

LIST OF CONTENTS

	Page #
LIST OF FIGURES	I
LIST OF TABLES	II
SUMMARY	III-IV
ACKNOWLEDGMENTS	V
LIST OF ABBREVIATIONS & SYMBOLS	VI-VII
INTRODUCTION	1-3

SECTION: 1

REVIEW OF LITERATURE	4-31
CHAPTER I	
AUDITORY SYSTEM	4-19
ANATOMY OF HUMAN EAR	4-16
EXTERNAL EAR	4
Pinna	4
External Auditory Canal	4
Tympanic Membrane	4
MIDDLE EAR	5
Tympanic Cavity	5
Auditory Ossicles	5
Eustachian Tube	5
Oval and Round Windows	5
INNER EAR	7-16
Osseous Labyrinth	7
Membranous Labyrinth	8-14
Sensory Epithelia	8
Organ of Corti	9
Sensory Cells	11
Inner Hair Cells	11
Outer Hair Cells	11
Ion Transport Epithelia	13
Interciliary Links of Stereocilia and Mechanotransduction	14
PHYSIOLOGY OF HEARING	17-19
EVENTS IN SOUND TRANSDUCTION PATHWAY	17

CHAPTER II

MOLECULAR BASIS OF DEAFNESS	20-28
PREVALENCE.....	20
CLASSIFICATION	20-22
HISTORY OF GENETIC DEAFNESS.....	22
MOLECULAR BASIS OF HEREDITRY DEAFNESS	22
NONSYNDROMIC AUTOSOMAL RECESSIVE DEAFNESS	25

CHAPTER III

LINKAGE ANALYSIS” A KEY TOOL FOR HUNTING DISEASE GENES	29-31
LINKAGE ANALYSIS	29
RECOMBINATION FRACTION	29
LOD SCORE	30
MULTIPOINT MAPPING	31
DNA POLYMORPHISMS - A TOOL FOR LINKAGE ANALYSIS.....	31

SECTION: 2

MATERIALS & METHODS	32-59
FIELD WORK.....	32-39
IDENTIFICATION AND ENROLLMENT OF FAMILIES	32
CLINICAL EVALUATION.....	33-39
Clinical Assessment of Hearing Loss	33-36
Clinical Assessment of Vestibular Function.....	37
Clinical Assessment of Retinitis Pigmentosa (RP).....	37-39
LAB WORK.....	39-59
DNA EXTRACTION	39-41
From Blood Samples.....	39
From Buccal Swabs	40
QUANTIFICATION OF DNA.....	41-42
PREPARATION OF REPLICA DNA PLATES	42
LINKAGE ANALYSIS FOR REPORTED DFNB LOCI.....	42-47
Genotyping STR Markers by Polymerase Chain Reaction.....	43
GENOME WIDE SCAN	48-51
Multiplex PCR Protocol.....	48
SAMPLE PREPARATION FOR ABI PRISM® 3100 GENETIC ANALYZER.....	52

PRINCIPLE OF AUTOMATED FLUORESCENT GENOTYPING	52
HAPLOTYPE ANALYSIS	53
DATA ORGANIZATION AND LOD SCORE CALCULATION	53-56
Data Sheet	53
Ranges Sheet	54
The Macros of the Software	54
LOD Score Calculation by FASTLINK	55
LOD Score Calculation by EASYLINKAGE	56
DNA SEQUENCING	56-59
Amplification of PCR Fragments	56
Purification of PCR Product	57
Sequencing Reaction	57
Preparation of Product for Sequencing	58
Analysis of DNA Sequences	58

SECTION: 3

RESULTS	60-93
----------------------	-------

CHAPTER I

LINKAGE ANALYSIS FOR REPORTED DFNB LOCI	60-79
PREFACE	60
LINKAGE TO DFNB1/ <i>GJB2</i>	61-65
PKDF131	61
PKDF1103	61
PKDF1094	61
LINKAGE TO DFNB4/ <i>SLC26A4</i>	66-67
PKSR14A	66
LINKAGE TO DFNB9/ <i>OTOF</i>	68-70
PKDF339	68
PKDF1088	69
LINKAGE TO DFNB29/ <i>CLDN14</i>	71-77
PKDF315	71
PKDF361	71
PKDF1092	75
PKDF797	75
Haplotype Analysis of Recurrent Mutations of <i>CLDN14</i>	78

CHAPTER II

MAPPING OF A NEW AUTOSOMAL RECESSIVE NONSYNDROMIC DEAFNESS LOCUS DFNB88 AT CHROMOSOME 2p11.2.....	79-93
PREFACE.....	79
PKDF468	80-87
Clinical Evaluation.....	80
Linkage Analysis for Reported Loci.....	80
Genome-Wide Linkage Analysis for Mapping new Locus	81
LOD Score Calculations	84
Haplotype Analysis of PKDF468	84
Further Evidence of DFNB88 LINKAGE.....	88-89
PKSR11b.....	88
Haplotype Analysis of PKSR11b.....	88
REFINED LINKAGE INTERVAL OF DFNB88.....	90
CANDIDATE GENES IN DFNB88 REGION	91

SECTION: 4

DISCUSSION.....	94-102
------------------------	---------------

SECTION: 5

REFERENCES.....	103-116
------------------------	----------------