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Genomics of cardiovascular measures of autonomic tone

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Abstract

The autonomic nervous system exerts broad control over the involuntary functions of the human body via complex equilibrium between sympathetic and parasympathetic tone. Imbalance in this equilibrium is associated with a multitude of cardiovascular outcomes, including mortality. The cardiovascular static state of this equilibrium can be quantified via physiological parameters such as heart rate, blood pressure and by spectral analysis of heart rate variability.

Here we review the current state of knowledge of the genetic background of cardiovascular measurements of autonomic tone. For most parameters of autonomic tone a large portion of variability is explained by genetic heritability. Many of the static parameters of autonomic tone have also been studied via candidate gene approach, yielding some insight into how genotypes of adrenergic receptors affect variables such as heart rate. Genome-wide approaches in large cohorts similarly exist for static variables such as heart rate and blood pressure, but less is known about the genetic background of the dynamic and more specific measurements, such as heart rate variability. Furthermore, because most autonomic measures are likely polygenic, pathway analyses and modeling of polygenic effects are critical. Future work will hopefully explain the control of autonomic tone and guide individualized therapeutic interventions.

Subject Codes

Autonomic Nervous System; Cardiovascular Disease; Genetics

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Introduction

The autonomic nervous system (ANS) exerts intricate, nearly global control of all involuntary functions of the human body. Through reciprocal and cooperative activation of the two divisions of the ANS, the sympathetic and parasympathetic pathways, the ANS plays a critical role in homeostatic regulation.(1) In addition to regulating homeostasis, the ANS generates rapid hemodynamic and neuroendocrine responses to stressors.(2) Though the ANS regulates a diverse group of functions ranging from pupillary diameter to genitourinary function,(3) autonomic control of cardiovascular function has received increased interest. Autonomic function has been hypothesized to be central to the pathophysiology of heart failure,(4) hypertension,(5) and arrhythmias.(6, 7) While aspects of autonomic function are heritable and may predispose individuals to disease states,(8) very little is known about the genetic underpinnings of autonomic function. With the development of affordable assays to measure not just the overall genetic contribution to physiologic variables but also test for association with candidate genes or perform hypothesis - generating genome wide association studies (Table 1), the understanding of the genetic underpinning of autonomic function is gradually emerging. In this review, we outline the measurement of autonomic function, implications for disease pathogenesis, and the current state of knowledge regarding heritability and genetic determinants of autonomic function, with a focus on cardiovascular disease.

Autonomic Tone: Definition, measurement, heritability, and uses as prognostic markers

Defined simply, “autonomic tone” can be conceptualized as a rheostat balancing the two ANS divisions—the sympathetic and parasympathetic pathways. Though much of the autonomic nervous system trafficking is processed via reflex mechanisms, this likely omits a great deal of higher-order physiologic complexity in autonomic regulation.(9) In the following section, we will outline a number of cardiovascular measures of autonomic tone, their utility as markers of health and disease, and available evidence regarding their heritability.

1. Heart Rate

Heart rate—the number of times per minute that the heart generates an electrical depolarization—is largely under control of the sinoatrial node, which is reciprocally regulated by autonomic effects on spontaneous diastolic depolarization. In general, sympathetic stimulation results in an increase in heart rate, whereas parasympathetic stimulation results in a decrease in heart rate.(10) Interestingly, while sympathetic stimulation shortens action potential duration (APD) in both ventricular and atrial myocardium, parasympathetic stimulation prolongs APD and effective refractory period (ERP) in the ventricles, but shortens APD and ERP in the atria. This phenomenon may account for the fact that vagal stimulation is arrhythmogenic in the atria, but anti-arrhythmic in the ventricles.(6)

Resting heart rate may serve as a potential marker of health and/or disease. In patients with cardiovascular disease, increased resting heart rate was associated with worsened cardiovascular outcomes.(11) Additionally, increased resting heart rate was also predictive of incident heart failure in a population without known cardiac disease,(12) as well as all-cause mortality in individuals over age 60.(13) Interestingly, increased resting heart rate is also associated with chronic orofacial pain.(14, 15) Conversely, a low-resting heart rate is associated with later development of atrial fibrillation.(16) Taken together, this suggests that shifts of autonomic tone toward sympathetic predominance may increase risk or progression of sympathetically mediated conditions, such as heart failure and chronic pain, whereas excessive parasympathetic tone may act as a trigger for atrial arrhythmias. While age and sex differences exist in resting heart rate,(13) the genetic underpinnings of these differences remain unclear.

a. Heritability of resting HR—Several authors have assessed the heritability of resting HR. A higher correlation was found between the resting HR of siblings than spouses of participants in the Framingham Heart Study.(17) Similarly heritability was estimated to explain 40% of the variability in resting HR comparing related to unrelated individual in a study of Chinese and Japanese cohorts.(18) A study comparing ECG measurements between 251 pairs of twins found that heritability explained 77% of the variability in HR.(19) Similarly, a study comparing the correlation of both resting HR and HR following a mental calculation task between 372 pairs of monozygous and dizygous twins suggested that heritability explained about 63–69% of the variability in both variables.(20)

b. Candidate gene studies of resting HR—Several candidate genes have been suggested to affect resting HR, especially within the adrenergic receptors (Table 2). A variant (Ser49Gly) within the beta-1 adrenergic receptor was found to be associated with resting heart rate in a cohort of 1348 Chinese/Japanese individuals.(18) The same variant was also associated with resting HR in hypertensive African-Americans and Caucasian individuals taking beta-blockers in cohorts of 1337 and 1685 individuals, respectively.(21) Other variants of beta-1 receptors have additionally been associated with a differential response to beta-blocking therapy.(22) Other variants in the alpha-2 receptor was similarly associated with resting HR in subpopulations of Caucasian and African-American individuals.(21)

c. Genome-wide studies of resting HR—Multiple genome-wide association studies have been performed on resting HR in several populations (Table 2). The first association identified via GWAS of two populations with 10,000 individuals each was with rs365990, a missense variant in the myosin heavy chain alpha isoform (*MYH6*).(23) Later studies expanded the cohorts used in the original GWAS studies to include a total of 181,171 individuals.(24) These confirmed prior loci and added 14 additional loci, with loci also associated with dilated, hypertrophic and arrhythmogenic right ventricular cardiomyopathy, regulation of heart contraction, cell adhesion, energy metabolism and Alzheimer's disease. Most recently, 64 loci, including 46 not previously described, were found to be significantly associated with resting heart rate in a study of 19.9 million variants in up to 265,046 individuals.(25) These included multiple loci on all but three autosomal chromosomes.

Interestingly none of the variants identified via GWAS approach include beta-adrenergic receptors, the focus of candidate approaches. This highlights the utility of using data-driven approaches to identify novel pathways associated with cardiovascular and autonomic phenotypes.

2. Blood Pressure, systemic vascular resistance, and baroreceptor response

The autonomic nervous system exerts complex control over blood pressure through regulation of cardiac function, vascular resistance, intravascular volume, and integration of sensory inputs.(26) Short-term perturbations of blood pressure are sensed in large part by arterial baroreceptors, which then modulate efferent sympathetic and parasympathetic trafficking. While chronotropic responses to changes in blood pressure largely rely on the parasympathetic nervous system, the sympathetic nervous system exercises greater control over peripheral vascular tone as well as cardiac function.(27) Indeed, neurodegenerative disorders affecting the sympathetic nervous system often result in symptomatic hypotension due to failure of part of the baroreceptor reflex arc.(28) The role of the sympathetic nervous system in chronic blood pressure elevation is well appreciated, with numerous studies demonstrating sympathetic hyperactivity in patients with both early and established hypertension.(29) Indeed, many pharmacologic treatments for hypertension aim to reduce the sympathetic hyperactivity that is thought to play a central role in the pathogenesis of hypertension.(30) Additionally, emerging non-pharmacologic strategies for the management of hypertension include modulation of sympathetic tone.(27)

The role of blood pressure as a marker of health and disease is well established. Orthostatic hypotension is associated with a higher risk of incident stroke and coronary artery disease.(31) Similarly, failure to appropriately augment blood pressure in response to physical exercise is associated with higher cardiovascular morbidity and mortality.(32) Hypertension—elevated resting blood pressure—is an extremely common medical condition that increases risk of stroke, myocardial infarction, heart failure, and renal disease.(33) To mitigate these risks, current guidelines recommend careful treatment of hypertension,(34) though recent trials might result in changes in target blood pressure.(35) Evidence suggests that gender and race may impact adrenergic receptor responsiveness, thereby mediating vascular resistance.(36)

a. Heritability of resting blood pressure, systemic vascular resistance, and baroreceptor response—Heritability in measurements of both systolic (SBP) and diastolic (DBP) blood pressure has been established, with the correlation of both resting BP and BP responses to a mental stressor (mental arithmetic) using twin pairs, revealed that 49–72% of the variability in DBP and SBP was explained by heritability.(20) Similarly, utilizing a high-density SNP genotyping in two large cohorts, 20–27% and 39–50% of the variability in SBP and DBP was explained by heritability.(37) In a family study with 444 individuals, both 23% of blood pressure and 39% variability in pulse pressure was found to be explained by heritability.(38) In 172 pairs of twins utilizing a non-invasive measurement of cardiac output, the heritability of systemic vascular resistance was found to be 59%.(39) Finally, heritability explained 36–44% of the variability in measurements of baroreceptor sensitivity,

measured as the slope between instantaneous blood pressure and subsequent R-R interval in a study of 149 twin pairs.(40)

b. Candidate gene studies of resting blood pressure—Few authors have attempted association of plausible candidates to blood pressure variation (Table 2). Screening individuals from the Framingham heart study for variants in genes associated with salt handling known to cause familial hyper-or hypotension (*SLC12A3, SLC12AI, KCNJ1*), 138 coding sequence variants were identified in 2,492 individuals.(41) Individuals carrying the rare variants had a significantly lower SBP than individuals without them. Additionally, variants within 160 genes with a biological link to hypertension were assessed for association with measurements of blood pressure in three cohorts, revealing only a weak association for variants with two of the genes (*LEPR, ADRA2A*) and blood pressure.(42) There was only a weak association between homozygotes for variants in the Rho/rho kinase isoform 2 gene (*ROCK2*) and systemic vascular resistance.(39) Baroreceptor reflex, measured as the blood pressure response to a Valsalva maneuver, differed between variants in the aldosterone synthase (*CYP11B2*).(22) Another study, quantifying baroreceptor reflex sensitivity by measuring the fluctuation between systemic blood pressure and R-R interval, also identified association between the response and variants in the *CYP11B2* gene and both the bradykinin B2 receptor (*BDKRB2*) and the endothelial nitrous oxide (*NOS3*) synthase gene.(43)

c. Genome-wide studies of blood pressure—Original genome-wide approaches in a sample of 14,000 individuals identified no genetic regions associated with a diagnosis of hypertension.(44) Increasing the number of patients by combining multiple large consortia of individuals have subsequently identified more than 60 loci associated with quantitative measurements of blood pressure, each with a relatively small contribution to the phenotype (Table 2).(45–47) This highlights the challenges in mapping and understanding how very complex genetic interactions contribute to blood pressure regulation.

3. Heart Rate Variability (HRV)

As one of the primary controllers of heart rate, the autonomic nervous system plays a large role in dictating the length of the inter-beat interval—the length of time between each heartbeat. These beat-to-beat fluctuations in heart rate can be measured with a variety of technologies, and interpreted over short (i.e. 5 minutes) or long (i.e. 24 hours) periods of time. Short recordings are typically analyzed using frequency-domain measures, which group inter-beat fluctuations into several defined frequency spectra of high frequency (HF), low frequency (LF), and very low frequency (VLF) (Figure 1a). Additionally, normalized measurements of high frequency (HF/HF+LF), low frequency (LF/HF+LF) and ratio of LF/HF have been utilized as surrogate markers of autonomic tone. The quantification of the fluctuation within each frequency spectra can then be utilized for analysis of the genetic background of autonomic tone (Figure 1b). Similarly, long recordings of inter-beat intervals may be analyzed using frequency domain or time-domain techniques, which quantitatively describe the variability as normal-normal intervals.(48) The variability is then traditionally described as standard deviation of normal-normal interval (SDNN), root mean square of successive differences (RMSSD) and percentage of successive intervals with more than 50

ms difference (pNN50). Additionally, multiple novel analytic techniques, which are beyond the scope of this review, may provide insight into autonomic tone.(49) In both healthy controls(50) and patients with risk factors for cardiovascular disease,(51) levels of adrenergic hormones correlate with frequency domain measures of HRV. Similarly, cardiac norepinephrine spillover correlates with non-linear measures of HRV complexity.(52)

Analysis of heart rate variability may provide valuable insights in a variety of settings.(53) Multiple studies have suggested that decreased heart rate variability may predict worsened outcomes in patients with congestive heart failure or after acute myocardial infarction.(54) Frequency-domain measures of HRV predict dysrhythmias in both ambulatory patients(16, 55) and patients after major thoracic surgery.(56) In patients with chronic pain(57) and chronic headaches,(58) frequency-domain measures of HRV suggest decreased vagal function compared to healthy controls. Additionally, reduced heart rate complexity is predictive of mortality in both critically ill patients(59) and trauma patients, regardless of injury mechanism.(60) Interestingly, gender and ethnic differences exist in frequency-domain measures of HRV,(61) though the genetic underpinnings of these differences remain unclear.

Another tool used to assess baroreceptor sensitivity is heart rate turbulence, which measures the variability in the beat-to-beat duration following a single premature ventricular beat.(62) This variable is thought to reflect the reflex activation of the vagus nerve to control sinus rhythm.(63) Several studies have associated heart rate turbulence with morbidity from cardiovascular diseases.(64, 65) This could partially be due to differences in intrinsic cardiac innervation during electrical remodeling of diseased myocardium, as well as mediated via autonomic influences on ion channels contributing to arrhythmogenesis. (62)

1. Heritability of HRV—A sub-study of the Framingham heart study found a higher correlation in several measurements of HRV between siblings than spouses of individuals included in the study, indicating a genetic contribution to the parameter. (17) Similarly, the twins heart study found that there was a higher correlation between indices of HRV between monozygous twins than heterozygous twins.(66) Ambulatory HRV, assessed at four periods in the day by SDNN and RMSSD from 24h ECG measurements, has also been compared between monozygous twins and dizygous twins/singleton siblings in a study of 772 individuals.(67) The genetic contribution to ambulatory HRV ranged from 35% to 48%. Recently the heritability of multiple indices of HRV (HR, SDNN, RMSSD, pNN50, LF, HF, LF/HF) was assessed in a large sample of 1060 adult twins, revealing that heritability explained approximately 50–60% of the variability of all HRV measurements performed. (68) This indicates that a portion of inter-individual variability in HRV is mediated by shared genome rather than shared environment.

2. Candidate Gene Approaches—Several studies have attempted to associate variants in individual genes or regions with measurements of HRV, mostly variants within the acetylcholinergic pathway. A study identified an association between a variant in the choline transporter gene (*SLC5A7*) and HRV assessed by both LF power and LF/HF ratio.(69) Variants in the brain-derived neurotrophic factor (*BDNF*) were associated with both HF power and LF/HF ratio in a sample of 211 Chinese Han individuals. (70) The largest study

to date combined genetic and HRV information for 6740 individuals from 7 smaller studies into discovery and replication cohorts and then tested for association of 443 variants within genes related to acetylcholine pathway (*CHAT, SLC18A3, SLC5A7, CHRNB4, CHRNA3, CHRNA, CHRM2* and *ACHE*) and measurements of HRV assessed by RMSSD.(71) After correcting for multiple testing, no variant was found to be associated with HRV. The authors suggested that even though acetylcholine pathways might be involved in the physiology of HRV, their epigenetic interactions with other pathways controlled by other genes might not be fully understood. Identifying genes and pathways associated with HRV therefore likely requires an unbiased high-resolution genome-wide approach in an adequately powered cohort with high quality HRV phenotypes coupled with new and emerging bioinformatic and statistical procedures that permit the examination of gene-gene interactions.

3. Genome-wide association studies—The first attempted genome wide scan for HRV-associated traits was a linkage scan of individuals from the Framingham Heart Study, associating genetic regions with measurements of HRV (VLF power, LF power and HF power).(72) This identified two genetic regions on chromosomes 2 and 15. The region on chromosome 15 is in proximity with a cluster of genes coding for the nicotinic acetylcholine receptor. However, a follow-up 100 kb SNP resolution genome-wide scan of HRV (assessed by LF/HF power and total power) did not identify any variants associated with HRV in a cohort of 548 individuals from the offspring substudy of the Framingham study.(73) A recent meta-analysis utilizing 17 genome-wide association studies assessed the genetic contribution to HRV.(74) This was done mostly through studies measuring inter-beat interval variability (SDNN and RMSSD) on short or ultra-short (10 second) ECGs, although these variability measurements are more traditionally done on ECG measurements of longer duration. This study identified that genetic risk scores by combination of risk alleles only predicted 0.9–2.6% of the variability in these measurement, but also identified 8 loci with genome-wide associations. As expected there was a strong association between these measurements of HRV and heart rate, and several loci associated with heart rate were identified. These include pathways affecting acetylcholine release in the sinoatrial node and genes coding for muscarinic adrenergic potassium channels (*GIRK*).(74)

4. Lessons from monogenic diseases affecting cardiovascular tone—Several monogenic diseases have shed light on potential mechanisms affecting cardiovascular presentation of autonomic tone. Patients with dopamine beta-hydroxylase deficiency suffer from severe orthostatic hypotension in addition to other symptoms of lack of sympathetic tone, such as hypothermia.(75) The disease is due to mutations in the dopamine beta-hydroxylase (*DBH*) gene responsible for conversion of dopamine to norepinephrine.(75) Similarly, patients with mutations in the norepinephrine-transporter gene (*NET/SLC6A2*) impairing the reuptake of norephinephrine into the releasing neuron. This results in increased activity and spillage of norepinephrine into circulation, resulting in elevated baseline heart rate and a profound response to orthostatic challenge.(76) Pathogenic mutations affecting the expression or increased copy numbers of the Parkinson disease 1 or 4 gene (*SNCA*, *PARK1, PARK4*) result in abnormally high expression of the alpha-synuclein protein, interacting with dopamine metabolism and affecting downstream generation of noradrenaline. In addition to causing early-onset Parkinsons disease, these

patients will frequently have dysregulation in peripheral adrenergic receptors and symptoms of severe orthostatic hypotension.(77) These diseases all highlight the importance of metabolism of adrenergic neurotransmitters in modulating autonomic cardiovascular tone.

4. Autonomic Response to Physical Stress

a. Heritability of autonomic response to physical stress—Compared to the available data on heritability and the genetic background of HR, BP and HRV, less is known about the response to physical stressors. Several studies have tested the heritability of blood pressure response to orthostatic challenge, such as a head-up table tilting, is the most commonly applied physical stress. The heritability of blood pressure response to head-up table test was compared in a cohort of 444 individuals from five multi-generational families.(38) Heritability was assumed to explain about 14–19% of the variability in the DBP and SBP response to the head-up table test. Similarly, heritability was estimated to explain 25% of the change in SBP from an orthostatic challenge in a cohort of 767 families.(78) A total of 40% of the variability in HR change in response to cold pressor test was found to be heritable in a study of 576 individuals from twin and sibling pairs.(79) Another study found that 12–25% of the blood pressure response to cold pressor test was due to genetic effects in a family cohort of 835 individuals.(80)

b. Candidate gene studies of autonomic response to physical stress—In a cohort of 3630 untreated hypertensive patients, individuals homozygous for the Arg389/Gly variant in the beta-1 adrenergic receptor were found to have a greater change in SBP following an orthostatic challenge.(81) Polymorphisms in *GNAS1*, another gene in the sympathetic nervous system, were also found to be associated with differential response to orthostatic challenge in a cohort of 415 individuals.(82) No association was found with variants within genes involved in the renin-angiotension-aldosterone pathway. A weak association between orthostatism and a variant in the *NEDD4L* gene, that regulates expression of a sodium channel in the kidney, was also found in a study of 793 individuals.(83) Variants in the *EBF1* and *CYP17A1* genes were associated with a diagnosis of orthostatic hypotension in a study that tested the association of 31 variants associated with blood pressure or hypertension in genome-wide analysis in cohort of 38,970 individuals from 5 populations.(84) Multiple variants within sympathetic pathway have been associated with differential response to the cold pressor test (Table 2). Amongst those are variants in the *CYB561* gene, a transporter gene in the sympathetic pathway,(79) as well as variants in the tyrosine hydroxylase (*TH*) gene, involved in catecholamine biosynthesis.(85) Polymorphism in the beta-2 adrenergic receptor was also associated with the blood pressure response in a cohort of young twins.(86) Furthermore genes involved in intracellular signal transduction and its response to salt load, namely *ADD1* and *GNB3*, and in genes (*AGT*, *AGTR1*) within renin-angiotensin-aldosterone pathway were also associated with the response to the cold pressor test in a Chinese Han population.(87, 88)

c. Genome-wide association studies of autonomic response to physical stress—A genome-wide study of changes in hypertension with orthostatic challenge in two Korean populations totaling approximately 6000 individuals identified multiple variants within the *CTNNA2* gene, previously unassociated with any autonomic phenotypes, and

changes in SBP.(89) Variants in *PIK3AP1* were also associated with changes in SBP, and variants in *ACTBL2, STAR* and *MYLK4* were associated with changes in DBP. None of these variants have been previously associated with autonomic tone. No variant was associated with a diagnosis of orthostatic hypotension. A genome-wide linkage study followed by single nucleotide polymorphism screen of linked regions identified variants in the *MCM8, SLC23A2* and *STK35* genes associated with the blood pressure response to the cold pressor test, via unknown pathways.(90)

5. Autonomic Response to Mental Stress

The heritability of the hemodynamic response to mental stressors has been assessed. In addition to baseline measurements, heritability was found to explain 44–74% of the HR and BP response to both a reaction time task and calculation task in a twin study with 373 twin pairs.(20) Another study found no significant increase in heritability in the response of HF and RMSSD measurements of HRV when 735 twin pairs were exposed to virtual reality driving stressor, video game or a social competence interview. This indicates that the same genes regulate the HRV under rest and stress.(91) However, a subset of the individuals also underwent 24h blood pressure measurement to assess hemodynamic response to real-life stressors. This indicated that a substantial fraction of the variability in hemodynamic response was unexplained by genes explaining baseline HRV.(92) Thus far, no candidate gene studies or genome-wide association studies on the hemodynamic effects of mental stress exist.

Conclusions and Future Directions

Autonomic tone is a paramount physiological variable associated with multiple cardiovascular outcomes of clinical interest. Cardiovascular measures of autonomic tone involve both basic measurements of the static components such as heart rate and blood pressure as well as more complex measurements of the dynamic components of autonomic tone such as different spectra of heart rate variability. Furthermore, the effects of physiological and psychological strain on these measurements can be quantified.

Both the heritability and genetic background of the static aspects of cardiovascular measurements of autonomic tone, such as resting heart rate and blood pressure, have been thoroughly studied. As highlighted here, this has revealed a substantial genetic component of these static variables, both when studied macroscopically by shared variability between twins and in high-resolution genome-wide association studies. Interestingly, there is no overlap where associations between these measurements and plausible candidate genes identified via candidate gene studies have not been identified or confirmed in a hypothesis-free genome-wide association studies. Furthermore, the identified variants generally did not conform to a single cellular signaling or metabolic pathway. This indicates that there is likely a multifactorial genetic contribution to these variables.

Furthermore, heritability represents a large component of the variability in measurements of the dynamic phase of autonomic tone, namely heart rate variability and changes in heart rate, blood pressure and heart rate variability with physical and psychological stressors. However, there is currently a lack of high-resolution genome-wide association studies with a high-

quality phenotyping of these important variables. Furthermore, novel bioinformatical methods, such as functional group/pathway analysis and modeling of polygenic effects, should be applied to the results of genome-wide association analyses to reveal effects that are not able to pass conservative significance thresholds typically applied to the genome-wide analyses. Comprehensive functional annotation of genetic variants via bioinformatic databases (such as tissue-specific gene expression and DNA methylation maps) is needed to understand how identified variants mediate their biological effects. Finally, limited work exists on modification of autonomic tone to affect the associated cardiovascular outcomes. These could include heart rate modulation by blockade of beta-receptor or calcium channels. It is likely that only a subset of the patients would have benefit from such interventions, and perhaps these patients could be identified in the future from their genetic background. It is likely that such studies will follow, given the utility of such information for cardiovascular risk prognostication and development of novel therapeutics.

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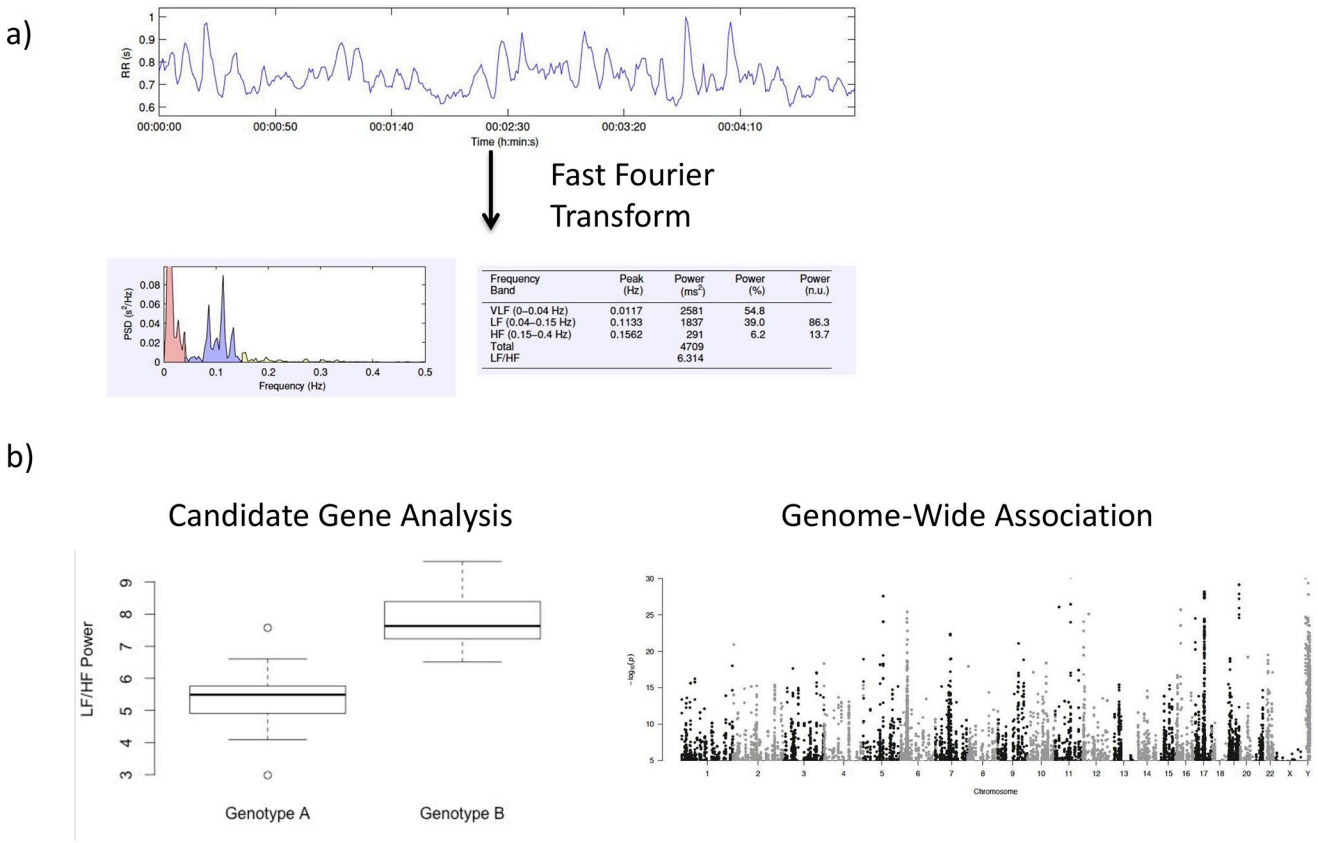

Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0–0.04 Hz)	0.0117	2581	54.8	
LF (0.04–0.15 Hz)	0.1133	1837	39.0	86.3
HF (0.15–0.4 Hz)	0.1562	291	6.2	13.7
Total		4709		
LF/HF		6.314		

Figure 1.

Example of the analysis of the genetic background of heart rate variability: a) RR interval (time between heart beats) are collected over 5 minutes, and spectral analysis performed by fast Fourier transform of the signal to describe the data in domains of High frequency (HF), low frequency (LF), very low frequency (VLF) and LF/HF ratio. b) The quantified measurements of heart rate variables are then compared between different genotypes of candidate genes or different alleles of single nucleotide polymorphisms evenly distributed throughout the genome in an unbiased genome-wide approach.

Table 1

Methods to study genetic association with physiologic variables or pathologic states.

Measurement	Description
Heritability study	For continuous variables (such as heart rate) The covariance of the dizygous twins accounts for environmental influences, and a portion of the genetic influences on the variable (since they share 50% of the DNA). The difference between the covariance in a group of monozygous twins and the covariance in a group of dizygous twins is an estimate of the genetic contribution to the variable.
Candidate gene study	A list of biologically plausible genes is generated from existing literature (i.e. genes involved in the acetylcholine pathway). The outcome variable is correlated with the genotype of variants (i.e. single nucleotide polymopisms) within these genes.
Genome-wide association study	The genotype of genetic variants (such as single nucleotide polymorphisms or microsatellite markers) distributed around the genome is compared between cases and controls. Most commonly non-protein coding variants. Areas with different frequency genotypes between cases and controls are potentially involved in pathogenesis of disease.

Table 2

List of identified genetic variants associated with variables describing autonomic tone, associated genes, key publication describing each variant, and minor allele frequency (MAF) of variants found in Caucasian population. Note that more than one publication can include a description of variant. Also note that several genes can be adjacent to a single nucleotide variant associated with a physiological parameter. All studies were population based, there were no familial studies.

SNP	Feature	Associated.Gene	Publication	Type of study
rs1799998	Baroreceptor sensitivity	*CYP11B2*	Ylitao et al. and Xing-Sheng et al.	Candidate gene
NA	Baroreceptor sensitivity	*NOS3*	Xing-Sheng et al.	Candidate gene
NA	Baroreceptor sensitivity	*BDKRB2*	Xing-Sheng et al.	Candidate gene
rs11195419	Blood pressure	*ADRA2A*	Sober et al.	Candidate gene
rs10077885	Blood pressure	*TRIM36*	Ehret et al.	GWAS
rs10760117	Blood pressure	*PSMD5*	Ehret et al.	GWAS
rs10889553	Blood pressure	*LEPR*	Sober et al.	Candidate gene
rs11105354	Blood pressure	*ATP2B1*	Ehret et al.	GWAS
rs11128722	Blood pressure	*FGD5*	Ehret et al.	GWAS
rs11195417	Blood pressure	*ADRA2A*	Sober et al.	Candidate gene
rs11556924a	Blood pressure	*ZC3HC1*	Ehret et al.	GWAS
rs1156725	Blood pressure	*PLEKHA7*	Ehret et al.	GWAS
rs11953630	Blood pressure	*EBF1*	Ehret et al.	GWAS
rs12243859	Blood pressure	*CACNB2*	Ehret et al.	GWAS
rs12247028	Blood pressure	*SYNPO2L*	Ehret et al.	GWAS
rs12627651	Blood pressure	*CRYAA–SIK1*	Ehret et al.	GWAS
rs12656497	Blood pressure	*NPR3–C5orf23*	Ehret et al.	GWAS
rs12705390	Blood pressure	*PIK3C G*	Ehret et al.	GWAS
rs12940887	Blood pressure	*ZNF652*	Ehret et al.	GWAS
rs12958173	Blood pressure	*SETBP1*	Ehret et al.	GWAS
rs13107325a	Blood pressure	*SLC39A8*	Ehret et al.	GWAS
rs1327235	Blood pressure	*JAG1*	Ehret et al.	GWAS
rs1361831	Blood pressure	*RSPO3*	Ehret et al.	GWAS
rs1371182	Blood pressure	*FIGN–GRB14*	Ehret et al.	GWAS
rs1450271	Blood pressure	*ADM*	Ehret et al.	GWAS
rs1458038	Blood pressure	*FGF5*	Ehret et al.	GWAS
rs1620668	Blood pressure	*ST7L–CAPZA1–MOV10*	Ehret et al.	GWAS
rs17010957	Blood pressure	*ARHGAP24*	Ehret et al.	GWAS
rs17037390a	Blood pressure	*MTHFR–NPPB*	Ehret et al.	GWAS
rs17080093	Blood pressure	*PLEKHG1*	Ehret et al.	GWAS
rs17097182	Blood pressure	*LEPR*	Sober et al.	Candidate gene
rs17608766	Blood pressure	*GOSR2*	Ehret et al.	GWAS
rs17638167	Blood pressure	*ELAVL3*	Ehret et al.	GWAS

SNP	Feature	Associated.Gene	Publication	Type of study
rs1799945a	Blood pressure	*HFE*	Ehret et al.	GWAS
rs1975487	Blood pressure	*PNPT1*	Ehret et al.	GWAS
rs2187668	Blood pressure	*BAT2–BAT5*	Ehret et al.	GWAS
rs2272007a	Blood pressure	*ULK4*	Ehret et al.	GWAS
rs2291435	Blood pressure	*TBC1D1–FLJ13197*	Ehret et al.	GWAS
rs2493134a	Blood pressure	*AGT*	Ehret et al.	GWAS
rs2521501	Blood pressure	*FURIN–FES*	Ehret et al.	GWAS
rs2586886	Blood pressure	*KCNK3*	Ehret et al.	GWAS
rs2594992	Blood pressure	*HRH1–ATG7*	Ehret et al.	GWAS
rs2891546	Blood pressure	*TBX5–TBX3*	Ehret et al.	GWAS
rs2898290	Blood pressure	*BLK–GATA4*	Ehret et al.	GWAS
rs2969070	Blood pressure	*CHST12–LFNG*	Ehret et al.	GWAS
rs3184504a	Blood pressure	*SH2B3*	Ehret et al.	GWAS
rs3735533	Blood pressure	*HOTTIP–EVX*	Ehret et al.	GWAS
rs3741378a	Blood pressure	*SIPA1*	Ehret et al.	GWAS
rs3752728	Blood pressure	*PDE3A*	Ehret et al.	GWAS
rs4245739	Blood pressure	*MDM4*	Ehret et al.	GWAS
rs4247374	Blood pressure	*INSR*	Ehret et al.	GWAS
rs4691707	Blood pressure	*GUCY1A3–GUCY1B3*	Ehret et al.	GWAS
rs592373	Blood pressure	*LSP1–TNNT3*	Ehret et al.	GWAS
rs6026748	Blood pressure	*GNAS–EDN3*	Ehret et al.	GWAS
rs6271a	Blood pressure	*DBH*	Ehret et al.	GWAS
rs633185	Blood pressure	*FLJ32810–TMEM133*	Ehret et al.	GWAS
rs6442101a	Blood pressure	*MAP4*	Ehret et al.	GWAS
rs6779380	Blood pressure	*MECOM*	Ehret et al.	GWAS
rs6891344	Blood pressure	*CSNK1G3*	Ehret et al.	GWAS
rs6919440	Blood pressure	*ZNF318–ABCC10*	Ehret et al.	GWAS
rs7076398	Blood pressure	*C10orf107*	Ehret et al.	GWAS
rs7103648	Blood pressure	*RAPSN*	Ehret et al.	GWAS
rs711737	Blood pressure	*SLC4A7*	Ehret et al.	GWAS
rs7213273	Blood pressure	*PLCD3*	Ehret et al.	GWAS
rs740746	Blood pressure	*ADRB1*	Ehret et al.	GWAS
rs7515635	Blood pressure	*HIVEP3*	Ehret et al.	GWAS
rs751984	Blood pressure	*LRRC10B*	Ehret et al.	GWAS
rs772178	Blood pressure	*NCAPH*	Ehret et al.	GWAS
rs880315	Blood pressure	*CASZ1*	Ehret et al.	GWAS
rs918466	Blood pressure	*ADAMTS9*	Ehret et al.	GWAS
rs932764a	Blood pressure	*PLCE1*	Ehret et al.	GWAS
rs936226	Blood pressure	*CYP1A1–ULK3*	Ehret et al.	GWAS

SNP	Feature	Associated.Gene	Publication	Type of study
rs943037	Blood pressure	*CYP17A1–NT5C2*	Ehret et al.	GWAS
rs1042713	Cold pressor test	*ADRB2*	Li et al.	Candidate gene
rs16887217	Cold pressor test	*STAR*	Hong et al.	GWAS
rs16991617	Cold pressor test	*MCM8*	Yang et al.	GWAS
rs17020502	Cold pressor test	*CTNNA2*	Hong et al.	GWAS
rs2006765	Cold pressor test	*AGT*	Wang et al.	Candidate gene
rs2326373	Cold pressor test	*SMOX*	Yang et al.	GWAS
rs3087776	Cold pressor test	*CYB561*	Zhang et al.	Candidate gene
rs4681443	Cold pressor test	*AGTR1*	Wang et al.	Candidate gene
rs4959677	Cold pressor test	*MYLK4*	Hong et al.	GWAS
rs6052943	Cold pressor test	*SLC23A2*	Yang et al.	GWAS
rs6356	Cold pressor test	*TH*	Rao et al.	Candidate gene
rs6715049	Cold pressor test	*CTNNA2*	Hong et al.	GWAS
rs6736587	Cold pressor test	*CTNNA2*	Hong et al.	GWAS
rs6756959	Cold pressor test	*CTNNA2*	Hong et al.	GWAS
rs6892553	Cold pressor test	*ACTBL2*	Hong et al.	GWAS
rs7098785	Cold pressor test	*PIK3AP1*	Hong et al.	GWAS
rs1050288	Heart rate	*KLHL42*	Eppinga et al.	GWAS
rs10739663	Heart rate	*MAPKAP1*	Eppinga et al.	GWAS
rs10841486	Heart rate	*PDE3A*	Eppinga et al.	GWAS
rs10880689g	Heart rate	*ALG10B*	Eppinga et al.	GWAS
rs11083258	Heart rate	*CDH2*	Eppinga et al.	GWAS
rs11118555	Heart rate	*CD46*	den Hoed et al.	GWAS
rs11454451	Heart rate	*GPATCH2*	Eppinga et al.	GWAS
rs11563648	Heart rate	*ZNF800*	Eppinga et al.	GWAS
rs11920570	Heart rate	*CCDC58*	Eppinga et al.	GWAS
rs12501032	Heart rate	*PPARGC1A*	Eppinga et al.	GWAS
rs12576326	Heart rate	*TP53I11*	Eppinga et al.	GWAS
rs12579753	Heart rate	*PPFIA2*	Eppinga et al.	GWAS
rs1260326	Heart rate	*GCKR*	Eppinga et al.	GWAS
rs12713404	Heart rate	*BCL11A*	Eppinga et al.	GWAS
rs12721051	Heart rate	*APOE; APOC1; PVRL2*	Eppinga et al.	GWAS
rs12889267	Heart rate	*NDRG2; ARHGEF40; ZNF259*	Eppinga et al.	GWAS
rs13165531	Heart rate	*CDH6*	Eppinga et al.	GWAS
rs138186803	Heart rate	*MKLN1*	Eppinga et al.	GWAS
rs145358377	Heart rate	*RNF207; ICMT*	Eppinga et al.	GWAS
rs1468333f	Heart rate	*CDC23*	Eppinga et al.	GWAS
rs1483890	Heart rate	*FRMD4B*	Eppinga et al.	GWAS
rs1549118	Heart rate	*ADCK1*	Eppinga et al.	GWAS

SNP	Feature	Associated.Gene	Publication	Type of study
rs16974196	Heart rate	*C19orf47; MAP3K10*	Eppinga et al.	GWAS
rs17180489	Heart rate	*RGS6*	Eppinga et al.	GWAS
rs17265513	Heart rate	*ZHX3; EMILIN3*	Eppinga et al.	GWAS
rs1801252	Heart rate	*ADRB1*	Eppinga et al., Ranade et al, Wilk et al.	GWAS
rs2076028	Heart rate	*SUN2; CBY1; FAM227A; JOSD1; TOMM22; DDX17; GTPBP1*	Eppinga et al.	GWAS
rs2152735	Heart rate	*LMO4*	Eppinga et al.	GWAS
rs2283274	Heart rate	*CACNA1C*	Eppinga et al.	GWAS
rs2358740	Heart rate	*CACNA1D*	Eppinga et al.	GWAS
rs236349	Heart rate	*PPIL1*	Eppinga et al.	GWAS
rs272564	Heart rate	*RNF220*	Eppinga et al.	GWAS
rs365990	Heart rate	*MYH6*	Holm et al.	GWAS
rs3749237	Heart rate	*IP6K1; GMPPB; FAM212A; DAG1; KLHDC8B; LAMB2; PRKAR2A; QRICH1*	Eppinga et al.	GWAS
rs3915499	Heart rate	*MYH11*	Eppinga et al.	GWAS
rs41312411	Heart rate	*SCN5A*	Eppinga et al.	GWAS
rs41748	Heart rate	*MET*	Eppinga et al.	GWAS
rs4608502	Heart rate	*COL4A3*	Eppinga et al.	GWAS
rs4900069	Heart rate	*C14orf159*	Eppinga et al.	GWAS
rs56233017	Heart rate	*PLEC*	Eppinga et al.	GWAS
rs564190295	Heart rate	*WIPF1*	Eppinga et al.	GWAS
rs58437978	Heart rate	*TBX20*	Eppinga et al.	GWAS
rs61735998	Heart rate	*FHOD3*	Eppinga et al.	GWAS
rs6845865	Heart rate	*ARHGAP10; EDNRA*	Eppinga et al.	GWAS
rs7194801	Heart rate	*CDH11*	Eppinga et al.	GWAS
rs75190942	Heart rate	*KCNJ5; C11orf45*	Eppinga et al.	GWAS
rs79121763	Heart rate	*TEKT3; PMP22*	Eppinga et al.	GWAS
rs867400	Heart rate	*RASSF3*	Eppinga et al.	GWAS
rs907683	Heart rate	*SPEG; DES*	Eppinga et al.	GWAS
rsl015451	Heart rate	*GJA1*	den Hoed et al.	GWAS
rsl3245899	Heart rate	*ACHE*	den Hoed et al.	GWAS
rsl7287293	Heart rate	*LINC00477 (C12orf67)*	den Hoed et al.	GWAS
rsl74549	Heart rate	*FADS1*	den Hoed et al.	GWAS
rs11153730	Heart rate	*SLC35F1*	den Hoed et al.	GWAS
rs12974991, rs12974440, rs12980262	Heart rate	*NDUFA11*	Nolte et al.	GWAS
rs10842383	Heart rate variability	*LINC00477 (C12orf67)*	Nolte et al.	GWAS
rs236349	Heart rate variability	*PPIL1*	Nolte et al.	GWAS
rs7980799, rs13311682, rs13245988	Heart rate variability	*SYT10*	Nolte et al.	GWAS

SNP	Feature	Associated.Gene	Publication	Type of study
rs4262, rs180238	Heart rate variability	*GNG11*	Nolte et al.	GWAS
rs4899412, rs2052015, rs2529471, rs36423	Heart rate variability	*RGS6*	Nolte et al.	GWAS
rs2680344	Heart rate variability	*HCN4*	Nolte et al.	GWAS
rs1812835	Heart rate variability	*NEO1*	Nolte et al.	GWAS
rs6123471	Heart rate variability	*KIAA1755*	Nolte et al.	GWAS
rs11191548	Orthotatism	*CYP17A1*	Fedoeowski et al.	Candidate gene
rs11953630	Orthotatism	*EBF1*	Fedoeowski et al.	Candidate gene
rs4149601	Orthotatism	*NEDD4L*	Luo et al.	Candidate gene
NA	Orthotatism	*GNB3*	Tabara et al.	Candidate gene
NA	Orthotatism	*GNAS1*	Tabara et al.	Candidate gene