A recurrent deletion mutation in OPA1 causes autosomal dominant optic atrophy in a Chinese family

Liping Zhang1,*, Wei Shi2,*, Liming Song3, Xiao Zhang1, Lulu Cheng1, Yanfang Wang4, Xianglian Ge1, Wei Li5, Wei Zhang5, Qingjie Min6, Zi-Bing Jin1, Jia Qu1 & Feng Gu1

1School of Ophthalmology and Optometry, Eye Hospital, Wenzhou Medical University, State Key Laboratory Cultivation Base and Key Laboratory of Vision Science, Ministry of Health and Zhejiang Provincial Key Laboratory of Ophthalmology and Optometry, Wenzhou, Zhejiang 325027 China, 2National Key Discipline of Pediatrics, Ministry of Education, Department of Ophthalmology, Beijing Children’s Hospital, Capital Medical University, Beijing 100045, China, 3Department of Urology, Beijing Chao-yang Hospital, Capital Medical University, Beijing 100020 China, 4Zhejiang Key Laboratory of Medical Genetics, School of Laboratory Medicine and Life Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325027 China, 5Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101 China, 6Institute of Genomic Medicine, Wenzhou Medical University, Wenzhou, Zhejiang 325027 China.

Autosomal dominant optic atrophy (ADOA) is the most frequent form of hereditary optic neuropathy and occurs due to the degeneration of the retinal ganglion cells. To identify the genetic defect in a family with putative ADOA, we performed capture next generation sequencing (CNGS) to screen known retinal disease genes. However, six exons failed to be sequenced by CNGS in optic atrophy 1 gene (OPA1). Sequencing of those exons identified a 4 bp deletion mutation (c.2983-1_2985del) in OPA1. Furthermore, we sequenced the transcripts of OPA1 from the patient skin fibroblasts and found there is six-nucleotide deletion (c.2984-c.2989, AGAAAG). Quantitative-PCR and Western blotting showed that OPA1 mRNA and its protein expression have no obvious difference between patient skin fibroblast and control. The analysis of protein structure by molecular modeling suggests that the mutation may change the structure of OPA1 by formation of an alpha helix protruding into an existing pocket. Taken together, we identified an OPA1 mutation in a family with ADOA by filling the missing CNGS data. We also showed that this mutation affects the structural intactness of OPA1. It provides molecular insights for clinical genetic diagnosis and treatment of optic atrophy.

Autosomal dominant optic atrophy (ADOA) is the most frequent form of hereditary optic neuropathy. It is characterized by optic nerve pallor, central or centrocecal visual field loss, color vision deficits and progressive loss of visual acuity in the early decades of life due to the degeneration of the retinal ganglion cells1. In most cases, ADOA patients experience a slowly progressive and insidious decrease of their quality of vision, which is irreversible2. The disease prevalence is between 1 in 5,000 to 1 in 50,000 in different populations3,4.

Since this disease has no effective treatment, accurate molecular diagnosis is a crucial step for preimplantation genetic diagnosis or prenatal screening.

To date, two genes (OPA1 and OPA3) and three loci (OPA4, OPA5 and OPA8) have been associated with autosomal dominant optic atrophy. OPA2, OPA6 and OPA7 mutations are responsible for X-linked or recessive optic atrophy2. However, OPA1 (NM_130837) is the major gene responsible for ADOA, which was first localized on 3q28 in 1996, followed by the discovery of the OPA1 gene sequence5,6. OPA1 is widely expressed, but most abundant in the retina5. It consists of 31 exons with the last exon as non-coding exon and by alternative splicing from exons 4 to 5b, it produces eight mRNA isoforms7. OPA1 encodes a large GTPase related to dynamins, anchored to the mitochondrial cristae inner membrane, controlling the shape of mitochondrial cristae and keeping their junctions tight during apoptosis8.

OPA1 cleavage has been reported9. Under conditions of stress, it is cleaved by OMA1 (overlapping with the m-AAA protease 1 homolog) to generate shorter isoforms, which trigger mitochondrial fragmenation9. Under high oxidative phosphorylation conditions, it is cleaved by Ymel, the human orthologue of the Yme1 subunit of the yeast i-AAA complex, which stimulates mitochondrial inner membrane fusion10. OPA1 also has been reported to be involved in the maintenance of the cristae structure11.
The other gene responsible for ADOA is OPA3 (NM_001017989), which encodes a mitochondrial inner membrane protein with unknown function. The mutation in OPA3 displayed optic atrophy plus a syndrome consisting of early onset bilateral optic atrophy, later onset spasticity, extrapyramidal signs and cognitive deficit. In the present study, a patient diagnosed with putative ADOA was recruited. We sought to identify the genetic defect and dissect the molecular consequence of the identified mutation. By capture next generation sequencing (CNGS) and Sanger sequencing, the mutation associated with ADOA in this patient was identified. To dissect the molecular consequence of the mutation, the structure of mitochondria was examined in fibroblasts from patient skin biopsy; the gene and protein expression of OPA1 was tested by quantitative (Q)-PCR and Western blotting, respectively; and the structural changes in OPA1 protein were assessed by molecular modeling.

Results
Clinical data. The family in this study comprised six affected individuals from a three generation pedigree (Fig. 1). The proband was a 35 year-old female (marked with a black arrow in Fig. 1). The present vision of the proband is about 20/400. Fundus examination indicated the optic disk in both eyes was well-defined and presented with a bilateral and symmetrical pallor (Fig. 2 A, B, C). 3-D optical coherence tomography (OCT) scans of the optic nerve head revealed the thickness of retinal nerve fiber layer (RNFL) above and below the optic disk and partial temporal sides was obviously attenuated in both eyes (Fig. 2 D, E). OCT scans showed that the macular central fovea had no obvious abnormality in either eye, but RNFL at the (rostral) nasal side and (macular) parafovea region had a tendency to be thinner (Fig. 2 F,G). Flash visual evoked potential (F-VEP) showed P2 wave latencies in both eyes were normal, but amplitude was decreased, indicating defective conduction of the optic nerves (Fig. 2H).

Taken together, based on the clinical manifestations and pedigree, the diagnosis of the patient from this family is putative ADOA.

Identification of the disease-causing gene. To identify the ADOA-causing gene in this family, we performed capture next generation sequencing (CNGS) to screen a panel of genes previously reported to be retinal disease genes (Fig. 3A, Table S1,S4), including the two known genes (OPA1 and OPA3) linked with ADOA. However, we did not detect any disease-causing gene mutations but identified 6 SNPs (Table S2), which includes two novel DNA variants. We rationalize that the mutation may be located in the region of missing coverage or beyond of the panel of the captured genes (Table S1). To rule out the first possibility, we retrieved the data from the CNGS and observed there was no missing coverage in OPA3 but missing coverage of six exons and a low depth of coverage of ten exons in OPA1 (NM_130837). It indicates that no reliable data of more than half of the coding exons (16 of 30) has been obtained from CNGS. To fill in the missing or verify these data, we designed specific primers (Table S3) to amplify these fragments and then sequenced with Sanger sequencing. The mutation analysis led to identification of 4-bp deletion mutation (gAGA, g is part of intron, AGA is part of exon 30, c.2983-1_2985del) in OPA1 (Fig. 3B). We searched for mutations identified to date in the literature and found this mutation present vision of the proband is about 20/400. Fundus examination indicated the optic disk in both eyes was well-defined and presented with a bilateral and symmetrical pallor (Fig. 2 A, B, C). 3-D optical coherence tomography (OCT) scans of the optic nerve head revealed the thickness of retinal nerve fiber layer (RNFL) above and below the optic disk and partial temporal sides was obviously attenuated in both eyes (Fig. 2 D, E). OCT scans showed that the macular central fovea had no obvious abnormality in either eye, but RNFL at the (rostral) nasal side and (macular) parafovea region had a tendency to be thinner (Fig. 2 F,G). Flash visual evoked potential (F-VEP) showed P2 wave latencies in both eyes were normal, but amplitude was decreased, indicating defective conduction of the optic nerves (Fig. 2H).

Taken together, based on the clinical manifestations and pedigree, the diagnosis of the patient from this family is putative ADOA.

Identification of the disease-causing gene. To identify the ADOA-causing gene in this family, we performed capture next generation sequencing (CNGS) to screen a panel of genes previously reported to be retinal disease genes (Fig. 3A, Table S1,S4), including the two known genes (OPA1 and OPA3) linked with ADOA. However, we did not detect any disease-causing gene mutations but identified 6 SNPs (Table S2), which includes two novel DNA variants.

We rationalize that the mutation may be located in the region of missing coverage or beyond of the panel of the captured genes (Table S1). To rule out the first possibility, we retrieved the data from the CNGS and observed there was no missing coverage in OPA3 but missing coverage of six exons and a low depth (<5) of coverage of ten exons in OPA1(NM_130837). It indicates that no reliable data of more than half of the coding exons (16 of 30) has been obtained from CNGS. To fill in the missing or verify these data, we designed specific primers (Table S3) to amplify these fragments and then sequenced with Sanger sequencing. The mutation analysis led to identification of 4-bp deletion mutation (gAGA, g is part of intron, AGA is part of exon 30, c.2983-1_2985del) in OPA1 (Fig. 3B). We searched for mutations identified to date in the literature and found this mutation
has been previously reported in the Italian population\textsuperscript{14}, although the same mutation was named as c.2819-1\_2821del due to using another isoform for the mutation annotation. The identification of the same variant in the affected members of the Italian and Chinese pedigrees provides support for its pathogenic nature, since it arose independently in different genetic and ethnic backgrounds.

We also scanned c.2983-1\_2985del in two public DNA databases (1000 Genomes Project and ESP6500 Genomes Project) and one in-
Skin fibroblasts from the ADOA subject have abnormal mitochondrial morphology. Although clinical examination indicated degeneration of the retinal ganglion cells of the ADOA patient, it is difficult to directly study patient-specific ganglion cells in vitro or in vivo. As skin fibroblasts are readily accessible by biopsy, we selected this cell type for further study. The mitochondria of the skin fibroblasts were labeled by mitotracker and then their morphology was observed using confocal microscopy.

As shown in Fig. 4A–D, the morphology of mitochondria in patient-derived fibroblasts and control is dramatically different. Specially, control fibroblasts have spotty distribution of mitochondria (here we define “spotty” as length of mitochondrion < 6.9 μm, Fig. 4A, C), however, patient-derived fibroblasts have tubular distribution of mitochondria (“tubular” as length > 6.9 μm, Fig. 4B, D). Statistically, compared with spotty mitochondria in control, only 4.8% ± 2.5% of them from the patient are spotty and the rest (95.2% ± 2.5%) are tubular (Fig. 4A–E). Furthermore, the mitochondrial lengths in the fibroblasts of patient were much larger than that of control (patient, 28.4 ± 5.8 μm versus control, 6.9 ± 1.4 μm, Fig. 4A–D,F). As OPA1 contributes to mitochondrial structure and biogenesis, it would not be surprising if a mutation in this gene alters mitochondrial morphology, and therefore contribute to the pathogenesis of ADOA. Interestingly, the growth rate of the patient fibroblasts was much slower than that of control (data not shown), but no obvious skin disorder was observed in this patient.

Effect of the mutation on OPA1 transcription, protein expression and protein three-dimensional structure. To assess the specific consequence of the c.2983-1_2985del mutation, we extracted mRNA from the patient skin fibroblasts, and amplified OPA1 from the cDNA derived from these cells. These amplified fragments were inserted into a cloning vector followed by sequencing the individual clones carrying the amplified fragments. The sequencing results showed the mutant allele was transcribed and the six nucleotide deletion (c.2984-c.2989, AGAAAG) was present (Fig. 5A), which produced a two lysine residue deletion (995–996 deletion) and a missense mutation (Val997Ile) (Fig. 5B). This showed that the genetic deletion mutation in OPA1 creates a new splicing acceptor (Fig. S1). Since both the wild-type and mutant alleles appear to be transcribed, we counted the numbers of wild type and mutant clones we obtained, and found no significant difference in their numbers (30 clones of wild type versus 22 mutant) (Fig. 5C). This indicates that there is no significant difference at steady-state transcript levels of OPA1 between the wild type and mutant allele.

We then compared the level of OPA1 mRNA expression in the patient skin fibroblasts and control. A slight decrease but no significant of OPA1 mRNA expression was observed in patient skin fibroblasts (Fig. 5D). Western blotting analysis of protein expression extracted from the patient and control fibroblasts.
showed the same level of OPA1 protein expression (Fig. 5E, F). Furthermore, several different isoforms of OPA1 (approximately 73 KDa, 55 KDa and 37 KDa) were detected.

To dissect the molecular mechanism at the level of protein structure, we firstly mapped the mutant residue to the OPA1 protein and found it was located at the C-terminus (Fig. 6A). Multiple sequence alignments were performed and we found that codons 995–997, where the mutation occurred, were located within an extremely conserved region in various species (Fig. 6B).

We predicted the secondary structure of human wild-type and mutant OPA1 using I-TASSER online software. In secondary structure prediction, the C-terminal part of the OPA1 protein (991–1010) forms an alpha helix (Fig. 6B). The 3D model generated by I-TASSER suggests that this alpha helix protrudes into a pocket (Fig. 6C), which will potentially affect the structure of the full protein with functional consequences.

**Discussion**

Optic atrophy is a group of highly heterogeneous inherited diseases\(^{15}\). Clinical variability, both within and among families with the same disease, often makes recognition and classification difficult. Traditionally, classification has relied on the recognition of similar characteristics and similar patterns of transmission, but genetic analysis now permits the diagnosis of this disease in the absence of family history or in the setting of unusual clinical presentations\(^{16}\). Thus, we initially performed CNGS to identify the genetic defects in this family, but failed to discover any mutation in retinal disease gene. According to the previous study, some captured region may be missing in these tested genes\(^{17}\). Thus, to identify the causative mutation for the disease, filling the missing data may be necessary. Here we showed a case of filling missing CNGS data to search the causative mutation for ADOA, which raises more concern for the clinical application of the next generation sequencing.

In most cases, ADOA presents as a non-syndromic, solely bilateral optic neuropathy, but some patients have associated extra-ocular features including sensory-neural hearing loss, myopathy and peripheral neuropathy\(^{18–20}\). At least five mutations in OPA1, p.Arg445His, p.Gly401Asp and p.Leu243*, p.Arg437Glu and p.Ala357Leufs*4 have been reported in patients affected with both optic atrophy and hearing loss\(^{21–23}\). However, the proband bearing the same mutation (c.2983-1_2985del) as identified in the present study in Italian family presented optic atrophy plus phenotype, including the mild bilateral temporal pallor of the optic disc, a thinning of the peripapillary bundle nervous layers in both superior and inferior temporal quadrant bilaterally. The Italian patient also displayed a mild bilateral ptosis, ophthalmoparesis, pes cavus, the left side with a decreased/absent Achilles tendon reflex bilaterally. In our study, the patient only had a progressive decrease of vision with no other symptoms, which indicates the same OPA1 mutation may manifest itself differently and be patient dependent and confirms the heterogeneity of this disease. However, further studies are needed to provide insights into the detailed molecular pathogenesis of the retinal ganglion cells affected by this mutation.

The mutation reported in this study occurs at an intron/exon boundary and we would predict it to affect splicing. One possible splice form (S1, Fig. S1–2) is a result of the destruction of the canonical splice acceptor and creating a new splice acceptor insert site. The second possible splice form (S2, Fig. S2) results from skipping exon 30, in other words, a new transcript with a splicing of exon 29 with exon 31 will be generated (Fig. S2). Sequencing of OPA1 cDNA obtained from skin fibroblasts showed that a new splice acceptor site is created resulting in the deletion of two lysine residues and a missense mutation (Fig. S1–2). The same splicing form has been detected in skeletal muscle of the Italian patient\(^{14}\), which reveals the present mutation does change the splicing both in ectoderm and mesoderm derived tissues.

**Figure 5** | OPA1 mRNA and protein expression in patient skin fibroblasts. (A) Sequencing of clones from OPA1 cDNA PCR products. (B) OPA1 mutation analysis. A two residue deletion (995Lys–996Lys) and a missense mutation (Val997Ile) were observed. (C) Relative OPA1 mRNA expression levels in patient skin fibroblasts (HF-M, human skin fibroblasts with mutation) and control. (D) The transcription of the wild type and mutant allele in patient skin fibroblasts. RT-PCR products, harbors the mutation sequence, were cloned into pET vector; individual clones were picked and then Sanger sequenced. (E) Western blotting for OPA1. (F) The quantitative analysis of Western blotting result was performed using Image J software.
Furthermore, the mutation does not affect the mRNA stability or protein expression. So far, two theories address the cause of ADOA: haploinsufficiency and dominant negative effects. A dominant negative effect is likely to be the case in this family because both the wild-type and mutant allele appear to have similar levels of steady-state transcription, the patient and control fibroblasts have the same level of OPA1 protein expression.

In summary, this study identified a recurrent mutation in OPA1 in an ADOA family. Our study demonstrates a case of filling missing data of CNGS to search the causative mutation for ADOA, which raises more concern for the clinical application of the next generation sequencing. We also showed the potential molecular consequence of the mutation by protein structural modeling and provided more evidence to support a dominant negative effect to explain the disease pathogenesis. Further detailed functional studies are needed to provide further insights to this inherited disease.

Methods

Patient Recruitment. This study conformed to the tenets of the Declaration of Helsinki. It was approved by the Ethics Committee of Eye Hospital, Wenzhou Medical University. Written informed consent was obtained from the recruited individuals. All experiments were performed in accordance with the approved guidelines. Optical coherence tomography (OCT), flash visual evoked potential (F-VEP) and fundus examination were performed as routine retinal ophthalmic examination. A five ml venous blood sample was drawn into an ethylenediaminetetraacetic acid (EDTA) sample tube. Genomic DNA was extracted from peripheral blood leukocytes using the standard phenol/chloroform extraction protocols.

![Figure 6 | Mutant OPA1 protein analysis. (A) Multiple-sequence alignment of OPA1 from different species. The red square indicates the location of the deletion and missense mutation we identified in OPA1 (B) Alpha helical structure of OPA1. The upper sequence is the control; the lower is the OPA1 with deletion/missense mutation. The arrow indicates the location of the deletion/missense mutation in OPA1. The region containing the deletion/missense mutation is predicted to form an alpha helical structure, which was absent from the wild type. (C) In secondary structure prediction, the C-ter part (991–1010) forms an alpha helix. The model generated by I-TASSER suggests that this conserved helix (shown in orange), where the mutation is located, protrudes into a pocket. Interruption between this helix and the rest of the pocket will potentially affect the structural intact of the protein.](www.nature.com/scientificreports)
cDNA synthesis was carried out with M-MLV reverse transcriptase (Invitrogen, cat. No.15596-026) following the manufacturer's instructions. Generation Sequencing was performed as previously described 17. The enriched patient skin fibroblasts and control skin fibroblasts were obtained from skin study are shown in Table S3. For quantitative PCR, the cycling conditions were 95°C for 10 min, followed by 40 cycles of 95°C for 10 s and 60°C for 60 s. qPCR data was captured and analyzed using StepOne software (ver. 2.0). qPCR performed using SYBR® Premix Ex Taq™ II (TaKaRa, cat NO RR820A). The OPA1 relative mRNA expression level in the normal and patient fibroblasts were obtained by normalization to ACTB using the formula 1/Ctmean, minus Ctcontrol. All qPCR data was performed in triplicate.

### Western blotting

For Western blotting, total proteins were extracted from the patient and control skin fibroblasts using RIPA buffer, then fractionated in a 10% SDS-PAGE gel and transferred to PVDF membranes. OPA1 was detected using a mouse anti-OPA1 monoclonal antibody (Santa Cruz, cat No.SC323936) followed by anti-mouse IgG, coupled to IRDye 800CW (Liric Biosciences, cat No. 926-32210). GAPDH was detected using a rabbit anti-GAPDH monoclonal antibody (Biowordpress, cat No. AP0063), followed by anti-rabbit IgG, coupled to IRDye 680 (Liric Biosciences, cat No. 926-68071). Western blotting data was analyzed using Image J software.

| Gene | Exon | Physical location | Length | Sequencing Depth |
|------|------|-------------------|--------|------------------|
| OPA1 | 1    | chr:19331117-193311247 | 130   | 60               |
| OPA1 | 2    | chr:19333251-193332830 | 319   | 18               |
| OPA1 | 3    | chr:19333446-193335375 | 129   | 10               |
| OPA1 | 4    | chr:19334955-193350855 | 130   | 3               |
| OPA1 | 5    | chr:19335534-193356644 | 130   | 10               |
| OPA1 | 6    | chr:19336626-193367676 | 130   | 10               |
| OPA1 | 7    | chr:19334387-193344000 | 129   | 18               |
| OPA1 | 8    | chr:19334936-193349492 | 130   | 2               |
| OPA1 | 9    | chr:19335319-193353323 | 129   | 0                |
| OPA1 | 10   | chr:19335692-193357091 | 129   | 0                |
| OPA1 | 11   | chr:19335732-193357582 | 130   | 36               |
| OPA1 | 12   | chr:19336059-193360658 | 129   | 2                |
| OPA1 | 13   | chr:19336076-193360865 | 129   | 4                |
| OPA1 | 14   | chr:19336113-193361262 | 130   | 2                |
| OPA1 | 15   | chr:19336130-193361431 | 130   | 2                |
| OPA1 | 16   | chr:19336176-193361894 | 131   | 9                |
| OPA1 | 17   | chr:19336333-193363442 | 129   | 2                |
| OPA1 | 18   | chr:19336348-193363617 | 129   | 2                |
| OPA1 | 19   | chr:19336486-193349476 | 130   | 4                |
| OPA1 | 20   | chr:19336582-193365955 | 129   | 3                |
| OPA1 | 21   | chr:19336557-193366868 | 129   | 0                |
| OPA1 | 22   | chr:19337265-193372816 | 166   | 8                |
| OPA1 | 23   | chr:19337486-193375021 | 153   | 0                |
| OPA1 | 24   | chr:19337665-193376794 | 129   | 9                |
| OPA1 | 25   | chr:19337724-193377375 | 130   | 5                |
| OPA1 | 26   | chr:193380610-193380751 | 141   | 20               |
| OPA1 | 27   | chr:19382662-19382791 | 129   | 0                |
| OPA1 | 28   | chr:19384066-19384196 | 130   | 20               |
| OPA1 | 29   | chr:19384894-19385078 | 129   | 6                |
| OPA1 | 30   | chr:193409819-193409948 | 129   | 0                |

**OPA1**

| Gene | Exon | Physical location | Length | Sequencing Depth |
|------|------|-------------------|--------|------------------|
| OPA1 | 1    | chr:194605671-194605716 | 398   | 220              |
| OPA1 | 2    | chr:194608880-194608822 | 142   | 109              |

**Patient skin fibroblasts and control skin fibroblasts were obtained from skin biopsies.**

Capture Next Generation Sequencing and Bioinformatics Analysis. Capture Next Generation Sequencing was performed as previously described. The enriched patient skin fibroblasts and control skin fibroblasts were obtained from skin study are shown in Table S3. For quantitative PCR, the cycling conditions were 95°C for 10 min, followed by 40 cycles of 95°C for 10 s and 60°C for 60 s. qPCR data was captured and analyzed using StepOne software (ver. 2.0). qPCR performed using SYBR® Premix Ex Taq™ II (TaKaRa, cat NO RR820A). The OPA1 relative mRNA expression level in the normal and patient fibroblasts were obtained by normalization to ACTB using the formula 1/Ctmean, minus Ctcontrol. All qPCR data was performed in triplicate.

### Western blotting

For Western blotting, total proteins were extracted from the patient and control skin fibroblasts using RIPA buffer, then fractionated in a 10% SDS-PAGE gel and transferred to PVDF membranes. OPA1 was detected using a mouse anti-OPA1 monoclonal antibody (Santa Cruz, cat No.SC323936) followed by anti-mouse IgG, coupled to IRDye 800CW (Liric Biosciences, cat No. 926-32210). GAPDH was detected using a rabbit anti-GAPDH monoclonal antibody (Biowordpress, cat No. AP0063), followed by anti-rabbit IgG, coupled to IRDye 680 (Liric Biosciences, cat No. 926-68071). Western blotting data was analyzed using Image J software.
Acknowledgments

We thank the families for their participation in this project. We are indebted to Dr. Jinyu Wu (Institute of Genomic Medicine, Wenzhou Medical University, China) for scanning the present mutation in in-house exome database and Dr. Ji Sun (Department of Pharmacology, University of Washington, Seattle, WA, USA) for structural modeling. This work was supported by grants from the Chinese National Program on Key Basic Research Project (973 Program, 2013CB967502, FG), Natural Science Foundation of China (81201181/H1818, FG), Zhejiang provincial & Ministry of Health research fund for medical sciences (WKJ2013-2-023, FG), Medical Scientific Projects from Health Bureau of Zhejiang Province (2011ZDA016, WL), Wenzhou Medical University Grant (QTJ 12011, FG and KYQD131102, LPZ).

Author contributions

F.G. conceived the idea and supervised the research. L.P.Z., W.S., L.M.S., X.Z., L.L.C., X.L.G., Y.F.W., W.L., W.Z. and Z.B.J. collected the samples and performed the experiments. Q.J.M., J.Q. and F.G. performed data analyses, F.G. wrote the manuscript. All authors have read and approved the final manuscript.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Zhang, L. et al. A recurrent deletion mutation in OPA1 causes autosomal dominant optic atrophy in a Chinese family. Sci. Rep. 4, 6936; DOI:10.1038/srep06936 (2014).

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder in order to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-sa/4.0/