Original article

A common variation in *HCN1* is associated with heart rate variability in schizophrenia

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Abstract

Background: There is growing evidence for a shared genetic basis between schizophrenia risk and cardiovascular disease. Reduced efferent vagal activity, indexed by reduced heart rate variability (HRV), has been consistently described in patients with schizophrenia and may potentially contribute to the increased cardiovascular risk in these patients. In this study, we tested the hypothesis whether the established schizophrenia risk variant *HCN1* rs16902086 (A>G) is associated with reduced HRV.

Methods: We analyzed the risk status of *HCN1* rs16902086 (AG/GG vs. AA genotype) in 83 unmedicated patients with schizophrenia and 96 healthy controls and investigated genotype-related impacts on various HRV parameters.

Results: We observed significantly increased resting heart rates and a marked decrease of vagal modulation in our patient cohort. Strikingly, *HCN1* rs16902086 (A>G) was associated with reduced HRV parameters in patients only. A trend towards more pronounced HRV deviations was observed in homozygous (GG) compared to heterozygous patients (AG).

Conclusion: We present first evidence for a genetic risk factor that is associated with decreased vagal modulation in unmedicated patients with schizophrenia. Moreover, our findings suggest that *HCN1* might be involved in reduced vagal modulation and possibly in increased cardiac mortality in schizophrenia patients. Thus, our data indicate that reduced vagal modulation might be an endophenotype of schizophrenia.

1 Introduction

Schizophrenia has a highly polygenic architecture, involving thousands of common single nucleotide polymorphisms (SNPs) with very small individual effects (Purcell et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics, 2014). Large-scale genome-wide association studies have identified more than 100 SNPs that are significantly associated with an increased risk of developing schizophrenia (Pardiñas et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics, 2014). However, the contributions of such common variants to schizophrenia-associated symptoms are largely unknown (Carter et al., 2017). Studying neurocognitive or neurophysiological endophenotypes may provide new insights into biological processes underlying schizophrenia (Greenwood et al., 2019).

Cardiovascular diseases (CVD) are distinctly more common in schizophrenia patients and contribute to the shortened life expectancy of about 15 to 20 years in these patients (Azad et al., 2016; Ifteni et al., 2014; Kugathasan et al., 2018; Ringen et al., 2014). Beyond effects by lifestyle and antipsychotic medication (Laursen et al., 2014), several lines of evidence suggest a shared pathophysiology between schizophrenia and cardiovascular disease (Ringen et al., 2014). For instance, it has been observed that cardiovascular disease and schizophrenia risk might have common genetic origins (Andreassen et al., 2013; De Hert et al., 2018; So et al., 2019). The most obvious link lies in the relation between heart rate variability alterations (Bär, 2015) and the development of CVD. In these patients, parasympathetic (vagal) function is reduced and sympathetic modulation seems to be elevated. This constellation is known to be associated with the development of cardiac diseases including coronary heart disease (Jensen et al., 2013a). This altered balance is reflected in decreased heart rate

variability (HRV), which has been consistently described in schizophrenia patients both at first manifestation as well as during chronic disease (Bär et al., 2007; Bär et al., 2005; Castro et al., 2009; Clamor et al., 2016; Mujica-Parodi et al., 2005; Valkonen-Korhonen et al., 2003). Interestingly, milder forms of HRV alterations have even been demonstrated in healthy first-degree relatives of schizophrenia patients suggesting a genetic basis (Bär et al., 2010; Berger et al., 2010; Jauregui et al., 2011; Schulz et al., 2015). Therefore, reduced vagal sinoatrial activity meets all asserted major criteria for an endophenotype of schizophrenia (Clamor et al., 2016; Gottesman and Gould, 2003).

Rapid advances in the genetic architecture of schizophrenia provide new insights how schizophrenia and low vagal cardiac modulation might be linked. Various genes among schizophrenia-associated loci are involved in cardiac pace-making and conduction as well as vagal modulation. Among them *HCN1*, which encodes a potassium channel forming subunit, is a major contributor to the inward hyperpolarization-activated cation current (I_h). I_h regulates neuronal excitability, synaptic plasticity and serves as a pacemaker in cardiac tissue. Furthermore, *HCN1* is among schizophrenia-associated genes that were highlighted to be of particular interest with respect to current hypotheses of schizophrenia etiology and treatment (Pardiñas et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics, 2014).

In the present study we investigated a possible association of *HCN1* with HRV in unmedicated patients with schizophrenia. Therefore, we genotyped the most significant schizophrenia-associated SNP rs16902086 in *HCN1* (intronic variant, p=5,55E-11) that was recently highlighted in a meta-analysis of genome-wide genotype data for schizophrenia cases (Pardiñas et al., 2018).

Our first aim was to analyze the main effect of diagnosis on HRV parameters, in order

to corroborate previous findings and being the basis of the genetic analysis. Secondly, we tested for associations of schizophrenia risk status in *HCN1* rs16902086 (defined by AG and GG carriers) on HRV measures in patients and controls.

Finally, we tested for potential differences in HRV parameters between individual genotypes (AA vs. AG vs. GG) in patients and healthy controls.

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2 Participants and Methods

2.1 Participants

83 patients suffering from paranoid schizophrenia and 96 control subjects were included in this study (Table 1).

Patients were recruited when fulfilling inclusion criteria (see below) in the acute stage upon admission to the hospital or the outpatient department of the University Hospital, Jena. Patients were included in the study only, when they had not taken antipsychotic medication for at least 8 weeks prior to the study. Control subjects were recruited from hospital staff, medical students and the local community.

All subjects underwent a screening program consisting of a drug screening for drug residues, legal and illegal substances, a full clinical examination, a baseline ECG and routine laboratory parameters to exclude any other mental disorder or somatic disease such as a history of hypertension, diabetes, or other cardiovascular diseases. Moreover, subjects of non-Caucasian origin were not included. The screening program was carried out by a staff psychiatrist prior to the autonomic assessment. Patients or controls taking any medication influencing heart rate or blood pressure regulation (e.g. beta-blockers, antiarrhythmics, tranquillizers, antidepressants) were not included. All subjects were asked to refrain from smoking, heavy eating or exercising 2 h prior to the investigation. The diagnosis was established by a staff psychiatrist when patients fulfilled DSM-IV criteria (Diagnostic and statistical manual of mental disorders, 4th edition, published by the American Psychiatric Association) as assessed by the Structured Clinical Interview for DSM-IV (SCID) and was confirmed by an independent

psychiatrist. In case of first-episode psychosis, the diagnosis was re-evaluated by a staff psychiatrist after 3 months. Psychotic symptoms were quantified by a staff psychiatrist after the screening procedure using the positive and negative symptom scale (PANSS) (Kay et al., 1987). All subjects were informed about the nature of the procedures one day in advance. All subjects gave written informed consent to a protocol approved by the Ethics Committee of the University Hospital, Jena, Germany. Furthermore, patients were advised that refusal of participating in the study would does not affect any future treatment in our hospital. Every effort was made to ensure that patients were able to give informed consent. Patients were only included after a psychiatrist had certified their ability to give full informed consent to the study protocol.

2.2 Assessment of autonomic function

Examinations were performed between 1 and 6 p.m. in a quiet room which was kept comfortably warm (22–24°C). Subjects were asked to relax, breathe regularly and move as little as possible. We used the MP150 system (BIOPAC Systems Inc, Goleta, CA, USA) for recording of physiological signals at 1000 Hz sampling frequency for 30 minutes. The ECG was acquired arranging three electrodes on the chest according to an adjusted Einthoven triangle. ECG signals were band-pass filtered between 0.05 and 35 Hz. Automatically detected RR-interval time series were afterwards checked manually for ectopic beats or artifacts that were replaced using linear interpolation (Lippman et al., 1994).

We computed standard measures of HRV in the frequency domain according to relevant guidelines (Malik, 1996). We integrated spectral power after Fast Fourier transformation of RR-interval time series, within the low-frequency band (LF; 0.04–

0.15 Hz) and the high-frequency band (HF; 0.15–0.40 Hz). As the HF component is related to cardiovagal modulation and LF is linked to both sympathetic and parasympathetic influence, the LF/HF ratio has been proposed as a measure of sympatho-vagal balance with high values indicating sympathetic dominance (Furlan et al., 2000; Montano et al., 2009). Although, there is still no consensus on the exact interpretation of LF power (Billman, 2013; Pagani et al., 2012; Reyes del Paso et al., 2013), LF/HF is frequently used to assess the sympatho-vagal balance (Rajendra Acharya et al., 2006).

Additionally, root mean square of the successive differences (RMSSD) was calculated. Fast fluctuations of heart rate as quantified by RMSSD are supposed to indicate parasympathetic cardiac function (Malik, 1996).

2.3 Genetic Analyses and Identification of Subgroups

Genotyping was performed using high-throughput technology (Illumina's Infinium PsychArray-24 Kit®), which includes 265,000 proven tag SNPs found on the Infinium Core-24 Bead Chip, 245,000 markers from the Infinium Exome-24 BeadChip and 50,000 additional markers associated with mental disorders. These SNPs were used as a basis for imputation on a 1000Genomes backbone. Genotyping was performed for each participant for rs16902086.

Depending on the rs16902086 genotype, patients with schizophrenia and healthy controls were divided in two genotype subgroups per diagnostic group, i.e. GG AND AG vs. AA.

2.4 Statistical Analysis

2.4.1 Main effect of diagnosis on HRV parameters

For statistical analyses, SPSS for Windows (version 23.0) was used. First, a multivariate analysis of variance (Boiko et al.) was performed to identify differences between patients with schizophrenia and healthy controls regarding HRV parameters mHR (mean heart rate), LF/HF and RMSSD. Follow-up univariate analysis of variance (ANOVAs) were performed for each parameter. Cohen's d was calculated for significant differences.

2.4.2 Associations between HCN1 rs16902086 risk status and HRV parameters

To compare mHR, LF/HF and RMSSD between genotype risk groups in *HCN1* rs16902086 (AG/GG vs. AA) in patients and healthy controls separately, additional MANOVAs and follow-up univariate ANOVAs were performed for each parameter.

2.4.3 Associations between HCN1 rs16902086 genotype and HRV parameters

Another MANOVA and follow-up ANOVAs were performed to compare mHR, LF/HF and RMSSD between genotypes in *HCN1 rs16902086* (AA vs. AG vs. GG) in patients and healthy controls. To reveal differences between respective genotypes for single parameters, a Bonferroni-Holm corrected pair-wise comparison was performed as a pot hoc analysis.

3 Results

Distribution of allele frequencies and sociodemographic data are shown in Table 1 and Table 2. In the patient cohort, there were more smokers in the AA-no-risk genotype group.

3.1 Main effects of diagnosis on HRV parameters

We first tested the main effect of diagnosis on HRV parameters. Using MANOVA to compare patients with healthy controls, we found a significant main effect for the between-subjects factor GROUP (patients with schizophrenia versus healthy controls) [$F(3,139) = 6.77$, $p < 0.001$]. Follow-up univariate ANOVAs showed significant main effects for mHR, RMSSD and LF/HF indicating reduced HRV in patients compared to controls (Table 1).

3.2 Associations between rs16902086 risk status and HRV parameters

We further tested whether risk status (RISK) in *HCN1* rs16902086 (AG/GG vs. AA) has an impact on HRV parameters.

Initially we tested the interaction effect RISK x GROUP on HRV parameters. We found a significant interaction effect for mHR [$F(3,175) = 22.95$, $p < 0.001$], LF/HF [$F(3,175) = 12.42$, $p < 0.001$] and RMSSD [$F(3,175) = 13.3$, $p < 0.001$]. Next we tested the main effect for the between-subjects factor RISK (AG plus GG genotype versus AA genotype) on HRV parameters in all subjects (patients plus healthy controls) [$F(3,175) = 3.25$, $p = 0.023$]. Follow-up univariate ANOVAs showed significant main effects for

mHR [F(1,177) = 4.33, p = 0.039] and LF/HF [F(1,177) = 9.07, p = 0.003], but not for RMSSD [F(1,177) = 3.04, p = 0.083] comparing RISK in all subjects.

Subsequently, we tested the main effect of RISK on HRV parameters separately in patients and healthy controls. MANOVAs showed significant main effects for RISK in patients [F(3,79) = 4.93, p = 0.004], but not in healthy controls [F(3,92) = 0.81, p = 0.494]. Comparing RISK in patients only, follow-up ANOVAS revealed significant main effects for all HRV-parameter including increased heart rates (mHR) [F(1,81) = 5.62, p = 0.020], reduced vagal modulation (RMSSD) [F(1,81) = 11.49, p = 0.001] and a shift of sympathovagal balance in favor of sympathetic modulation (LF/HF) [F(1,81) = 7.42, p = 0.008] (Figure 1). Finally, we performed another MANOVA to compare PANSS subscales (PANSSpos, PANSSneg, PANSSgeneral) between RISK in patients and found no significant differences [F(3,79) = 0.83, p = 0.485].

3.3 Associations between HCN1 rs16902086 genotype and HRV parameters

In a further step, we performed another MANOVA to test the main effect of GENOTYPE (AA vs. AG vs. GG) on HRV parameters in all subjects. We found a significant main effect for the between-subjects factor GENOTYPE [F(6, 348) = 2.17, p = 0.046]. Follow-up univariate ANOVAs showed significant main effects for LF/HF [F(2, 176) = 4.93, p = 0.008], but not for mHR [F(2, 176) = 2.19, p = 0.115] and RMSSD [F(2, 176) = 2.72, p = 0.069] comparing GENOTYPE in all subjects.

Finally, we tested for the main effect of GENOTYPE on HRV parameters separately in patients and healthy controls. MANOVAs showed significant main effects for GENOTYPE in patients [F(6,156) = 2.48, p = 0.026], but not in healthy controls

[F(6,182) = 0.88, p = 0.512]. Comparing GENOTYPE in patients only, follow-up ANOVAS showed significant main effect for all HRV parameters mHR [F(2,80) = 3.70, p = 0.029], RMSSD [F(2,80) = 3.24, p = 0.045] and LF/HF ratio [F(2,80) = 5.27, p = 0.007]. Post-hoc-t-tests showed significant increased mHR in schizophrenic GG-homozygotes compared to AA-homozygotes (p = 0,050) and a significant increased LF/HF ratio in patients with AG-genotype compared to AA-homozygotes (p = 0.006) (Figure 2).

4 Discussion

This is the first study to demonstrate that unmedicated schizophrenia patients with identified *HCN1* rs16902086 risk status reveal robust HRV alterations. Furthermore, our data underline evidence for a distinct genetic contribution of reduced cardiac vagal modulation in these patients, which stipulates the assumption that low HRV is an endophenotype of the disorder (Clamor et al., 2016).

To our knowledge, this is the largest HRV-investigation in unmedicated patients with schizophrenia so far. In accordance with previous reports, here we demonstrate increased heart rates and reduced RMSSD suggesting low vagal function at rest in schizophrenia patients as compared to healthy controls. The increased LF/HF ratio in patients indicates a shift in autonomic balance in favor of sympathetic modulation as it has already been described previously in smaller samples of patients (Bär, 2015; Montaquila et al., 2015). However, underlying mechanisms remained unclear so far. It is therefore intriguing that our data might suggest a potential role of *HCN1* for vagal modulation in schizophrenia.

The main finding of our study is that HRV is significantly decreased in unmedicated schizophrenia patients with identified *HCN1* rs16902086 (A>G) psychosis risk status. The genotype-related impact on HRV measures was even more pronounced in patients carrying the homozygous (GG) compared to the heterozygous (AG) risk genotype. Thus, patients with *HCN1* rs16902086 (A>G) seem to be predisposed to reduced vagal modulation in our study. This is of interest since decreased vagal activity has been identified as an independent risk factor for a shortened life expectancy in various diseases (Ernst, 2017; Jensen et al., 2013b).

Due to distinct increased cardiac morbidity and mortality in schizophrenia patients, it is of major clinical relevance to identify patients with increased cardiovascular risk. Although further studies on the genetic influences on HRV in schizophrenia will be needed, genotyping *HCN1* rs16902086 may be a first step towards this direction.

Remarkably, we observed differences in HRV parameters only in patients with genetic risk status, whereas no significant differences could be found between genotype subgroups in healthy controls. Thus, mechanisms contributing to low vagal modulation presented in schizophrenia patients appear to be complex. Epistasis, epigenetics and/or environmental factors might additionally contribute to HRV alterations in patients with schizophrenia. Notably, we were unable to find a substantial difference between *HCN1* rs16902086 risk status in patients with respect to the presented psychopathology. Thus, long-lasting stressful experiences associated with the psychotic state may have milder impacts on the observed HRV alterations in schizophrenia than genetic factors. Interestingly, there were more smokers in the AA-no-risk genotype subgroup among patients. This is of interest, since there are some indications for an association between chronic and current smoking and reduced vagal modulation (Hayano et al., 1990; Minami et al., 1999; Yotsukura et al., 1998). Due to various central and peripheral effects of cigarette smoking the definite influence cannot be reliably determined. However, since there are more smokers in the no-risk genotype subgroup, the observed HRV reductions are very unlikely due to smoker status.

By demonstrating an association between an established schizophrenia risk variant and alterations in HRV our data underline that reduced vagal modulation has to be considered as an endophenotype of the disorder (Clamor et al., 2016). As HRV analyses provide reliable measures, they are less subjective than heterogeneous clinical symptoms used for diagnosis and might be more promising. Moreover,

analyzing interactions between HRV and other neuropsychological symptoms associated with schizophrenia, such as executive functioning (Clamor et al., 2016; Neill and Rossell, 2013; Thayer et al., 2009), may uncover common underlying mechanisms. In line with this, our findings suggest a potential involvement of *HCN1* in HRV alterations in schizophrenia. Other authors proposed a role for *HCN1* in established schizophrenia-related endophenotypes, such as spatial memory (Greenwood et al., 2019). Understanding the molecular basis of these endophenotypes could provide the opportunity to detect novel antipsychotic targets. *HCN1* can homodimerize or heterodimerize with other pore-forming subunits to form a hyperpolarization-activated cation channel (HCN) (Benarroch, 2013). Depolarizing currents through HCN channels are implicated in generating spontaneous electrical activity (so called “pacemaker current”) in both, sinoatrial and neuronal cells (Ravindran et al., 2016). There is growing evidence that HCN channels play an essential role in mental disorders and stress sensitivity (Arnsten, 2011; Ku and Han, 2017; Paspalas et al., 2013). *HCN1* is highly expressed in brain areas substantially involved in the pathogenesis of schizophrenia, like the hippocampus and the prefrontal cortex, regulating neuronal excitability, rhythmic activity and synaptic plasticity (Benarroch, 2013; Bender et al., 2001; Santoro et al., 2000). Furthermore, it has been demonstrated that Hcn1-deficient mice suffer from sinus node dysfunction with bradycardia and sinus dysrhythmia (Fenske et al., 2013). The authors proposed that the HCN1-channel stabilizes the leading pacemaker region within the sinoatrial node and hence is essential for the regulation of beat-to-beat variation (Fenske et al., 2013). However, the specific functional relevance of rs16902086 is yet to be clarified. As rs16902086 is a common deep intronic variant that is not located at a splice site, its functional relevance is difficult to assess. It is conceivable that the variant lies within a

cis-regulatory element, affecting gene expression of *HCN1,* though there are no reported regulatory elements in close proximity to the variant until now (Jia et al., 2017). Apart from that, rs16902086 could be located within a splicing regulatory element, which could lead to an isoform with altered electrophysiological characteristics in brain and/or heart tissue contributing to observed HRV alterations in patients with schizophrenia. *HCN1* rs16902086 could also be coupled with another SNP which was not genotyped. Further studies are needed to explore the molecular role of *HCN1* in the disease architecture of schizophrenia and cardiac autonomic dysfunction.

Our study has several limitations. First, in order to get the largest possible sample size, we could not match patients and healthy controls. Thus, there are significant differences between patients and controls such as age, smoking behavior, physical activity and coffee consumption, potentially influencing autonomic function. Secondly, the number of subjects was still relatively small. Although only unmedicated patients were included in our study, which is an advantage, further independent patient cohorts are mandatory to validate our findings in future studies. Third, the association of *HCN1* rs16902086 with reduced vagal modulation needs to be replicated in another sample. Moreover, other SNPs in *HCN1* should be examined for associations with altered heart rate variability in patients with schizophrenia. Fourth, HRV parameters were derived from ECG recordings over a time period of 30 minutes. Long-term measurements for 24 hours would be necessary to be able to take circadian influences into account. Finally, despite of toxicological testing and precise medical records on an antipsychotic-free interval of at least 8 weeks, possible drug residues or adjustment compensatory processes by previous medication affecting autonomic function cannot completely excluded.

5 Conclusions

This is the first study to describe a potential mechanism contributing to reduced vagal modulation in unmedicated patients with schizophrenia. Patients with a risk variant in *HCN1* rs16902086 (A>G) seem to be predisposed to reduced vagal modulation according to our study, which might partly be responsible for increased cardiac mortality in schizophrenia. Future studies are warranted to validate and further investigate the potential pathophysiological function of *HCN1* in schizophrenia disease.

Contributors

AR: acquisition of the data, analysis and interpretation of the data, preparing the manuscript; HC: preparing the manuscript, critical revision; SK: participated in data acquisition, quality checking and preparation, and assisted in literature search, critical revision; AS: analysis and interpretation of the data, critical revision; TM: critical revision; MN: performed genotyping as well as further preparation and quality control of the genetic data, critical revision; CH: study conception, critical revision; KB: design and study conception, critical revision.

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Conflict of interest

All authors are declare to not have any actual or potential conflict of interest including any financial, personal or other relationships, that could inappropriately influence, or be perceived to influence, the work.

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Table and Figure legends

Table 1

Sociodemographic/genetic data and main effect of diagnosis on HRV parameters

Distribution of allele frequencies. Other data expressed as mean (SD). P-values resulting from ANOVAs.

Abbrev.: Minor Allele Frequency (MAF), Mean Heart Rate (mHR), Heart Rate Low Frequency/ High Frequency-ratio (LF/HF), Root Mean Sum of Squared Differences (RMSSD).

Table 2

Sociodemographic and clinical data of genotype subgroups.

Data expressed as mean (SD). P-values resulting from ANOVAs; BMI: Body mass index; PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987).

Figure 1

A, B, C. Scatter diagram illustrating significant differences in mHR (bpm) (A), RMSSD (B) and LF/HF (C) in unmedicated patients with the rs16902086 risk genotype, * $p < 0.05$, p-value resulting from the ANOVAs.

Figure 2

A, B, C. Bar chart showing mHR (A), RMSSD (B), LF/HF (C) for the respective genotypes AA, AG and GG in patients and controls, * $p < 0.05$, p-value resulting from post-hoc-t-tests are only shown for the comparison of the genotypes in the patient group.

Table 1

Sociodemographic/genetic data and main effect of diagnosis on HRV parameters

	diagnostic group		p	Cohens' d
	healthy controls	patients		
N	96	83		
age (y)	25.28 ± 3.94	33.27 ± 10.95	<0.001	0.97
gender (f/m)	48/48	36/47	n.s.	
smoker status (y/n)	18/78	30/53	0.040	0.13
cig. per day	1.25 ± 3.34	6.92 ± 10.87	<0.001	0.83
cups of coffee a day	1.0 ± 1.3	2.0 ± 1.4	0.037	0.76
BMI (m/kg^2)	22.69 ± 3.03	22.83 ± 9.5	n.s.	
hours of sport per week	2.8 ± 2.0	0.8 ± 1.3	0.003	1.3
MAF	G = 0.42 (80/192)	G = 0.34 (57/166)		
AA	0.58 (34/96)	0.66 (33/83)		
AG	0.36 (44/96)	0.30 (43/83)		
GG	0.06 (18/96)	0.04 (7/83)		
mHR	64.5 ± 1.07	76.58 ± 1.14	<0.001	1.14
RMSSD	73.02 ± 4.24	36.28 ± 4.53	<0.001	0.66
LF/HF	1.56 ± 0.19	2.86 ± 0.20	0.001	0.89

Distribution of allele frequencies. Other data expressed as mean (SD). P-values resulting from ANOVAs.

Abbrev.: Minor Allele Frequency (MAF), Mean Heart Rate (mHR), Heart Rate Low Frequency/High Frequency-ratio (LF/HF), Root Mean Sum of Squared Differences (RMSSD).

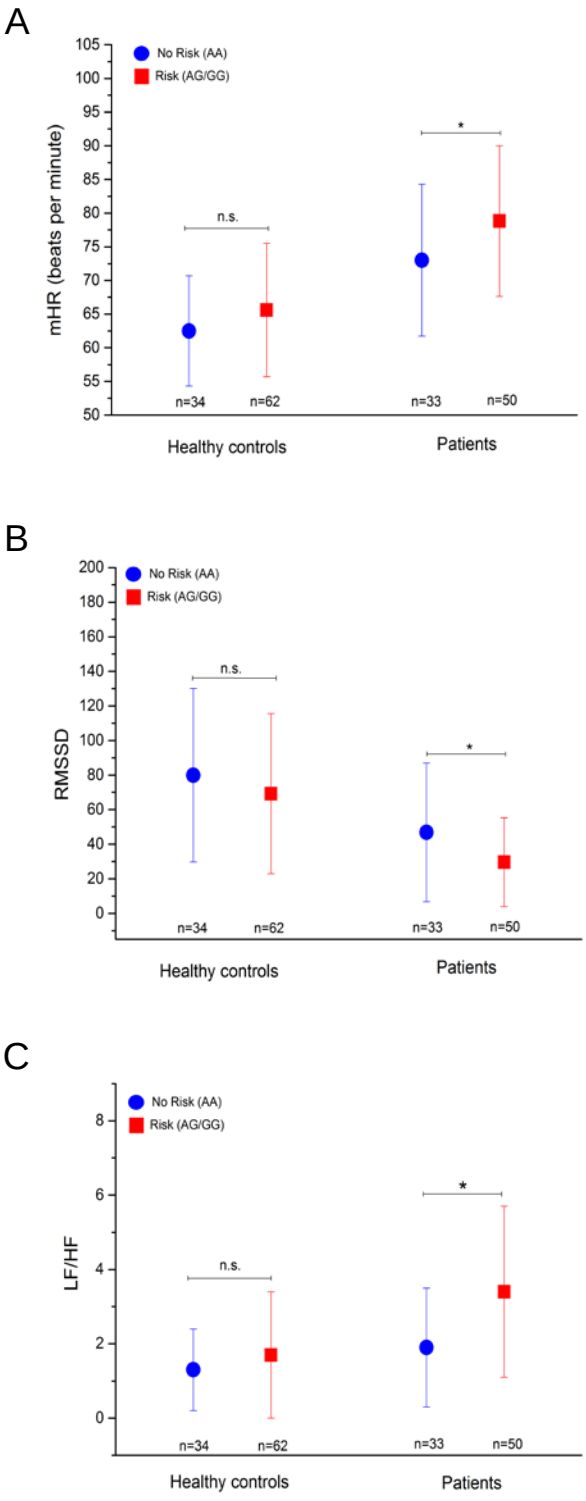
Table 2

Sociodemographic and clinical data of genotype subgroups.

healthy controls	**genetic groups**		p
	AA	AG/GG	
N	34	62	
age (y)	25.7 ± 4.4	25.1 ± 3.7	n.s.
gender (f/m)	17/17	31/31	n.s.
smoker status (y/n)	6/28	12/50	n.s.
cig. per day	0.9 ± 2.4	1.4 ± 3.8	n.s.
cups of coffee a day	0.9 ± 1.0	1.0 ± 1.5	n.s.
BMI (m/kg^2)	22.7 ± 3.3	22.7 ± 2.9	n.s.
hours of sport per week	2.3 ± 1.9	3.1 ± 2.0	n.s.
patients	**genetic groups**		p
	AA	AG/GG	
N	33	50	
age (y)	33.9 ± 12.2	32.7 ± 11.2	n.s.
gender (f/m)	15/18	21/29	n.s.
smoker status (y/n)	15/18	15/35	0.008
cig. per day	7.7 ± 10.5	6.5 ± 11.5	n.s.
cups of coffee a day	0.9 ± 1.5	0.5 ± 0.9	n.s.
BMI (m/l^2)	23.7 ± 8.5	22.5 ± 7.2	n.s.
hours of sport per week	0.9 ± 1.5	0.5 ± 0.9	n.s.
PANSS general	39.8 ± 10.4	44.41 ± 13.0	n.s.
PANSS pos	21.5 ± 6.0	21.7 ± 5.5	n.s.
PANSS neg	21.6 ±9.7	22.9 ± 7.9	n.s.

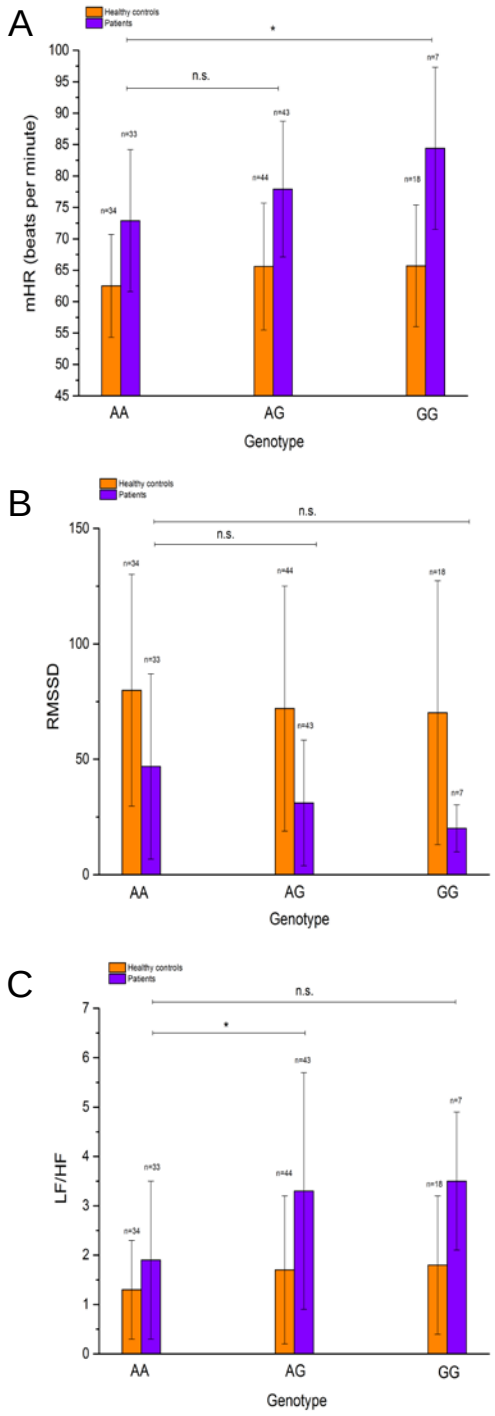
Data expressed as mean (SD). P-values resulting from ANOVAs; BMI: Body mass index; PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987).

Figure 1



A, B, C. Scatter diagram illustrating significant differences in mHR (bpm) (A), RMSSD (B) and LF/HF (C) in unmedicated patients with the rs16902086 risk genotype, * $p < 0.05$, p-value resulting from the ANOVAs.

Figure 2



A, B, C. Bar chart showing mHR (A), RMSSD(B), LF/HF (C) for the respective genotypes AA, AG and GG in patients and controls, * $p < 0.05$, p-value resulting from post-hoc-t-tests are only shown for the comparison of the genotypes in the patient group.

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