The common variant rs1805128 in the *KCNE1* gene is an independent risk allele 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

- The common variant p.Asp85Asn in *KCNE1* (rs1805128, NM_000219.5: c.253G>A) is widely considered to be a benign/likely benign variant.
- However, previous functional assays have demonstrated that p.Asp85Asn modestly reduces the slow (IKs) and rapid (IKr) rectifier potassium current in vitro and is associated with QTc prolongation and risk of drug-induced torsades de pointes.
- Furthermore, previous reports in a small cohort suggested that p.Asp85Asn may lead to a mild form of Long QT Syndrome (LQTS).
- As a result, the variant has received conflicting interpretations in ClinVar based on ACMG variant interpretation guidelines that range from benign to pathogenic. To test the hypothesis that the p.Asp85Asn variant confers increased risk for cardiac arrhythmias, we examined whether the variant is over-represented in patients referred for LQTS testing compared to controls.

METHODS

- We performed a retrospective review of 84,758 de-identified patients who underwent diagnostic testing at Invitae, identifying two cohorts (Table 1).
- The first consisted of 7,545 patients with various cardiovascular phenotypes for whom *KCNE1* sequencing was performed as part of a comprehensive cardiovascular genetics panel consisting of 150 genes or as part of a smaller LQTS-specific panel consisting of 17 genes.
- We also analyzed two nested sub-cohorts of these 7,545 patients: 1,821 patients, specifically tested for the LQTS panel and 1,439 of these 1,821 subjects tested for the LQTS panel who had no pathogenic/likely pathogenic (P/LP) variants detected besides rs1805128.
- The second cohort consisted of the remaining 77,213 patients without a known cardiovascular phenotype, and for whom *KCNE1* was not requisitioned but sequenced incidentally, thus serving as an internal patient control group.
- The allele frequency of rs1805128 was determined in all patient cohorts and compared to gnomAD as a second, population-based, control group.
- Odds Ratios (OR) with 95% confidence intervals were calculated according to Sheskin DJ (2011).

RESULTS

- The rs1805128 variant was detected in 251/7,545 (3.33%) patients for whom *KCNE1* was ordered and in 1706/77,213 (2.21%) of the internal patient control group.
- The rs1805128 variant was over-represented at a statistical significance level of p<0.0001 in patients for whom *KCNE1* was ordered for any reason (OR 1.52, 95% C.I. 1.33-1.74), even more so among patients in whom LQTS was suspected (OR 2.65, 95% C.I. 2.16-3.21), and most highly enriched in patients in whom no other explanatory variants were found in the LQTS genes (OR 2.91, 95% C.I. 2.35-3.58).
- When compared to gnomAD data, (2637/282814 alleles; 0.93%), rs1805128 was statistically significantly over-represented at p<0.0001 in patients for whom *KCNE1* was ordered for any reason (OR 1.83, 95% C.I. 1.60-2.09), even more so among patients in whom LQTS was suspected (OR 3.11 95% C.I. 2.55-3.77), and was most highly enriched in patients in whom no other explanatory variants were found in the LQTS genes (OR 3.42, 95% C.I. 2.76-4.20).
- Although limited statistics did not allow for a meaningful analysis in different ethnic groups, an analysis that was restricted to only self-reported white/caucasians showed consistent results with p<0.001 for all six ORs

Table 1

KCNE1 rs1805128 status (homozygous, heterozygous or negative) in Cases vs Internal Controls

	rs1805128 hom	rs1805128 het	rs1805128 negative	Total
KCNE1 requisitioned for any reason as part of a comprehensive panel	5	246	7,249	7,545
LQTS specifically requisitioned due to suspicion of LQTS	3	99	1,719	1,821
LQTS specifically requisitioned and no other genetic cause of arrhythmia found	3	85	1,351	1,439
Internal Patient Control	10	1696	75,507	77,213

Figure 1

Graphic representation of the MAF analysis and the determination of "OR" for the *KCNE1* rs1805128 variant for the three patients cohorts and the two cohorts of controls.

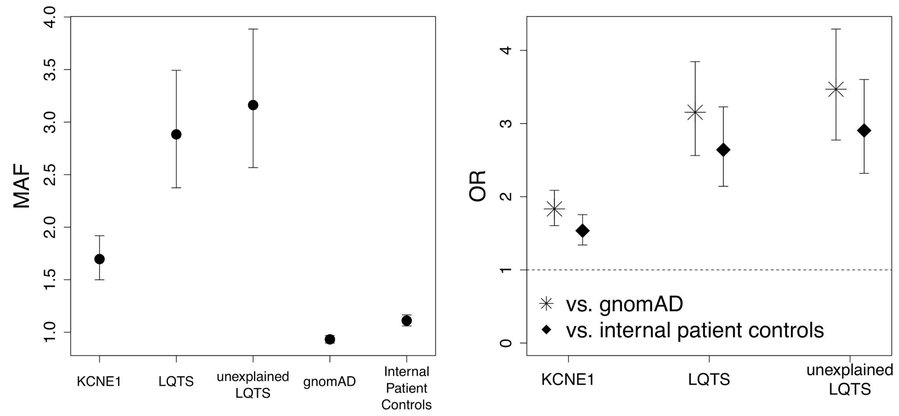

Table 2

OR calculation and 95% CI interval determination for the *KCNE1* rs1805128 variant in Cases vs Internal Controls

	Versus internal Patient Controls		
	OR	95% C.I.	p
KCNE1 requisitioned for any reason as part of a comprehensive panel	1.54	1.34-1.75	<0.0001
LQTS specifically requisitioned due to suspicion of LQTS	2.64	2.14-3.23	<0.0001
LQTS specifically requisitioned and no other genetic cause of arrhythmia found	2.91	2.32-3.60	<0.0001

Table 3

OR calculation and 95% CI interval determination for the *KCNE1* rs1805128 variant in Cases vs External Controls (gnomAD)

	Versus gnomAD		
	OR	95% C.I.	p
KCNE1 requisitioned for any reason as part of a comprehensive panel	1.83	1.60-2.09	<0.0001
LQTS specifically requisitioned due to suspicion of LQTS	3.15	2.56-3.85	<0.0001
LQTS specifically requisitioned and no other genetic cause of arrhythmia found	3.47	2.77-4.29	<0.0001

CONCLUSIONS

- rs1805128 is enriched among patients referred for clinical genetic testing in whom LQTS is suspected compared to internal controls and compared to the gnomAD population cohort.
- rs1805128 is not a benign variant, but instead a risk allele for susceptibility to cardiac arrhythmias.
- The data presented here about rs1805128 calls for a unifying classification of this variant in large databases such as ClinVar.
- Large case/control data provide evidence that common functional variants can confer a significant risk to human health and their classification should be revised accordingly.

References:
1. Nishio Y, Makiyama T, Itoh H, et al., D85N, a KCNE1 polymorphism, is a disease-causing gene variant in long QT syndrome. J Am Coll Cardiol. 2009 Aug 25;54(9):812-9. doi: 10.1016/j.jacc.2009.06.005. PMID: 19695459
2. Kääb S, Crawford DC, Sinner MF, et al., A large candidate gene survey identifies the KCNE1 D85N polymorphism as a possible modulator of drug-induced torsades de pointes. Circ Cardiovasc Genet. 2012 Feb 1;5(1):91-9. doi: 10.1161/CIRCGENETICS.111.960930. Epub 2011 Nov 18. PMID: 22100668
3. Hasegawa K, Ohno S, Itoh H, et al. A rare KCNE1 polymorphism, D85N, as a genetic modifier of Long QT Syndrome. Journal of Arrhythmia, 30 (2014): 161-166. doi: 10.1016/j.joa.2013.08.004.

Disclosures: Authors are stockholders and employees of Invitae.