LONG QT INTERVAL IN TURNER SYNDROME – A HIGH PREVALENCE OF LQTS GENE MUTATIONS

Christian Trolle, MD[1], Kristian Havmand Mortensen, MD[2], Lisbeth Nørum Pedersen, MSc, PhD[3], Agnethe Berglund, MD[1], Henrik Kjærulf Jensen, MD, PhD[4], Niels Holmark Andersen, MD, PhD[4] and Claus Højbjerg Gravholt, MD, PHD[1]

(1)Department of Endocrinology and Internal Medicine and Medical Research Laboratories, Aarhus University Hospital, Aarhus, Denmark, (2)Department of Radiology, Cambridge University Hospitals, Cambridge, United Kingdom, (3)Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark, (4)Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

1 Background

QT interval prolongation of unknown etiology is common in Turner syndrome (TS).

This study set out to explore the presence of known pathogenic long QT (LQT) mutations in TS and to examine the corrected QT interval (QTc) over time and relate the findings to the TS phenotype.

2 Methods

Adult females with Turner syndrome (n=88) were examined thrice and 68 age-matched healthy controls were examined once. QTc was measured by one blinded reader (intra-reader variability: 0.7%), and adjusted for influence of heart rate by Bazett's (bQTc) and Hodges's formula (hQTc).

The prevalence of mutations in genes related to Long QT syndrome was determined in females with Turner syndrome and a QTc >432.0 milliseconds (ms).

Echocardiographic assessment of aortic valve morphology, 24-hour blood pressures and blood samples were done.

3 Results

The mean hQTc in females with Turner syndrome (414.0±25.5 ms) compared to controls (390.4±17.8 ms) was prolonged (p<0.001) and did not change over time (416.9±22.6 vs. 415.6±25.5 ms; p=0.4).

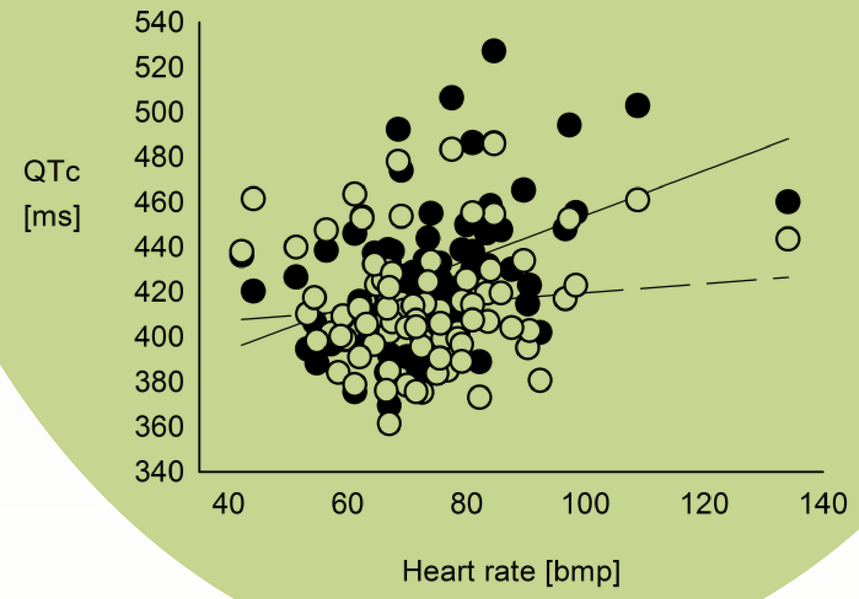
45,X karyotype was associated with increased hQTc prolongation compared to other Turner syndrome karyotypes (418.2±24.8 vs. 407.6±25.5 ms; p=0.03).

In females with Turner syndrome and a bQTc >432 ms, 7 had mutations in major Long QT syndrome genes (SCN5A and KCNH2) and one in a minor Long QT syndrome gene (KCNE2).

4 Figures

Mutations	QTc [ms]	
	Bazett	Hodges
KCNH2 (Definitely pathogenic)	468.7	444.3
KCNH2 (Uncertain pathogenic) KCNE2 (Likely pathogenic)	465.2	433.9
KCNH2 (Uncertain pathogenic)	464.8	435.8
KCNH2 (Uncertain pathogenic)	458.3	434.6
KCNH2 (Uncertain pathogenic)	453.5	427.6
SCN5A (Uncertain pathogenic)	453.4	452.6
SCN5A (Definitely pathogenic)	443.4	424.8
KCNH2 (Uncertain pathogenic)	432.0	415.6

Figure below. QTc in females with TS. Hodges's formula (open circles, dashed regression line, r2=0.012; p=0.3) compared to Bazett's formula (filled circles, solid regression line, r2=0.200; p<0.001).



5 Conclusion

There is a high prevalence of mutations in the major LQTS genes in females with TS and prolonged QTc.

However, it remains to be settled, whether these findings are related to the unexplained excess mortality in Turner women

Funding:
Danish Ministry for Science and Technology and Innovation, The Danish Heart Foundation, Novo Nordisk Foundation, Aase og Ejnar Danielsen Foundation, Korning Foundation, Hede Nielsens Foundation, Eva og Henry Frænkels Minde Foundation and Snedkermester Sophus Jacobsen og hustru Astrid Jacobsens Foundation