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Exome Sequencing and Congenital Heart Disease in Sub-Saharan Africa

Ekanem N Ekure [#] [1], Adebowale Adeyemo [#] [2], Hanhan Liu [3], Ogochukwu Sokunbi [1], Nnenna Kalu [1], Ariel F Martinez [4], Babajide Owosela [4], Cedrik Tekendo-Ngongang [4], Yonit A Addissie [4], Akinsanya Olusegun-Joseph [5], Desmond Ikebudu [6], Seth I Berger [7], Maximilian Muenke [4], Zhe Han [3], Paul Kruszka [4]

Affiliations

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Abstract

Background: Congenital heart disease (CHD) is the most common birth defect and affects roughly 1% of the global population. There have been many large CHD sequencing projects in developing countries but none in sub-Saharan Africa. In this exome sequencing study, we recruited families from Lagos, Nigeria, affected by structural heart disease.

Methods: Ninety-eight participants with CHD and an average age of 3.6 years were recruited from Lagos, Nigeria. Exome sequencing was performed on probands and parents when available. For genes of high interest, we conducted functional studies in *Drosophila* using a cardiac-specific RNA interference-based gene silencing system.

Results: The 3 most common CHDs were tetralogy of Fallot (20%), isolated ventricular septal defect (14%), and transposition of the great arteries (8%). Ten percent of the cohort had pathogenic or likely pathogenic variants in genes known to cause CHD. In 64 complete trios, we found 34 de novo variants that were not present in the African population in the Genome Aggregation Database (v3). Nineteen loss of function variants were identified using the genome-wide distribution of selection effects for heterozygous protein-truncating variants (s_{het}). Nine genes caused a significant mortality when silenced in the *Drosophila* heart, including 4 novel disease genes not previously associated with CHD (*UBB, EIF4G3, SREBF1*, and *METTL23*).

Conclusions: This study identifies novel candidate genes and variants for CHD and facilitates comparisons with previous CHD sequencing studies in predominantly European cohorts. The study represents an important first step in genomic studies of CHD in understudied populations. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01952171.

Keywords: Drosophila; Nigeria; Tetralogy of Fallot; exome; heart disease.

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