



شبكة المعلومات الجامعية

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Ain Shams University Information Network
جامعة عين شمس

شبكة المعلومات الجامعية

@ ASUNET



شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأفلام بعيدا عن الغبار

في درجة حرارة من ١٥-٢٥ مئوية ورطوبة نسبية من ٢٠-٤٠%

To be Kept away from Dust in Dry Cool place of
15-25- c and relative humidity 20-40%

بعض الوثائق الأصلية تالفة



بالرسالة صفحات لم ترد بالاصل

HEARING LOSS AND GENETICS IN HUMANS

AN ESSAY

Submitted in partial fulfillment of Master's Degree In Audiology

BY

Mona Ahmed El-Akkad

(MB, Bch)

SUPERVISED BY

Prof Dr Ahmad Sameh Farid

Professor of ENT and Audiology
Head of Audiology Department
Faculty of Medicine
Cairo University

Prof Dr Mohamed Ibrahim Shabana

Professor Of Audiology
Faculty of Medicine
Cairo University



**Faculty of Medicine
Cairo University
2002**

مختصر

اجتماع لجنة الحكم على الرسالة المقدمة من
الطالبة / منى أحمد البتة
توطئة للحصول على درجة الماجستير /
في أمراض السمع والسمع

Hearing Loss & Genetics in Humans

باللغة الانجليزية

باللغة العربية

بناءً على موافقة الجامعة بتاريخ ٢٠٠٢ / ٢ / ٣ تم تشكيل لجنة الفحص والمناقشة للرسالة
الذاتية أمسالة على النحو التالي :-

١) أ.د / أحمد سامح فريد - أستاذ الانف والحنجرة كلية الطب - جامعة القاهرة - من المشرفين

٢) أ.د / محمد طارق غنم - أستاذ مساعد - أمراض السمع والسمع كلية الطب - جامعة القاهرة - متحقق داخلي

٣) أ.د / علي عبدالدايم علي - أستاذ مساعد - كلية الطب - جامعة الأزهر - متحقق خارجي

بعد فحص الرسالة بواسطة كل عضو من الأعضاء وكتابة تقارير منفردة لكل منهم إنشأت اللجنة لجنة فنية
مؤلفة من الأخصائيين بتاريخ ٢٠٠٢ / ٣ / ٣ بتسمي السمعيات - مديح العياد الخارجية

كلية الطب - جامعة القاهرة وذلك لإفادة الطالب في جلسة علمية في موضوع الرسالة ولتفادي التي تفضل
لها وكذلك لأخص العيادة التي قام بها البحث .

رأب اللجنة :-

توزيعات أعضاء اللجنة :-

المشرفون

أ.د / أحمد سامح فريد
أستاذ الانف والحنجرة
كلية الطب - جامعة القاهرة

المشرفون الداخليين

أ.د / محمد طارق غنم
أستاذ مساعد أمراض السمع والسمع
كلية الطب - جامعة القاهرة

المتحققون الخارجيين

أ.د / علي عبدالدايم علي
أستاذ السمعيات
كلية الطب - جامعة الأزهر

Abstract

The academic basis of Mandel's inheritance patterns, chromosomes, molecular biology science and technology were the basis to decipher causes and types of genetic mutations, prospectives of the international gene project as well as gene mapping. The clinical aspect of the study included definition of genetic hearing loss, prevalence and the clinical presentation in all ages with special details of the commonest classifications. Combined clinical biology and biomolecular technology aspects in identifying genes with special details about connexin 26 expression and functions were detailed. The last chapter included clinical and laboratory diagnosis and Future insight in gene therapy.

Key Words

Gene – Extrons – Introns – Mutations – Hearing loss – Nucleic Acid – Molecular Biology Technology – Molecular Biology Diagnosis – Chromosomes – Genetic Engineering – Deafness – Syndrome – Genetic counseling – Gene therapy – Connexines

CONTENTS

	<i>Page</i>
Acknowledgment	
List of Tables	
List of Figures	
List of Abbreviations	
Introduction and Aim of Work.....	1
Historical background of inheritance (GENETICS)	2
Inheritance Patterns (Mandelian Pattern of Inheritance)	4
Molecular Biology	10
Main Biochemical Functions of DNA	23
DNA Mutations and chromosomal abnormalities	
Abnormal gene structure and abnormal gene expression.....	34
Technology of molecular biology.....	40
Human Gene Project.....	52
Clinical aspects in view of molecular technology	55
Hearing Loss.....	59
The common causes of deafness according to clinical presentation	65
What Clinical Conclusion can We Draw So Far?.....	110
Molecular Biology of Connexin 26	113
Genetic Evaluation and Counseling for Hearing Loss	118
Molecular Biology Therapy	124
Modern Science in Clinical Genetics	140
Summary	143
References	145
Arabic Summary	

LIST OF TABLES

	<i>Page</i>
Table (1): Classification of repetitive DNA sequences.....	16
Table (2): Prevalence of genetic deafness.....	62
Table (3): Different degrees of hearing impairment prevalence per 100,000 live births.....	64
Table (4): Common causes of conductive hearing loss.....	65
Table (5): Common causes of sensorineural hearing loss	85
Table (6): Common causes of mixed hearing loss.....	101
Table (7): Autosomal dominant disorders	104
Table (8): Autosomal recessive disorders.....	105
Table (9): Sex linked disorders.....	105
Table (10): Autosomal chromosomal syndromes.....	106
Table (11): Mitochondrial disorders.....	106
Table (12): Multifactorial genetic hearing loss.....	106
Table (13): Locus, Gene, Connexins & clinical presentation	112
Table (14): Incidence of mutation of GJB2 gene of connexin26, percentage, and race	113
Table (15): Vectors for gene therapy.....	130
Table (16): Candidate diseases for gene therapy.....	135

LIST OF FIGURES

<i>Figure</i>		<i>Page</i>
1	Autosomal recessive inheritance	5
2	Autosomal dominant inheritance.....	6
3	X-linked recessive inheritance	6
4	X-linked dominant inheritance.....	7
5	Base-pairing role of DNA	10
6	DNA double helix and base pair	10
7	One DNA strand	12
8	Coding length in a gene	13
9	Gene language.....	13
10	Codons of amino acids.....	14
11	Model of nucleosomes	18
12	Electron micrograph of nucleosomes.....	18
13	Karyotyping	20
14	Two sisters chromatids	20
15	Diagrammatic structure of a human chromosome.....	20
16	Nomenclature of chromosomal parts.....	21
17	Cell cycle.....	24
18	Stages of mitosis in animal cells	24
19	DNA replication is semi conservative.....	25
20	Diagrammatic representation of transcription and translation.....	28
21	Transcription and translation.....	28
22	Polymerization of nucleotides in transcription.....	30
23	Splicing	32
24	Splicing and alternative splicing	32
25	Equal crossover.....	36
26	Un-equal crossover	36
27	Paternal imprinting	39
28	Maternal imprinting.....	39
29	Southern blot.....	41

Figure		Page
30	Identification of a DNA by hybridization	43
31	Recombinant DNA.....	44
32	Down syndrome	66
33	Down child syndrome simian crease	67
34	Crouzon's disease.....	69
35	Treacher Collins' disease.....	69
36	Marfan syndrome.	70
37	Marfan lens.....	70
38	Treacher Collins' faces.....	71
39	Dental malocclusion.....	71
40	Cleft palate	72
41	Clubfoot.....	73
42	Cub-shaped external ears.....	73
43	Achondroplasia.....	74
44	Duane.....	75
45	Classic Apert profile	75
46	Fusion of fingers (syndactyly) in Apert' syndrome.....	76
47	Osteogenesis imperfecta	77
48	Otosclerosis.....	79
49	Cleft palate	80
50	Cholesteatoma	82
51	Paget disease.....	83
52	Neurofibromatosis	83
53	Goldenhar 'syndrome.....	84
54	Klippel feil web neck.....	88
55	Klippel feil tuft hair lumbosacral	88
56	Hydrops fetalis turner.....	88
57	Turner.....	89
58	Usher' RP	91
59	Waardenburg syndrome.....	93
60	Joint hyper-mobility in Stickler Syndrome.....	94
61	Stick-retin-detach	95

LIST OF ABBREVIATIONS

A.....	Adenine
ASHG.....	American Society of Human Genetics
Bp.....	Base pair
C.....	cytosine
COL IA2.....	Collagen type I, -2 chain
COL.....	Collagen
D.....	Deaf (moderate)
d.....	Deaf (severe to profound)
DNA.....	deoxyribonucleic acid
EEG.....	Electroencephalogram
FAD.....	Flavine adenine dinucleotide
G.....	Guanine
HL.....	Hearing loss
HSCR.....	Hirshsprung Disease
IDEA.....	Individual with disability education acts
IRP.....	Institutional Review Board
Kbp.....	Kilo pair
LINES.....	Long interspersed
m RNA.....	Messenger RNA
NAD.....	Nicotineamide dinucleotide
P.....	Long arm of chromosomes
PCR.....	Polymerase chain reaction
PPR.....	Progressive pigmentary retinopathy
q.....	short arm of chromosomes
r RNA.....	ribosomal RNA
RFLP.....	Restriction fragment length polymorphism
RNA.....	ribonucleic acid
SINES.....	Short interspersed repeats
SNHL.....	Sensorineural hearing loss
STL.....	Stickler syndrome
t RNA.....	transfer RNA
T.....	Thymine
USH.....	Usher
VNTRs.....	variable number tandem repeats
WS.....	Waardenburg syndrome

INTRODUCTION

Genetic hearing loss approximately accounts for fifty percent of all childhood deafness. A large size of genetic cases is reported, as the cause is unknown because the pedigree may not be obvious.

Hearing loss may cause infants and toddlers to be at risk for speech and language impediments. This makes them feel frustrated, angry, or isolated from their family, peers, and community.

The clinical spectrum of inherited deafness is broad and ranges from simple deafness without other clinical abnormalities to genetically determined syndromes affecting several different body systems in which deafness is only one of many signs, which together comprise the syndrome (*Willems, 2000*).

Understanding of the academic basis of biochemistry molecular biology together with appropriate investigation may be of great help to reach diagnosis to choose the specific investigation needed and hence therapy.

AIM OF THE WORK

To study

- 1- the biochemical basis for genetic diseases for hearing loss.
- 2- the applications of molecular genetics to understand heritable hearing loss and to use these advances in the practice of medicine.
- 3- to focus on the approaches to diagnosis, genetic counseling.
- 4- screening of individuals at risk for genetic diseases which have been revolutionized by the application of molecular genetics.

HISTORICAL BACKGROUND OF INHERITANCE (GENETICS)

There has been a growing recognition of the influence of genetic factors in human diseases. At the same time revolutionary developments have occurred in the basic science of genetics.

Principles of hereditary, Mandel's law, were first declared 1903 sixteen years after his death. He described dominant and recessive traits as well as the laws of homozygous and heterozygous. The pairing and splitting of chromosomes at cell division was proposed in 1903. The materials of chromosomes were found to be composed of DNA and protein. Tatium and Leadcerberg discovered that the genetic information was carried and transmitted through DNA protein, deoxynucleoprotein, in 1946. Franklin invited X-ray crystallography for DNA was invited in 1950 by Franklin. Crick and Watson received Nobel Prize in 1962 for their proposal of the double helical structural formula and the base pairing role of DNA in 1953, while RNA has only one strand.

Chromosome duplication and cell division was further discovered to be caused by DNA replications. This DNA replication is a complex biochemical process involving many enzymes including DNA polymerase and RNA polymerase [discovered in 1958 and 1966] respectively. Another Nobel Prize for molecular biologists was awarded in 1978 for Hamilton and Daniel for their discovery of restriction endo-nucleases and ligases enzymes.

Important steps in molecular biology (biomedical engineering), was the laboratory ability to determine the base sequence of RNA [Northern blot] and the amino acid sequence of proteins [Western blot]. These sequences in terminology because DNA leads to 3 RNAs synthesis which in turn lead to protein synthesis (*Sandra et al., 1999*).

Thus human genetic studies had been involved through three complementary systems.