A gain of function *SLC4A3* mutation causes short QT syndrome

From molecular analysis to phenotypic expression and novel diagnostic testing

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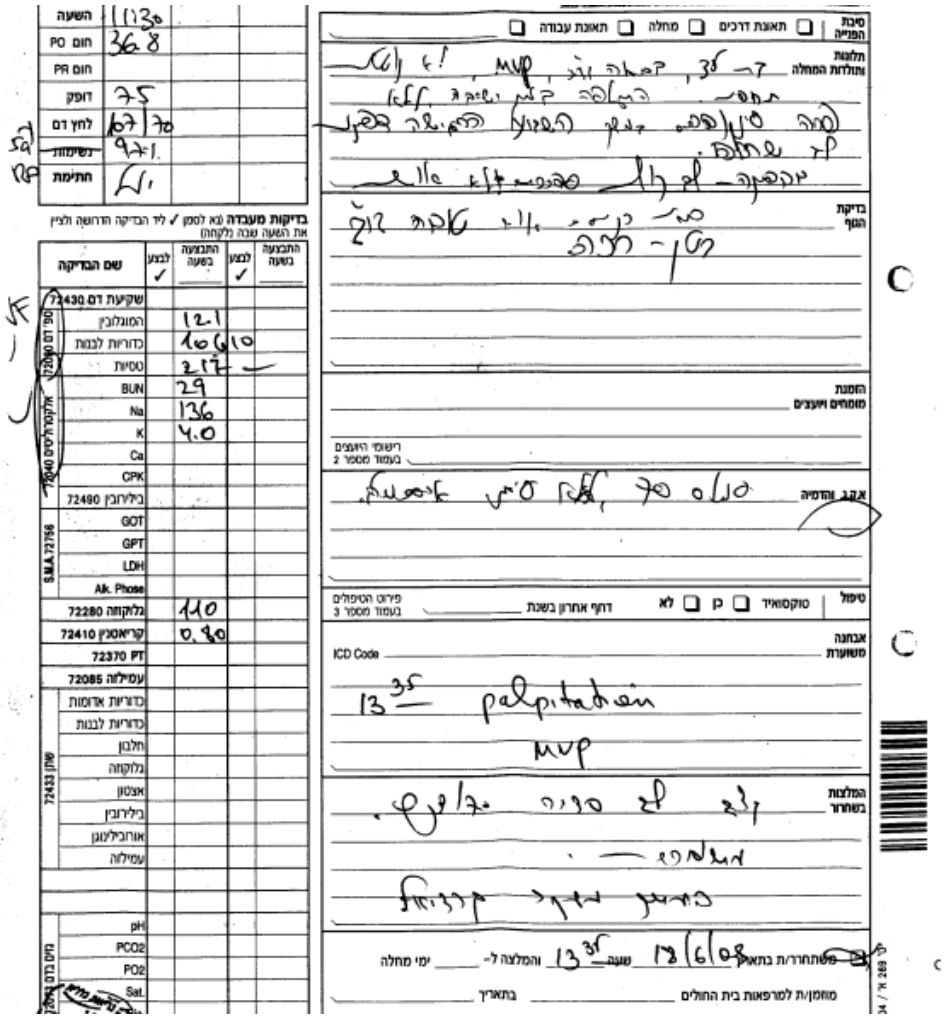
The proband

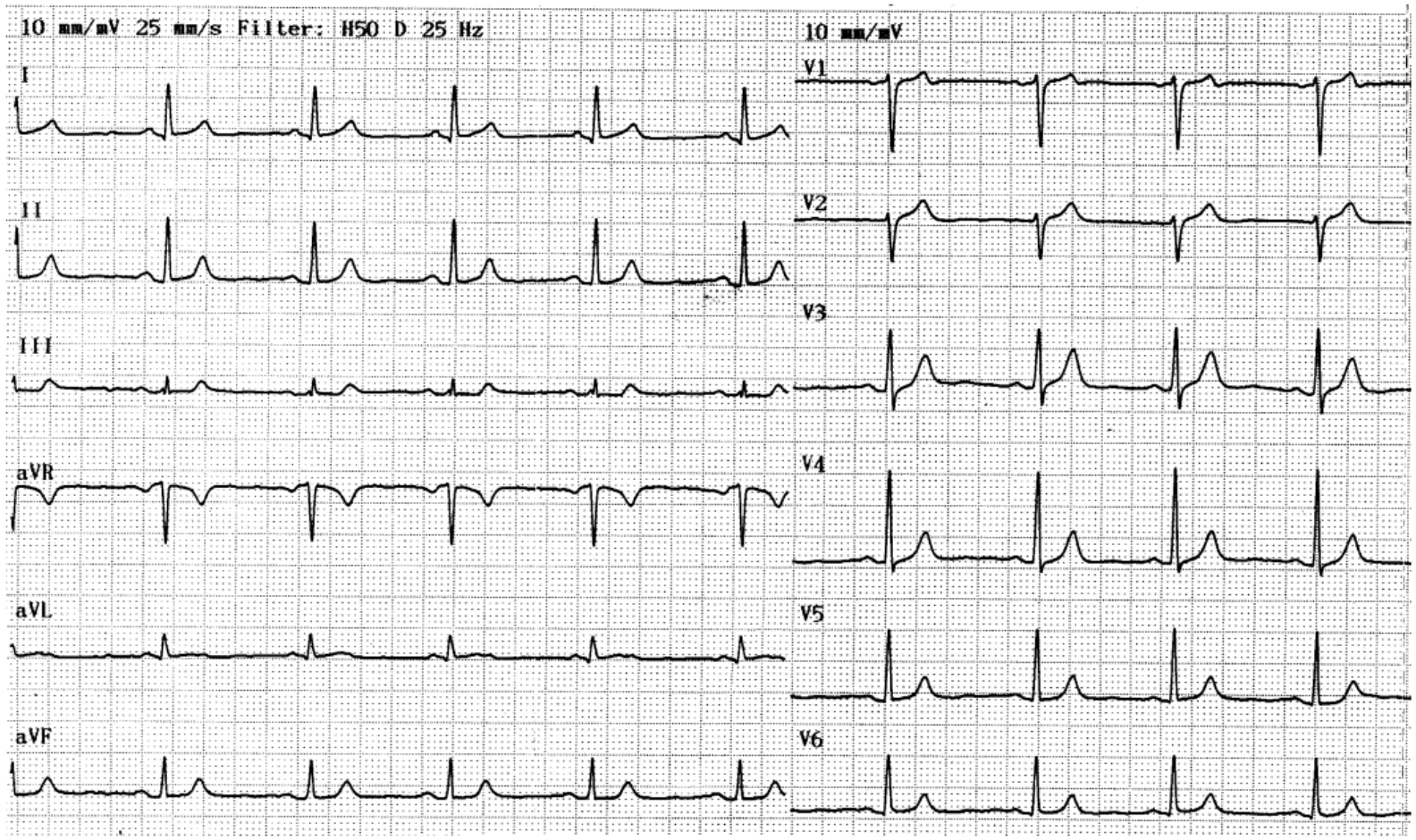
- Female, age 35
- Syncope during a phone conversation
- Discharged for further work-up

A.H.,
Female,
age 35



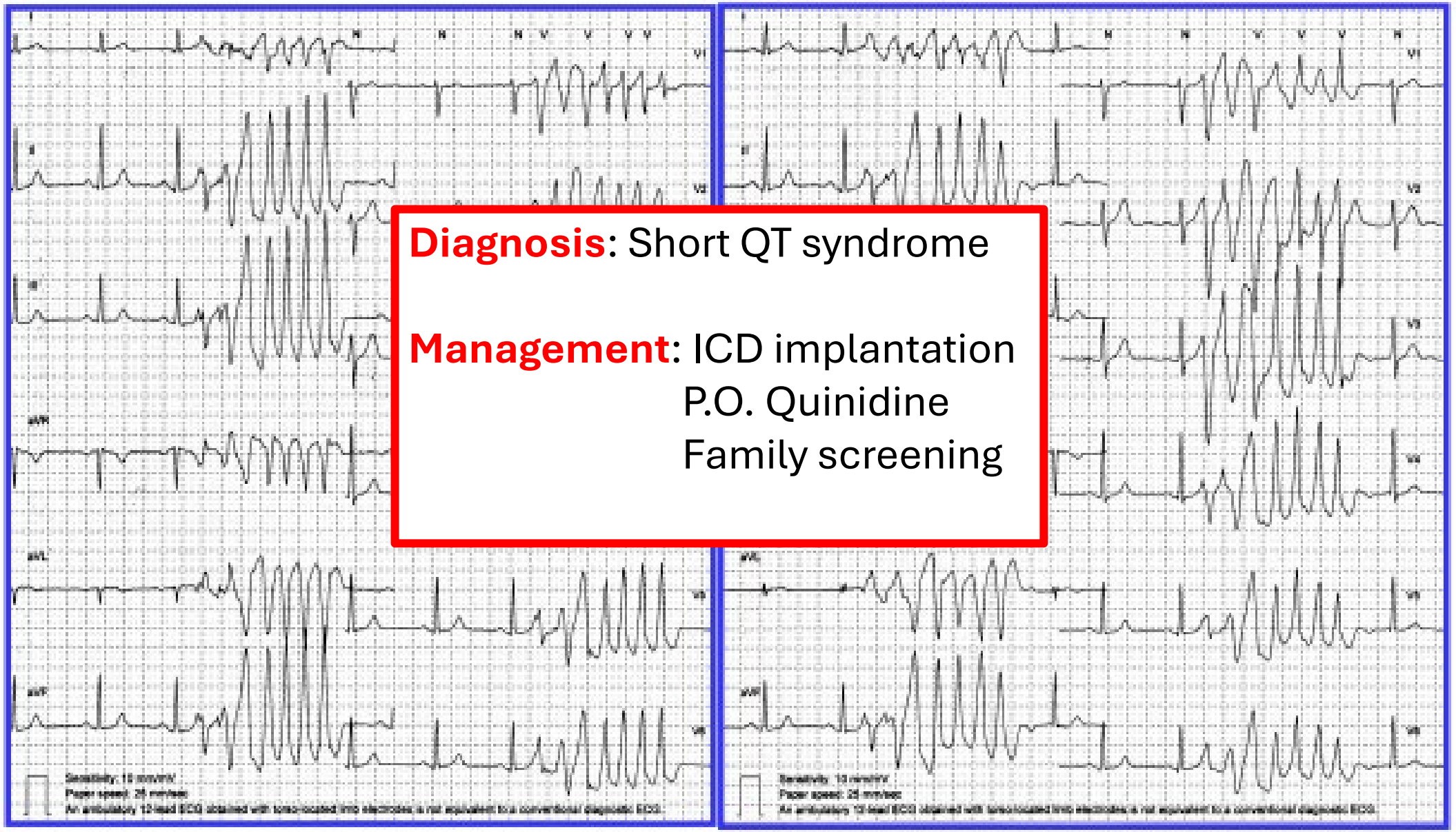
With courtesy of Prof. Sami Viskin

Resting ECG



RR 960 msec, QT 350 msec, **QTc 357 msec**

With courtesy of Prof. Sami Viskin



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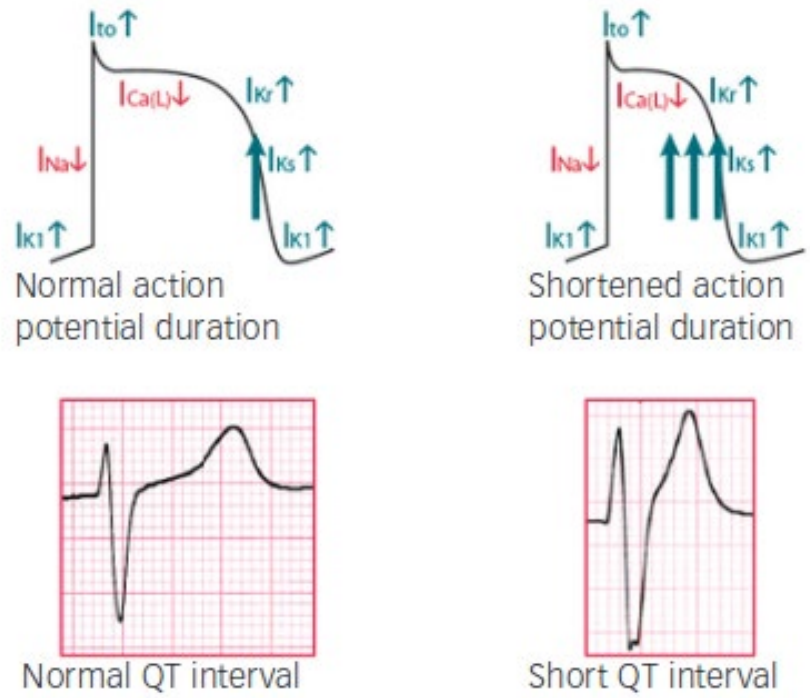
Congenital short QT syndrome (SQTS)

- A rare, heterogeneous genetic disorder first described two decades ago
- Poses a high risk of cardiac arrhythmias (AF, VT)
- May present as syncope cardiac arrest
- Initially classified as “channelopathy” (<u>increased</u> K^+ currents, <u>decreased</u> Ca^{2+} or Na^+ currents)
- Recently, mutations in *SLC4A3*, encoding anion exchanger 3 (AE3), were described



SHORT QT SYNDROME

Short QT syndrome is very rare compared to LQTS. The QTc is <360 ms and usually <300 ms. The genetic abnormality causes a gain of function of the potassium channel (I_{Kr}) or reduced inward depolarizing currents. The abnormality is associated with atrial fibrillation, polymorphic VT, and sudden death.

Fiorenzo Gaita et al. Circulation 2003

Hancox et al. Journal of Congenital Cardiology, 2019

Diagnosis of SQTS

Two QTc cut-off thresholds:

A. QTc ≤320 ms

or

B. QTc ≤360 ms combined with one or more of the following:

(a) a pathogenic mutation,

(b) a family history of SQTS,

(c) survival from a VT/VF episode in the absence of heart disease

Diagnosis		
It is recommended that SQTS is diagnosed in the presence of a QTc ≤360 ms and one or more of the following: (a) a pathogenic mutation, (b) a family history of SQTS, (c) survival from a VT/VF episode in the absence of heart disease.[1061,1068]	I	C
SQTS should be considered in the presence of a QTc ≤320 ms.[1064–1067,1073,1074]	IIa	C
SQTS should be considered in the presence of a QTc ≥320 ms and ≤360 ms and arrhythmic syncope.	IIa	C
SQTS may be considered in the presence of a QTc ≥320 ms and ≤360 ms and a family history of SD at age <40 years.	IIb	C

ESC Clinical Practice Guidelines, 2022

Pedigree and variant analysis

- A significant overlap of the QTc values between carriers and non-carriers

- A non-conservative *SLC4A3* mutation was identified and initially classified as a VUS

- R1016G was predicted to alter protein function by bioinformatic tools

Structure-function analysis

- An AE3 ”heterodimer” was modelled using SWISS-MODEL.

- R1016 is conserved and involved in conformational changes.

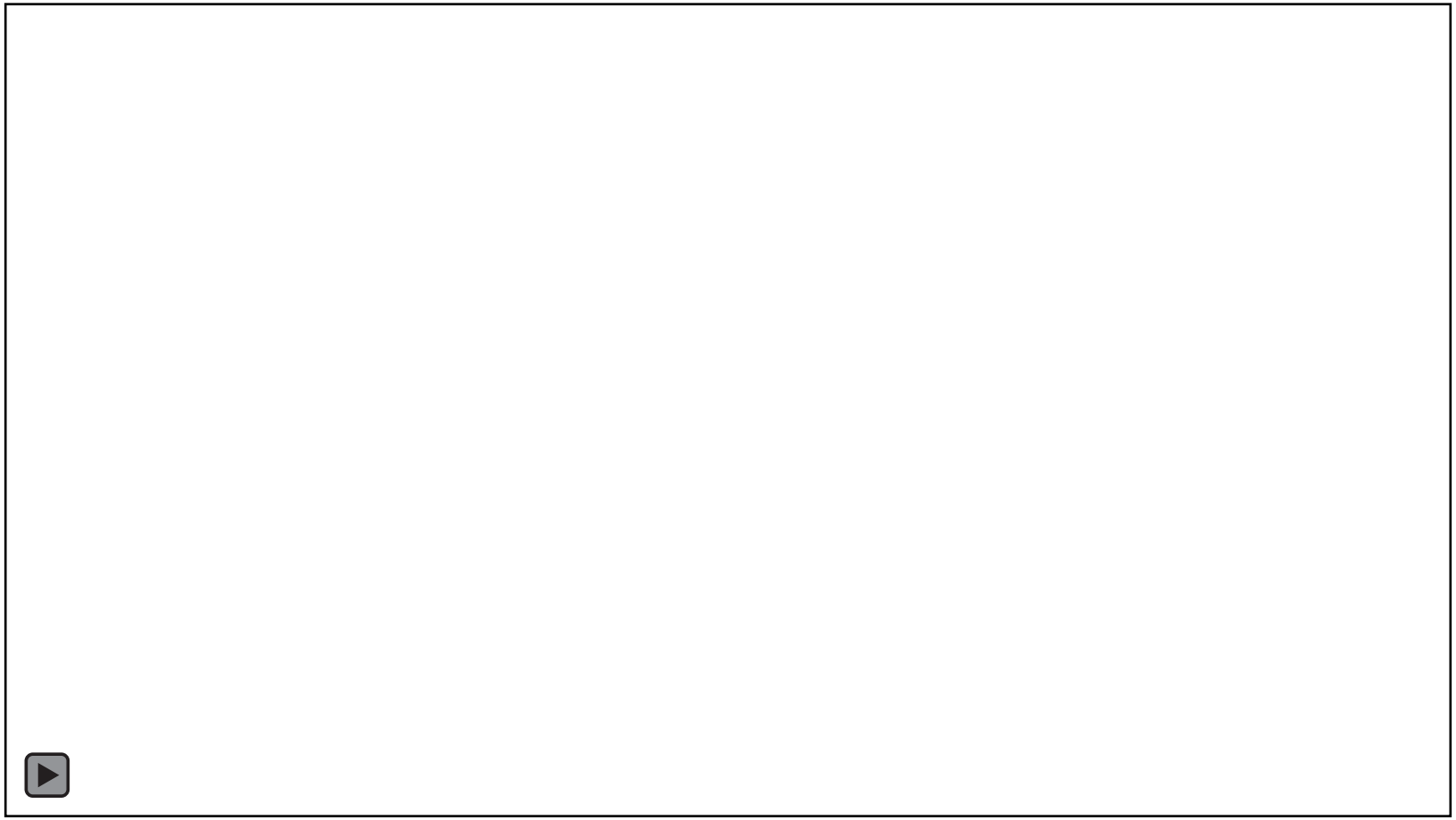
- R1016G results in a *gain of function* as opposed to previously described *loss of function* AE3 variants.

Diagnostic testing – resting ECG *vs* Holter

- Although statistically significant differences are observed, the populations largely overlap

- The difference is mainly derived from the males

The Ippon test



Provocative testing provides high diagnostic accuracy

Conclusions

- SQTS is characterized an increased risk for atrial and ventricular arrhythmias
- We identified a novel *SLC4A3* variant that causes a *gain of function* of the AE3
- We developed the “Ippon test” for the bedside diagnosis of SQTS, exposing insufficient QT-lengthening upon heart rate deceleration.
- Our novel provocative test allowed the identification of affected family members with high diagnostic accuracy.

Acknowldegments

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