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REVIEW ARTICLE

Genetic characterization and disease mechanism of retinitis pigmentosa; current scenario

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Abstract Retinitis pigmentosa is a group of genetically transmitted disorders affecting 1 in 3000–8000 individual people worldwide ultimately affecting the quality of life. Retinitis pigmentosa is characterized as a heterogeneous genetic disorder which leads by progressive devolution of the retina leading to a progressive visual loss. It can occur in syndromic (with Usher syndrome and Bardet-Biedl syndrome) as well as non-syndromic nature. The mode of inheritance can be X-linked, autosomal dominant or autosomal recessive manner. To date 58 genes have been reported to associate with retinitis pigmentosa most of them are either expressed in photoreceptors or the retinal pigment epithelium. This review focuses on the disease mechanisms and genetics of retinitis pigmentosa. As retinitis pigmentosa is tremendously heterogeneous disorder expressing a multiplicity of mutations; different variations in the same gene might induce different disorders. In recent years, latest technologies including whole-exome sequencing contributing effectively to uncover the hidden genesis of retinitis pigmentosa by reporting new genetic mutations. In future, these advancements will help in better understanding the genotype–phenotype correlations of disease and likely to develop new therapies.

Keywords Retinitis pigments · Autosomal dominant · Autosomal recessive · Whole-exome sequencing · X-linked

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Introduction

More than 240 genetic mutations are involved in inherited retinal dystrophies which are an overlapping group of genetic and clinical heterogeneous disorders (El-Asrag et al. 2015). Retinitis pigmentosa is a heterogeneous genetic disorder which is characterized by progressive devolution of the retina, affecting 1 in 3000–8000 people worldwide (Hamel 2006; Hartong et al. 2006); starting in the mid-fringe and advances towards the macula lutea and fovea. Symptoms include diminishing visual fields that lead to Kalnienk vision, ultimately leading to legal blindness or complete blindness (Hartong et al. 2006). Retinitis pigmentosa is also depicted as rod-cone dystrophy because of primarily degeneration of photoreceptor rods along with secondary degeneration of cones; eventually causing complete blindness. Photoreceptor rods are appeared to be more affected than cones. The rod-cone sequences elaborate why the night blindness is initially appeared in patients and in later life patients suffer from visual disability in periodic conditions (Hamel 2006). Diseased photoreceptors face apoptosis (Marigo 2007), which is resulted in reducing the thickness of the outer nuclear layer in the retina, and retinal pigments with abnormal structural changes are deposited in the fundus.

Clinical phenotypes may include, (1) abnormal absence of a-waves and b-waves in electroretinogram results, (2)

reduced field vision. Symptoms appear in early teenage but severe visual impairment occurs by 40–50 years of age (Hamel 2006). In a multicentre study, 999 patients (age 45 or older) were evaluated for visual acuity, carrying multiple genetic subtypes of retinitis pigmentosa revealed that 69% patients had visual acuity of 20/70 or better, 52% of 20/40 or better, 25% of 20/200 or worse and 0.5% had no light sensing in both eyes (Grover et al. 1999). Genetic nature of retinitis pigmentosa is heterogeneous. In 1984, after first reported linkage of retinitis pigmentosa locus to a DNA marker on chromosome X (Bhattacharya et al. 1984), currently mutation over 58 genes are known to cause retinitis (Table 1).

In retinitis pigmentosa carriers, the nature of the disease can be non-syndromic (limited to the eye), or it can appear in syndromic nature. For example, in the case of syndromic nature of the disorder, patients carrying Usher syndrome express the combination of retinitis pigmentosa and hearing impairment (Mathur and Yang 2015). Approximately 20–30% of patients carrying retinitis pigmentosa has an association with the non-ocular disorder, and would be categorized as carrying syndromic retinitis pigmentosa. For an instant, missense mutations of the *BBS2* gene cause Bardet-Biedl syndrome (retinitis pigmentosa, obesity, mental retardation and polydactyl) or non-syndromic retinitis pigmentosa (Shevach et al. 2015). Non-syndromic retinitis pigmentosa may be inherited as autosomal recessive, autosomal dominant digenic, X-linked and even mitochondrial patterns (Ferrari et al. 2011). Overall percentage prevalence of non-syndromic and syndromic retinitis pigmentosa is shown in Table 2. The most patronize types of syndromic retinitis pigmentosa are Usher syndrome and Bardet-Biedl syndrome (Ferrari et al. 2011).

Genetic characterizations of retinitis pigments are complicated, so authorized genotype–phenotype correlation is impossible to define. In addition to numerosity of variations, as a matter of fact, different disorders may be caused by the different mutations in the same gene and same mutations can cause inter-familial and intra-familial phenotypic variability. For example, the vast majority of rhodopsin mutations depict a classical autosomal dominant pattern of inheritance, leading to retinitis pigmentosa. However, low numbers of mutations depict autosomal recessive patterns of inheritance (Berger et al. 2010). Likewise, major X-linked recessive retinitis pigmentosa gene—RPGR—is linked with the mutations in male patients and no phenotypic male-to-male characteristics have ever been reported to transmit. The current review focuses on the genesis on the retinitis pigmentosa and how mutations lead to pathophysiological effects. For the accurate outcomes, mutations frequency of the genes will be evaluated that are associated with retinitis pigmentosa and how these mutations lead to retinal degradation; ultimately inducing retinitis pigmentosa.

Table 1 Genes associated with retinitis pigmentosa (adapted from; Retnet)

Disease category	Genes and loci (total number)	No. of identified genes
Autosomal dominant retinitis pigmentosa	23	22
Autosomal recessive retinitis pigmentosa	37	36
X-linked retinitis pigmentosa	5	2

Visual phototransduction

To better understand how the mutations in genes associated with retinitis pigmentosa influence the functions of proteins, the molecular basis of the visual phototransduction is needed to be understood. Visual phototransduction is a biological process through which light signals are converted into electrical signals in the light-sensitive cells(rod and cone photoreceptors) in the retina of the eye. The photoreceptors cells are the polarized type of neurons in the retina that is capable of phototransduction. Photoreceptors cells consist of a cell body, an inner segment, an outer segment and synaptic region. Inner segment is connected to the outer segment via cilium. The molecular machinery

Table 2 Overall percentage prevalence of retinitis pigmentosa

Pattern of inheritance	Type of disease	Prevalence	References
Systematic or syndromic retinitis pigmentosa	Bardet-Biedl syndrome	5%	Ferrari et al. (2011), Daiger et al. (2007), Bowne et al. (2006), Schwartz et al. (2003)
	Usher syndrome	10%	
Non-syndromic retinitis pigmentosa	Autosomal recessive	15–20%	
	Autosomal dominant	20–25%	
	X-linked	10–15%	
	Digenic	Very rare	
	Leber congenital amaurosis	4%	

resides within the inner segment that is involved in the biosynthesis, membrane trafficking and the energy metabolism system. Outer segment is comprised of membranous discs circumvented by a plasma membrane. Over 90% of the total protein in the outer segment is rhodopsin. Vision begins via an apoprotein (opsins) and a chromophore (11-cis, derived from vitamin A) attached to the opsin by Schiff base bond. Isomerization of 11-cis retinal is induced via light absorption by rhodopsin protein to all-trans retinal, ultimately conformation of the opsin is changed, hence vision is initiated. In photoreceptor cells, all-trans retinal that is released from opsin is reduced to all-trans retinol and then moved to the pigmented layer of the retina. For the continuity of vision, in retinal pigment epithelium the 11-cis retinal is produced again from all-trans-retinol. This process is accomplished by 65 kDa isomerohydrolase expressed in retinal pigment epithelium known as RPE65 (Daiger et al. 2007; Redmond et al. 1998). Rhodopsin acts and triggers its GTP-binding protein, transducin, and canonical second-messenger signaling pathway is initiated with help of heterotetrameric phosphodiesterase 6 complexes.

Clinical description of retinitis pigmentosa

Retinitis pigmentosa develops over multiple decades; long lasting disease. Even so in extreme cases rapid development has also been shown. Retinitis pigmentosa can be handily classified into three stages; (1) the early stage, (2) the middle stage, and (3) the end stage.

Early stage

A major symptom of early stage retinitis pigmentosa is night blindness; may be appeared at different stages of life; from the first years of age, or during the second decade of life or even later. Patients carrying mild night blindness often ignore it, and it appears in teen ages, in dim light. At this stage, defects like peripheral visual field appear in dim light, but in daylights patients spent normal life and intensity of these defects are minimal. At the early stage of retinitis pigmentosa it is difficult to diagnose, especially when any kind of familial history is not available. Clinical examination of the fundus may appear normal (Fig. 1a); the optic disc is normal, no bone-spicule shaped pigment deposits are present, retinal arterioles fading is at a modest level, and color vision is normal. In the visual field tests under scotopic conditions, scotomas are revealed, but this test is usually carried out in mesopic conditions. Electroretinogram is a key test to better understand the prevailing conditions. Mostly, low amplitude b-waves are shown in results that dominate in scotopic conditions.

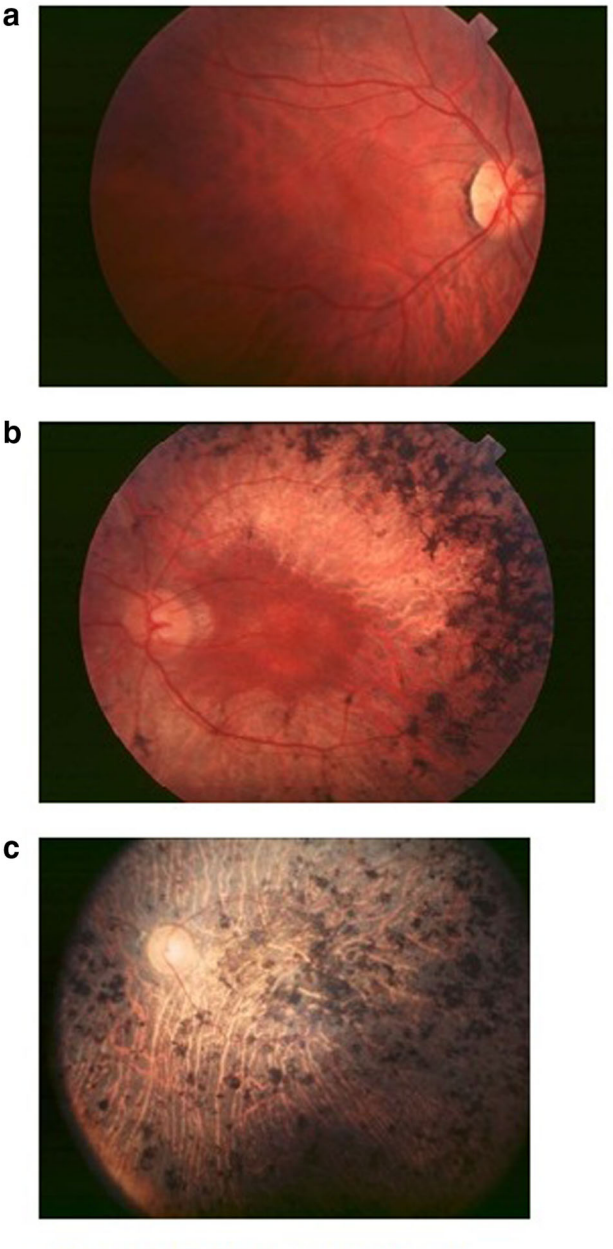

Fig. 1 **a** Early stage fundus of patients carrying retinitis pigmentosa. **b** Mid stage fundus of patients carrying retinitis pigmentosa. **c** End stage fundus of patients carrying retinitis pigmentosa

However, if the retina partially defects, electroretinogram may appear normal.

Middle stage

Patients become cognizant of the loss of peripheral visual field in daylight conditions; patients miss hands in handshaking, during drive they cannot see side-coming cars. Night blindness is evident; with troubles to drive during night, walking at evening or in dark staircases.

Dyschromatopsia to very light colors (yellow and blue hues) is present. Photophobic conditions appear, particularly in diffuse lights, leads to reading problems because of the narrow window between too bright light and insufficient light, also because of lower visual acuity. Clinical examination of fundus discloses the retinal atrophy along with bone-spicule shaped pigments in the mid-periphery (Fig. 1b). The optic disc is fairly pale and retinal vessels narrowing are apparent. In scotopic conditions electroretinogram is commonly unrecordable, and at 30 Hz flickers, bright light cone responses are hypo voluted.

End stage

Without external control, patients cannot move from one place to other, because of peripheral vision loss. Reading is difficult without magnifying glasses (reading become impossible when central visual field vaporizes), and photophobia is intense. Clinical examination of the fundus (Fig. 1c) reveals the macular area with widespread pigment deposits. The optic disc has impressible achromasia and blood vessels are thin. Electroretinogram is unrecordable.

Genetic characterization of retinitis pigmentosa

Non-syndromic retinitis pigmentosa

Autosomal dominant retinitis pigmentosa

So far mutations in 24 different genes have been associated with autosomal dominant retinitis pigmentosa (RetNet 2015) but only a few genes account for a relevant percentage of the retinitis pigmentosa cases, these include, *RHO* (26.5%), *RPRH2* (5-9%), *PRPF31* (8%) and *RP1* (3-5%) (Ferrari et al. 2011). Table 3 shows the genes that are associated with autosomal dominant retinitis pigmentosa.

PRPF31 (Pre-mRNA processing factor 31) Mutation in *PRPF31* (Pre-mRNA splicing factor of 61 kDa) is currently proposed to play a vital role in autosomal dominant retinitis pigmentosa, inducing 1–8% cases of autosomal dominant retinitis pigmentosa (Audo et al. 2010a; Venturini et al. 2012).

Apparently *PRPF31* is one of the three pre-mRNA splicing factors inducing autosomal dominant retinitis pigmentosa, two other factors are *PRPF3* (1% of all cases) and *PRPF8* (3% of all cases). One of the unique characteristics of mutations in *PRPF31* is the incomplete penetrance. Mode of inheritance may be complicated to determine if symptomless carriers have affected parents and children, because of that genetic counseling of family is hindered. Symptomatic patients have been reported to experience night blindness and loss of visual field in teenage, and are generally reported as blind, when they are in the 30 s. Comparison of haplotype analysis of asymptomatic and symptomatic patients reveals that both types inherit different wild-type allele. Wild-type allele with a high level of expression may adjust for the nonfunctional mutated allele, but wild-type allele with low expression is unable to reach the activity threshold level of required photoreceptor-specific *PRPF31* (Waseem et al. 2007; Vithana et al. 2003).

RP1 (retinitis pigmentosa 1) By positional cloning *RP1* gene was first time reported by linkage testing in large autosomal dominant retinitis pigmentosa family south-eastern Kentucky. Mutations in *RP1* gene induce both dominant and recessive types of retinitis pigmentosa (Blanton et al. 1991; Field et al. 1982). 240-kD retinal photoreceptor-specific protein is encoded by RP1 gene and the expression of *RP1* in very prominent. Clinical diagnosis of patients carrying *RP1* mutated gene shows reduced visual field diameters. Generally genetic disorders are thought to be caused by environmental factors, allelic heterogeneity and genetic variations, but for RP1 disorders, genetic variants are thought to important because of the severity of disorder variety reveals the patients with the same primary mutation.

RHO (rhodopsin) The first component of visual transduction pathway is rhodopsin and when the light is absorbed by the rod cell of the retina, it is activated (Murray et al. 2009). With more than 100 mutations, approximately 30–40% cases of autosomal dominant retinitis pigmentosa are induced due to mutations in *RHO* gene. Autosomal recessive retinitis pigmentosa and autosomal dominant congenital night blindness can also be induced by the mutations in *RHO* gene. Murray and colleagues reported the autosomal dominant retinitis pigmentosa case resulted from *RHO* gene mutation, which nominated a protein with no 6th and 7th transmembrane, including the 11-cis retinal binding site (Rosenfeld et al. 1992). In a mouse model experiment carrying dominant retinitis pigmentosa, improved retinal function was achieved, following subretinal administration of recombinant are non-associated virus vectors containing RNAi-based suppressors (Chadderton et al. 2009). Latterly, restoration of visual function was achieved in P23H transgenic rats following subretinal administration of recombinant are non-associated virus vectors containing Bip/Grp78 gene (Gorbatyuk et al. 2010). In spite of all knowledge in autosomal dominant retinitis pigmentosa induced by the *RHO* gene mutation,

Table 3 Genes associated with autosomal dominant retinitis pigmentosa (adapted from; GeneCards, Retnet and OMIM)

Identified gene	Chromosomal location	Function of gene	Other phenotypes	References
SPP2	2q37.1	It could coordinate an aspect of bone turnover	None	Liu et al. (2015)
OR2W3	1q44	Initiate a neuronal response that triggers the perception of a smell	None	Ma et al. (2015)
HK1	10q22.1	Helps in glycolysis and gluconeogenesis, energy pathway	Excessive nonspherocytic hemolytic anemia, recessive hereditary neuropathy (Russe)	Sullivan et al. (2014), Wang et al. (2014)
BEST1	11q12.3	Provides instructions for making Bestrophin	Recessive retinitis Pigmentosa	Burgess et al. (2008), Davidson et al. (2009)
CA4	17q23.2	Involves in respiration, calcification, acid–base balance	None	Kohn et al. (2008), Alvarez et al. (2007)
CRX	19q13.32	Maintain normal rod and cone function	Dominant Leber congenital amaurosis	Menotti-Raymond et al. (2010)
TOPORS	9p21.1	It has the ability to interact with the tumor suppressor protein P53	None	Chakarova et al. (2007), (2011)
FSCN2	17q25.3	Acts as an actin bundling protein	None	Zhang et al. (2007a), Wada et al. (2001, 2003)
GUCA1B	6p21.1	Stimulates guanylyl cyclase 1 and guanylyl cyclase 2	Dominant macular dystrophy	Sato et al. (2005), Payne et al. (1999)
IMPDH1	7q32.1	Catalyzes the conversion of inosine 5′-phosphate (IMP) to xanthosine 5′-phosphate	Dominant Leber congenital amaurosis	Mortimer et al. (2008), Mortimer and Hedstrom (2005)
NRL	14q11.2	Transcription factor which regulates the expression of RHO and PDE6B genes	Autosomal recessive retinitis pigmentosa	Mears et al. (2001), Bessant et al. (1999)
NR2E3	15q23	Rod development and repressor of cone development	Recessive retinitis pigmentosa	Escher et al. (2009), Coppieters et al. (2007), Gire et al. (2007)
SEMA4A	1q22	Cell surface receptor	Dominant cone-rod dystrophy	Abid et al. (2006), Rice et al. (2004), Kumanogoh et al. (2002)
RHO	3q22.1	Required for photoreceptor cell viability after birth	Recessive retinitis pigmentosa	Dryja et al. (1993), Rosenfeld et al. 1992), Dryja et al. (1991)
PRPH2	6p21.1	Essential for disk morphogenesis	Digenic forms with ROM1	Boon et al. (2009), Chang et al. (2002), Ali et al. 2000)
RPE65	1p31.2	Roles in the production of 11-cis retinal and in visual pigment regeneration	None	Acland et al. (2001), Lotery et al. (2000)
PRPF8	17p13.3	Functions as a scaffold that mediates the ordered assembly of spliceosomal proteins and snRNAs	None	McKie et al. (2001), Kojis et al. (1996), Goliath et al. (1995)
ROM1	11q12.3	Essential for disk morphogenesis	Digenic retinitis pigmentosa with PRPH2	Yang et al. (2008), Zhang et al. (2007b)
PRPF31	19q13.42	Involved in pre-mRNA splicing	None	Venturini et al. (2012), Sullivan et al. (2006b)
KLHL7	7p15.3	mediates'Lys-48'-linked ubiquitination	None	Friedman et al. (2009)
RP1	8q12.1	Required for the differentiation of photoreceptor cells	Recessive retinitis pigmentosa	Avila-Fernandez et al. (2012), Riazuddin et al. (2005)
PRPF4	9q32	Participates in pre-mRNA splicing	None	Chen et al. (2014)
PRPF3	1q21.2	Participates in pre-mRNA splicing	None	Chakarova et al. (2002), Heng et al. (1998)
RDH12	14q24.1	Key enzyme in the formation of 11-cis-retinal from 11-cis-retinol during regeneration of the cone visual pigments	Recessive leber congenital amaurosis	Fingert et al. (2008), Perrault et al. (2004), Janecke et al. (2004)

Table 3 continued

Identified gene	Chromosomal location	Function of gene	Other phenotypes	References
PRPF6	20q13.33	Participates in pre-mRNA splicing	None	Tanackovic et al. (2011)
RP9	7p14.3	Roles in B-cell proliferation in association with PIM1	None	Sullivan et al. (2006a), Maita et al. (2004), Keen et al. (2002)
SNRNP200	2q11.2	Involves in spliceosome assembly, activation and disassembly	None	Benaglio et al. (2011), Li et al. (2010b), Zhao et al. (2009)

therapeutical approaches did not proceed at the same pace.

PRPH2 (Peripherin 2) The *PRPH2* (Peripherin 2) gene, once recognized as *RDS* (retinal degeneration slow) gene containing 3 exons and encoded 346 amino acid protein (39-kDa integral membrane glycoprotein). The protein is reported at the outer segment disc of cone and rod photoreceptor, containing one intradiscal domain (D2) and four transmembrane domains (known as M1–M4). The protein in combination with another protein (ROM1) forms homotetrameric and heterotetrameric complexes and also forms a homo-oligomeric structure with itself (Loewen et al. 2001). In 1991, *PRPH2* mutations inducing retinitis pigmentosa were first time reported and cause about 5-9% of autosomal dominant retinitis pigmentosa cases. Mutation in *PRPH2* gene and *ROM1* gene has been observed to cause digenic retinitis pigmentosa (Dryja et al. 1997).

Autosomal recessive retinitis pigmentosa

For autosomal recessive retinitis pigmentosa, over 40 genes have been mapped (Table 4) and most of the genes are rare and cause 1% of fewer cases. Some genes like *RP25*, *PDE6A*, *RPE65*, *and PDE6B* have higher prevalence percentage up to 2–5% of all cases.

Rp25 Mutations that are rare to another geographical region can be the common reason to cause autosomal recessive retinitis pigmentosa in particular populations, for example the *RP25* locus has been reported for causing 10-20% of autosomal recessive retinitis pigmentosa cases in Spanish populations (Barragán et al. 2008).

PDE6 (PDE6A, PDE6B, PDE6G) One α, β and two γ subunits are important parts of the *PDE6* complex; which encode a protein that has a vital function in rod photoreceptor visual phototransduction. Intracellular cGMP level is maintained by the complex by the hydrolyzing process of cGMP, due to G protein light activation(Tsang et al. 1998). In retinitis pigmentosa case, processes are unknown that induce rod photoreceptor death, but it is thought that low PDE6 activity may lead to rode-cone devolution. For proper photoreceptor function every subunit of *PDE6* complex is necessary, in fact for autosomal recessive retinitis pigmentosa, mutations in *PDE6A* and *PDE6B* genes are second most familiar cause for inducing disease. Visual loss is the main risk for heterozygous carriers, carrying mutations in *PDE6* gene, when *PDE6* is inhibited using drugs like revatio, cialis, or levitra (Tsang et al. 2008). Latterly *PDE6G* gene is reported with a mutation, causing autosomal recessive retinitis pigmentosa (early onset) (Dvir et al. 2010).

Rpe65 *RPE65* (an enzyme by which all-trans-retinyl esters in hydrolyzed into 11-cis-retinol) is vital for the reformation of the visual pigments essential for rod-mediated and cone-mediated vision and it is expressed in the pigmented layer of the retina. *RPE65* gene has been reported for approximately 60 mutations and causing recessive retinitis pigmentosa (2%) and leber congenital amaurosis (16%) (Cai et al. 2009). In three pre-clinical experiments, patients with leber congenital amaurosis were injected with adeno-associated viral vectors comprising the human *RPE65* cDNA. Modest level improvements were achieved in visual acuity (Bainbridge et al. 2008; Cideciyan et al. 2008; Maguire et al. 2008).

X-linked retinitis pigmentosa

X-linked retinitis pigmentosa patients exhibit severe phenotypes in early phases of disorder development and account approximately 10–15% of all retinitis pigmentosa cases. In some cases, deafness, abnormal sperm development and defective respiratory tract were noticed (Veltel and Wittinghofer 2009). Only two gene loci (*RP2 and RP3*) have been recognized so far out of six mapped gene loci (*RP2*, *RP6*, *RP23*, *RP24*, *RP34 and RPGR*) on X-chromosome (Table 5). More than 70% patients carrying X-linked retinitis pigmentosa have mutations in RP3 gene, and *RP3* gene product is located on an external segment of rod photoreceptor (Vervoort et al. 2000). Approximately 10–15% patients carry X-linked retinitis pigmentosa due to mutations in *RP2* gene (Veltel and Wittinghofer 2009).

Table 4 Genes associated with autosomal recessive retinitis pigmentosa (adapted from; GeneCards, Retnet and OMIM)

Identified gene	Gene function	Chromosomal location	Phenotypes other than recessive retinitis pigmentosa	References
ADIPOR1	Receptor for ADIPOQ, required for normal glucose and fat homeostasis	1q32.1	Bardet-Biedl like	Xu et al. (2016a)
POMGNT1	Participates in O-mannosyl glycosylation	1p34.1	None	Xu et al. (2016b)
ZNF408	May be involved in transcriptional regulation	11p11.2	Dominant familial exudative vitreoretinopathy	Avila-Fernandez et al. (2015), Collin et al. (2013)
NEUROD1	Neurogenesis regulator D1, acts as a transcriptional activator	2q31.3	None	Wang et al. (2015)
IFT172	Necessary for cilia maintenance and formation. Plays an indirect role in hedgehog signaling	2p33.3	Recessive Bardet-Biedl syndrome	Bujakowska et al. (2015)
IFT140	Component of the IFT complex A, important role in proper development and function of ciliated cells and maintenance of ciliogenesis and cilia	16p13.3	Recessive Mainzer-Saldino syndrome, recessive Leber congenital amaurosis	Xu et al. (2015b), Schmidts et al. (2013)
HGSNAT	Participates in glycosaminoglycan degradation and glycan structures degradation	8p11.21	Recessive mucopolysaccharidosis	Haer-Wigman et al. (2015)
RDH11	Shows an oxidoreductive catalytic activity for retinoids, involves in the metabolism of short-chain aldehydes	14q24.1	None	Xie et al. (2014)
DHX38	Embryogenesis, spermatogenesis, and cellular growth and division	16q22.2	Early onset with macular coloboma	Ajmal et al. (2014)
KIZ	Required for stabilizing the expanded pericentriolar material around the centriole	20p11.23	None	El Shamieh et al. (2014)
BEST1	Anion channel	11q12.3	Dominant retinitis Pigmentosa	Burgess et al. (2008), Davidson et al. (2009)
ABCA4	Retinal metabolism	1p22.1	Recessive macular dystrophy	Maugeri et al. (2000), Zhang et al. (1999)
ARL2BP	Role in the nuclear translocation	16p13.3	None	Davidson et al. (2013)
C2orf71	Might have an important role in developing of normal vision	2p23.2	None	Downs et al. (2013), Nishimura et al. (2010)
C8Oorf37	Unknown	8q22.1	None	van Huet et al. (2013), Estrada-Cuzcano et al. (2012)
CERKL	Tissue maintenance and development	2q31.3	None	Aleman et al. (2009), Tuson et al. (2004
CLRN1	Conjugation	3q25.1	None	Khan et al. (2011), Adato et al. (2002)
CNGA1	Phototransduction	4p12	None	Dryja et al. (1995), Griffin et al. (1993
CNGB1	Phototransduction	16q13	None	Bareil et al. (2001), Ardell et al. (2000)
CRB1	Tissue maintenance and development	1q31.3	Recessive leber congenital amaurosis	McKay et al. (2005
DHDDS	Catalysis	1p36.11	None	Zuchner et al. (2011), Zelinger et al. (2011)
DHX38	ATP-binding RNA helicase involves in pre-mRNA splicing	16q22.2	None	Ajmal et al. (2014)
EMC1	Unknown	1p36.13	None	Abu-Safieh et al. (2013)
EYS	Protein of the extracellular matrix	6q12	Unknown	Audo et al. (2010b), Barragán et al. (2008)

Table 4 continued

Identified gene	Gene function	Chromosomal location	Phenotypes other than recessive retinitis pigmentosa	References
FAM161A	Unknown	2p15	Unknown	Langmann et al. (2010), Bandah-Rozenfeld et al. (2010b)
GPR125	Orphan receptor	4p15.2	None	Abu-Safieh et al. (2013)
IDH3B	Involved in Krebs cycle	20p13	Unknown	Hartong et al. 2008
IMPG2	Component of the retinal intercellular matrix	3q12.3	Unknown	Bandah-Rozenfeld et al. (2010a)
KIAA1549	Unknown	7q34	None	Abu-Safieh et al. (2013)
KIZ	Unknown	20p11.23	None	Tuz et al. (2014), Shaheen et al. (2014), Akizu et al. (2014)
LRAT	Retinal metabolism	4q32.1	Recessive leber congenital amaurosis	Xiao et al. (2011
MAK	An important function in spermatogenesis	6p24.2	None	Stone et al. (2011)
MERTK	Transmembrane protein	2q13	None	Mackay et al. (2010)
MVK	Regulatory site in cholesterol biosynthetic pathway	12q24.11	None	Siemiatkowska et al. (2013)
NEK2	Involves in control of centrosome separation and bipolar spindle formation	1q32.3	None	Nishiguchi et al. (2013)
NR2E3	Transcription factor	15q23	Dominant retinitis pigmentosa, Recessive enhanced S-cone syndrome	Escher et al. (2009), Coppieters et al. (2007), Gire et al. (2007)
NRL	Tissue maintenance and development	14q11.2	Dominant retinitis pigmentosa	Mears et al. (2001), Bessant et al. (1999)
PDE6A	Phototransduction	5q33.1	None	Dryja et al. (1999)
PDE6B	Phototransduction	4p16.3	Dominant congenital stationary night blindness	Chang et al. (2006)
PDE6G	Phototransduction	17q25.3	None	Dvir et al. (2010)
PRCD	Unknown	17q25.1	Unknown	Nevet et al. (2010)
PROM1	Cellular structure	4p15.32	Recessive retinitis pigmentosa with macular degeneration	Yang et al. (2008)
RBP3	Retinal metabolism	10q11.22	Unknown	Parker et al. (2009)
RGR	Retinal metabolism	10q23.1	Dominant choroidal sclerosis	Morimura et al. (1999)
RHO	Phototransduction	3q22.1	Dominant retinitis pigmentosa	Dryja et al. (1993), Rosenfeld et al. (1992), Dryja et al. (1991)
RLBP1	Retinal metabolism	15q26.1	Recessive Bothnia dystrophy	Eichers et al. (2002
RP1	Tissue maintenance and development	8q12.1	Dominant retinitis pigmentosa	Avila-Fernandez et al. (2012), Riazuddin et al. (2005), Liu et al. (2002)
RPE65	Retinal metabolism	1p31.2	Recessive leber congenital amaurosis	Acland et al. (2001), Lotery et al. (2000)
SAG	Phototransduction	2q37.1	Recessive Oguchi disease	Nakazawa et al. (1998)
SLC7A14		3q26.2	None	Jin et al. (2014)
SPATA7	Unknown	14q31.3	None	Wang et al. (2009)
TTC8	Cellular structure	14q32.11	Recessive Bardet-Biedl syndrome	Riazuddin et al. (2010)

Table 4 continued

Identified gene	Gene function	Chromosomal location	Phenotypes other than recessive retinitis pigmentosa	References
TULP1	Tissue maintenance and development	6p21.31	Recessive leber congenital amaurosis	Hanein et al. (2004)
USH2A	Cellular structure	1q41	Recessive Usher syndrome	Seyedahmadi et al. (2004), Bhattacharya et al. (2002)
ZNF513	Expression factor	2p23.3	None	Naz et al. (2010), Li et al. (2010a)

Table 5 Genes associated with X-linked retinitis pigmentosa (GeneCards, Retnet and OMIM)

Identified gene	Gene Function	Chromosomal location	Phenotypes	References
OFD1, *RP23*	Involves in biogenesis of the cilium	Xp22.2	None	Webb et al. (2012), Coene et al. (2009)
RP2	Involved in beta-tubulin folding	Xp11.23	None	Hardcastle et al. (1999), Mears et al. (1999)
RPGR	Intraflagellar transport	Xp11.4	X-linked cone dystrophy, X-linked congenital stationary night blindness	Branham et al. (2012), Pelletier et al. (2007)
RP6	Unknown	Xp21.3-p21.2	None	Breuer et al. (2000), Musarella et al. (1990)
RP24	Unknown	Xq26-q27	None	Gieser et al. (1998)
RP34	Tissue development and maintenance	Xq28-qter	None	Melamud et al. (2006)

Syndromic retinitis pigmentosa

Retinitis pigmentosa is generally an isolated problem; the only eye is affected, but in other various rare cases retinitis pigmentosa is also linked to other disorders. Examples may include Usher syndrome, refsum syndrome, Bardet-Biedl syndrome.

Usher syndrome

Usher syndrome is an autosomal recessive disorder, in which retinitis pigmentosa, hearing impairment and sometimes vestibular dysfunction are associated. Deaf-blindness is the most common disorder due to this syndrome. Prevalence is 1:12,000–1:30,000 individuals in different populations. 10–30% of autosomal recessive retinitis pigmentosa cases are caused due to usher syndrome (Millan et al. 2011). In clinical manners, usher syndrome is separated into three types, (1) usher type I (severe form), (2) usher type II (moderate to severe form) and (3) usher type III. To date 12 genes have been reported for usher syndrome; 7 genes for usher type I, 3 genes for usher type II and 2 genes for usher type III (Table 6).

Bardet-Biedl syndrome

Bardet-Biedl syndrome is defined a recessive inherited disorder with symptoms of obesity (72%), learning difficulties, abnormalities of the fingers/toes, kidney disease, rod-cone dystrophy (>90%) and renal abnormalities. Bardet-Biedl syndrome affects 1: 120,000 Caucasians, but high prevalence (1:13,000) has been reported in a population of north Atlantic (Moore et al. 2005) and within the Bedouins (1:13500-1:16900) (Teebi 1994). Children carry Bardet-Biedl syndrome has a poor visual prognosis. Night blindness is usually apparent by age 7 to 8 years (Heon et al. 2005; Azari et al. 2006). To date, 21 genes have been associated with Bardet-Biedl syndrome (Table 7).

Whole-exome sequencing as an effective tool in clinical and symptomatic genetics

Advancement in DNA sequencing has become the most efficient resources for basic biological and clinical research, and has been applied in various fields such as biological systematics, diagnostics, biotechnology, parental testing and forensic identifications. The combination

Table 6 Genes identified for Usher syndrome (adapted from; GeneCards, Retnet and OMIM)

Disease	Identified gene	Chromosomal location	Gene Function	References
Usher type I	*MYO7A*	11q13.5	An important role in the renewal of the outer photoreceptor disks, Mediates mechanotransduction in cochlear hair cells	Gibbs et al. (2003), (2004)
	CDH23	10q22.1	Maintain a proper system of the stereocilia bundle of hair cells in the cochlea, Mediates mechanotransduction in cochlear hair cells	Zheng et al. (2005), Astuto et al. (2002)
	PCDH15	10q21.1	Maintain normal retinal and cochlear function	Ahmed et al. (2001), (2003)
	USH1C	11p15.1	Required for normal hearing, Mediates mechanotransduction in cochlear hair cells	Ebermann et al. (2007a), Ouyang et al. (2002)
	USH1G	17q25.1	Develop and maintain cochlear hair cell bundles	Weil et al. (2003), Kikkawa et al. (2003)
	CIB2	15q25.1	Important for proper photoreceptor cell maintenance and function	Riazuddin et al. (2012)
	CLRN1	3q25.1	Role in the excitatory ribbon that conjugates hair cells and cochlear ganglion cells	Khan et al. (2011), Adato et al. (2002)
Usher type II	*USH2A*	1q41	Involves in hearing and vision	Seyedahmadi et al. (2004), Bhattacharya et al. (2002
	GPR98	5q14.3	Receptor may have a crucial role in the development of the central nervous system	Hilgert et al. (2009), Ebermann et al. (2009)
	DFNB31	9q32	Essential for elongation and sustainment of inner and outer hair cells in the organ of Corti	Ebermann et al. (2007b), Mburu et al. (2003)
Usher type III	*HARS*	5q31.3	Responsible for the synthesis of histidyl-transfer RNA	Puffenberger et al. (2012)
	ABHD12	2p11.21	May regulate endocannabinoid signaling pathway	Eisenberger et al. (2012), Fiskerstrand et al. (2010)

of chain termination sequence (Mullis et al. 1992) and polymerase chain reaction (Sanger et al. 1977) established many of the prominent events such as the completion of the Human Genome Project that provided barely ample references to study the genetic modifications in associated phenotypes (Venter 2003; Sachidanandam et al. 2001). Recently new technologies for whole-genome sequencing and whole-exome sequencing replaced the traditional methods with low-cost sequencing cost per exome/genome. These advanced next-generation sequencing technologies, revolutionized the clinical structure to improve human health, although there are many problems to be addressed like, the high cost of the procedure, user-friendly software to analysis raw genetics and sequence data and the ethical issues that are related to gathering genetic data.

Role of whole-exome sequencing in human genetic disorders

According to OMIM Statistics presently, over 6000 presumptively single gene disorders have been reported, but the molecular basis of nearly two-third of disorders has not been described. Finding phenotypic variants and causative genes help in understanding the pathogenic mechanism of the prevailing disorder. In patients or small families with newly identified variants, genetic diagnosis is difficult to conceivable just on the basis of variant finding. It is much difficult to find more patients if the disorder is very rare. Recently reported variants are needed to validate for having pathologic effect with the help of functional experiments; biochemical confirmatory experiments are allowed to execute if the mutated gene has delimitated function in a well-known pathway associated with the disease. Novel genes identification causing rare single gene disorders is important to apprehend the biological pathways causing disorder as well as therapeutic management. Recent studies emphases that whole-exome sequencing is a powerful technique to find out casual genes responsible for Mendelian disorders (Rabbani et al. 2012); Fig. 2 shows the combination of exome sequencing and filtering strategy is helpful to distinguish the fundamental gene causing Mendelian disorders.

Heterogeneous single gene phenotypes

There are many genetically heterogeneous disorders like retinitis pigmentosa, intellectual disability, hereditary hearing impairment, and autistic spectrum disorder.

Table 7 Genes identified for autosomal recessive Bardet-Biedl syndrome(adapted from; GeneCards, Retnet and OMIM)

Identified gene	Chromosomal location	Gene function	References
ARL6	3q11.2	Requires for proper retinal function and organization	Chiang et al. (2004)
BBIP1	10q25.2	Regulates cytoplasmic microtubule constancy and acetylation	Scheidecker et al. (2014)
BBS1	11q13	BBSome requires for ciliogenesis but unnecessary for centriolar satellite function	Mykytyn et al. (2002)
BBS2	16q12.2		Katsanis et al. (2001)
BBS4	15q24.1	Requires for microtubule anchoring at the centrosome	Katsanis et al. (2001)
BBS5	2q31.1	BBSome requires for ciliogenesis but unnecessary for centriolar satellite function	Li et al. (2004)
BBS7	4q27		Badano et al. (2003)
BBS9	7p14.3		Nishimura et al. (2005)
BBS10	12q21.2	Helps in folding of proteins ATP hydrolysis	White et al. (2006)
BBS12	4q27		Stoetzel et al. (2007)
CEP290	12q21.32	Triggers ATF4-mediated transcription	Leitch et al. (2008)
IFT27	22q12.3	Possesses GTPase activity	Aldahmesh et al. (2014)
INPP5E	9q34.3	Particular for lipid substrates	Bielas et al. (2009)
KCNJ13	2q37.1		Lindstrand et al. (2014)
LZTFL1	3p21.31	May function as a tumor suppressor	Marion et al. (2012)
MKKS	20p12.2	Helps in folding of proteins ATP hydrolysis	Katsanis et al. (2001)
MKS1	17q22	Requires for cell branching morphology	Leitch et al. (2008)
NPHP1	2q13	Control epithelial cell polarity in combination with BCAR1	Lindstrand et al. (2014), Mollet et al. (2002)
SDCCAG8	1q43	Establish cell polarity and epithelial lumen formation	Chaki et al. (2012)
TRIM32	9q33.1	May mediate biological activity of the HIV-1	Chiang et al. (2006)
TTC8	14q32.11	Requires for ciliogenesis but unnecessary for centriolar satellite function	Riazuddin et al. (2010)

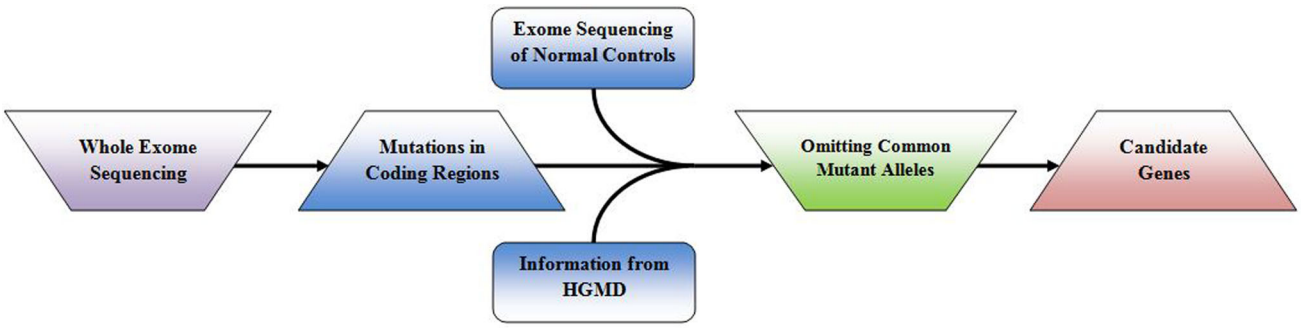

Fig. 2 Filtering methodologies and exome sequencing

Whole-exome sequencing has successfully resulted to distinguish various genes causing retinal disorders. Table 8 shows the role of whole-exome sequencing in identifying de novo genes in retinal disorders.

Future concerns

In near future it is hoped that, new strategies will be introduced for molecular diagnosis of retinitis pigmentosa for clinical practices, and disease inducing variations in genes will be discovered. But for this hope to come true, specific conditions are needed to meet; (1) All disease-causing variations in genes should possibly be reported, (2) techniques for molecular diagnosis should be low-cost, authentic, quick and widely available, (3) clinical should have the ability to understand the molecular information provided by a molecular diagnosis of disease. Currently reliable technologies are available and new technologies are rising that enhance the chances to report new mutations in individuals. For known mutations detection, currently array-based diagnostic technology is available for several retinal diseases. Next-generation sequencing is allowing the researchers to identify disease-causing variants and to

Table 8 De novo genes of retinal disorders reported by whole-exome (adapted from; GeneCards, Retnet and OMIM)

Disorder (type of retinal disorder)	Chromosomal location	Gene identified	References
Recessive macular dystrophy	1p13.3	*DRAM2*	El-Asrag et al. (2015)
Recessive achromatopsia	1q23.3	*ATF6*	Ansar et al. (2015), Kohl et al. (2015), Xu et al. (2015a)
Dominant retinitis pigmentosa	1q44	*OR2W3*	Ma et al. (2015)
Recessive Bardet-Biedl syndrome; recessive retinitis pigmentosa	2p33.3	*IFT172*	Bujakowska et al. (2015)
Recessive retinitis pigmentosa	2q31.3	*NEUROD1*	Wang et al. (2015)
Dominant retinitis pigmentosa	2q37.1	*SPP2*	Liu et al. (2015)
Recessive oculoauricular syndrome	4p16.1	*HMX1*	Gillespie et al. (2015)
Recessive microcephaly, growth failure and retinopathy	4q28.2	*PLK4*	Martin et al. (2014)
Recessive retinitis pigmentosa, non-syndromic recessive mucopolysaccharidosis	8p11.21	*HGSNAT*	Haer-Wigman et al. (2015)
Recessive retinal dystrophy with iris coloboma	9q21.12	*MIR204*	Conte et al. (2015)
Dominant retinitis pigmentosa; recessive nonspherocytic hemolytic anemia, recessive hereditary neuropathy	10q22.1	*HK1*	Sullivan et al. (2014), Wang et al. (2014)
Dominant familial exudative vitreoretinopathy; recessive retinitis pigmentosa with vitreal alterations	11p11.2	*ZNF408*	Avila-Fernandez et al. (2015), Collin et al. (2013)
Recessive cone-rod dystrophy; recessive Joubert syndrome	12q21.33	*POC1B*	Beck et al. (2014), Durlu et al. (2014), Roosing et al. (2014)
Recessive retinitis pigmentosa	14q24.1	*RDH11*	Xie et al. (2014)
Recessive cone and cone-rod dystrophy	14q24.3	*TTLL5*	Sergouniotis et al. (2014)
Recessive chorioretinopathy and microcephaly	15q15.3	*TUBGCP4*	Scheidecker et al. (2015)
Recessive retinal dystrophy and cerebellar dysplasia	18p11.31-p11.23	*LAMA1*	Aldinger et al. (2014)
Recessive Boucher-Neuhauser syndrome with chorioretinal dystrophy	19p13.2	*PNPLA6*	Kmoch et al. (2015), Synofzik et al. 2013, Topaloglu et al. (2014)
Recessive retinitis pigmentosa	20p11.23	*KIZ*	El Shamieh et al. (2014)
Recessive Usher syndrome	20q11.22	*CEP250*	Khateb et al. (2014)

report novel genes for the specific disease. The latest techniques have recently been utilized to detect genes and variants causing autosomal dominant retinitis pigmentosa against the conventional methods (Daiger et al. 2010; Bowne et al. 2011).

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interests.

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