Whole-exome sequencing identifies OR2W3 mutation as a cause of autosomal dominant retinitis pigmentosa

Xiangyu Ma1,*, Liping Guan2,*, Wei Wu3, Yao Zhang1, Wei Zheng4, Yu-Tang Gao5, Jirong Long4, Na Wu1, Long Wu1, Ying Xiang1, Bin Xu1, Miaozhong Shen2, Yanhua Chen2, Yuenwen Wang5, Ye Yin5, Yingrui Li2,6, Haiwei Xu3, Xun Xu2† & Yafei Li1†

1Department of Epidemiology, College of Preventive Medicine, Third Military Medical University, Chongqing, People’s Republic of China, 2BGI-Shenzhen, Shenzhen, People’s Republic of China, 3Southwest Hospital/Southwest Eye Hospital, Third Military Medical University, Chongqing, People’s Republic of China, 4Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA, 5Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People’s Republic of China, 6BGI-Tech, Shenzhen, People’s Republic of China.

Retinitis pigmentosa (RP), a heterogeneous group of inherited ocular diseases, is a genetic condition that causes retinal degeneration and eventual vision loss. Though some genes have been identified to be associated with RP, still a large part of the clinical cases could not be explained. Here we reported a four-generation Chinese family with RP, during which 6 from 9 members of the second generation affected the disease. To identify the genetic defect in this family, whole-exome sequencing together with validation analysis by Sanger sequencing were performed to find possible pathogenic mutations. After a pipeline of database filtering, including public databases and in-house databases, a novel missense mutation, c. 424 C>T transition (p.R142W) in OR2W3 gene, was identified as a potentially causative mutation for autosomal dominant RP. The mutation co-segregated with the disease phenotype over four generations. This mutation was validated in another independent three-generation family. RT-PCR analysis also identified that OR2W3 gene was expressed in HESC-RPE cell line. The results will not only enhance our current understanding of the genetic basis of RP, but also provide helpful clues for designing future studies to further investigate genetic factors for familial RP.

Methods

Subjects and clinical evaluation. We recruited a four-generation Chinese family from Chongqing in Southwest China. Six of nine members in the second generation affected RP (Figure 1-A). All participants underwent a full ophthalmologic examinations, including slit-lamp biomicroscopy, fundus examination, visual field test, and full-field flash electroretinography (ERG). Blood-derived DNA was available from five cases II-1, II-2, II-3, II-4, II-7 and from twelve healthy family members including II-8, II-9, III-1, III-2, III-3, III-15, III-16, IV-1, IV-2, IV-
Whole-exome sequencing. The whole-exome sequencing approach was employed to identify the disease-associated genes in five subjects, including four RP cases (II-2, II-3, II-4, and II-7) and one healthy control (II-9) by BGI, Shenzhen, China. Thirty microgram (μg) human genomic DNA was extracted from peripheral venous blood samples of each participant. Qualified genomic DNA sample was randomly fragmented by Covaris Acoustic System. Then adapters were ligated to both ends of the resulting fragments. Extracted DNA was then amplified by ligation-mediated PCR (LM-PCR), purified, and hybridized to the Nimblegen SeqCap EZ Library v3.0 (Roche/NimbleGen, Madison, WI) for enrichment. Both non-captured and captured LM-PCR products were subjected to quantitative PCR to estimate the magnitude of enrichment. Each captured library was then loaded on HiSeq2500 platform (Illumina, San Diego, CA). We performed high-throughput sequencing for each captured library to ensure that each sample meets the desired average sequencing depth (90×). Raw image files were processed by Illumina base calling Software 1.7 for base-calling with default parameters and the sequences of each individual were generated as 90 bp pair-end reads.

Bioinformatics analysis. The clean reads were aligned to the human reference genome (GRCh37, UCSC hg19) by SOAPaligner (soap2.21)16. Based on the results from SOAPaligner, software SOAPsnp (version 1.03) was used to assemble the consensus sequence and call genotypes in target regions20. When analyzing indel, mapping reads were used for subsequent analysis. Coverage and depth calculations were based on all mapped reads and the exome region. All variants were first filtered against several public databases for the minor allele frequency (MAF) > 0.5%, including dbSNP135, 1000 genomes data (pilot1, 2, 3), hapmap (release 24), YH project22, then against two in-house databases (sample size were 7,000 from Vanderbilt Epidemiology Center and 1,414 from BGI, respectively; samples of both databases come from Chinese population, which have the similar genetic background with the subjects in current study).

Mutation validation. To determine whether any of the remaining variants co-segregated with the disease phenotype in this family, the mutations were then confirmed in all other family members that DNA samples were available by Sanger sequencing. Direct polymerase chain reaction (PCR) products were sequenced using ABI 3730 Genetic Analyzer. Sequencing data were compared pair-wisely with the Human Genome database (GRCh37, UCSC hg19) to detect mutations. The possible causative mutation was further confirmed using RP pedigree database of GBI.

Cell culture, differentiation and identification. The HESC line H1 was induced to differentiate into retinal pigmented epithelium cells (HESC-RPE) as described previously23. Immunofluorescence analysis was performed according previous methods24. In brief, the HESC-RPE cells were fixed with 4% paraformaldehyde for 20 min, permeabilized using 0.1% Triton X-100 in PBS for 15 min and blocked for 30 min in 3% BSA. The following primary antibody were used: Mitf (Abcam, 1:50), Pax6 (Abcam, 1:50), zonula occludens-1 (ZO-1, Invitrogen, 1:400).

Reverse transcription-polymerase chain reaction (RT-PCR). Total RNA of HESC-RPE on 60 day, 80 d and 100 d were extracted using an RNAprep Pure Cell Kit (Sangon Biotech, CHN) according to the manufacturer’s instructions. Total RNA (approximately 1–2 μg per 20 μl reaction) was reverse transcribed using a PrimeScript® RT Reagent Kit (Takara, JPN). PCR amplification of OR2W3 gene (primers: F-TGGTGTTTATCTCTGTCCCTAAC, R- CTCCTGTTCTCTAGGG-TGTAGATG) was performed by the CFX96 Real-Time PCR System (Bio-Rad, USA) using a PCR Mix (Dongsheng Biotech, CHN) according to the manufacturer’s instructions.

Results

Clinical characteristics. Figure 1-A presents the pedigree of the four-generation Chinese family, which was consistent with autosomal dominant inheritance. Totally there are 7 members in this family affected RP, including two deceased members (I-1 and
II-5). The two deceased members showed similar clinical symptoms and pathogenesis with other 5 alive members (II-1, II-2, II-3, II-4, II-7). Night blindness appeared first, followed by progressive reduction of visual acuity, peripheral visual field, and photophobia. Fundus photography revealed similar clinical features for the affected individuals, including attenuation of retinal vascular, bone-spicule pigmentation, chorioretinal degeneration with peripapillary atrophy, optic disc pallor, and enlarged optic cups, comparing with the normal subject (Figure 1-B, 1-C). ERG records showed no detectable cone or rod responses in the patients.

**Mutation screening.** To find the causative mutations and exclude the known genes, we sequenced all exons and the flanking intronic splicing sites of the previously known causative genes of RP (Supplementary Table 1) among one RP case (II-1) and one healthy control (II-8), and confirmed by Sanger sequencing. All genes showed no pathogenic mutations, indicating the possibility of the familial cases in current study were caused by mutations in unknown genes.

**Whole-exome sequencing.** Whole-exome sequencing was performed upon five healthy control, including four RP cases (II-2, II-3, II-4, and II-7) and one healthy control (II-9). An average of 11,747 MB raw data was generated with a mean depth of 101.74-fold for the target regions. Approximately 98.64% of the targeted bases (64,482,551 bp in length) were covered sufficiently to pass our thresholds for calling SNPs and indels. We identified 144,701–150,367 SNPs and 15,368–16,173 indels for the five sequenced targets regions. Approximately 98.64% of the targeted bases (64,482,551 bp in length) were covered sufficiently to pass our thresholds for calling SNPs and indels. We identified 144,701–150,367 SNPs and 15,368–16,173 indels for the five sequenced targets. For rare inherited diseases, the frequency of the possible pathogenic variants in healthy population should be very low. Furthermore, two in-house databases were used to filter the remaining variants, which resulted that 10 SNPs were left (OR2W3 R142W, DNMT2 R297H, ROBO2 P1106S, CSMD3 K3075Q, ZHX2 G799R, PALM3 E658Q, HAP1 E269Q, BRIPI N775S, INT52 I775L, and TSSC4 H81R).

### Table 1 | Characteristics of 5 alive affected individuals from RP pedigree

| Characteristics | II-1   | II-2   | II-3   | II-4   | II-7   |
|-----------------|--------|--------|--------|--------|--------|
| Age (years)     | 64     | 60     | 58     | 54     | 46     |
| Gender          | Female | Male   | Male   | Male   | Female |
| Age of night blindness onset (years) | 20     | 30     | 21     | 20     | 30     |
| Visual field    | None   | None   | None   | None   | None   |
| Optic disc      | pallor | pallor | pallor | pallor | pallor |
| Artery attenuation | Yes   | Yes    | Yes    | Yes    | Yes    |
| Pigment deposits | Yes   | Yes    | Yes    | Yes    | Yes    |
| Electroretinography | non-detectable | non-detectable | non-detectable | non-detectable | non-detectable |

### Table 2 | Number of candidate variants filtered against several public variation databases

| Feature_SNP                     | control:II-9 | case:II-2 | case:II-3 | case:II-4 | case:II-7 |
|---------------------------------|---------------|------------|------------|------------|-----------|
| Total_SNPs1                     | 150367        | 146587     | 149036     | 144701     | 147040    |
| Functional_SNPs2                | 15982         | 15944      | 15897      | 15814      | 15847     |
| Filtered_DBsnp                  | 13286         | 13229      | 13202      | 13084      | 13195     |
| Filtered_DBsnp_1000gene         | 2857          | 2834       | 2804       | 2716       | 2709      |
| Filtered_DBsnp_1000gene_Hapmap  | 2817          | 2793       | 2763       | 2678       | 2670      |
| Filtered_DBsnp_1000gene_Hapmap_YH| 2664         | 2638       | 2609       | 2524       | 2515      |
| Filtered_DBsnp_1000gene_Hapmap_YH:II-9| 0          | 870        | 840        | 786        | 850       |
| Share_all_cases                 | 72            |            |            |            |           |
| Filtered_Housedatabase          | 10            |            |            |            |           |
| Genotype & phenotype cosegregation | 1 (OR2W3 R142W) |        |            |            |           |

1) Total SNPs detection were performed on the targeted exome regions and flanking regions within 200 bp. SNP types include variants of nonsense, missense, splicing site, 5’UTR, 3’UTR, NR_exon, synonymous-coding, intron, intergenic.
2) Functional_SNPs include variants of nonsense, missense, splicing site.
3) In this step, variants were filtered by mutations of healthy control. 

**Phenotype & genotype co-segregation and validation of the mutations.** The ten remaining mutations were then confirmed in other twelve family members that DNA samples were available by Sanger sequencing to co-segregate with the disease phenotype (Figure 2). Genetic analysis demonstrated that only OR2W3 (Olfactory receptor 2, W3) R142W was carried by affected patients and absent in healthy controls. Therefore, OR2W3 R142W mutation was also observed in another three-generation RP family (Figure 1-D), including 3 cases (II-1, II-2, III-1) and 1 control (I-1); three RP cases were found to carry the same mutation and one healthy control does not. Furthermore, immunolocalization analysis of HESC-RPE revealed the expression of RPE cells markers (Mift, PAX6, and ZO-1), while RT-PCR analysis showed that HESC-RPE expressed OR2W3 (Figure 3).

**Conservation of R142W in OR2W3 gene.** Pathogenicity assessment of OR2W3 R142W mutation was undertaken by evaluation of amino acid evolutionary conservation and in-silico prediction studies. Using UCSC Genome Browser (http://genome.ucsc.edu/cgi-bin/hgGateway), we found the variant was highly conserved in nine primate species, including human, chimp, gorilla, orangutan, baboon, rhesus, ab-eating macaque, baboon, green monkey, and bushbaby, although not conserved in non-primate mammals. According to two web-based topology prediction package: TMPred (http://www.ch.embnet.org/software/TMPRED_form.html) and TopPred (http://mobyle.pasteur.fr/cgi-bin/portal.py?forms=toppred), OR2W3 R142W mutation is located in a transmembrane domain of OR2W3 (Figure 2).
gene. The variants was also predicted to have a deleterious effect by Mutation Taster26. Exome Variant Server (EVS) database retrieval didn’t find this variant.

Discussion

RP, the most frequent inherited retinal degeneration, has become one of the commonest causes of genetic visual dysfunction27. Since RP1 identified by linkage study in 199128, 56 susceptibility genes/loci for RP have been subsequently discovered by different approaches. However, due to the enormous heterogeneity of the disease pathogenesis, a large part of the familial cases still could not be explained. In this study, using a whole exome sequencing approach, we identified a novel missense mutation, c. 424 C > T transition (p.R142W) in OR2W3 gene, associated with autosomal dominant RP in a large Chinese family. This mutation was validated in another independent three-generation family. RT-PCR analysis also identified that OR2W3 gene was expressed in HESC-RPE cell line. To the best of our knowledge, OR2W3 gene was identified to be associated with RP for the first time.

Table 3 | Number of candidate Indels filtered against several public variation databases

| Feature_Indel                  | control: II-9 | case: II-2 | case: II-3 | case: II-4 | case: II-7 |
|-------------------------------|---------------|------------|------------|------------|------------|
| Total_Indels                  | 16173         | 15403      | 16053      | 15368      | 15772      |
| Functional_Indels             | 2053          | 1976       | 2058       | 1996       | 2089       |
| Filtered_DBsnps               | 586           | 576        | 582        | 570        | 565        |
| Filtered_DBsnps_1000gene      | 337           | 346        | 323        | 325        | 327        |
| Filtered_DBsnps_1000gene_Hapmap | 337           | 346        | 323        | 325        | 327        |
| Filtered_DBsnps_1000gene_Hapmap_YH | 335           | 344        | 321        | 324        | 325        |
| Filtered_DBsnps_1000gene_Hapmap_YH_Ile-9 | 0            | 159        | 147        | 146        | 151        |
| Shared_all_cases              | 15            |            |            |            |            |
| Housedatabase_filter          | 0             |            |            |            |            |

1Total_Indels detection were performed on the targeted exome regions and flanking regions within 100 bp. Indel types include variants of frameshift, cds-Indel, spliceSite, 5-UTR, 3-UTR, intron, promoter, intergenic.
2Functional_Indels include variants of frameshift, cds-Indel, spliceSite.
3In this step, variants were filtered by mutations of healthy control: II-9.

Figure 2 | Sanger sequencing of OR2W3 R142W mutation.

Figure 3 | Identification of HESC-RPE cells. (A) Immunocytochemistry of HESC-RPE cells demonstrating the expression of Mitf, Pax6 and ZO-1. (B) RT-PCR analysis of OR2W3 in HESC-RPE. Cropped gel has been run under the same experimental conditions. Full-length blot is presented in Supplementary Figure S1.
The olfactory receptors (ORs), including OR2W3, were first defined as a supergene family that encodes G-protein coupled receptor proteins (GPCRs) in olfactory epithelium of the rat in 1991.29,30. Zhao et al. explored the physiological function of ORs in initiating transduction in olfactory receptor neurons34. However, ORs were not exclusively expressed in the olfactory epithelium. Recent studies have demonstrated ORs were expressed in a broad variety of other tissues, including autonomic nervous system, brain, tongue, erythroid cells, prostate, placenta, gut and kidney35. Furthermore, RNA sequencing of 16 different human tissues by Next Generation Sequencing (NGS) revealed OR2W3 gene were expressed in 9 different tissue samples, and most highly expressed in thyroid36. These indicated the different potential functions of OR2W3 gene in different human biological process.

OR2W3 gene, which was located in 1q44, has an intron-free reading frame of 942 nucleotides that encodes 314 amino acids. UCSC Genome Browser13 showed that OR2W3 shares exons with Trim58 (Tripartite motif-containing protein 58). When we used SWISS-MODEL server37 to model the structure of OR2W3 protein, JAGGED-1 (PDB ID: 2vj2B)36, which was also associated with one kind of autosomal dominant inherited disease - Alagille syndrome37, showed the biggest sequence identity with OR2W3. Recent studies also revealed that the biological functions of OR2W3 gene was not only restricted to olfactory system, like G-protein coupled receptor activity and olfactory receptor activity. Aston et al.38 and Plaske et al.39 found OR2W3 rs11204546 was associated with both azoospermia and oligozoospermia risk; a mutation in OR2W3 gene (chr1:248059606, p.T240P) was associated with the metastasis of pancreatic ductal adenocarcinoma40; expression of OR2W3 was also identified to be associated with long-term schizophrenia41, variability in response tob-blockers42, and the changes in global gene-expression profiles in human cervical cancer HeLa cells exposed to non-activated Dendrimers and Dendriplexes43. However, through epidemiological survey and Medical record retrieval, all the subjects in current study don’t have related diseases and mutations.

Vision and olfaction are two of the major sensory systems, which coordinate and integrate the information to provide us a unified perception of our environment. Studies showed that they share many links and common points in different aspects, including neuroanatomical pathways44, cross-modal links and the extension of this notion to goal-directed actions45, pathogenic or biological genes46–48. Woodard et al.49 found rdgB (retinal degeneration B), a gene required for normal visual system physiology, was shown to be necessary for olfactory response of both adult flies and larvae, indicating that rdgB was required for both visual and olfactory physiology. Loss of olfactory receptor genes were also found to coincide with the acquisition of full trichromatic vision46. In this study, we revealed a novel missense mutation in OR2W3 gene, was associated with autosomal dominant RP. This finding may indicate the essential links between Vision and olfaction, and strongly suggested an exchange in the importance of these two senses.

As we mentioned above, RP refers to a highly clinical and genetic heterogeneous group of inherited ocular diseases. Inheritance patterns included autosomal dominant, autosomal recessive, and X-linked models. In this study, we presumed autosomal dominant to be the inheritance pattern of this family basing on two reasons. First, both the first two generations have affected patients. We excluded the possibility of intermarriage through intensive epidemiologic survey. Second, high prevalence rate (6/9 = 66.7%) in the second generation. Nevertheless, we also analyzed the data based on the autosomal recessive model, including homozygous inheritance model and compound heterozygous model, but no promising mutations were detected. One limitations of this study is that due to patient’s refusal for retinal biopsy, the results could not be strengthened by RNA analysis of this gene or immune-localisation of the protein using multiple tissues including the retina and retinal pigment epithelium(RPE) cells.

Conclusion

A novel missense mutation (OR2W3 R142W) was identified to be associated with RP by whole-exome sequencing. Our findings expand the phenotypic and mutation spectrum of RP and provide helpful clues for designing future studies to further investigate genetic factors for familial RP.

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Author contributions

I.Y., X.X., X.H., M.X. and G.L designed the experiments; M.X., G.L., W.W., Z.Y., W.N., X.H., S.M. and L.Y. performed the investigations and experiments; M.X. and G.L. analyzed the data; L.L., Z.W., G.L., Y.Y. and L.Y. provided technical and material support. M.X. and G.L. wrote the manuscript; all authors reviewed the manuscript.

Additional information

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