Assessment of Gene Mutations Causing Retinal Degeneration

A Thesis

Submitted to the Faculty of Science, Cairo University in Partial Fulfillment of the Requirements for the Degree of M.Sc. in Zoology

(Cell Biology, Histology & Genetics)

By

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Department of Zoology

Faculty of Science

Cairo University

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To my Mother

To the spirit of my Father

To my Sister

To the spirit of my Grandmother

And to my dearest uncle Abdel-Azeem

Abstract

Student name: Reem Mahmoud Mebed

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The inherited retinal degenerative diseases are a genetically and phenotypically diverse group of inherited diseases that leads to visual impairment. Retinitis pigmentosa (RP) is a major cause of progressive retinal disease. It was found that the rhodopsin gene (*RHO*) represents one of the causative genes for autosomal dominant RP as well as rare cases of autosomal recessive RP. In this study a high percentage of autosomal recessive cases were reported (٥٦.٧%). Also a high parental consanguinity rates were evident (٦٦.٦%). Autosomal dominant cases represented ١٦.٦% of total cases. Sequencing of *RHO* gene revealed no mutations among the study population. This may be attributed to the high percentage of the autosomal recessive inheritance.

Keywords: Retinal degeneration, retinitis pigmentosa, inheritance patterns, rhodopsin gene.

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Contents

Abstract

Acknowledgements

List of figures……i

Introduction……..١

Review of literature……..٢

١. Retinitis Pigmentosa……..٢

١.١. Inheritance patterns of RP……..٤

١.٢. Causative genes……..٥

٢. Physiology & Anatomy of the retina……٧

٣. Overview on rhodopsin structure and function……٩

٤. Possible factors leading to photoreceptor cell death……١٢

٥. The Effect of mutant rhodopsin on photoreceptors……١٧

٦. Gene therapy……١٩

٦.١. Insertion of the wild-type gene……..٢٠

٦.٢. Silencing the expression of the mutant allele……٢١

The Aim of the Study……٢٣

Materials and Methods……..٢٤

١. Description of the study population……..٢٤

١.١. Clinical investigations……٢٤

١.٢. Genetic counseling……..٢٤

٢. Sample collection……...…٢٥

٣. Extraction of genomic DNA……...…...٢٥

٤. PCR procedure……..…….٢٨

٥. Agarose gel electrophoresis……...……٢٩

٦. Purification of PCR products……..…٣١

٧. Sequencing the PCR products……...٣١

Results…….…..…٣٣

١. Study population……٣٣

٢. Clinical examinations……٣٣

٣. Genetic counseling……٣٤

٤. Rhodopsin gene amplification using PCR……٤٧

٥- Sequence analysis……٥٠

Discussion……..……...٥٤

Summary……..٥٨

References……٥٩

List of figures

Figure:
١.....٣٧

Showing flash ERG of RP patient

Figure:
٢.....٣٨

Showing the patients' age of diagnosis

Figure:
٣.....٣٩

Showing the patient's visual acuity of the right eye

Figure:
٤.....٤٠

Showing the patient's visual acuity of the left eye

Figure:
٥.....٤١

Showing family pedigree of a simplex case

Figure:
٦.....٤٢

Showing family pedigree of an autosomal dominant case

Figure:
٧.....٤٣

Showing family pedigree of an autosomal recessive case

Figure:

٨……٤٤

Showing autosomal recessive inheritance

Figure:

٩…… i ……٤٥

Showing the frequency of the different RP inheritance patterns

Figure:

١٠……..٤٦

Illustrate the parental consanguinity among the study population

Figure:

١١……..٤٨

Agarose gel electrophoresis of the PCR products of exon ٢

Figure:

١٢……..٤٨

Agarose gel electrophoresis of the PCR products of exon ٤

Figure: ١٣……٤٩

Agarose gel electrophoresis of the PCR products of exon ٥

Figure:

١٤……..٥١

Illustrate blasting exon ٢ of the patients' rhodopsin with genomic rhodopsin (GenBank NT_٠٠٥٦١٢.١٦).

Figure:

١٥……..٥٢

Illustrate blasting exon ٤ of the patients' rhodopsin with genomic rhodopsin (GenBank NT_٠٠٥٦١٢.١٦).

Figure:

١٦……..٥٣

Illustrate blasting exon ٥ of the patients' rhodopsin with genomic rhodopsin (GenBank NT_٠٠٥٦١٢.١٦).

Introduction

Retinitis pigmentosa is a clinically and genetically heterogeneous group of inherited retinal degenerations that is estimated to affect more than ١.٥ million people worldwide (**Hartong *et al.,*** ٢٠٠٦). It is characterized by progressive photoreceptor cell death and diminished or non-detected electroretinogram. Eventually, it can lead to complete blindness (**Neidhardt *et al.,*** ٢٠٠٥). At this time, there is no effective treatment for RP (**Chen *et al.,*** ٢٠٠٦).

Over ١٠٠ causative genes have been implicated in hereditary retinal degenerations. To date, up to ٤٥ causative genes/loci have been identified in RP (**Hartong *et al.,*** ٢٠٠٦**; Delyfer *et al.,*** ٢٠٠٤). One is the rhodopsin gene, which encodes a photo-pigment constituting >٩٠% of the protein content in rod photoreceptor outer segments. This protein is responsible for the initiation of the visual transduction cascade upon the incidence of a photon of light (**Palczewski** ٢٠٠٦). Up to ١٥٠ mutations have been characterized in the *RHO* gene. Most of which are single nucleotide polymorphisms (http://www.sph.uth.tmc.edu/RetNet/). Previous studies have correlated between the phenotypic variability and distinct amino acid substitutions (**Neidhardt *et al.,*** ٢٠٠٥**; Iannaccone *et al.,*** ٢٠٠٦). The majority of rhodopsin mutations lead to misfolding of the protein. However, the mechanisms by which this misfolded and/or misrouted protein lead to photoreceptor cell death remains to be determined (**Saliba *et al.,*** ٢٠٠٢).

This study aimed to identify the associated mutations in the gene coding for human rhodopsin and leads to retinal degeneration in RP Egyptian patients. This might help understanding the genetic causes of photoreceptor degeneration, hopping to pave the way for future therapeutic approaches.

Review of literature

Retinal degenerative diseases are a major cause of visual disability and blindness in human. In the majority of inherited photoreceptor degenerations both cone and rod photoreceptors die, but the degree to which these cell types are affected differs between the various disorders. In general, photoreceptor degenerations are classified according to the particular cell type or the anatomical region that is first to degenerate. Retinitis pigmentosa is generally associated with predominant initial loss of rod photoreceptors in the mid-peripheral retina resulting in night blindness as a first symptom (**Pacione *et al.,* ٢٠٠٣**).

١. Retinitis pigmentosa

Retinitis pigmentosa is the most common form of inherited retinopathies. It is characterized by retinal pigment deposits visible on fundus examination, abnormal electroretinogram (ERG), progressive retinal dysfunction which initially affects the peripheral retina, atrophy of the retinal tissue accompanied by a secondary degeneration of the tissue underlying the retina, the retinal pigmented epithelium (RPE) (**Chen *et al.,* ٢٠٠٦; Hamel ٢٠٠٦; Phelan *et al.,* ٢٠٠٠**).

In typical cases, known as rod-cone RP, rods are the predominantly affected photoreceptor cells. Consequently, this generates a number of characteristic clinical symptoms including night blindness at an early age or stage of the disease, bilateral symmetric loss of the mid-peripheral visual fields and eventually develops tunnel vision. As the disease progress, cone photoreceptors are also affected and day vision and central visual acuity are compromised. However, the rate of visual failure is variable, but total