International Journal of Medical Laboratory 2020;7(1):9-14.

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Original Article

Study of Patterns of Inheritance in Affected Patients with Retinitis Pigmentosa in Iranian Populations

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ABSTRACT

Article history
Received 24 Aug 2019
Accepted 13 Jan 2020
Available online 1 Mar 2020

Key words
Bardet-Biedl syndrome
Patterns of inheritance
Retinitis pigmentosa

Background and Aims: Retinitis pigmentosa (RP) is the most common form of inherited retinal degeneration, photoreceptors loss of which in the retina causes visual loss. The purpose of the present study was to determine patterns of inheritance in RP patients in Yazd to help the health professional for designing suitable laboratory testing for the high risk families.

Materials and Methods: Thirty affected RP patients referred to the Genetics Clinic of Research and Clinical Center for Infertility, in Yazd Medical Sciences University from 2010-2016. Full medical and family histories were taken from all family members. Ophthalmology examinations were performed in members of the families including electroretinogram, fundus photography, visual-field measurements and spectral domain optical coherence tomography.

Results: In this study, the most commonly pattern was inheritance of autosomal recessive. The patients were diagnosed as having Usher syndrome, Bardet-Biedl syndrome and Posterior Column Ataxia with Retinitis Pigmentosa. The study also reported a patient with Kreans-Sayer syndrome, a mitochondrial disease.

Conclusions: We identified different inheritance patterns in RP patients. Identifying patterns of inheritance is important for pre-marriage and pre-conception genetic counselling.

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[DOI: 10.18502/ijml.v7i1.2465]

Introduction

The prevalence of retinitis pigmentosa (RP) is reported to be 1 case per 3000 to 7000 individuals [1]. At first, RP disease was described in 1853 [2]. RP is the most common heterogeneous group of inherited retinal disorders caused by damage to the light-sensitive rods and cones located in the retina, the back part of eyes. Rods, which provide side (peripheral) and night vision, are affected more than the cones that provide color and clear central vision [3, 4]. The first sign of affected individuals is night blindness, followed by decline of the peripheral visual field known as tunnel vision [3]. If RP disease involved vision alone, it is referred to as nonsyndromic RP and comprises about 70-80% of RP patients, are included but if the disease occurs systemically, it is termed syndromic RP. The most common forms of syndromic RP are Usher syndrome and Bardet-Biedl syndrome [5]. Bardet-Biedl syndrome is RP with autosomal recessive pattern characterized by cardinal features of postaxial polydactyly, retinitis pigmentosa, kidney defects, obesity and mental retardation as well as hypogonadism [6]. Usher syndrome is RP with hearing disorders and congenital [7]. Several methods for classifying RPs exist including electroretionogram test that measures electrical responses of photoreceptors in retina; ophthalmoscopic (fundoscopic) examination to distinguish degenerative changes in retina and retinal pigment epithelium and patterns of inheritance [8]. To date, over 260 genes have been involved in inherited retinal disorders. Among these, 88 genes have been identified to be associated with non-syndromic RP. At least 29, 54, and 5 genes/loci have been described to induce autosomal dominant RP (adRP), autosomal recessive (arRP), and X-linked (XLRP), respectively (RetNet database; https://sph.uth. tmc.edu/RetNet/). Next generation sequencing is one of the best approaches for identification of the genetic causes of Mendelian inherited RP [9]. Mutations in some of genes cause arRP pattern including *CEP290*, *CRB1*, *ABCA4* and *USH2A* [6]. Pattern of adRP is the mildest inheritance pattern [10]. The genes responsible for mutations with adRP are *RHO*, *RP1*, *PRPH2* and *PRPF31* [6]. The genes that account for xIRP are *RPGR* and *RP2* [6] (Table1). Vision defects caused by the mutations may be associated with apoptosis, light damage, ciliary transport dysfunction, and endoplasmic reticulum stress pathways. Common result of the pathways is rod photoreceptors loss [11].

Material and Methods

Thirty Iranian families affected with RP referred to the Genetics Clinic of the Research and Clinical Center for Infertility in Yazd Medical Sciences University from 2010-2016. This study was approved by the Ethics Committee of Shahid Saduoghi University of Yazd Medical Sciences. All the subjects provided written informed consent.

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[DOI: 10.18502/ijml.v7i1.2465]

Table 1. The most common genes responsible for mutations with different patterns of inheritance

Genes	Protein	Patterns of inheritance	OMIM	Mutations
RHO	Rhodopsin	adRP	180380,613731	161
RPGR	X-linked retinitis pigmentosa GTPase regulator		300029,312610	151
PRPH2	Peripherin-2	adRP	179605,608133	123
RP1	Oxygen regulated protein 1	adRP	180100,603937	67
RP2	Retinitis pigmentosa 2 (X-linked)	X-linked	300757,312600,	76
PRPF8	Pre-mRNA-processing-splicing factor 8	adRP	600059,607300	21
USH2A	Usherin	arRP	608400,613809	392
NR2E3	Nuclear receptor subfamily 2 group E3	adRP	604485,611131	45
CRX	Cone-rod otx-like photoreceptor homeobox transcription factor	adRP	120970,602225,	51
PDE6B	Rod cGMP phosphodiesterase beta subunit	arRP	180072,613801	39
RPE65	Retinoid isomerohydrolas	adRP: arRP	180069,613794	134
EYS	Eyes shut/spacemaker (*Drosophila*) homolog	arRP	602772,612424	118
BEST1	Bestrophin 1	adRP: arRP	607854,613194	232
CRB1	Crumbs homolog 1	arRP	600105,604210	183
CLRN1	Clarin-1	arRP	606397,614180	23
RDH12	Retinol dehydrogenase 12	adRP: arRP	607854,613194	66
ABCA4	ATP-binding cassette transporter – retinal	arRP	601691,601718	680
PRPF31	Human homolog of yeast pre-mRNA splicing factor 31	adRP	600138,606419	65

adRP=Autosomal dominant retinitis pigmentosa; arRP= Autosomal recessive retinitis pigmentosa

Full medical and family histories were taken from all families' members. The pedigree chart from all of the Iranian families was displayed and ophthalmologic examinations

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[DOI: 10.18502/ijml.v7i1.2465]

were performed. The samples were divided into two groups: group 1 including patients with non-syndromic RP, without systemic involvement, and group 2 including patients with syndromic RP. The clinical symptoms and inheritance patterns in families were checked out.

Results

In the present study, almost all of the patients in the families affected with RP were born from consanguineous marriages and unaffected parents. Ophthalmological examination revealed visual disturbance during the first decade of life, and visual acuity and visual fields declined with increasing age in affected individuals of the family. Progressive peripheral visual loss and fundus photography indicated extensive bone spicule in periphery, narrowing arteries and veins, and pale and waxy optic disc. The samples included females (53%) and males (47%). Molecular studies performed showed the patients suffering from Usher syndrome, Bardet-Biedl syndrome, Posterior Column Ataxia with Retinitis Pigmentosa and a patient with Kreans-Sayer syndrome, a mitochondrial disease. Autosomal recessive inheritance pattern bore the highest rate of inheritance pattern among the patients (Table 2).

Table 2. Patterns of inheritance found in families

Pattern of inheritance	Type of disease	Prevalence (%)
Systemic or syndromic RP	Usher syndrome	3.3
	Bardet-Biedl syndrome	6.6
Non-syndromic RP	Autosomal recessive RP	76
	Autosomal dominant RP	23
	X-linked RP	10
	Mitochondrial	3.3
	Digenic	0

RP=Retinitis pigmentosa

Discussion

RP is the most common heterogeneous group of inherited retinal disorders [4]. RP is transmitted by all types of inheritance patterns mostly including autosomal dominant, autosomal recessive and X-linked forms. In addition complex and mitochondrial patterns occur rarely [12, 13]. The study of RP in the world has revealed predominant types of inheritance patterns to be different in each region [14]. In the present study, patients with autosomal recessive inheritance had the highest rate compared with patients having a different pattern of inheritance. Our results regarding pattern of inheritance revealed to be in line with that of reported from Norway study [15]. A study in 2013, also identified autosomal recessive as the most common pattern of inheritance. This study demonstrated the

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[DOI: 10.18502/ijml.v7i1.2465]

importance of the evaluation of the affected family with a different pattern of inheritance, and according to the type of RP and the technology used, mutations in 30-80% cases were detected [14]. Finding the pattern of RP inheritance is very important for pre-marriage and better following molecular base of the disease processes. Clinical findings, patterns of inheritance and genetic of patient is an important step in the diagnosis of RP disease.

Conclusion

Worldwide RP studies have showed the differences in predominant type of inheritance in each region. These differences may be cause to epidemiological diversity. In our study, we reported that autosomal recessive pattern was the most common pattern. This study demonstrated the requirement genetic studies in all populations to give an accurate prognosis of the disease. Identifying affected genes in rare disorders leads to an accurate genetic counselling and a better follow-up of the disease. Molecular and clinical studies expand prognostic information for clinician and family.

Conflicts of Interest

The authors declare no conflict of Interest.

Acknowledgements

We are thankful to the patients and their families for their cooperation. The results described in this paper were extracted from a Ph.D. thesis and this article was supported by Yazd University of Medical Sciences with the grant No. 4929.

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