Insights into the genetic architecture underlying complex, critical congenital heart disease

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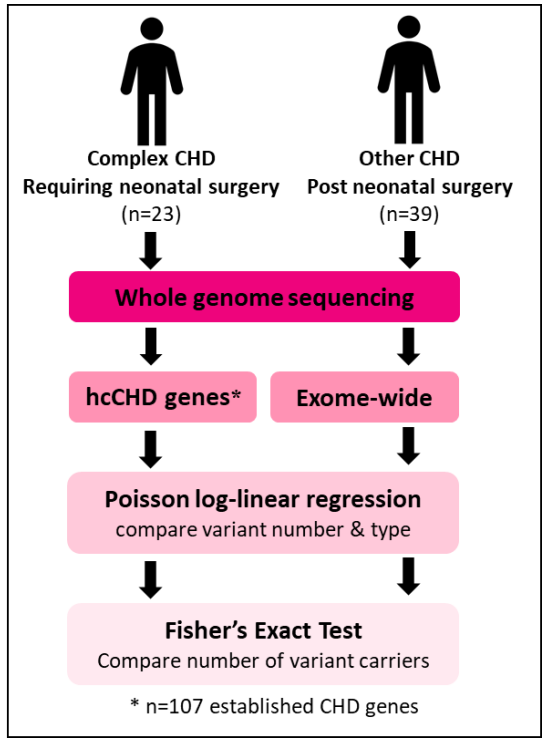
Background

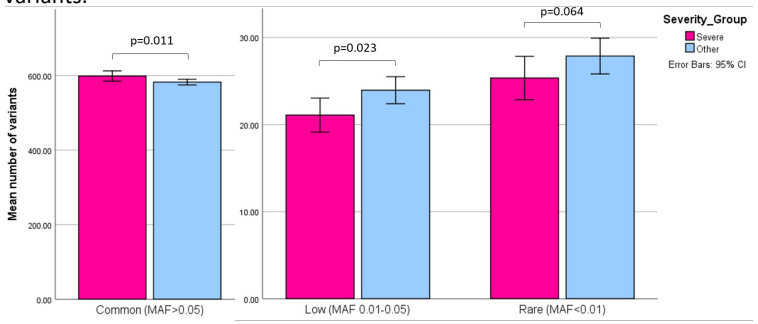
Congenital heart disease (CHD) has a multifactorial aetiology, raising the possibility of an underlying genetic burden, predisposing to disease but also variable expression, including variation in disease severity, and incomplete penetrance. Understanding the heritable component contributing to reduced penetrance and variable expression to prevent/ameliorate disease severity in future generations, is important and relevant to the aging CHD population.

Method

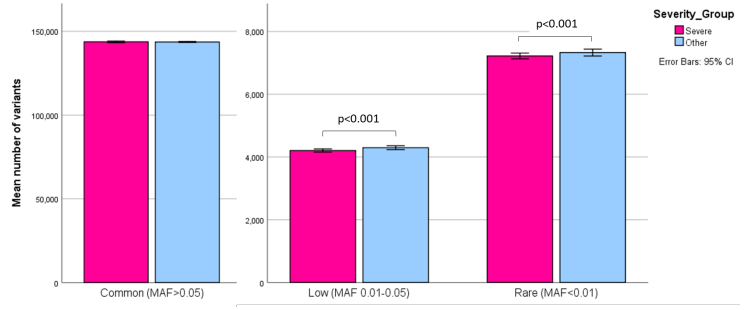


Results

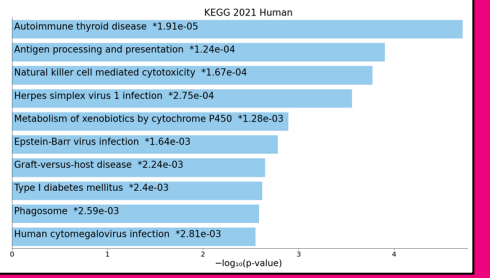
hcCHD gene analysis: Significantly more common variants in severe CHD compared with other CHD and significantly fewer rare and low-frequency variants.



Exome-wide analysis: Significantly less rare and low-frequency variants in severe CHD cases compared with other CHD.



Gene-based variant burden: Significantly implicated pathways among rare and low-frequency variants, included '*Autoimmune thyroid disease*' and '*Type 1 Diabetes Mellitus*'.



Conclusion

These preliminary findings suggest that the genetic architecture of complex, critical CHD is distinct from other types of CHD due to a significant increase in common variation, specifically among hcCHD genes. Further, these findings highlight associations with regulatory genes and environmental 'stressors' (modifiable factors affecting the fetal-placental-maternal environment) involved in the final presentation of disease. Validation in larger cohorts, may clarify the contribution of modifying variants and their effects on variable expression, specifically relating to disease severity.

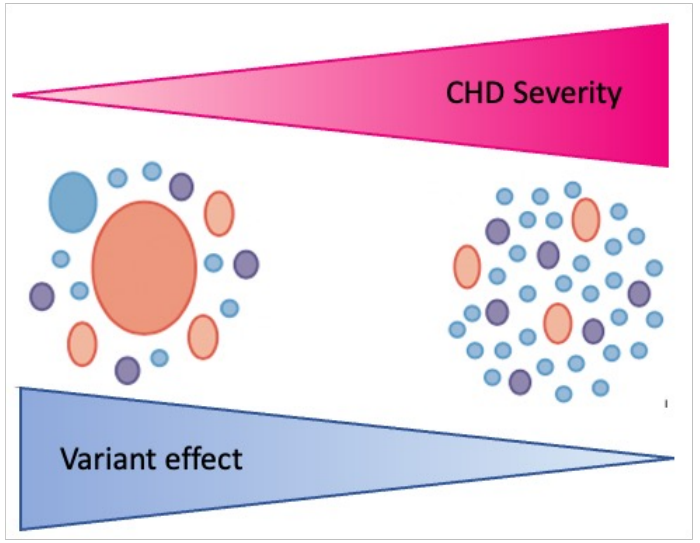


Figure description: Variant effect sizes and association with disease severity where each circle represents a contributing variant, and its size the effect of the variant on the phenotype.

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