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LETTER TO THE EDITOR

Contribution of rare genetic variants to heart failure and cardiomyopathy in the UK Biobank

Heart failure (HF) is a major global health burden.[1] HF risk factors are hypertension, coronary heart disease, diabetes, obesity and valvular heart disease. HF aggregates in families and genome wide association studies have identified several HF variants.[1] Cardiomyopathy is a relatively rare disease of the heart muscle and is one of many causes of HF. Cardiomyopathy is classified into dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy.[2] Many genes and rare genetic variants have been linked to cardiomyopathy. Whether rare variants also are involved in HF is unknown.[1] Few large-scale whole exome sequencing (WES) studies have been published until Wang *et al*. reported the relationships between rare protein-coding variants and 17 361 binary phenotypes using WES data from 269 171 UK Biobank participants (https://azphewas.com/).[3] Gene-based collapsing analyses revealed 1703 statistically significant gene–phenotype associations for binary traits. Recently, Karczewski *et al*. also determined gene-based association investigating 4529 phenotypes in 394 841 UK Biobank exomes (https://app.genebass.org/).[4]

We used the two published UK Biobank portals (https://azphewas.com/ and https://app.genebass.org/)[3,4] to access gene-collapsing analysis of rare variation for HF and cardiomyopathy (*Table 1*). We therefore did not obtain ethical approval. The significance levels used in the two portals and published studies were stringent.[3,4] In order not to discard potential candidate genes, we present genes with *P*-vales $<0.05/20\ 000$ genes $= 2.5 \times 10^{-6}$ commonly used for WES studies. In *Table 1*, only the genes with genome wide significant results are shown with *P*-values for the best significant model. Four previously identified cardiomyopathy genes (*TTN*, *MYH7*, *MYBPC3* and *DSP*) and one novel candidate cardiomyopathy gene (*MAGOHB*) were identified. Six novel genes were associated with common HF (*TTN*, *FLNC*, *TET2*, *ASXL1*, *MYBPC3* and *SEMA3G*). *TTN*, *MYBPC3* and *FLNC* genes have previously been linked to cardiomyopathy suggesting similar mechanisms to be involved in HF. *SEMA3G* has

Table 1 Results of gene collapsing analysis of rare variants for heart failure (HF) and cardiomyopathy according to three-digit ICD-10 codes

ICD-10 codes and names of studied phenotypes	Astra Zeneca portal	Genebass (LOF)	Genebass (missense/LC)
I11 Hypertensive heart disease	NS	NS	NS
I13 Hypertensive heart and renal disease	NS	ND	ND
I42 Cardiomyopathy	*TTN* 2.16e-60[a] *MYBPC3* 7.28e-24[a] *MYH7* 3.40e-15[a] *DSP* 8.19e-11[a]	*MYBPC3* 2.09e-27[a] *DSP* 2.11e-7[a]	*MYH7* 4.12e-13[a] *MAGOHB* 3.51e-7
I43 Cardiomyopathy in diseases classified elsewhere	NS	ND	ND
I50 Heart failure	*TTN* 5.97e-27[a] *FLNC* 6.17e-7[a] *TET2* 6.54e-7[b] *ASXL1* 1.05e-6[b]	*MYBPC3* 2.03e-6[a]	*SEMA3G* 2.17e-6
J81 Pulmonary oedema	NS	NS	NS

Union was used to define phenotypes for https://azphewas.com. Only genome wide significant associated genes are shown (best model), that is, $P < 2.5 \times 10^{-6}$. Significance threshold was *P*-values $<0.05/20\ 000$ genes $= 2.5 \times 10^{-6}$ commonly used for whole exome sequencing (WES) studies. For Genebass portal (https://app.genebass.org), the highest values for SKAT-O, SKAT or burden test are shown. For Astra Zeneca portal (https://azphewas.com), the highest *P*-value of the 12 tested models is shown.
ICD-10, International Classification of Diseases 10th Revision; LoF, high-confidence loss of function variants indicated by LOFTEE[4]; Missense/LC, missense variants are grouped with in-frame insertions and deletions, as well as low-confidence LoF variants filtered out by LOFTEE.[4] The latter have a frequency spectrum consistent with missense variation and affect a set of amino acids in a similar way;[4] ND, not determined; NS, no genome wide significant gene.
[a]Genes previously linked to cardiomyopathy according to OMIM (https://www.omim.org/).
[b]*TET2* and *ASXL1* genes have been associated with myelodysplastic syndrome (MDS) (https://www.omim.org/) and clonal haematopoiesis of indeterminate potential (CHIP).[5]

previously not been linked to any disease (https://varsome.com/ and https://www.omim.org/). *TET2* and *ASXL1* genes have been linked to myelodysplastic syndrome and mastocytosis (https://varsome.com/ and https://www.omim.org/). Interestingly, clonal haematopoiesis of indeterminate potential defined as clonally expanded leukemogenic sequence variations (in *DNMT3A*, *TET2*, *ASXL1* and *JAK2*) have been associated with HF.[5]

In conclusion, five genes were associated with cardiomyopathy and six genes with HF in UK Biobank. This suggests that rare variation in several genes is linked both to cardiomyopathy and HF. Classical cardiomyopathy genes may be involved in heart failure. The association with *TET2* and *ASXL1* suggests clonal haematopoiesis of indeterminate potential might be involved in HF.

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