Session P05 - Cardiovascular disorders

Add To Itinerary

P05.61A - Determination of disease-associated genes and gene-sets in Tetralogy of Fallot

June 16, 2019, 10:15 AM - 11:15 AM | Posters P05

Authors

R. Manshaei[1], M. S. Reuter[1,2], B. A. Mojarad[3], G. Pellecchia[2], M. Zarrei[2], R. Chaturvedi[1,4], A. S. Bassett[5,6,7,8], R. Kim[1,9,10], D. Merico[2,11];

[1]Ted Rogers Centre for Heart Research, Cardiac Genome Clinic, The Hospital for Sick Children, Toronto, ON, Canada, [2]The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, ON, Canada, [3]Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada, [4]Labatt Heart Centre, Division of Cardiology, The Hospital for Sick Children, Toronto, ON, Canada, [5]Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada, [6]Division of Cardiology, Toronto Congenital Cardiac Centre for Adults at the Peter Munk Cardiac Centre, Department of Medicine, University Health Network, Toronto, ON, Canada, [7]The Dalglish Family 22q Clinic for Adults with 22q11.2 Deletion Syndrome, Department of Psychiatry, and Toronto General Research Institute, University Health Network, Toronto, ON, Canada, [8]Department of Psychiatry, University of Toronto, Toronto, ON, Canada, [9]Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, ON, Canada, [10]Fred A. Litwin Family Centre in Genetic Medicine, University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada, [11]Deep Genomics Inc., Toronto, ON, Canada.

Disclosures

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Abstract

Introduction: Genes and pathways are analyzed for excess of ultra-rare truncating and missense variants in Tetralogy of Fallot using a binomial test comparing observed variation rates to background de-novo mutation rates. This method doesn't require matched controls. **Materials and Methods:** Since original background mutation rates were estimated for de-novo variants, we applied a scaling factor to obtain new probabilities P'=k*P; factor k was computed so that the number of predicted and observed ultra-rare variants match. We applied the same method pooling expected probabilities and observed variants by pathway, to boost power. We addressed the problem of gene-set correlations by using a greedy-step-down-aggregation approach; and computed a sampling-based FDR only for aggregated gene-sets. We tested gene-sets derived from Gene Ontology and pathways, and MPO annotation of human orthologs in mouse. **Results:** By applying this method to genes predicted haploinsufficient, we found significant genes: FLT4 (BH-FDR~0%), NOTCH1 (BH-FDR~0.5%), and etc. For Gene Ontology and pathways, we found the VEGF and related pathways (FDR~0%, including FLT4,KDR, ⋯), Cardiac Vascular Smooth Muscle Cell Differentiation, and related pathways (FDR~0.08%, including NOTCH1 gene, ⋯). For MPO terms, we found abnormal vitelline vascular remodeling and related pathways (FDR~0%, including FLT4,KDR,FOXO1, ⋯), delayed heart looping and related pathways (FDR~0.05%, including NOTCH1 gene, ⋯). **Conclusions:** FLT4,KDR,FOXO1, and NOTCH1 genes were in line with manual gene curation findings. Also, pathways results confirm manual curation findings which support dysregulated VEGF signaling as a novel mechanism contributing to the pathogenesis of TOF. Funded by Ted-Rogers Centre for Heart Research, and CIHR (MOP-89066).