Dedication

This thesis is dedicated proudly to my guiding stars and soul
Father and Mother
whose love, encouragement, and sacrifices have been the motivation for my accomplishments and honors. I hope I was your good daughter, making you proud in every endeavor I pursue.

Hiba Almaadani

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This is to certify that the thesis entitled "***Computational investigation on the biomarkers and the role of SHANK3 in Autism Spectrum Disorder***" submitted to the School of Sciences, Tezpur University, in partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology is a record of original research work carried out by **Ms. Hiba Almaadani** under my personal supervision and guidance.

All helps received by her from various sources have been duly acknowledged. No part of this thesis has been reproduced elsewhere for the award of any other degree.

Date : 05/09/2019
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(Dr. Venkata Satish Kumar Mattaparthi)
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Declaration

I hereby declare that the thesis entitled ***"Computational investigation on the biomarkers and the role of SHANK3 in Autism Spectrum Disorder"*** has been submitted to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences for partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology.

I am the sole author of this thesis. This is a true copy of the original work carried out by me including any required final revisions, as accepted by my examiners.

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This is to certify that the thesis entitled ***"Computational investigation on the biomarkers and the role of SHANK3 in Autism Spectrum Disorder"*** submitted by Ms. Hiba Almaadani to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences in partial fulfillment of the requirement for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology has been examined by us on and found to besatisfactory.

The committee recommends the award of the degree of Doctor of Philosophy.

Signature of:

Principal Supervisor	**Principal Co-Supervisor**	**External examiner**
Date:	**Date:**	**Date:**

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Hiba Almaadani

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List of Abbreviations

1CSSI	One-Character Secondary Structure Information
3DFFT	Three-Dimensional Fast Fourier Transform
A	Alanine
Å	Ångstrom
aa	Amino acids
AD	Autism Disorder
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention-Deficit/Hyperactivity Disorder
AMBER	Assisted Model Building with Energy Refinement
AMPA	Glutamatergic α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid
AMPAR	Glutamatergic α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid Receptor
ARR	Ankyrin Repeat Region
ASD	Autism spectrum disorder
atm	Atmosphere pressure
ATP	Adenosine Tri Phosphate
BBB	Blood-Brain Barrier
BP	Biological Processes
Ca^{2+}	Calcium ion
αCaMKII	Ca2+/calmodulin-dependent kinase IIα
CAF	Cafeteria diet
CC	Cellular Components
CCL2	C-C motif chemokine ligand 2
CDC	Centers for Disease Control and Prevention
CDCS	Cri-Du-Chat Syndrome

List of Abbreviations

CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CSPGs	Chondroitin Sulfate Proteoglycans
CTNND2	delta-catenin
CXCL12	C-X-C motif chemokine ligand 12
DAVID	Database for Annotation, Visualization, and Integrated Discovery
DEGs	Differentially Expressed Genes
DLPFC	DorsoLateral Prefrontal Cortex
DNA	Deoxyribonucleic acid
DSSP	Dictionary of Secondary Structure for Protein
E	Glutamic acid
E/I	Excitatory/Inhibitory
EAATs	Excitatory Amino Acid Transporters
ERK	Extracellular signal-Regulated Kinases
FDR	False Discovery Rate
ff99SBildn	force field 99 with the Smith and Barber modifications and improved side-chain torsion potentials
FFT	Fast Fourier Transform
FMR1	Fragile X Mental Retardation 1
FXS	Fragile X syndrome
GABAergic	Gamma-Aminobutyric Acid
GEO	Gene Expression Omnibus
GFAP	Glial Fibrillary Acidic Protein
GFP-SPN	Green Fluorescent Protein is fused to the SPN domain
GO	Gene Ontology
GRIP	Glutamate Receptor Interacting Protein

List of Abbreviations

GSEA	gene set enrichment analysis
GTPases	Guanosine TriphosPhate hydrolase
GWAS	Genome-Wide Association Studies
HA	Hydrogen Acceptor
HD	Hydrogen Donor
IFN-γ	Interferon gamma
IL-1	Interleukin-1
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
IL-6	Interleukin-6
INDT-ASD	INCLEN Diagnostic Tool for Autism Spectrum Disorder
INDT-ASD	INCLEN Diagnostic Tool for Autism Spectrum Disorder
K	Kelvin
KEGG	Kyoto Encyclopedia of Genes and Genomes
KO	knock-out
L	Leucine
LFC	log-fold change
LPS	Lipopolysaccharide
LTCCs	L-type calcium channels
LTD	long-term depression
LTP	long-term potentiation
M	Methionine
M1	Microglia classical activation state
M2	Microglia alternative activation state
MAPK	Mitogen-activated protein kinase

List of Abbreviations

MC	Monte Carlo simulation
MCP-1	Monocyte Chemoattractant Protein-1
MD	MD= Molecular Dynamics
MF	Molecular Function
MIA	Maternal Immune Activation
N	Asparagine
NF-κB	NuclearKappa Factor B
NIH	National Institutes of Health
NMR	Nuclear Magnetic Resonance
No	Number
NPT	Constant number (N), pressure (P), and temperature (T)
ns	nanosecond
NVE	Microcanonical Ensemble
NVT	Constant number (N), volume (V), and temperature (T)
ORA	over-representation analysis
P	Proline
PBC	Periodic Boundary Conditions
PDB	Protein Data Bank
PDD-NOS	Pervasive Developmental Disorder- Not Otherwise Specified
PDZ	PSD-95/Discs large/ZO-1 domain
PMB	Post-Mortem Brain
PME	Particle Mesh Ewald
PPIs	Protein-protein interactions
ps	picosecond
PSD	Post-Synaptic Density

List of Abbreviations

PTVs	Protein-Truncating Variants
P-value	Probability value
R	Arginine
RBVI	Resource for Biocomputing, Visualisation, and Informatics
RCSB	Research Collaboratory for Structural Bioinformatics
Rg	Radius of gyration
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
RNA	Ribonucleic acid
ROS	Reactive Oxygen Species
S	Serine
SAM	Sterile Alpha Motif;
SAPAP1	SAP90/PSD-95-Associated Protein 1
SCFA	Short-Chain Fatty Acid
SHANK3	SH3, and multiple ankyrin repeat domains 3
SNPs	Single Nucleotide Polymorphisms
SPCE	Extended Simple Point Charge model
SPN	Shank/ProSAP N-terminal domain
TD	Typically Developing
TIP3P	Transferable Intermolecular Potential with 3 Points
TNF-α	Tumour Necrosis Factor alpha
TSPO	Translocator Protein 18 kDa
Ubl	Ubiquitin-Like
UCL	University College London
UCSF	University of California, San Francisco

List of Abbreviations

WT	Wild Type
αCaMKII	α-subunit of the calcium-/calmodulin dependent kinase II
βUP	beta-Ureidopropionase enzyme

List of Publications

1. **Almaadani, H. K.,** and Mattaparthi, V. S. K. Impact of E71S Mutation on SHANK3 Conformational Dynamics at the SPN-ARR Interface. *Biointerface Research in Applied Chemistry* (officially accepted for publication on 11th of May, 2024).
2. **Almaadani, H. K.**, and Mattaparthi, V. S. K. Effect of N52R mutation at the SPN-ARR interface on the conformational dynamics of SHANK3. *Current Proteomics* (officially accepted for publication on 16th of June, 2024).
3. **Almaadani, H. K**., and Mattaparthi, V. S. K. Computational investigation on the impact of point mutations on the N-terminal domain of SHANK3, indicating distinct synaptopatheies in Autism Spectrum Disorder. *Indian Journal of Biochemistry & Biophysics* (officially accepted for publication).

List of Publications

List of Publication under communication

1. **Almaadani, H. K**. The role of neuroinflammation pathomechanism on autism spectrum disorder and unraveling potential biomarkers for early detection. *Cytokine.*

List of Conferences

Almaadani, H. Baruah, S. “Early detection of autism spectrum disorder: Meta-analysis of RNA-seq to determine the role of cytokines in ASD pathogenesis” National Seminar on “Emerging trends in biological sciences: A North East India perspective” held at NIH University, Shillong, India on 28th Febreuary-01th March, 2023. (Poster Presentation)