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**PhD Dissertation Defense**

Entitled

*GENOMIC AND CELLULAR STUDIES ESTABLISH THE PATHOGENESIS AND CELLULAR  
MECHANISMS OF DISEASE-CAUSING MUTATIONS IN FAMILIES WITH AUTOSOMAL RECESSIVE  
DISORDERS*

by

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Abstract

The majority of the reported genetic disorders in the UAE population are of the autosomal recessive type, which is mainly due to high rates of consanguinity within the UAE national population, and within a significant proportion of other UAE expatriate communities; such as Arabs and Pakistanis. It is estimated that more than 50% of all marriages among Emiratis occur between biologically related couples, with first cousin marriages being the highest. That could be attributed to sociocultural values in the region. Successful management of genetic diseases can be achieved by the implementation of effective preventative programs that could help reduce the number of new cases, and provide early diagnosis to potentially improve disease management. For these desired outcomes to be achieved, it is imperative to identify the molecular causes (i.e. disease-causing genes and mutations) of such disorders. Therefore, the aim of this study is to elucidate the molecular pathology and cellular mechanisms of a group of recessive disorders affecting Emirati and expatriate families in the UAE. Whole exome sequencing, together with homozygosity mapping and segregation analyses, were performed on the recruited families to elucidate the causative genes and mutations. Where necessary, bioinformatics *in silico* analyses coupled with cellular and other functional studies were performed to confirm pathogenicity and uncover the cellular mechanisms of the studied disease phenotypes. In this dissertation, I report the identification of two novel compound heterozygous mutations in Multiple PDZ domain (*MPDZ*) gene causing congenital hydrocephalus, and provide experimental evidence on their pathogenesis and mechanisms. In addition, I report the identification of a novel mutation in Xylosyltransferase I (*XYLT1*) gene responsible for Desbuquois dysplasia II (DBQDII), and provide evidence on the involvement of the endoplasmic reticulum (ER) quality control in the cellular mechanism of several DBQDII-causing mutations, including, the newly identified one. Furthermore, I provide preliminary data on candidate genes in two families affected by suspected monogenic intellectual disability syndromes. Overall, this dissertation provides evidence on the pathogenicity of several mutations and associated cellular mechanisms. The outcomes of this project will likely be valuable for implementing effective preventive strategies at least for the extended family members of the affected individuals.

**Keywords:** Autosomal recessive disorders, Desbuquois dysplasia II (DBQDII), congenital hydrocephalus, *XYLT1*, *MPDZ*, whole exome sequencing.