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RESPONSE TO LETTER TO THE EDITOR

Response by Wilde and Gollob to Letter Regarding Article, "Reappraisal of Reported Genes for Sudden Arrhythmic Death: Evidence-Based Evaluation of Gene Validity for Brugada Syndrome"

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In Response:

Dr London expresses concerns regarding the conclusion that the *GPD1L* gene lacks sufficient evidence to support causality for Brugada syndrome (BrS).[1] We are pleased to elaborate on the details leading to this unanimous conclusion from 19 authors, including genomic scientists, clinical geneticists, genetic counsellors, and inherited arrhythmia specialists. In their 2007 article reporting *GPD1L* as a causative gene in familial BrS, London and colleagues indicated that fine mapping reduced a linked region of 15 cM to a region of 1 million base pairs (bp), although no details are provided.[2] The authors state that 6 genes were within their reported 1 million bp–linked region: *KCNH8, DNLC1, PLCD1, GPD1L, TGFB2* (presumably *TGFBR2* as *TGFB2* is on chromosome 1), and *C3orf3* (now known as *HHATL*).[2] The structure of the human genome on chromosome 3 incorporating these reported linked genes does not seem compatible with a shared region of only 1 million bp. The genome maps of 2006 and 2018 are in agreement, indicating that the 2 most distant linked genes (*KCNH8* and *HHATL*) are at least 23 million bp apart and encompass >300 genes.[3] Furthermore, within this 23–million bp region resides *SCN5A*, the most common cause for BrS. Dr London and colleagues state that *SCN5A* was ruled out as a cause (in addition to being considered not within the shared region) by screening the gene by using denaturing high-performance liquid chromatography. This mutation-screening technique has been shown to have a sensitivity as low as 70% for mutation detection.[4] The common frequency of their reported p.A280V-*GPD1L* variant causing 16 affected cases in a family is challenging to reconcile with the high general population frequency of this variant observed in the gnomAD database (1/2500 Europeans). A disease-causing variant so common would suggest a significant role for *GPD1L*, and even this specific variant, as a cause for BrS, yet variants in *GPD1L* do not occur at any excess frequency in BrS cases versus controls, and penetrant families with *GPD1L*-related BrS have never again been reported or identified in hundreds of cases followed in the clinics from our authors. Finally, reporting alterations in sodium channel current cannot be considered evidence for causality, because even common polymorphisms within *SCN5A* induce functional changes consistent with those reported for putative mutations.[5]

Dr London suggests that genes lacking rigorous scientific evidence to support causality should remain on clinical testing panels and that removing them may adversely affect care. To this sentiment, we cannot disagree strongly enough. Applying a genetic test that may conclude a life-changing diagnosis, require intervention, create life-long anxiety, and impact asymptomatic family members should mandate that such a test meets a standard of clinical validity before use in patient care. Otherwise, the risk of undue

harm from incorrect interpretation cannot be justified. The large-volume clinics in Amsterdam and Toronto only test *SCN5A* in BrS, despite the option for large panel testing. Recognition in clinical genetics of genes with questionable disease causality in all areas of medicine spurred the National Institutes of Health funding of $25 million to serve the mandate of now 750 investigators reevaluating reported gene-disease associations.

ARTICLE INFORMATION

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Disclosures

None.

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