Common variants in the KCNE1 and KCNH2 genes are independent risk alleles for cardiac arrhythmias.

Matteo Vatta[1], Rebecca Truty[1], John Garcia[1], Tom Callis[1], Swaroop Aradhya[1], Robert Nussbaum[1]

[1]Invitae, San Francisco, CA

BACKGROUND

- Three common variants, *KCNE1* p.Asp85Asn (rs1805128), *KCNH2* p.Arg176Trp (rs36210422) and *KCNH2* p.Lys897Thr (rs1805123), are widely classified as benign or likely benign.
- However, previous functional in vitro assays demonstrating various degrees of altered slow (IKs) and rapid (IKr) rectifier potassium current, as well as INa sodium current, suggests they may confer arrhythmia susceptibility.
- As a result, these variants have received conflicting interpretations based on current guidelines.

OBJECTIVE

- To test the hypothesis that these variants confer an increased risk for cardiac arrhythmias.

METHODS

- We performed a retrospective review of over 90,000 de-identified patients who underwent diagnostic testing at Invitae.
- We identified a cohort of 1,987 subjects who had been specifically tested for the LQTS panel (including *KCNE1* and *KCNH2*) and a subcohort of 1,571 out of the 1,987 patients who were found not to have any pathogenic/likely pathogenic (P/LP) variants detected in the LQTS panel.
- The remaining patients without a known cardiovascular phenotype and who had *KCNE1* or *KCNH2* genes sequenced in the background served as an internal patient control group.
- The allele frequencies of rs1805128, rs36210422 and rs1805123 were determined in each of these patient cohorts and also in gnomAD to serve as a second, population-based, control group.
- A limitation of this analysis is that there is insufficient data on the ethnic background of the tested patients to assess or correct for stratification.
- Odds Ratios with 95% confidence intervals were calculated according to Sheskin DJ (2011).

RESULTS

- The rs1805128, rs36210422 and rs1805123 variants were detected in 109 (5.5%), 12 (0.6%) and 611 (30.7%) of the 1,987 subjects specifically tested for the LQTS panel respectively.
- When compared to our internal patient controls, rs1805128 and rs36210422 minor alleles were statistically significantly over-represented with p<0.0001 in patients for whom LQTS was ordered and even more so among patients in whom no other explanatory variants were found in the LQTS genes.
- In contrast, rs1805123 is under-represented with OR 0.806, in patients for whom LQTS was ordered, and more so among patients in whom no other explanatory variants were found in the LQTS genes.
- When compared to the gnomAD data, these variants were statistically significantly over/under-represented in patients for whom LQTS was suspected as well as in patients in whom no other explanatory variants were found in the LQTS genes.

Table 1. Analysis of functional SNPs in our cohort of subject for whom LQTS test was ordered and subject with negative LQTS panel compared to Internal controls and population controls (gnomAD)

Variant	Cohort	Internal control OR	95% C.I.	gnomAD OR	95% C.I.
rs1805128	LQTS ordered	2.65	2.16-3.21	3.11	2.55-3.77
rs1805128	Undiagnosed LQTS	2.91	2.35-3.58	3.42	2.76-4.20
rs36210422	LQTS ordered	9.83	4.81-18.48	7.45	3.58-14.38
rs36210422	Undiagnosed LQTS	11.41	5.40-21.92	8.65	4.02-17.04
rs1805123	LQTS ordered	0.81	0.74-0.88	0.91	0.83-0.99
rs1805123	Undiagnosed LQTS	0.79	0.72-0.87	0.89	0.81

Figure 1. MAF and OR for the *KCNE1* p.Asp85Asn (rs1805128) variant for the three patients cohorts and the two control cohorts.

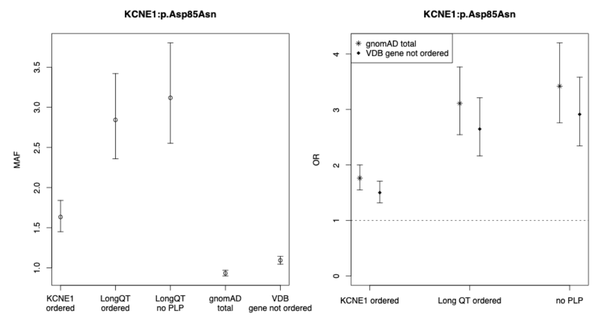


Figure 2. MAF and OR for the *KCNH2* p.Arg176Trp (rs36210422) variant for the three patients cohorts and the two control cohorts.

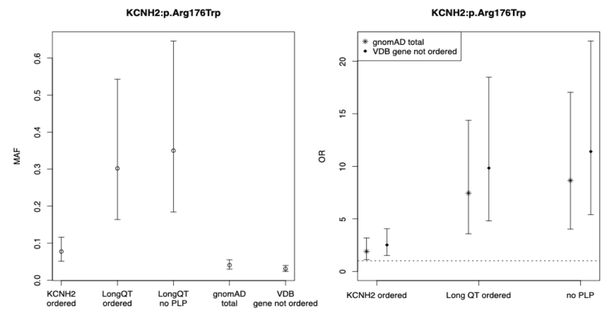
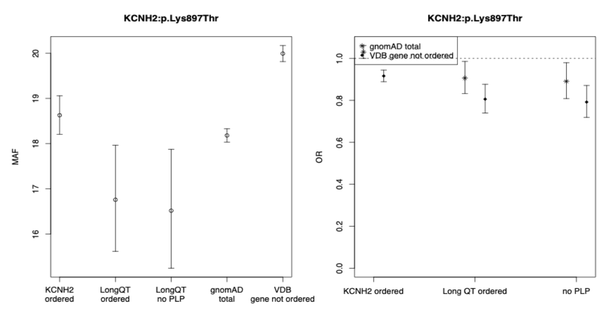


Figure 3. MAF and OR for the *KCNH2* p.Lys897Thr (rs1805123) variant for the three patients cohorts and the two control cohorts.



ADDITIONAL ANALYSIS

- In addition to the variants in *KCNE1* (p.Asp85Asn) and *KCNH2* (p.Arg176Trp and p.Lys897Thr), we sought to determine whether other previously published variants associated with cardiac arrhythmias could be independent risk alleles.
- We analyzed the following variants in *KCNE2* (p.Gln9Glu, p.Ile57Thr, and p.Thr8Ala), *KCNH2* (p.Arg1047Leu), *KCNQ1* (p.Gly643Ser), and *SCN5A* (p.Arg1193Gln, p.Arg481Trp, p.His558Arg, p.Pro1090Leu, p.Pro2006Ala, p.Ser1103Tyr, p.Ser1787Asn, p.Ser524Tyr)
- However, none of those variants reached statistical significance when in the LQTS cohort compared to internal and general controls

CONCLUSIONS

- This study suggests that the minor alleles in rs1805128 and rs36210422 and the major allele in rs1805123 are enriched among patients in whom LQTS is suspected compared to a patient control groups or the gnomAD population cohort.
- It suggests rs1805128 and rs3621042 are independent risk alleles for the susceptibility to cardiac arrhythmias, rather than being benign variants. In contrast, the minor allele in rs1805123 may be protective against LQTS.
- This study indicates that case/control data from a clinical testing laboratory may be used to provide evidence that common functional variants can have a significant impact on the risk for LQTS and the classification of these common functional variants should be revised accordingly.

Reference: Sheskin DJ (2011) Handbook of parametric and nonparametric statistical procedures. 5th ed. Boca Raton: Chapman & Hall /CRC

Disclosures: M.V., R.T., J.G., T.C., S.A, and R.N. are stockholders and employees of Invitae.