont fréquemment rapportées chez les patients atteints de schizophrénie. Cependant, la distinction entre phénotypes et endophénotypes reste floue.

Méthodes: Dans cette revue, nous avons synthétisé les données cliniques, neurobiologiques et génétiques afin d'évaluer les altérations cardiaques dans la schizophrénie et leur potentiel en tant qu'endophénotypes.

Résultats: Le dysfonctionnement autonome, en particulier la réduction de la variabilité de la fréquence cardiaque (HRV) et l'altération de la régulation parasympathique, apparaît comme le phénotype cardiaque le plus constant et le seul à répondre aux critères d'un endophénotype. En revanche, les anomalies électrophysiologiques telles que la prolongation du QT/QTc, les modifications de l'onde T, ainsi que certaines anomalies structurelles du cœur présentent des associations génétiques avec la schizophrénie, mais ne disposent pas de données suffisantes en termes d'héritabilité et de suivi longitudinal pour être classées comme endophénotypes.

Conclusion: Parmi toutes les anomalies cardiaques rapportées dans la schizophrénie, le dysfonctionnement autonome, et en particulier la diminution de l'HRV, est le seul à répondre aux critères d'un endophénotype. Cependant, la grande majorité des études examinées étaient observationnelles, ce qui limite la solidité de nos conclusions. Des études futures portant sur l'héritabilité et utilisant des approches multi-omiques sont nécessaires pour mieux comprendre les interconnexions pathogénomiques complexes entre les maladies mentales et cardiaques.

Mots clés: Schizophrénie, cœur, anomalies, phénotypes, endophénotypes

Correspondance
Amine Larnaout
University of Tunis El Manar, Faculty of Medicine of Tunis, 1002, Razi Hospital, Department of Psychiatry D.
Email: larnaout.amin@gmail.com

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Introduction

Schizophrenia is a highly heritable psychiatric disorder. Most studies estimate its heritability to range from 60% to 80% (1). The onset age ranges from 21 to 25 in males, whereas it occurs between 25 and 30 in females (2). Advances in genetic research have facilitated the identification of multiple common and rare variants associated with vulnerability to schizophrenia (3). Despite these findings, the etiology of schizophrenia remains complex, involving intricate interactions between genetic predisposition and environmental influences. Neither genetic nor environmental components alone fully account for the pathogenesis of this disorder (4).

Despite considerable progress in genetic studies, pinpointing specific causal genes or genomic regions implicated in schizophrenia remains challenging (4). The emergence of genome-wide association studies (GWAS) has substantially contributed to the identification of susceptibility variants. The Psychiatric Genomics Consortium (PGC) has reported over 300 single-nucleotide polymorphisms (SNPs) linked to schizophrenia through meta-analyses of GWAS data (2). Nonetheless, the precise role of these variants in symptom manifestation remains unclear. Indeed, the complexity of the phenotype in psychiatry makes the phenotype-genotype correlation difficult to determine. Observable behaviors alone may not serve as reliable phenotypic markers for identifying underlying genetic determinants of schizophrenia (4). This is where endophenotypes and intermediate phenotypes come into play, serving as simplified traits that help guide the identification of genes of susceptibility for more complex abnormalities.

The concept of endophenotypes has gained prominence in the study of complex neuropsychiatric conditions. Endophenotypes represent internal or intermediate, quantifiable traits that serve as intermediary markers linking genetic predisposition to clinical manifestations. These markers could be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, and neuropsychological parameters. To be considered as an endophenotype, a trait has to be associated with illness in the population, be heritable, manifest in individuals independently of their illness state, and co-segregate with the disorder within families and subsequently be found in non-affected family members at a higher rate than in the general population (5). The utilization of endophenotypes supports the deconstruction of psychiatric diagnoses into more distinct components, facilitating targeted genetic investigations. Compared to broad disease symptoms, endophenotypes offer more precise indicators of genetic mechanisms (3). Beyond enhancing genetic analysis, endophenotypes contribute to improved classification systems, aid in the development of animal models, and refine diagnostic precision (4). The etymology and methodological applications of endophenotypes in neuropsychiatric research, as well as their broader relevance in disorders with complex genetic bases, have been extensively examined in the literature (4).

Schizophrenia is a neurodevelopmental multisystemic disorder. People with schizophrenia have comorbidities with many other disorders and show anomalies in many organs in addition to the brain, which leads to excess mortality (6). Epidemiological studies showed that people with schizophrenia have their life expectancy reduced by 15 to 20 years compared with the general population (7), and cardiovascular diseases account for the majority of these deaths (8). Regardless of their medication status, specific cardiac phenotypes and functional abnormalities have been described; few have been considered as endophenotypes. The importance of the study of cardiac phenotypes and endophenotypes in schizophrenia lies not only in reducing death tolls inherent to heart anomalies but also in helping understand the specific etiopathogenic link between both disorders, which will help develop further understanding of both conditions.

This review aims to expose cardiac phenotypes and endophenotypes in schizophrenia, providing a clearer distinction between both and an insight into their role in bridging genetic predisposition and clinical symptomatology.

Methods

This systematic review was conducted in accordance with the Cochrane Collaboration principles of Systematic Reviews and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

The protocol of this is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD420251011159). This systematic review does not have a comparator, as there is no intervention to consider for the review question.

A structured and systematic search was performed using the PubMed, Web of Science, and Embase databases. The search timeline included studies published between 2000 and 2025. An additional search has been conducted in Google Scholar with the feature of AskScispace.

The aim was to identify original reports. The bibliographies of all the identified original studies were analysed to check for additional studies of interest. Three independent investigators identified the potentially relevant papers. Two investigators independently reviewed the retrieved papers for the screening phase, then the inclusion phase.

Type of studies

All studies referencing adults with schizophrenia and cardiac evaluation were analysed. Primary and secondary studies were included. All types of studies were considered for inclusion, whether randomised controlled trial, non-randomised trial, or observational study.

Type of participants

Papers referencing adults with schizophrenia and cardiac evaluation, as already mentioned, were analysed, and only papers reporting independent results of treatment-naïve patients were included.

The diagnosis of schizophrenia is considered eligible if the

paper reports the definition according to the "Diagnostic and Statistical Manual of Mental Disorders, Fourth and Fifth Editions".
The cardiac evaluation of patients includes one or more of the following:
- Clinical examination
- Surface 12-lead ECG
- ECG-Holter monitoring
- Echocardiography
- Cardiac magnetic resonance imaging (MRI)
- Tilt test
- Exercise testing
- Genetic testing

Inclusion and exclusion criteria

Eligible studies included patients considered treatment-naïve or drug-free by the authors.
The main exclusion criteria related to the type of paper were:
- Systematic review or literature review
- No reported results for the unmedicated schizophrenic patients (as a group or subgroup)

The main exclusion criteria related to patients' selection were:
- Patients included younger than 18 years old
- Pregnant women
- Patients with a history of cardiac disease (cardiomyopathy; coronary artery disease; congenital heart disease; conduction system disease; arrhythmia; inherited arrhythmic syndrome; cardiac tumour)
- Patients taking anti-arrhythmic drugs or other drugs with potential cardiac effect
- Patients with a history of cancer treated with chemotherapy or radiotherapy in the thoracic region
- Patients with a history of cardiac surgery or thoracic surgery

The search was completed on July 30th, 2025

Type of outcome measures

The aim was to determine relevant reported cardiac features to be considered as phenotypes or endophenotypes in schizophrenia.

Primary outcomes
- De novo cardiac abnormality not considered secondary to any evident cause

Secondary outcomes
- Ventricular depolarisation and /or repolarisation abnormalities noted on the ECG recording (12-lead ECG or Holter monitoring; Tilt test; Exercise testing)
- Atrial depolarisation abnormalities noted on the 12-lead ECG
- Atrial or atrio-ventricular or ventricular conduction abnormalities noted on the 12-lead ECG or Holter monitoring or tilt test, or exercise testing
- Supraventricular tachycardia or other atrial arrhythmia or ventricular arrhythmia noted on the ECG recording (12-lead ECG or Holter monitoring; Tilt test; Exercise testing)
- Abnormal atrial contraction or ventricular contraction noted on the cardiac imaging (echocardiography, cardiac MRI)
- Abnormal cardiac wall hypertrophy noted on the cardiac imaging (echocardiography, cardiac MRI)
- Abnormal cardiac wall characterisation noted on cardiac MRI
- Abnormal blood pressure noted on the physical examination or during the tilt test, or during the exercise testing

Search methods for the identification of studies

Search strategy
All relevant studies were analysed independently of their publication status (published, in press, or unpublished)
Controlled vocabulary terms and free text terms were used according to each database, as described in Table I.

Database searches
The search terms, as described in Table I, were used in the following databases
- PubMed
- Embase
- Web of Science
- AI-powered Google Scholar search
A grey literature review was conducted through "Google Scholar" and Web of Science databases.

Table 1. Databases

Database	Terms used
PubMed	MeSH Search question*
OVID databases: -Embase	Emtree (Embase)
Web of Science	Free-text
Google Scholar	Free-text

***Search question**: « (("Cardiovascular Diseases"[tiab] OR "Heart Rate"[tiab] OR "QT Interval"[tiab] OR "Electrocardiography"[tiab] OR "Heart Failure"[tiab]"arrhythmias cardiac"[tiab] OR "cardiac arrhythmias"[tiab] OR "arrhythmia"[tiab] OR "arrhythmias"[tiab] OR "cardiac dysrhythmia"[tiab] OR "dysrhythmia cardiac"[tiab] OR "autonomic nervous system diseases"[tiab] OR "dysautonomia"[tiab] OR "blood pressure"[tiab] OR "arterial pressure"[tiab] OR "venous pressure"[tiab] OR "heart rate"[tiab] OR "heart conduction system"[tiab] OR "cardiac conduction system disease"[tiab]) AND ("schizophrenia"[tiab] OR "schizophrenia spectrum and other psychotic disorders"[tiab] OR "schizophrenia paranoid"[tiab] OR "schizophrenia disorganized"[tiab] OR "schizophrenia childhood"[tiab] OR "schizophrenia catatonic"[tiab] OR "schizophrenia treatment resistant"[tiab] OR "schizotypal personality disorder"[tiab])) »

Results

This systematic literature review yielded 17 studies after the identification phase (698 papers), then the screening phase (39 papers), as shown in the flowchart (Figure 1) (9). All these studies were observational studies except one experimental study. All papers had been reviewed in total except for one, which was reported as an abstract.

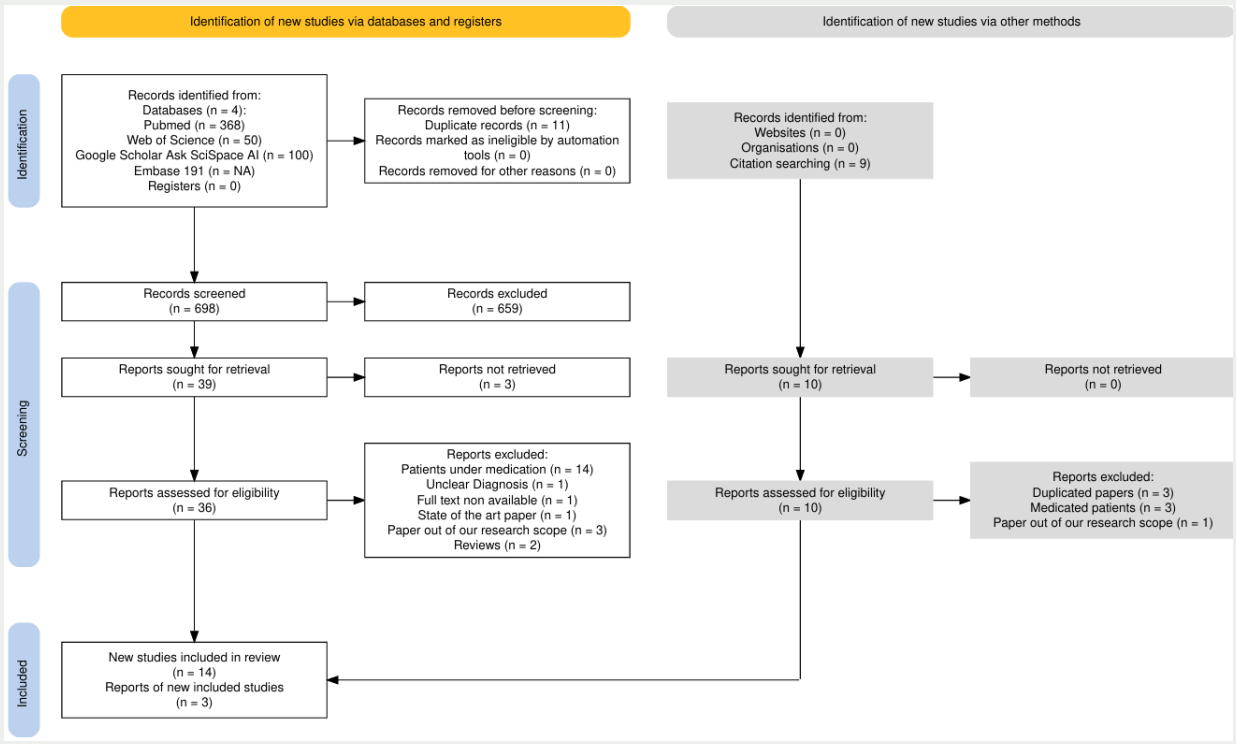

Figure 1. Flowchart of the systematic review

The total investigated schizophrenic patients was 1,117. One group of authors had 7 papers out of these 17, and in the last one published in 2024, they had the same population from a previously published paper. The total unmedicated patients was 1,052 (Figure 2 extracted from the data in Table I-II in supplementary data). Two studies did not include schizophrenic patients, one being the UK Biobank study from 2023, and the other one related to the first-degree relatives.

Comparison between healthy subjects and schizophrenic subjects was reported in 15 studies (Table I-II in supplementary data).

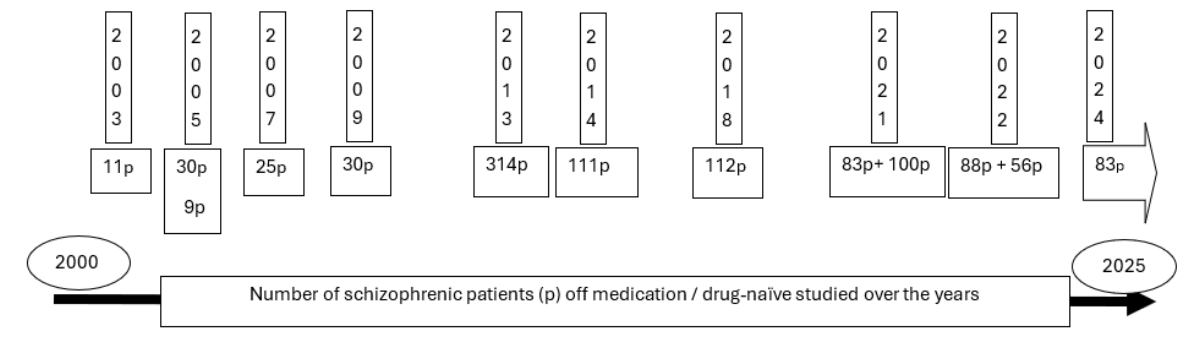

Figure 2. Timeline of the research relating the number of patients included within each study

P: Unmedicated patients

The cardiac features that were included were as follows (Table II in supplementary data):

- Heart Rate Variability (HRV) evaluated by long ECG recording (ranging from 5-min to 24h duration)
- Ventricular repolarization from a 12-lead ECG
- Cardiac structure and function phenotypes from a magnetic resonance imaging (MRI)
- Genes related to cardiac functionality (Excitability and repolarization)

Initial studies concerned testing HRV during stressful tasks. The trend for the latest studies was about genetics (Tables I-II in supplementary data).

Table II reports relevant population characteristics.

Table 2. Population characteristics

Authors	Total unmedicated schizophrenic patients	Female/Male	Mean age
Valkonen-Korhonen M et al.	11	Not mentioned	24
Bär KJ et al. 2005	30	11/19	34.2 ± 2.3
Mujica-Parodi LR et al.	9	4/5	36.5 ± 11.31
Bär KJ et al. 2007	25	9/16	30.8 ± 10.3
Chang JS et al.	30	13/17	33.9± 10.5
Castro MN et al.	22 (First-degree relatives)	7/15	45± 14
Chang HA et al.	314	151/163	37.16 ± 13.81
Fujii et al.	85	36/49	40.4 ± 14.6
Mäki-Marttunen T et al.	Computational modelling	-	-
Bär KJ et al. 2018	112	Not mentionned	Not mentionned
Refisch A et al. 2021	83	36/47	33.27 ± 10.95
Özsoy F et al.	100	14/86	40.92 ± 10.11
Refisch A et al. Feb 2022	88	41/47	32.3 ± 11.0
Refisch A et al. Nov 2022	77	45/32	33.1 ± 11.5
Balcioglu YH et al.	56	29/27	36.09 ± 10.81
Pillinger T et al.	32279	16625/15654	Not mentionned
Refisch A et al. 2024	83 (Same population as Refisch A et al. 2021)	36/47	33.27 ± 10.95

Heart variability in unmedicated schizophrenic patients

The HRV was considered in 12 out of the 17 studies. Linear parameters and nonlinear parameters were evaluated (Figure 3).

The mean HR was increased in unmedicated schizophrenic patients. The HRV in the Time-Domain analysis and Frequency-Domain analysis was in favor of unbalanced cardiac autonomic function with less vagal tone and more sympathetic arousal. One study featured the abnormal nocturnal sympathetic arousal. And additional stressful tasks were studied by four different authors. Those tasks varied from mental load (arithmetic load) to physiological load (orthoclinosthatic load). Related HRV during these tasks was lower.

Advanced HRV parameters (Nonlinear complexity) were included in 5 studies as more specific parameters for the HRV pattern. Their variance was also in favor of an increased sympathetic feature.

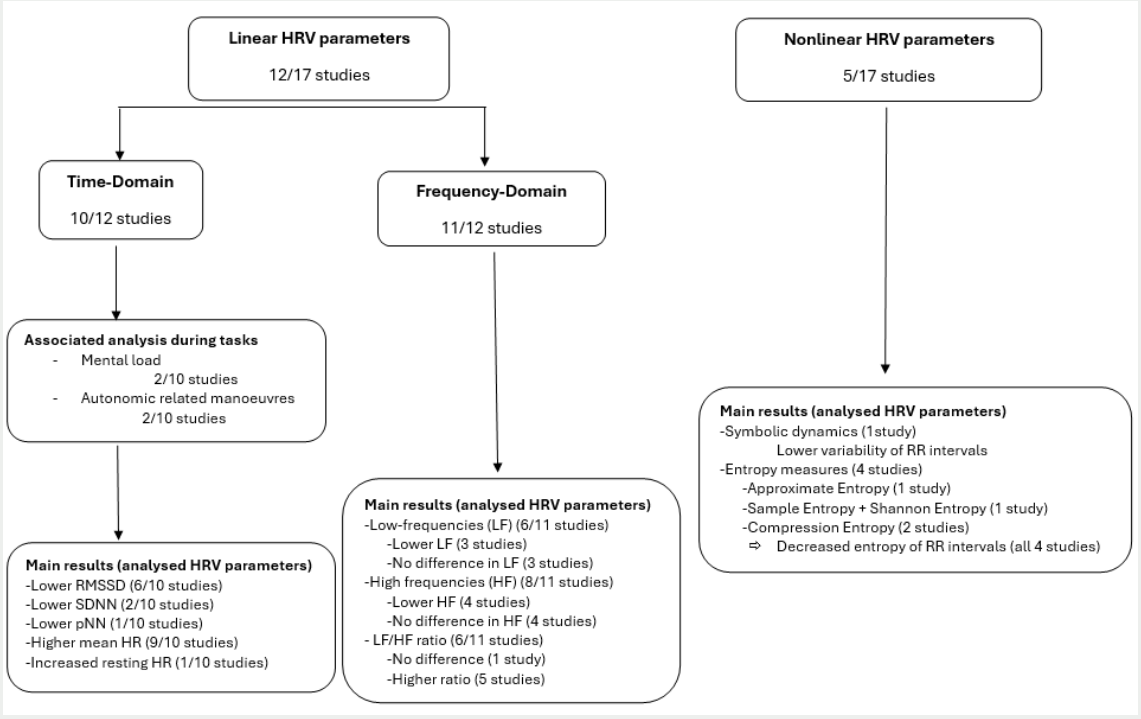

Figure 3. Different Heart Rate Variability parameters results

HF: High frequency (Frequency-Domain); **HR**: Heart rate; **HRV**: Heart Rate Variability; **LF**: Low frequency (frequency-Domain); **pNN**: percentage of successive normal sinus (NN) intervals; **RMSSD**: Root Mean Square of Successive Differences; **SDNN**: Standard Deviation of NN intervals;

Ventricular repolarization characteristics in unmedicated schizophrenic patients

From baseline 12-lead ECG, ventricular repolarization was evaluated in 5 studies, and P wave characterization was added in two of them (Figure 4). The QTc interval and the JTc interval were longer in unmedicated patients, with one study reporting that the sex difference in their QT was less relevant.

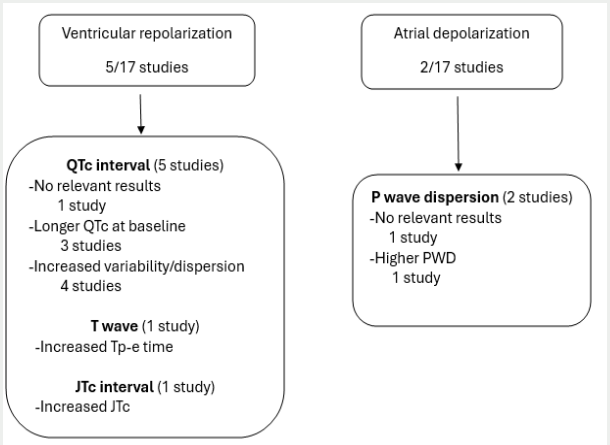

Figure 4. Different ECG features results

PWD: P wave dispersion

Association between schizophrenia gene-related and cardiac phenotypes

Genotyping for gene-related schizophrenia was an inclusion criterion in five papers (Figure 5), but four of them were almost from the same group of investigators. Relevant alleles from schizophrenic patients with the altered HRV pattern were the CHRM2 locus, CACNA1C, and KCNH2 SNPs.

The UK Biobank study was the only one studying cardiac imaging features.

Variants for Na+, HCN, and Ca2+ channels from the experimental study did alter cardiac cells' excitability and conductance.

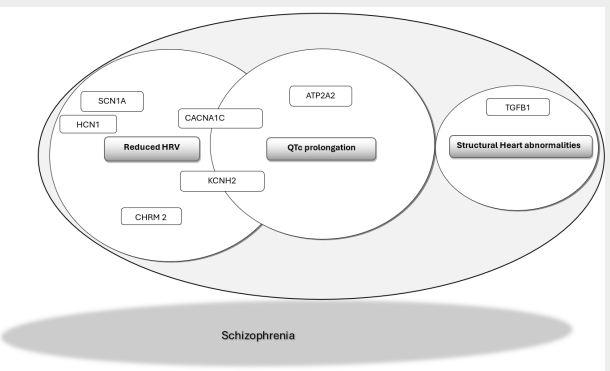

Figure 5. Relationship between schizophrenia-related genes and associated cardiac features

HRV: Heart Rate Variability

Discussion

Because of its neurodevelopmental underpinnings and genetic diversity, schizophrenia exhibits numerous morphological, neurochemical, and neurophysiological phenotypic anomalies. Cardiac phenotypes such as autonomic, electrophysiological, and structural domains represent some of the most frequently observed systemic anomalies in schizophrenia (6). This review aimed to examine the cardiac phenotypes and endophenotypes associated with schizophrenia and, to our knowledge, represents the first comprehensive analysis to delineate these two domains with a clear distinction between them.

Results revealed the most frequently cardiac features associated with schizophrenia were: autonomic dysfunction, repolarization anomalies with the QT and QTc prolongation, and structural and functional anomalies.

Autonomic dysfunction, particularly altered heart rate variability (HRV) characterized by reduced high-frequency power and elevated baseline heart rate, has been consistently reported in individuals with schizophrenia (15). This parameter reflects a decreased parasympathetic activation and a poor adaptability of the cardiovascular system to environmental stress (14). Studies have demonstrated that these alterations are also present in first-degree relatives, suggesting that protracted stress responses in schizophrenia may reflect a familial trait with a potential genetic background (15). It has been suggested that some brain structural abnormalities characterize schizophrenia, including the reduction of prefrontal cortex volume, the temporal lobe hippocampus, the parahippocampal gyrus, and amygdala volumes, play a role in the peripheral autonomic imbalance. In particular, a decreased activation of the amygdala-prefrontal circuits in patients with schizophrenia may be central in the impaired regulation of the autonomic output (27–29). Genetic studies have found a common genetic variant of the HCN1 gene to be associated with reduced heart rate variability in schizophrenia patients (20). Other genes, such as CACNA1C and KCNH2, appear to play a pleiotropic role, being associated with both schizophrenia risk and cardiac autonomic dysfunction (23).

Autonomic dysfunction thus represents a phenotype with clear familial aggregation. Probands of patients with schizophrenia also exhibit this phenotype, often with intermediate expression. Furthermore, the protracted autonomic response to psychological stress is an easily measurable trait that aligns well with established criteria for an endophenotype (30). Taken together, these findings indicate that heart rate variability fulfills the core criteria of an endophenotype, being heritable, present independently of disease state, and associated with increased illness risk, and can therefore be considered a valid endophenotype in schizophrenia (31).

The T wave is one of the most important markers of ventricular repolarization. In the absence of structural cardiac disease, the abnormalities of ventricular repolarization could be associated with heart arrhythmias

and a risk of torsade de pointes. Ventricular repolarization markers such as QT and QTc range, QT dispersion (QTd), T-wave peak to end (Tp-e) range, and Tp-e/QT ratio are all altered in patients with schizophrenia, making them highly predisposed to cardiac arrhythmias and sudden death (21). At the molecular level, accumulating evidence suggests that the genetic basis of QT prolongation in schizophrenia is increasingly evident. Ion channel proteins, such as KCNH2 (HERG1) and CACNA1C, both of which are present in myocardial tissue and play a role in cardiac repolarization, are also found in brain tissue. Their genetic variants are associated with the risk of schizophrenia, according to genome-wide association studies (17,32–34). Neuregulin 1 (NG1) is also another gene that could be associated with both the risk of schizophrenia and the QT interval prolongation. NG1 is also expressed in both the brain and the heart, where it plays a role in the control of cardiac autonomic nervous balance (35). Huertas-Vazquez et al. (36) found a link between a common missense variant of the NRG1 gene and both schizophrenia and sudden cardiac death. Other genes, particularly those encoding for subunits of voltage-gated Ca'2+, K+, and Na+ channels, as well as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and Ca'2+-transporting ATPases, appear to have a pleiotropic role, being associated with neuronal firing and cardiac pacemaking (18). Taken together, these data point toward a convergent genetic architecture, where ion channel and signaling pathway dysfunctions contribute to both schizophrenia susceptibility and repolarization abnormalities.

Nevertheless, despite this genetic convergence, electrophysiological traits such as QTc prolongation cannot be fully considered as endophenotypes of schizophrenia. According to classical criteria, an endophenotype must be heritable, present in unaffected relatives at higher rates than the general population, and largely independent of disease state (37). While QTc prolongation in schizophrenia appears to be partially influenced by genetic variants, current evidence does not fulfill the full heritability criteria. Furthermore, we found no studies reporting repolarization anomalies in first-degree relatives of patients with schizophrenia. Thus, ventricular repolarization abnormalities remain important phenotypes with genetic associations, but they do not yet qualify as validated endophenotypes.

Beyond QT prolongation, Brugada syndrome is characterized by an abnormal repolarization with demonstrated genetic underpinnings. Type 1 Brungada-ECG was described in up to 4% of patients with schizophrenia, compared to an estimated 0.05% prevalence in the general population (38). Among all arrhythmias, Brugada syndrome appears to have the most obvious genetic link with schizophrenia (39). The shared liability appears to be driven by genes related to immune processes and viral response mechanisms (39), but also genes coding for Na+, K+, and Ca2+ voltage-gated channels have been suggested to play a pleiotropic role in the excitable cells of the brain and heart (34).

Beyond these functional measures, structural cardiac alterations have also been documented. Cardiac magnetic resonance imaging and echocardiographic studies reveal subtle reductions in left ventricular mass, impaired myocardial strain, and altered chamber volumes in antipsychotic-naïve patients; changes that may reflect developmental or genetic influences rather than medication effects. TGF-β signaling and inflammatory pathways may be implicated, with emerging evidence of genetic overlap between these mechanisms and cardiac phenotypic variations (25).

Our observation supports the fact that brain disease and heart disease share common pathogenomic mechanisms. This convergence of autonomic (HRV), electrophysiological (QTc), and structural (ventricular morphology) traits, each with evidence for heritability or familial occurrence, strengthens the role of cardiac phenotypes and endophenotypes in understanding the inner foundations of schizophrenia. Such markers may unveil shared neurodevelopmental and cardiogenetic pathways underlying both psychosis vulnerability and cardiovascular risk and could ultimately pave the way to the discovery of genetic abnormalities contributing to schizophrenia.

The degree to which cardiac phenotypes satisfy known endophenotype criteria varies significantly, as described in Table 4. Heart rate variability (HRV) emerges as the most robust candidate, with consistent evidence for association with schizophrenia, state-independence, heritability, and presence in unaffected first-degree relatives. By contrast, repolarization and structural anomalies, while reproducibly associated with schizophrenia and supported by converging genetic findings (e.g., KCNH2, CACNA1C, NRG1), lack data on heritability and familial transmission, limiting their qualification as endophenotypes.

Limitations

Despite growing interest in cardiac manifestations in schizophrenia, the current evidence base has several important limitations. Most studies are cross-sectional, making it difficult to determine whether observed cardiac abnormalities are antecedent to or a consequence of illness progression or past treatment exposure. Otherwise, this review relies on studies from a few research groups, which raises the risk of publication bias and sample overlap. Medication confounding remains a major challenge, despite the fact that we selected only studies with unmedicated patients. Some cardiac changes can occur under antipsychotics and could persist for a long time even after treatment is stopped. Sample sizes in antipsychotic-naïve or drug-free populations are often small, limiting statistical power and findings' generalizability. Evidence for the heritability and state-independence of certain cardiac phenotypes remains limited, as few studies include unaffected relatives or employ longitudinal designs to confirm trait stability, preventing these phenotypes from being robustly defined as endophenotypes. Furthermore, structural and functional cardiac assessments are not standardized across studies, and measurement techniques vary widely, which could limit comparability.

Table 3. Cardiac phenotypes in schizophrenia mapped against classical endophenotype criteria

Phenotype	Association with illness	State-independence	Heritability / familial aggregation	Presence in unaffected relatives	Meets criteria as endophenotype?
Heart rate variability (HRV)	Strong Consistently reduced in schizophrenia	Yes	Supported by genetic variants (HCN1, CACNA1C, KCNH2); familial clustering	Yes (first-degree relatives show abnormal recovery/stress response)	**Yes**
QT/QTc prolongation	Reported in drug-free patients; associated with arrhythmia risk	Yes	Genetic overlap with schizophrenia (CACNA1C, KCNH2, NRG1)	Not demonstrated	No
Other repolarization markers (Tp-e, QT dispersion, Tp-e/QT ratio)	Abnormal in schizophrenia patients	Not well established	Suggested genetic links (ion channels, inflammatory pathways) with schizophrenia	Not studied	No
Brugada syndrome (Type 1 ECG)	Increased prevalence (≈4% in schizophrenia vs 0.05% in the general population)	Likely	Shared genetic liability (immune and ion channel genes) with schizophrenia	Not demonstrated	No
Structural anomalies (MRI/echo: ventricular volumes, strain, LV mass)	Subtle changes in drug-naïve schizophrenia and in high polygenic risk score (PRS) individuals	Unclear (few longitudinal data)	Evidence of overlap with schizophrenia polygenic risk (TGF-β, inflammatory pathways)	Not yet studied	No

Finally, the scarcity of integrated genomic and imaging studies limits the capacity to link cardiac phenotypes directly to underlying molecular mechanisms. Addressing these gaps will be essential for validating cardiac markers as true endophenotypes and for embedding them into both research and clinical practice.

Clinical Implications and Future Research Directions

Cardiovascular disease remains one of the leading causes of premature mortality in schizophrenia (7), yet current screening guidelines mainly focus on metabolic parameters but do not give importance to subclinical cardiac abnormalities. Taking into consideration this cardiac vulnerability status and knowing that the use of antipsychotics could be associated with cardiac toxicity, the choice of antipsychotics should be as judicious as possible. Antipsychotics with minimal anticholinergic effects and intrinsic serotonergic activity may result in a reduction of cardiac risk according to Chang et al. (16). Ultimately, including cardiac assessment in routine psychiatric care not only addresses a critical source of morbidity and mortality but also aligns with the multisystem model of schizophrenia that integrates brain and body health.

Future studies should focus further on longitudinal and family-based designs to clarify the temporal and heritable nature of cardiac phenotypes in schizophrenia. Tracking individuals from prodromal or high-risk states through illness onset will help determine whether specific cardiac markers precede, parallel, or follow psychotic symptom development. Large-scale integrative genomic and multi-omic analyses, combined with cardiac functioning and structural parameters, can provide a more comprehensive phenotyping, enabling the identification of pleiotropic variants and molecular pathways underlying both cardiac and neuropsychiatric traits. Additionally, standardizing cardiac assessment protocols will facilitate cross-cohort comparisons and meta-analyses. Predictive models for cardiovascular risk and psychosis susceptibility may be developed by integrating multimodal information using machine learning techniques, ultimately supporting the development of more concise precision psychiatry models.

Conclusion

Schizophrenia is increasingly recognized as a multisystem disorder, with cardiac abnormalities representing a clinically significant yet underexplored dimension. Evidence from autonomic, electrophysiological, and structural domains suggests that some of these abnormalities, particularly reduced heart rate variability, QTc prolongation, and subtle ventricular morphological changes, may represent candidate cardiac endophenotypes. Recognizing that these conclusions are primarily based on observational and cross-sectional studies, this may reduce the strength of our findings. However, the current state of knowledge indicates that only heart rate variability meets the criteria for an endophenotype. From a global point of view, these phenotypes and endophenotypes point toward shared genetic and developmental pathways linking cardiac and neuropsychiatric vulnerability.

Recognizing and validating these markers could transform both clinical care and research, enabling earlier cardiovascular risk detection and informing safer treatment choices. Future longitudinal, family-based, and integrative multi-omic studies are essential for a better understanding of the pathogenomic links between schizophrenia and heart anomalies and a deeper phenomenological insight into the complex interplay between brain and heart diseases.

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