

HBKU Thematic Research Grant 1st Cycle– Project Highlight

Project Title: Regulatory interactions of autism-associated neural enhancers implicate novel genes in autism etiology



LPI Name: Dr. Borbala Mifsud

Executive Summary

Autism spectrum disorders (ASD) are highly heterogeneous neurodevelopmental disorders that are clinically characterized by the manifestation of distinct behavioral, communication and social deficits. Genomic analyses of ASD families has led to the identification of several autism-associated genes, however it is likely that several hundreds of genes are involved in the complex ASD etiology. It is therefore important to identify further variants and genes that contribute to the development of ASD.

Here we propose to define autism-associated neuronal enhancers using two approaches. Firstly, we will use publicly available data from large whole-genome sequencing projects of autism families to find enhancers that harbor an excess number of *de novo* variants in ASD probands. Secondly, we will use Omni-C to investigate long-range regulatory interactions present in cortical neurons differentiated from patient-derived iPSC and identify enhancer elements that show allele-specific interactions in these cells. Subsequently, we will use these long-range regulatory interaction maps to determine the autism-associated enhancers' target genes. Novel candidate genes will be functionally characterized in *Drosophila* by knocking them down in the CNS of the embryo and subjecting the young flies to ASD-relevant behavioral assays, assessing habituation, social interaction and feeding.

Expected Outcome

Clinicians, researchers and families with autistic children will be beneficiaries of this project. It will aid identification of the genetic cause of ASD cases which so far have no known underlying genetic variant. It will also find novel ASD-associated genes and genomic regions.

Regulatory interactions can potentially be also used as biomarkers for ASD. An ASD-severity genetic and epigenetic panel could be designed based on these studies.

Collaborating HBKU entities: Qatar Biomedical Research Institute, HBKU.

Photos:



