

Identification of a New Causal Gene for Cardiac Arrhythmias

Institute of Human Genetics

In 2005 367,361 people died of cardiovascular diseases in Germany (1). In approx. 95 % of these cases the cause of death was a macroscopic heart disease, e.g. a heart attack. These diseases are very responsive to treatment, so that a fatal outcome can often be prevented or delayed by years. In the remaining 5 % of all cases diagnosis, therapy and prevention are more difficult. In those cases sudden cardiac death occurs – often without any preliminary warning – i.e. a directly life-threatening arrhythmia of the cardiac chambers. Although it tends to occur more frequently in young people and high-performing athletes, neither the blood analysis nor the ECG nor the heart ultrasound imaging allows any reliable risk forecasts.

Over the last decade several genetic arrhythmias have been elucidated with the help of family

surveys. This intensified the search for genetic factors for sudden cardiac death. It is difficult to examine large postmortal patient groups, but one parameter of the electrocardiogram (ECG), the QT interval, shows a clear association with sudden cardiac death.

Therefore, we investigated the genetics of the QT interval in the normal population. For this purpose the two KORA surveys F3 and S4 with a total of 6,500 participants as well as another 1,800 subjects from the Framingham Heart Study in the US were examined. We discovered a clear association with gene variants in the promoter of the NOS1AP gene, which codes for the nNOS activator protein (2). A frequent gene variant extends the QT interval by 3.5 ms (heterozygous genes) in 50 % of the population and by 7 ms (homozygous genes) in 10 % of the population. This makes it



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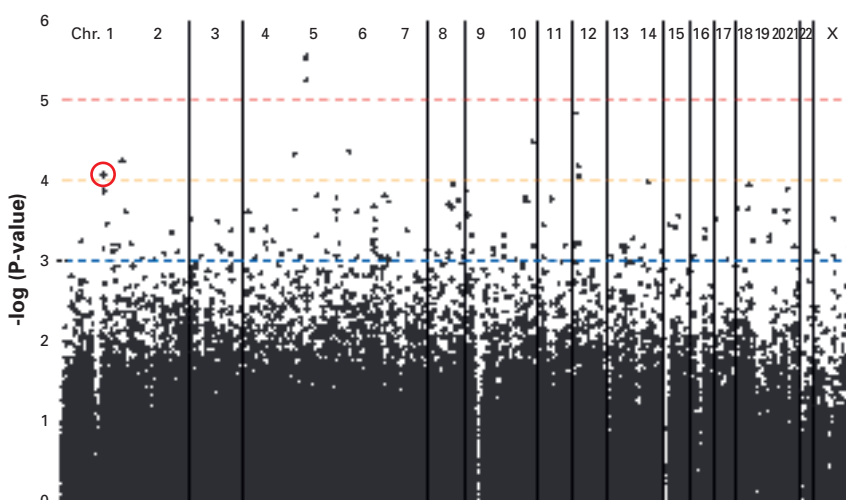
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the strongest known genetic factor for an ECG change.

Some first studies of a cohort of people who died of sudden cardiac death also showed an association in this respect. The risk of heterozygous carriers of the gene variant was 30 per cent higher than that of other people and that of homozygous carriers was nearly twice that of other people. We are currently conducting functional tests to elucidate the molecular mechanisms underlying this association.

Literature:

- (1) www.destatis.de
- (2) Arking, D.E., Pfeufer, A., Post, W., Kao, W.H.L., Newton-Cheh, C., Ikeda, M., West, K., Kashuk, C., Akyol, M., Perz, S., Jalilzadeh, S., Illig, T., Gieger, C., Guo, C.Y., Larson, M.G., Wichmann, H.E., Marbán, E., O'Donnell, C.J., Hirschhorn, J.N., Kääb, S., Spooner, P.M., Meitinger, M., Chakravarti, A.: A common genetic variant in the NOS regulator NOS1AP modulates cardiac repolarization, *Nature Genetics*, 2006; 38:644-651.



Level of significance for sequence variants influencing the QT interval:

Each dot stands for one of 100,000 sequence variants in the human genome (x-axis from chromosome 1 to the X chromosome). The corresponding P-values are plotted on the y-axis. The dot marked with a circle corresponds to the signal in the NOS1AP gene on chromosome 1.