Molecular Genetics & Genomic Medicine

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ORIGINAL ARTICLE OPEN ACCESS

A Novel Mutation of FOXC1 (P136L) in an Axenfeld–Rieger Syndrome Patient With a Systematized Delusion of Jealousy: A Case Report and Literature Review

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Received: 11 March 2024 | **Revised:** 20 August 2024 | **Accepted:** 23 August 2024

Funding: This research was supported by the Japan Society for the Promotion of Science 22K07562, 22K07597, 23K07016.

Keywords: Axenfeld–Rieger syndrome | FOXC1 | literature review | neuropsychiatric symptoms

ABSTRACT

Background: The main features of Axenfeld–Rieger Syndrome (ARS) are ocular, auditory, neurological, and morphological brain abnormalities. Mutations in forkhead box protein C1 (FOXC1) are among the responsible genes causing ARS, but neuropsychiatric features have rarely been reported. The case of an ARS patient (a 77-year-old man) with delusions of jealousy and impairment of working memory, in addition to the main clinical features, glaucoma and leukoencephalopathy, is presented.

Methods: The mutation in the patient's genome was found with whole exome sequencing and in silico analysis using PolyPhen-2 and SIFT. Furthermore, AlphaFold2 and PyMOL were used to predict the protein structure based on the mutation.

Results: A novel mutation at the forkhead domain of FOXC1 gene (c.408C>A, p.Phe136Leu) was found and confirmed in the patient's family, and it was predicted to cause protein damage; the SIFT score was 0, meaning deleterious, and the PolyPhen2 result also indicated damaging (score: 0.997). The predicted protein structure based on the novel mutation was different from that of the native structure. In the literature review, 6 of 95 (6.3%) cases showed neuropsychiatric features. Of them, 5 of 6 (83.3%) mutations were located in the forkhead domain.

Conclusion: A novel mutation was found in the FOXC1 gene (c.408C>A, p.Phe136Leu), which possibly induces delusions of jealousy and impairment of working memory, as well as features of ARS, by changing the protein structure. Mutations in that domain of the FOXC1 gene may be important not only for ocular abnormalities but also for brain function.

1 | Introduction

Axenfeld–Rieger syndrome (ARS) is an autosomal dominant disorder that potentially causes ocular, hearing, neurological, and morphological brain abnormalities (Muzyka et al. 2023). It is estimated that ARS affects 1 in 50,000–100,000 newborns (Seifi and Walter 2018). The corresponding genes are forkhead box protein C1 (FOXC1; 6p25) and pituitary homeobox 2 (PITX2; 4q25), and their functions are relevant to the regulation of ocular, craniofacial, neurological, and cardiovascular development (French 2021; French et al. 2014). The genetic variants related to ARS pathogenesis have been found, and each variant indicates several clinical features even in the same domain of the gene (Muzyka et al. 2023). Based on the clinical features, there are three types of ARS: type 1 (OMIM: 180500), ocular and systemic features; type 2 (OMIM: 601499), partial edentulism, microdontia, and early dedentation; and type 3 (OMIM: 602482), cardiac defects and/or sensorineural hearing loss (Seifi and Walter 2018; Chang et al. 2012). However, most case reports and series of ARS patients focused only on the ocular features. When focusing on genetic variants of FOXC1, several phenotypes including brain atrophy,

hydrocephalus, and leukoencephalopathy have been reported in addition to the main clinical features (Muzyka et al. 2023). FOXC1 belongs to the FOX class of transcription factors and has the forkhead domain (110 amino-acid DNA-binding domain), which binds to a conserved sequence and regulates target gene expressions.

FOXC1 mutations in the forkhead domain are well shown. However, the ages reported in previous reports were from relatively young patients, and the symptoms of old patients remain unknown. Furthermore, the neuropsychiatric features of ARS are still unclear but several previous reports showed neuropsychiatric changes including learning difficulties and epilepsy (D'Haene et al. 2011), intellectual disability (Souzeau et al. 2017; Reis et al. 2016), and impairment of working memory (Kumar, Chambers, and Dhamija 2017).

The aim of this study was to explore the genetic variant using whole exome sequencing (WES) in a family having at least two patients and to conduct in silico analysis to evaluate how the variant affects the protein structure. In addition, a literature review was conducted to elucidate possible neuropsychiatric features of ARS in old age.

2 | Case Presentation

2.1 | Medical History

The patient was a 77-year-old Japanese man. From the age of 72 years, delusions of jealousy in relation to his wife caused a major problem in his household. The subjects of the delusions of jealousy were strangers and his brother-in-law. The patient then visited the psychiatry department as an outpatient and was diagnosed as having dementia with Lewy bodies (DLB) due to visual hallucinations and delusions. Risperidone 1 mg/day was prescribed for the delusions of jealousy, but the symptoms remained. Finally, the subject of the delusions of jealousy became a systematized one which means severe and persistent, and the patient said “one person married my wife” and “the radio has reported that one person and his wife had a child”. He was referred to our university hospital for detailed examinations to make an accurate diagnosis. On the routine medical examination, there was impairment of working memory, but no other cognitive impairments, including disorientation and episodic memory, were found. Neuropsychological tests could not be conducted due to impaired vision and bilateral hearing loss.

2.2 | Family History

The family pedigree including the family history is shown in Figure 1A. His medical history included surgical procedures and diseases requiring medication. Bilateral glaucoma and an atrial septal defect were found at birth. He underwent surgery for appendicitis at the age of 17 years, for the atrial septal defect at the age of 27 years, and for a myelomeningocele at the age of 41 years. Bilateral hearing loss was diagnosed at 20 years of age, and it worsened when he was about 70 years old. At the age of 47 years, he was diagnosed with rheumatoid arthritis and is currently taking medication. The patient was referred to ophthalmology and otorhinolaryngology for detailed examinations in our university hospital. On ophthalmological examination, no morphological abnormalities, such as of the posterior embryonic ring, pupil, and iris atrophy, were found, although the iris showed mild atrophy. The patient was taking latanoprost timolol maleate and brinzolamide eye drops. However, his intraocular pressure was still high (35 mmHg), and there was a risk of blindness of the right eye if the intraocular pressure could not be decreased. On otorhinolaryngological examination, the patient was diagnosed as having bilateral sensorineural hearing loss. The pure tone audiometry showed the following: right, 96.7 dB; left, 100.0 dB (Figure 1B). In daily life, the patient was using a hearing aid.

Based on the previous report that FOXC1 mutation caused leukoencephalopathy (Kumar, Chambers, and Dhamija 2017), magnetic resonance imaging (MRI) was performed after the mutation in this case was detected. Leukoencephalopathy was found in addition to temporal and parietal atrophy (Figure 1C). On neurological examination, resting tremor and cogwheel rigidity of the elbow were found bilaterally. To exclude the Lewy body diseases (Parkinson's disease and DLB), the patient underwent dopamine active transporter single photon emission computed tomography (DaT scan) and ^{123}I-MIBG myocardial scintigraphy, and both examinations were normal (Figure 1D,E). It was concluded that the resting tremor and cogwheel rigidity of the elbow were caused by the antipsychotic risperidone.

There was limited information available for family members. I-3 had congenital glaucoma, but other features were uncertain. I-2, II-1, and II-2 were diagnosed as having dementia. Although II-1 had stolen money in the household and clothes in a shop, it is unclear whether the diagnosed dementia was a typical one such as Alzheimer's disease. III-3 showed congenital glaucoma and an atrial septal defect and had undergone surgical procedures for them. Furthermore, he was diagnosed with a major depressive disorder and was taking an antidepressant. Finally, the patient and two family members (II-3, II-4, and III-3) participated in genetic counseling at our university.

3 | Methods

3.1 | Whole Exome Sequencing

Extraction of gDNA was performed using the QIAamp DNA Blood Mini Kit (Qiagen; Tokyo, Japan) according to the manufacturer's protocol. Leukocyte DNA (proband and affected subjects: II-3 and III-3; unaffected subject: II-4) was submitted for WES (Macrogene Japan; Tokyo, Japan) to detect mutations of PITX2, FOXC1, and other genes. WES was performed using HiSeq 4000 (Illumina; San Diego, CA, USA). The libraries were prepared by SureSelect V6-Post before sequencing. The genome analysis pipeline was run based on the 1000 Genomes Project data and widely used software: bwa-0.7.17 (Li and Durbin 2009), picard-tools-2.18.2-SNAPSHOT (Picard Team), GATKv4.0.5.1 (McKenna et al. 2010), and SnpEff 4.3 (Cingolani 2022).

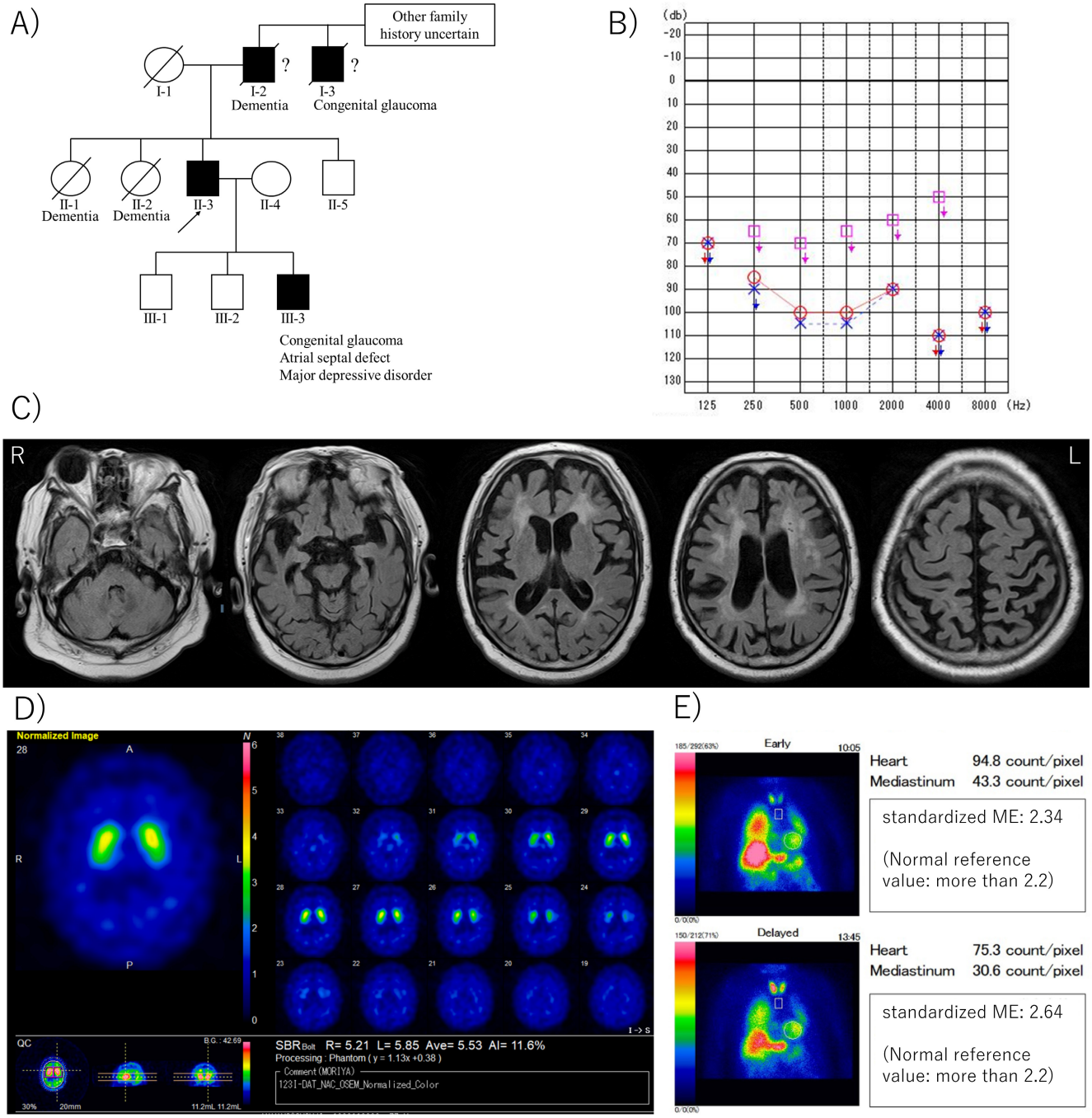

FIGURE 1 | Family pedigree and clinical features of the proband (II-3). (A) Family pedigree. Symbols for proband and affected individuals are colored in. The proband (II-3) and his son (III-3) have novel FOXC1 mutation by whole exome sequencing. (B) The audiogram shows bilateral sensorineural hearing loss (red, right ear; blue, left ear). (C) Brain magnetic resonance imaging data from the patient (T2-weighted-fluid-attenuated inversion recovery). A high-intensity area appears in the periventricular white matter. Representative dopamine active transporter single photon emission computed tomography (D) and ^{123}I-MIBG myocardial scintigraphy (E) show normal patterns. ARS, Axenfeld–Rieger Syndrome; MIBG, metaiodobenzylguanidine.

Paired-end sequences produced by the NovaSeq Instrument were first mapped to the human reference genome (hg38) using the mapping program 'BWA'. PCR duplicates were removed using MarkDuplicates.jar from the 'Picard-tools' package, which requires reads to be sorted. Based on the BAM file previously generated, variant genotyping for each sample was performed with Haplotype Caller of GATK. Filtered variants were annotated with another program called SnpEff and filtered with dbSNP 151.

3.2 | In Silico Prediction

To explore whether a variant causes protein damage, in silico analysis was performed using PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) and SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html). AlphaFold2 (Jumper et al. 2021) was used to evaluate how a variant affects protein structure. Then, the PDB file was visualized by PyMOL (The PyMOL Molecular Graphics System, Version 2.0, Schrödinger, LLC.).

TABLE 1 | Mutations in PITX2 and FOXC1 genes from whole exosome sequencing.

Gene symbol	Chromosome, position (GRCh38)	Protein domain	HGVS.c	HGVS.p	dbSNP151	II-3	II-4	III-3
PITX2	Chr4:110,620,968	Intron	c.411+196C>T		rs2278783	Heterozygous	Homozygous	Heterozygous
PITX2	Chr4:110,620,998	Intron	c.411+166C>T		rs2278782	Heterozygous	Heterozygous	Heterozygous
PITX2	Chr4:110,622,185	Intron	c.205+71A>G		rs28510307	Heterozygous	Heterozygous	Heterozygous
PITX2	Chr4:110,633,038	Intron	c.-10-30T>C		rs2276966	Heterozygous	Heterozygous	Heterozygous
FOXC1	Chr6:1,610,853	Exon 1 Forkhead	c.408C>A	p.Phe136Leu		Heterozygous		Heterozygous
FOXC1	Chr6:1,611,567	Exon 1	c.1139_1141dupGCG	p.Gly380dup	rs545470261;rs76840944	Heterozygous	Heterozygous	Homozygous
FOXC1	Chr6:1,611,782	Exon 1	c.1359_1361dupCGG	p.Gly454dup	rs572346201	Heterozygous		Heterozygous

Abbreviations: dbSNP, Single Nucleotide Polymorphism Database; GRCh, Genome Research Consortium human; HGVS, Human Genome Variation Society.

3.3 | Ethics Statement

This study was approved by the ethics review board of Ehime University Graduate School of Medicine (Approval Number: 31-K8), and informed consent was obtained from all participants.

4 | Results

4.1 | Whole Exome Sequencing

The average coverage for data was 99.77%, and the fraction of target regions covered with at least 10× and 20× was 98.90% and 93.80%, respectively. The known intron variants in PITX2 gene, a novel missense variant, and two insertions were found in FOXC1 gene (Table 1). No other genetic mutations that could cause these symptoms were found (Table S1). The novel single nucleotide variation (c.408C>A, p.Phe136Leu) and rs572346201 (c.1359_1361dupCGG, p.Gly454dup) in FOXC1 gene were found only in proband affected subjects (II-3 and III-3). Because previous reports have shown that rs572346201 is not a pathogenic variant (Medina-Trillo et al. 2016; Micheal et al. 2016), the other novel variant was selected for the following in silico analysis.

4.2 | In Silico Analysis

The FOXC1 gene is broadly expressed not only in the eye and the heart but also in the brain (https://www.genecards.org/). FOXC1 protein is constructed of active domain 1, forkhead domain, inhibition domain, and active domain 2. The patient's mutation was novel and located in the forkhead domain (Figure 2A). The SIFT score for the novel mutant was 0, which meant deleterious; the PolyPhen2 result also indicated damaging: HumVar (score: 0.997, sensitivity: 0.27, specificity: 0.98). In silico prediction of the 3D structure showed a difference between Phe136 and Leu136 (Figure 2B). The difference in the 3D structure was clear when both structures were merged (Figure 2C).

4.3 | Literature Review

A literature review was performed to determine whether FOXC1 mutations cause glaucoma, anterior segment dysplasia, cardiac abnormalities, facial/dental malformations, hearing loss, and neuropsychiatric findings. A total of 94 reports were found, and they and the present mutation are listed in order of amino acid position in Table 2. As expected, ocular information was abundant. However, in most cases, the age was unknown, although the age when glaucoma was diagnosed was well reported. In terms of neuropsychiatric findings, 6/95 (6.3%) showed neuropsychiatric features as follows: #35, learning difficulties; #50, epilepsy; #61, intellectual disability; #62, leukoencephalopathy and impairment of working memory; #88, mental retardation; and the present case. Of the mutations, 5 of 6 (83.3%) were located in the forkhead domain.

5 | Discussion

The present report is the first to describe an ARS patient having a systematized delusion and conduct a literature review to consider whether FOXC1 mutations cause neuropsychiatric symptoms.

The patient had been diagnosed with DLB due to visual hallucinations, parkinsonism (resting tremor and cogwheel rigidity of the elbow), and cognitive impairment. However, delusions of jealousy

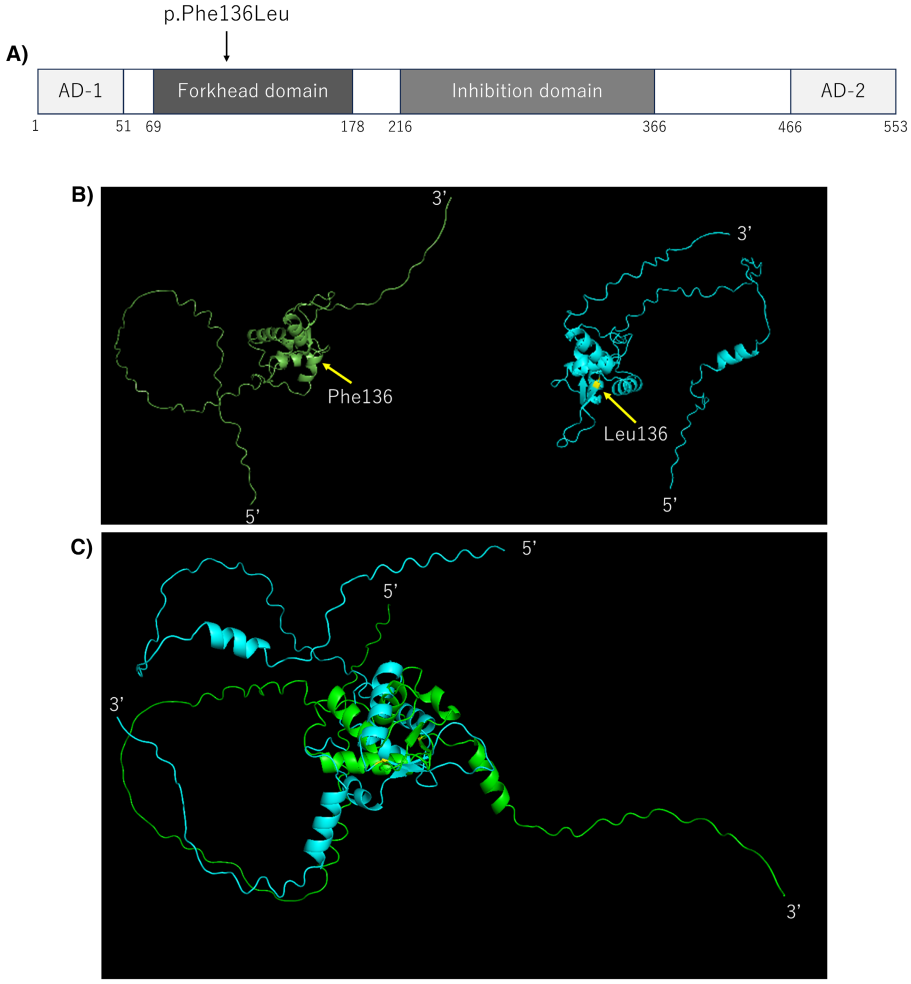

FIGURE 2 | The protein structure of FOXC1 and predicted protein structure based on the novel mutation. (A) The FOXC1 protein is constructed of active domain 1, forkhead domain, inhibition domain, and active domain 2. The novel mutation (c.408C>A, p.Phe136Leu) is located in the forkhead domain (black arrow). (B) The predicted protein structures for both patterns (Phe136, green; Leu136, cyan) and the mutation point (yellow arrow) are shown. (C) Merged predicted protein structure (Phe136, green; Leu136, cyan). FOXC1, forkhead box protein C1.

and Parkinsonism were misunderstood as visual hallucinations and side effects of risperidone, respectively. The cognitive impairment was only an impairment of working memory, and it did not fluctuate. Then, another disease was considered based on the criteria for the clinical diagnosis of DLB (McKeith et al. 2017). Furthermore, the association between rs2200733 in the PITX2 gene and dementia was reported (Rollo et al. 2015), but the mutation of rs2200733 was not found in this patient. Finally, the patient was diagnosed as having ARS type 3 because of the congenital glaucoma, atrial septal defect, and sensorineural hearing loss. Similar to the present case, leukoencephalopathy was reported in an 8-year-old girl, and she also had an impairment of working memory (Kumar, Chambers, and Dhamija 2017). Although leukoencephalopathy is caused as the phenotype of genetic reasons (Vanderver 2016), the association between FOXC1 mutations and MRI findings was not well discussed. In this case, considerable neurological findings by leukoencephalopathy were not found. Taken together, it was concluded that the novel mutation in the FOXC1 gene and/or leukoencephalopathy may cause delusions of jealousy and impairment of working memory.

The FOXC1 gene belongs to the forkhead box family, and the proteins are responsible for the regulation of several gene expressions as transcription factors. Most forkhead transcription factors share a highly conserved forkhead DNA-binding domain (110 amino acid) that binds to specific sequences of target genes. Furthermore, it has been reported that FOX proteins are connected to some transcription factors (e.g., GATA4 and NKX2.5) (Schmitt-Ney 2020). The novel mutation (c.408C>A, p.Phe136Leu) is located in the forkhead domain of the gene. Taken together, the novel mutation affects the regulatory function of downstream gene expressions and possibly causes neuropsychiatric symptoms and cognitive dysfunction. The predicted structure change also contributes to these symptoms by affecting protein function.

Surprisingly, only 5 of 95 (5.3%) reports included neuropsychiatric symptoms and cognitive dysfunction based on FOXC1 mutations. Those symptoms often emerge in old age, but the reported ages were relatively young (1-month-old to 77-year-old). It is possible that the reported cases may develop such symptoms in the future. Obviously, it is unclear whether FOXC1 mutations are relevant to the symptoms because the reported symptoms of all cases are from case reports or series. Interestingly, most of the mutations (5/6, 83.3%) related to neuropsychiatric findings including learning difficulties and epilepsy (D'Haene et al. 2011), intellectual disability (Souzeau et al. 2017), and impairment of working memory (Kumar, Chambers, and Dhamija 2017) in that gene were located in its forkhead domain. As mentioned above, the forkhead domain is a functionally important domain responsible for binding target genes and regulating expressions of those genes. These findings may suggest that mutations in the forkhead domain cause more neuropsychiatric symptoms than those in other domains when considering that the FOXC1 gene is broadly expressed in the brain in humans (https://www.genecards.org/).

TABLE 2 | Previous reports which found FOXC1 mutations and clinical features including neuropsychiatric findings.

#	HGVS.c	HGVS.p	Protein domain	Age when reported	Glaucoma	Anterior segment dysplasia	Cardiac	FacialDental	Hearing loss	Neuropsychiatric findings	PMID
1	c.4C>T	p.Gln2*	Active 1	10-year-old	+	+	NR	NR	NR	NR	12592227
2	c.12delC	p.Arg4fs	Active 1	NR	+	NR	NR	NR	NR	NR	18708620
3	c.26–47ins	p.Ser9fs	Active 1	13-year-old	+	+	NR	NR	NR	NR	11740218
4	c.67C>T	p.Gln23*	Active 1	NR in 9 subjects	+	+	+	+	+	NR	10713890
5	c.81_89del9	p.Arg28_30del	Active 1	NR	+	NR	NR	NR	NR	NR	18708620
6	c.92_100del	p.Ala31_ Ala33del	Active 1	4 and 9-year-old	+	+	NR	−	NR	NR	27463523
7	c.93_102del10	p.A31fs	Active 1	NR	+	+	−	−	−	NR	9792859
8	c.99_108del10	p.Gly33fs	Active 1	NR	+	+	NR	NR	NR	NR	11170889
9	c.100_109del10	p.Gly34fs	Active 1	25 and 34-year-old	−	+	NR	NR	NR	NR	28513611
10	c.116_123del8	p.A39fs	Active 1	NR	+	+	NR	NR	NR	NR	11170889
11	c.143C>A	p.Ser48*	Active 1	NR	+	+	−	−	−	−	16936096
12	c.153_163del11	p.Ala51fs	Active 1	NR in 3 subjects	NR	+	NR	NR	NR	NR	9620769
13	c.161T>A	p.Met161Lys		1-month-old	+	+	NR	NR	NR	NR	18484311
14	c.192C>G	p.Tyr64*		23-month-old	+	+	−	+	NR	NR	28432732
15	c.210_210delG	p.Gln70fs*	Forkhead	NR in 3 subjects	+	+	+	NR	+	NR	9620769 (10474162)
16	c.235C>A	p.Pro79Thr	Forkhead	1-month twin and 3-year-old	+	+	+	NR	NR	NR	11589884
17	c.236C>G	p.Pro79Arg	Forkhead	NR	+	+	−	+	−	NR	16936096
18	c.236C>T	p.Pro79Leu	Forkhead	NR	+	+	NR	NR	NR	NR	11170889
19	c.245G>C	p.Ser82Thy	Forkhead	NR in 5 subjects	+	+	+	−	+	NR	9792859
20	c.246C>A	p.Ser82Arg	Forkhead	7-year-old	+	+	+	+	−	NR	34715865
21	c.253G>C	p.Ala85Pro	Forkhead	3-year-old	+	+	+	NR	NR	NR	17653043
22	c.255GC>TT	p.Leu86Phe	Forkhead	More than 41-year-old	+	+	+?	+	NR	NR	14578375
23	c.256C4T	p.Leu86Phe	Forkhead	6 and 37-year-old	+	−	NR	NR	NR	NR	28513611
24	c.261C>G	p.Ile87Met	Forkhead	NR	+	+	NR	NR	NR	NR	9792859

(Continues)

TABLE 2 | (Continued)

#	HGVS.c	HGVS.p	Protein domain	Age when reported	Glaucoma	Anterior segment dysplasia	Cardiac	FacialDental	Hearing loss	Neuropsychiatric findings	PMID
25	c.262_265insC	p.Thr88fs	Forkhead	NR	+	+	NR	NR	NR	NR	11170889
26	c.268G>A	p.Ala90Thr	Forkhead	56-year-old	+	+	NR	NR	NR	NR	28513611
27	c.269C>A	p.Ala90Asp	Forkhead	0-year-old	+	+	+	NR	−	NR	30653210
28	c.272T>G	p.Ile91Ser	Forkhead	11-year-old	+	+	NR	NR	NR	NR	11740218
29	c.272T>C	p.Ile9lThr	Forkhead	NR in 10 subjects	+	+	NR	NR	NR	NR	15477465
30	c.286insG	p.Asp96fs	Forkhead	15-year-old	+	+	NR	NR	NR	NR	11740218
31	c.286dupG	p.Asp96fs	Forkhead	NR	+	+	−	−	−	NR	20881294
32	c.316C>T	p.Gln106*	Forkhead	NR	+	+	−	−	−	NR	20881294
33	c.316C>T	p.Gln106*	Forkhead	10, 13, 41, and 42-year-old	+	+	−	−	−	NR	28513611
34	c.317delA	p.Gln106Argfs	Forkhead	10, 11, 12, and 40-year-old	+	+	−	−	−	NR	23687430
35	c.325A>G	p.Met109Val	Forkhead	NR	+	+	−	+	+	Learning difficulties	20881294
36	c.335del	p.Phe112Sfs	Forkhead	NR	+	+	−	+	−	NR	20881294
37	c.335T>C	p.Phe112Ser	Forkhead	NR in 3 subjects	+	+	+?	NR	NR	NR	9620769 (10474162)
38	c.335T>C	p.Phe112Ser	Forkhead	12, 13, 37, 40, 76-year-old	+	+	+	+	NR	NR	12614756
39	c.339T>C	p.Tyr115Ser	Forkhead	NR in 2 subjects	+	+	−	−	+	NR	16936096
40	c.349delG	p.Asp117Thrfs	Forkhead	NR	+	+	−	+	−	NR	30653210
41	c.358C>T	p.Gln120*	Forkhead	15-year-old and NR in 4 subjects	+	+	+	−	−	NR	18498376
42	c.367C>T	p.Gln123*	Forkhead	NR in 3 subjects	+	+	NR	NR	NR	NR	12592227
43	c.378C>G	p.Ile126Met	Forkhead	NR in 2 subjects	NR	+	NR	NR	NR	NR	9620769
44	c.378A>G	p.His128Arg	Forkhead	NR	+	NR	NR	NR	NR	NR	18708620
45	c.380G>A	p.Arg127His	Forkhead	10-month-old	+	+	NR	NR	NR	NR	18484311
46	c.380T>G	p.Arg127Leu	Forkhead	NR	+	+	+	−	NR	NR	24914578
47	c.388C>T	p.Leu130Phe	Forkhead	NR in 2 subjects	−	NR	NR	NR	NR	NR	17210863

(Continues)

TABLE 2 | (Continued)

#	HGVS.c	HGVS.p	Protein domain	Age when reported	Glaucoma	Anterior segment dysplasia	Cardiac	FacialDental	Hearing loss	Neuropsychiatric findings	PMID
48	c.392C>T	p.Ser131Leu	Forkhead	NR	+	+	NR	NR	NR	NR	11170889
49	c.392C>A	p.Ser131*	Forkhead	NR	+	+	−	+	NR	Epilepsy	20881294
50	c.392C>G	p.Ser131Trp	Forkhead	NR	−	+	−	+	−	NR	20881294
51	c.402G>A	p.Cys135Try	Forkhead	NR	+	NR	NR	NR	NR	NR	18708620
52	c.408C>A	p.Phe136Leu	Forkhead	77-year-old and NR	+	−	+	−	+	Delusion of jealousy Impairment of working memory Major depressive disorder	Present study
53	c.409_411del	p.Val137del	Forkhead	NR	+	+	−	+	−	NR	30653210
54	c.412A>G	p.Lys138Glu	Forkhead	NR	+	+	−	−	−	NR	30653210
55	c.437_453del17	p.Pro146fs	Forkhead	38-year-old and NR in 4 family members	+	+	−	−	+	NR	17653043
56	c.446G>A	p.Gly149Asp	Forkhead	NR	+	+	+	−	−	NR	16936096
57	c.454T>C	p.Trp152Arg	Forkhead	9 and 13-year-old	+	+	NR	+	NR	NR	27463523
58	c.454T>G	p.Trp152Gly	Forkhead	0-year-old	+	+	NR	NR	NR	NR	19279310
59	c.456G>A	p.Trp152*	Forkhead	38-year-old and NR in 5 family members	+	+	−	+	−	NR	16638984
60	c.457A>C	p.Thr153Pro	Forkhead	NR in 4 family members	+	+	−	+	+	NR	30653210
61	c.457A>C	p.Thr153Pro	Forkhead	4, 17, 37, and 54-year-old	+	+	+	−	+	Intellectual disability	28513611
62	c.477C>G	p.Tyr159*	Forkhead	8-year-old	+	+	−	−	−	Leukoencephalopathy Impairment of working memory	27697311
63	c.481A>G	p.Met161Val	Forkhead	NR in 2 subjects	+	+	+	−	+	NR	16936096
64	c.482T>A	p.Met161Lys	Forkhead	NR in 3 subjects	+	+	NR	NR	NR	NR	12592227
65	c.482T>A	p.Met161Lys	Forkhead	NR in 3 subjects	+	+	NR	NR	NR	NR	12454026

(Continues)

TABLE 2 | (Continued)

#	HGVS.c	HGVS.p	Protein domain	Age when reported	Glaucoma	Anterior segment dysplasia	Cardiac	FacialDental	Hearing loss	Neuropsychiatric findings	PMID
66	c.487G>T	p.Glu163*	Forkhead	NR	+	+	−	−	+	NR	30653210
67	c.494G>C	p.Gly165Arg	Forkhead	50-year-old	+	+	−	+	−	NR	15277473
68	c.506G>C	p.Arg169Pro	Forkhead	5-year-old	+	+	−	−	+	NR	15277473
69	c.508C>T	p.Arg170Trp	Forkhead	NR in 5 subjects	+	+	+	−	−	NR	23239455
70	c.516_518delGCG	p.Arg173del	Forkhead	5-year-old	+	+	−	+	+?	NR	34809627
71	c.599_617del19	p.Gln200fs		26-year-old	+	+	−	−	−	NR	28513611
72	c.605delC	p.Pro202Argfs		NR	+	+	−	+	−	NR	20881294
73	c.609delC	p.Ala204Argfs		NR in 3 subjects	+	+	−	+	−	NR	21837767
74	c.666_681del16	p.Ile223Profs	Inhibition	1 and 28-year-old	+	+	+	−	−	NR	28513611
75	c.692_696del5	p.Gly231Valfs	Inhibition	NR	+	+	NR	NR	NR	NR	20881294
76	c.718_719delCT	p.Leu240Valfs	Inhibition	NR	+	+	−	+	−	NR	30653210
77	c.718_719delCT	p.Leu240Valfs	Inhibition	11-year-old	−	+	−	−	−	NR	16638984
78	c.719delT	p.Leu240Argfs	Inhibition	NR in 3 subjects	+	+	+	−	−	NR	30514661
79	c.738delG	p.Leu246fs	Inhibition	NR	+	+	−	+	−	NR	16936096
80	c.780dup	p.Asp261Argfs	Inhibition	NR	NR	NR	NR	NR	NR	NR	20881294
81	c.816_817delinsG NR	p.Ser272Argfs	Inhibition	NR	NR	NR	NR	NR	NR	NR	20881294
82	c.853dup25	p.Ala291fs	Inhibition	NR	+	NR	NR	NR	NR	NR	18708620
83	c.889C>T	p.Pro297Ser	Inhibition		+	+	−	−	−	NR	19793056
84	c.889C>T	p.Pro297Ser	Inhibition	+	+	NR	NR	NR	NR	NR	26220699
85	c.925_949del25	p.Ser309Cysfs	Inhibition	44, 46, 50, 69, and 77-year-old	+	+	−	−	−	NR	28513611
86	c.980_981del	p.Glu327Alafs	Inhibition	NR	NR	NR	NR	NR	NR	NR	20881294
87	c.1142_1144insGGC	p.Gly379Glyins		NR in 3 subjects	+	+	−	−	−	NR	26240509
88	c.1193_1196dup	p.Met400Serfs			+	+	−	−	+	Mentar retardation (IQ = about 60)	27272408
89	c.1265C>A	p.Ser422*		29 and 33-year-old	+	+	−	−	−	NR	28513611

(Continues)

TABLE 2 | (Continued)

#	HGVS.c	HGVS.p	Protein domain	Age when reported	Glaucoma	Anterior segment dysplasia	Cardiac	Facial	Dental	Hearing loss	Neuropsychiatric findings	PMID
90	c.1362_1364insCGG	p.Gly452insArg		NR in 2 subjects	+	+	–	–		–	NR	20881294
91	c.1491C>G	p.Tyr497*	Active 2	6 and 41-year-old	+	+	–	–		+	NR	28513611
92	c.1491C>G	p.Tyr497*	Active 2	NR	+	NR	–	+		–	NR	20881294
93	c.1494delG	p.Gly499Alafs*	Active 2	20, 45, and 85-year-old	+	+		+				
94	c.1511delT	Asn503fs	Active 2	NR	+	+	–	–		–	NR	16936096
95	c.1512delG	p.Phe504fs	Active 2	NR	+	+	NR	NR		NR	NR	11170889

Abbreviation: HGVS, Human Genome Variation Society.
*Indicates that the mutation results in a stop codon.

The finding that the patient's son with the same mutation in that gene showed depressive symptoms may confirm its involvement in the pathogenesis of brain dysfunction. Functional analysis including an animal model is necessary to determine the relationship between each mutation and neuropsychiatric features. Furthermore, examination of more reports of FOXC1 mutations will be important.

6 | Conclusions

A novel mutation in the FOXC1 gene (c.408C>A, p.Phe136Leu) was identified in an elderly man, and it may have induced delusions of jealousy, impairment of working memory, and leukoencephalopathy through a change in protein structure. Mutations in the forkhead domain of the FOXC1 gene may be important not only for ocular abnormalities but also for neuropsychiatric symptoms and cognitive dysfunction.

Author Contributions

Y.Y. designed the study, the main conceptual ideas, and the proof outline. Y.Y. and J.-i.I. collected the data. Y.Y., J.-i.I., and S.-i.U. aided in interpreting the results and worked on the manuscript. S.-i.U. supervised the project. Y.Y. wrote the manuscript with support from J.-i.I. and S.-i.U. All authors discussed the results and commented on the manuscript.

Acknowledgements

The authors would like to thank Chiemi Onishi for her technical assistance and all family members for their cooperation in this study. This work was partially supported by a Health and Labour Science Research Grant from the Japanese Ministry of Health, Labour and Welfare and a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology, JSPS KAKENHI grant numbers 22K07562, 22K07597, and 23K07016.

Data Availability Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Ehime University.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.