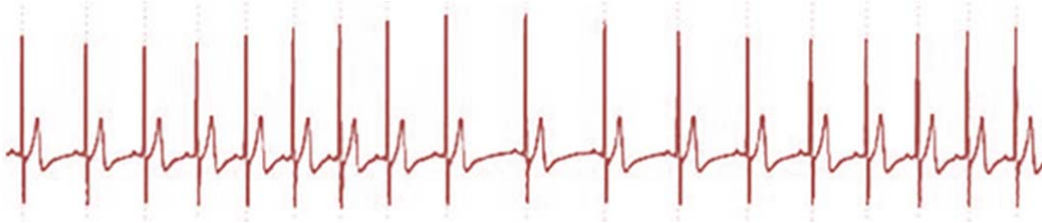


International consortium reports genetic variants that provide insight into the regulation of the heart rhythm in health and disease

Researchers find genes that influence heart rate variability



Normal beat-to-beat variation in heart rate; intervals between two consecutive beats can strongly vary.

The measurement of beat-to-beat variation in the period between two heart beats, known as heart rate variability, has long been in use as an assessment tool in clinical cardiology. Low heart rate variability is associated with risk of heart attacks and even death. Over the past decades interest in heart rate variability has spread to the social sciences because it can reflect the regulation of the heart by the autonomic nervous system. Heart rate variability has been used to predict sensitivity to stress in adults, as well as emotional and cognitive development in children.

An international collaboration on the genetics of heart rate variability led by Dutch researchers from the University Medical Center Groningen and the Vrije Universiteit Amsterdam, together with investigators from Europe and the USA, has obtained a breakthrough in identifying genetic variants that decrease heart rate variability. These variants appear associated with the genetic risk for high blood pressure and other dire cardiac outcomes.

The findings appear online today in *Nature Communications*. Researchers believe the findings represent a significant advance in the understanding of individual differences in activity of the cardiac vagal nerve, which is a crucial part of the ‘rest and digest’ branch of the autonomic nervous system that balances the activity of the opposite ‘fight and flight’ branch. The study also provides a greater understanding of the key mechanisms controlling rhythm generation in the pacemaker cells of the heart.

In the study, first author Ilja Nolte and colleagues report eight genomic loci harboring heart rate variability variants. Three of these variants are known to affect the expression of genes, two of which regulate the firing frequency of the pacemaker cells of the heart. These two genes, *GNG11* and *RGS6*, are active in the pathway that convert signals from the brain to the heart in rapid beat-to-beat changes. They are a plausible biological source for individual differences in heart rate variability.

The research brought together a large number of participants who had undergone an ECG recording and provided biomaterials for the extraction of their DNA. Their genetic profiles, based on millions of single nucleotide variants, were associated with heart rate variability, scored from ECG recordings that could be as short as ten seconds. An important strength of the study was that the findings replicated across three widely used measures of heart rate variability and were similar across different ethnic groups, i.e. the genetic effects on heart rate variability in individuals from a European, African-American and Hispanic-Latino background were very comparable.

“Discovery of genetic variants, the effects of which are plausibly localized in the heart tissue, provides a way to test causal hypotheses about the role of the vagal nerve of the autonomic nervous system in physical and mental health”, said senior author Prof. Eco de Geus, Ph.D., who specializes in autonomic nervous system regulation at the department of Biological Psychology of the Vrije Universiteit Amsterdam, which maintains the Netherlands Twin Register. “Using the new strategy of Mendelian Randomization in genetic epidemiology, true causal effects can be teased apart from those of confounding factors without having to perform expensive Randomized Controlled Trials. This strategy is particularly powerful when combined with the classical twin design.”

Nolte and colleagues also show that lower heart rate variability is associated with resting heart rate and blood pressure, two major risk factors for cardiovascular disease.

“The clear genetic association of heart rate variability with blood pressure is a breakthrough finding. It supports the potential causal role of the autonomic nervous system in the development of hypertension.”, said Prof. Harold Snieder from the department of Epidemiology at the University Medical Center Groningen, who was involved as the principal investigator on cardiovascular genetic epidemiology in the Lifelines Cohort Study, a very large study in the Northern part of the Netherlands that played a key role in the study.