

Table of Contents

Abbreviations	10
List of tables.....	11
List of figures	11
CHAPTER 1: LITERATURE REVIEW	12
1.1 Hearing and hearing loss	13
1.1.1 Hearing Loss: From past to present.....	13
1.1.2 Structure of ear:	13
1.1.3 Mechanisms of hearing:	14
1.1.4 Hearing loss:	16
1.2 Epidemiology and causes of hearing loss	18
1.2.1 Prevalence of Hearing loss:	21
1.2.2 Causes of Hearing loss	21
1.2.3 Deafness genes:	21
1.3 Gpr98 gene and its role in hearing loss	23
1.3.1 Gene structure:.....	26
1.3.2 Splice variants and protein isoforms:.....	26
1.3.3 Protein structure:	26
1.3.4 Expression of GPR98:.....	26
1.3.5 Pathology Action:	29
1.3.6 VLGR1 in usher syndrome:	30
1.3.7 Mice models with mutation in GPR98.....	31
1.4 Genetic diagnosis of HL and NGS	32
1.4.1 Overview on Next Generation Sequencing:	34
1.4.2 Targeted genomic enrichment:	34
1.4.3 NGS and deafness (MPS and novel deafness gene discovery).....	36
CHAPTER 2: Problem statement and objectives of the study	37
2.1 Introduction:.....	40
2.2 Problem statement.....	40
2.3 Objectives:	41
CHAPTER 3: MATERIALS AND METHODS	42
3.1 Materials:.....	43

3.2 Methodology:	44
3.2.1 Subjects:	44
3.2.2 Gene Exclusion:	44
3.2.3 Targeted genomic capture and massively parallel sequencing:.....	44
3.2.4 PCR amplification.....	46
3.2.5 Sanger sequencing.....	48
3.2.6 Taqman genotyping assay (Real time –PCR)	51
3.2.7 Functional assay: Study the effect of mutation on pre-mRNA splicing.....	52
3.2.8 Bioinformatics:	55
CHAPTER 4: RESULTS AND DISCUSSION	56
4.1 Identification a novel mutation in GPR98 gene.	56
4.2 Filtration of the novel mutation in Palestinian controls.	58
4.3 Effect of novel mutation of pre-mRNA splicing of GPR98.....	58
4.4 Prediction the effect of novel mutation on protein sequence of GPR98.....	61
REFERENCES	67
APPENDICES.....	71