Ph.D. Thesis proposal[1]

General Information		
Ph.D. Thesis Title	**Identification of candidate common genes in siblings with Lebanese ASD and study of their impact in cell culture model**	
USEK Doctoral Program	Ph.D. in Life and Earth Sciences	
Research Center		
Research Group	NND USEK / INSERM U1253 Faculty of Medicine Tours University	
Research Axis	Neurodevelopmental and Neuropsychiatric Disorders from genetic to pathophysiology	
PhD Supervisor	Name & Title: Pr. Walid Hleihel Email: walidhleihel@usek.edu.lb	University Address: Holy Spirit University of Kaslik- USEK
Co-supervisor (if applicable)	Name & Title: Pr. Christian Andres Email: christian.andres@univ-tours.fr	University Address: Tours University - France
Co-supervisor (if applicable)	Name & Title: Dr. Tania Bitar Email: taniabitar@usek.edu.lb	University Address: Holy Spirit University of Kaslik- USEK
Location (s)	Location 1: USEK, Lebanon	Work shift calendar /per year (%): 40%
	Location 2: France, Tours	Work shift calendar /per year (%): 60%
Potential funding and scholarship		

Applicant Profile and/or Special Requirements	Biology or Biochemistry background			
Comps Exam Language	☐ Arabic	☒ French	or	☒ English

Context of the Topic & Scientific Methods ***(Research impact, objectives, design, methods, and outputs)***
Autism spectrum disorders (ASD) are extremely variable conditions characterized by impairment in reciprocal social communication, restrictive and repetitive routines, typically manifesting before the age of 3 years. Studies have shown that ASD are multifactorial disorders including genetic and environmental factors. Variations in multiple genes give a strong evidence of the involvement of genetic factors that explain most of ASD risk. However, despite the great number of identified ASD susceptibility genes, only a small proportion of them were strongly validated, as such identifying specific causative genes is an important challenge. Thus, the aim of our study is to identify genetic mutations that are common in ASD sibling pairs and to validate the identified genes on cell models. Whole exome sequencing (WES) focuses on targeted sequencing of the protein coding regions of the genomic DNA and shows promise as a new tool in gene discovery for complex

[1] Thesis proposal should not exceed two pages.

diseases. WES has become the standard for causal gene detection in disease and treatment management. It permits the identification of small CNVs, SNVs, and indels in the genome associated with several disorders including ASD.

Our study will be divided into several parts:

First, the recruitment of ASD siblings' patients from NGOs and institutions specialized in mental disorders.

Second, extraction of DNA from the patients and their parents and non-autistic siblings will be performed, followed by WES to identify genetics variations and finally validation with Sanger sequencing. The analysis of the data could lead to the possible identification of common variations between ASD siblings.

Third, the identified gene variants will be validated on cell models (rodent primary neurons and neuronal cell lines in culture expressing plasmids containing the mutant cDNA or si RNA if the mutation is deleterious).

Taking the experience already gained in the precedent studies in ASD patients in the Holy Spirit University of Kaslik-Lebanon, this study has the potential to identify, with a higher confidence, candidate genes involved in the physiopathology of ASD and to validate their effect in a cell culture model which will be established in the INSERM Unit U1253-Tours, France.

Outcomes (OCs): What do we wish to achieve?	
OC1:	Detection of candidate genes in ASD with strong evidence of pathology
OC2:	A better understanding of the pathophysiology of ASD
OC3:	Providing a tool for an early diagnosis of ASD
OC4:	Providing a genetic counseling and personalized health maintenance measures and preventing the transmission of deafness genes

References (R) (5 most recent peer-reviewed publications in the field)	
R1:	Identification of rare copy number variations reveals PJA2, APCS, SYNPO, and TAC1 as novel candidate genes in Autism Spectrum Disorders. *T. Bitar et al. Journal of Pharmaceutical and Biomedical Analysis (2018)*
R2:	Proband Whole-Exome Sequencing Identified Genes Responsible for Autosomal Recessive Non-Syndromic Hearing Loss in 33 Chinese Nuclear Families. *S. Sang et al. Front. Genet. (2019)*
R3:	Gene-based and pathway-based testing for rare-variant association in affected sib pairs. *R. Romanescu et al. Genetic Epidemiology (2020)*
R4:	Whole exome sequencing in ADHD trios from single and multi-incident families implicates new candidate genes and highlights polygenic transmission. *B. Al-Mubarak et al. European Journal of Human Genetics (2020)*
R5:	Affected Sib-Pair Analyses Identify Signaling Networks Associated with Social Behavioral Deficits in Autism. *M. Pirooznia et al. Front. Genet., (2019)*