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Biomarker and therapeutic target discovery in DOCK8 deficiency

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Primary immunodeficiency (PID), a rare group of genetic disorders, is characterized by increased susceptibility to various infections, growth failure, eczema and malignancy. Hyper-IgE Syndromes (HIES) are a heterogeneous group of heritable inborn errors of immune function and include deficiencies in DOCK8, PGM3, STAT3 and severe atopic dermatitis. Lymphoblastoid cell lines were established from patients with HIES. Comprehensive "multi-OMICs" profiling using LC-MS/MS (metabolomics, proteomics), and RNA-Seq (transcriptomics) were performed on these cell lines. Multi-OMICs data was analyzed using differential expression, Ingenuity Pathway Analysis (IPA) as well as the Genomatix Pathway system tool which creates a network functionally related genes. Multiple canonical pathways, especially EIF2 signaling, P13/AKT signaling, epithelial adherences junction signaling and its remodeling, protein ubiquitination pathway, glycolysis as well as pathways of pyrimidine ribonucleotides were significantly perturbed with an impact on cellular growth and proliferation; amino Acid metabolism; DNA replication, recombination, and repair. Adenosine and homocysteine were most up-regulated while acetyl-L-carnitine, glutathione and several pyrimidine ribonucleotides. Infectious diseases and cancer were the top diseases identified by IPA analysis with MYC, 5-FU and sirolimus as the upstream regulators. Several interacting immune-modulators including IL6, 7, 17 and IFNG. DOCK8, STAT3 and ARHGEF2 isoforms were differentially expressed and appeared to be disease specific. Combined "multi-OMICs" analysis in DOCK8 deficiency identified apparently unique perturbations in multiple cellular processes and pathways leading to predisposition to infection and cancer.

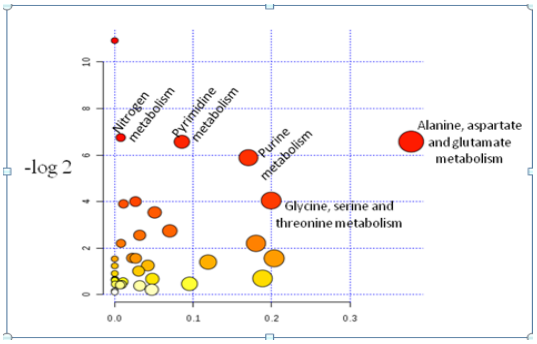

Figure-1: Significant changes in several pathways connected to DOCK8 deficiency.

Recent Publications

1. Yumi Mizano,Yuichi Ninomiya,Yutaka Nakachi, Mioko Iseki, Minnie Jacob, Fowzan S Alkuraya, et.al (2013) Tysnd1 Deficiency in mice interferes with the peroxisomal localization of PTS2 enzymes, causing lipid metabolic abnormalities and male infertility. *PLOS, Genet.*; 9(2): e1003286.
2. Osama Y Al-Dirbashi, Mohamed Rashed, Minnie Jacob, Lujane Y Al-Ahaideb (2008) Improved method to determine succinylacetone in dried blood spots for the diagnosis of tyrosinemia type 1 using UPLS-MS/MS. *Biomed chromatgr.*; 22(11): 1181-5.

Biography

Minnie Jacob works at the Newborn Screening and Biochemical Genetics Lab (NSBGL). She is currently pursuing her PhD at James Cook University, Australia. She is interested in metabolomics biomarker discovery in several Hyper IgE syndromes and in the Inborn Error of Metabolism (IEM). She has several publications to her credit.

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