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Original Article

Molecular Characterization of a Recurrent Pathogenic TYR Variant in a Consanguineous Family with Oculocutaneous Albinism Type 1

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ABSTRACT

Oculocutaneous albinism type 1 is a rare autosomal recessive disorder caused by pathogenic variants in the tyrosinase (TYR) gene, resulting in impaired melanin synthesis and characteristic cutaneous and ocular manifestations. This study aimed to investigate the molecular basis of oculocutaneous albinism type 1 in a consanguineous family through clinical evaluation, molecular genetic analysis, and bioinformatics approaches. Three affected male siblings from a consanguineous family underwent detailed clinical assessment. Genomic DNA was isolated from peripheral blood samples, and one affected individual was analyzed by whole exome sequencing (WES) to identify the disease-causing variants. Variant segregation within the family was confirmed by Sanger sequencing, while pathogenicity and evolutionary conservation were evaluated using established bioinformatics tools. Clinical examination revealed generalized hypopigmentation, white hair, photophobia, congenital nystagmus, and reduced visual acuity. A homozygous pathogenic missense variant, c.1255G>A (p.Gly419Arg) in the TYR gene, was identified and showed complete segregation with the disease phenotype. Bioinformatics analyses predicted the variant to be deleterious and demonstrated that the affected amino acid residue is highly conserved across vertebrate species. These findings provide molecular confirmation of a recurrent pathogenic TYR variant and expand the available genetic data for an underrepresented population, highlighting the importance of molecular diagnosis and genetic counselling in communities with a high prevalence of consanguineous marriages.

Keywords: Oculocutaneous Albinism Type 1, TYR Gene, Whole Exome Sequencing, Sanger Sequencing, Consanguinity, Pathogenic Variant.

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INTRODUCTION

Oculocutaneous albinism (OCA) is a genetically diverse autosomal recessive condition characterized by diminished or missing melanin production in the skin, hair, and eyes (Lee *et al*., 1994). Pathogenic variants in genes involved in the melanin biosynthetic pathway are the cause of the disorder, which can cause different levels of hypopigmentation and visual abnormalities. Patients with the disease often have white hair, hypopigmented skin, translucent irides, nystagmus, photophobia, foveal hypoplasia, decreased visual acuity, and a greater risk of developing skin damage from UV rays (Centurion & Schwartz, 2003). OCA is present in all parts of the world but is much more common in families where there is a high rate of consanguineous marriage and is a significant inherited disorder in many developing countries, including Pakistan. Oculocutaneous Albinism Type 1 (OCA1) is a subtype of OCA caused by deleterious mutations in the Tyrosinase (TYR) gene, responsible for encoding the key enzyme in melanin synthesis (Kamaraj & Purohit, 2014).

Tyrosinase facilitates the first hydroxylation of tyrosine to L-DOPA, followed by its oxidation to dopaquinone, both of which are essential processes in melanogenesis. The hypopigmentation and ocular abnormalities seen in OCA1 are caused by loss-of-function or decreased-function variants of TYR that prevent melanin production. So far, a variety of pathogenic variants of the TYR gene have been described in different populations, reflecting the genetic diversity of this disorder (Kausar *et al*., 2013; Ma *et al*., 2023; Neveu *et al*., 2022).

Consanguineous marriage is one of the highest in Pakistan and plays a significant role in the burden of autosomal recessive disorders, such as inherited retinal and pigmentation diseases. Although molecular diagnostic methods are becoming more available, genetic information on OCA1 is still scanty in several regions of Pakistan (Khan *et al*., 2025; Ullah *et al*., 2025). Families from the southern part of Khyber Pakhtunkhwa, including Dera Ismail Khan, have not been well represented in molecular genetic studies, and significant gaps remain in the knowledge of the Khyber Pakhtunkhwa regional mutation spectrum. We undertook extensive clinical, molecular, and bioinformatic studies on an OCA-1-affected consanguineous family from Dera Ismail Khan, in Pakistan (Ahmad *et al*., 2022; Chan *et al*., 2021; Muzammal, Hashmi, *et al*., 2025; Sajid *et al*., 2021).

Whole-exome sequencing identified a recurrent pathogenic variation, c.1255G>A(p. Gly419Arg) in the TYR gene (NM_000372), which was verified by Sanger sequencing in the family. Additional analyses of the variant using bioinformatics tools were also performed to examine the evolutionary conservation and the predicted functional effect. Despite advances in molecular genetic testing, the genetic basis of Oculocutaneous Albinism Type 1 remains poorly characterized in several regions of Pakistan, particularly in southern Khyber Pakhtunkhwa. Limited molecular data from Dera Ismail Khan restrict the understanding of the regional mutation spectrum and hinder accurate molecular diagnosis, carrier detection, and genetic counselling in affected families.

Research Gap

Although pathogenic variants of the TYR gene have been reported in different Pakistani populations, no detailed molecular characterization of Oculocutaneous Albinism Type 1 has been reported from consanguineous families in Dera Ismail Khan. This lack of regional genetic evidence represents an important knowledge gap that warrants investigation.

Research Objective

The objective of this study was to identify and molecularly characterize the disease-causing TYR gene variant responsible for Oculocutaneous Albinism Type 1 in a consanguineous family using clinical evaluation, whole-exome sequencing, Sanger sequencing, and bioinformatics analyses.

Research Question

What is the disease-causing genetic variant responsible for Oculocutaneous Albinism Type 1 in the investigated consanguineous family, and how does molecular and bioinformatics evidence support its pathogenicity?

MATERIALS AND METHODS

Ethical Approval and Study Participants

This study was approved by the Institutional Review Board. All participants signed informed consent forms before samples were collected and evaluated clinically. A family of three male siblings, all of them affected, was recruited from the Department of Ophthalmology and the Department of Pediatrics, Gomal Medical College, and was consanguineous with Saraiki language.

Clinical Evaluation

All affected persons had a thorough history taken and were examined physically and ophthalmologically. Phenotypic characteristics such as skin and hair pigmentation, ocular abnormalities (photophobia, nystagmus, strabismus, visual acuity, foveal hypoplasia), and the absence of syndromic characteristics were recorded. Informed consent was obtained for the representative clinical photographs taken.

Sample Collection and DNA Extraction

All available family members were sampled from the peripheral blood in EDTA vacutainer tubes (3 to 5 mL). Genomic DNA was isolated according to a standard salting-out procedure (Gaaib *et al*., 2011).

Whole Exome Sequencing (WES)

Whole-exome sequencing was performed on one affected proband according to the method of (Fatima *et al*., 2025; Khan *et al*., 2025; Rehman *et al*., 2024; Muzammal *et al*., 2024). The focus of prioritization was on rare, homozygous, protein-altering variants of known OCA genes, especially TYR.

Sanger Sequencing for Segregation Analysis

All family members were verified for the potential mutation discovered by WES using Sanger sequencing. Specific primers were constructed around the variant region of the TYR gene (NM_000372) and utilized for amplification of the area by PCR (Sanger *et al*., 1977).

Bioinformatics Analysis

Pathogenicity of the discovered variant was evaluated based on ACMG/AMP guidelines. The functional impact and protein stability were assessed using Silico prediction tools such as I-Mutant and Franklin, etc. Multiple sequence analyses across different vertebrate species were conducted using tools like Clustal Omega to analyze evolutionary conservation. Population frequency data were obtained from gnomAD, and variant databases (ClinVar, HGMD) were consulted (Razzaq *et al*., 2024; Vaser *et al*., 2016; Sievers & Higgins, 2014).

RESULTS AND FINDINGS

Clinical Findings

A consanguineous Saraiki-speaking family from Dera Ismail Khan (KP) was recruited for clinical and molecular investigation. The pedigree comprised four siblings, of whom three male siblings were affected, while both parents were phenotypically unaffected. Phenotypic characteristics were generalized milky-white skin, white or pale blonde hair, translucent irides, congenital horizontal nystagmus, strabismus, and significantly decreased visual acuity. Ophthalmological exam also showed foveal hypoplasia and binocular vision impairment. No evidence of bleeding disorders or immunodeficiency was seen in any affected family member. The clinical features of the affected patients are summarized in Table 1 and representative clinical photographs are shown in Figure 1.

Table 1

Clinical and phenotypic characteristics of the affected siblings with Oculocutaneous Albinism Type 1 (OCA1).

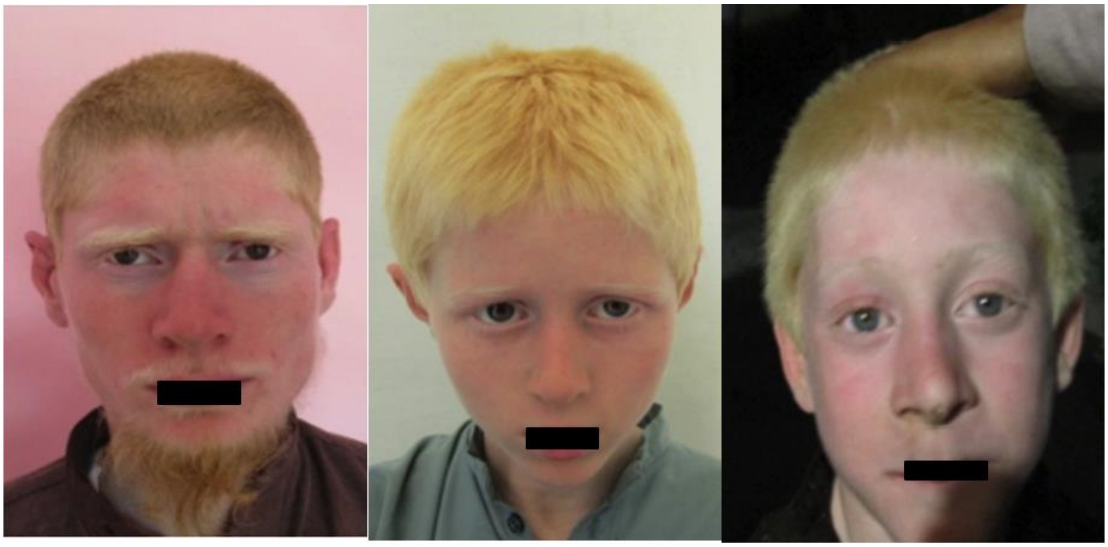
Parameter	IV:1	IV:2	IV:3
Age (Years)	15	13	12
Skin Pigmentation	Severe hypopigmentation (milky-white skin, prone to sunburn)	Severe hypopigmentation (milky-white skin)	Severe hypopigmentation (milky-white skin)
Hair Color	White / very pale blonde	Pale blonde/white	Pale blonde/white
Eye Pigmentation / Iris Translucency	Pale/translucent irides (blue-gray in ambient light, pinkish in bright light); visible choroidal vessels	Translucent irides (pale with pinkish hue)	Translucent irides (pale with pinkish hue)
Visual Acuity (OU)	worse	Worse	Worse
Photophobia	Severe	Severe	Severe
Nystagmus	Continuous horizontal	Continuous horizontal	Continuous horizontal
Strabismus	Alternating esotropia	Exotropia	Exotropia

Notes:

All individuals showed foveal hypoplasia and impaired binocular vision on ophthalmological evaluation. No syndromic features (e.g., bleeding tendency or immunodeficiency) were observed.

Figure 1

Facial Photographs of the Affected Members of the Family.

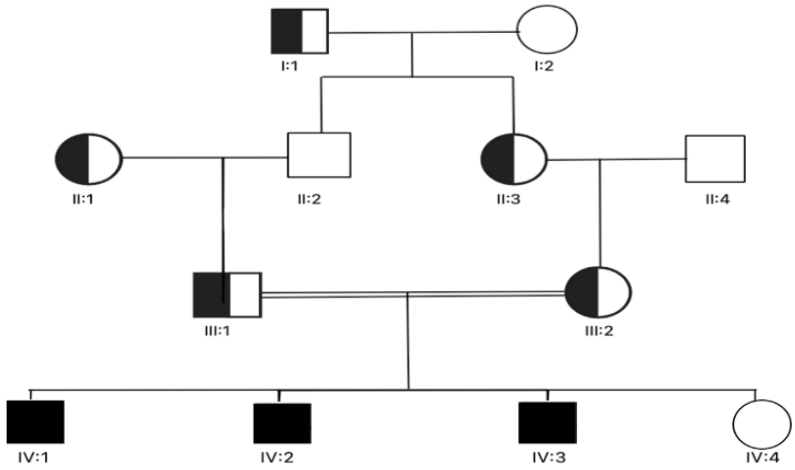


Pedigree Analysis

The data from pedigree analysis showed that the inheritance is autosomal recessive. All affected persons were born from consanguineous marriages, while both parents were clinically normal. The observed segregation pattern was consistent with inheritance of a recessive pathogenic variant, leading to the selection of whole-exome sequencing for molecular diagnosis (Figure 2).

Figure 2

A Family Tree Demonstrating an Autosomal Recessive Inheritance Pattern

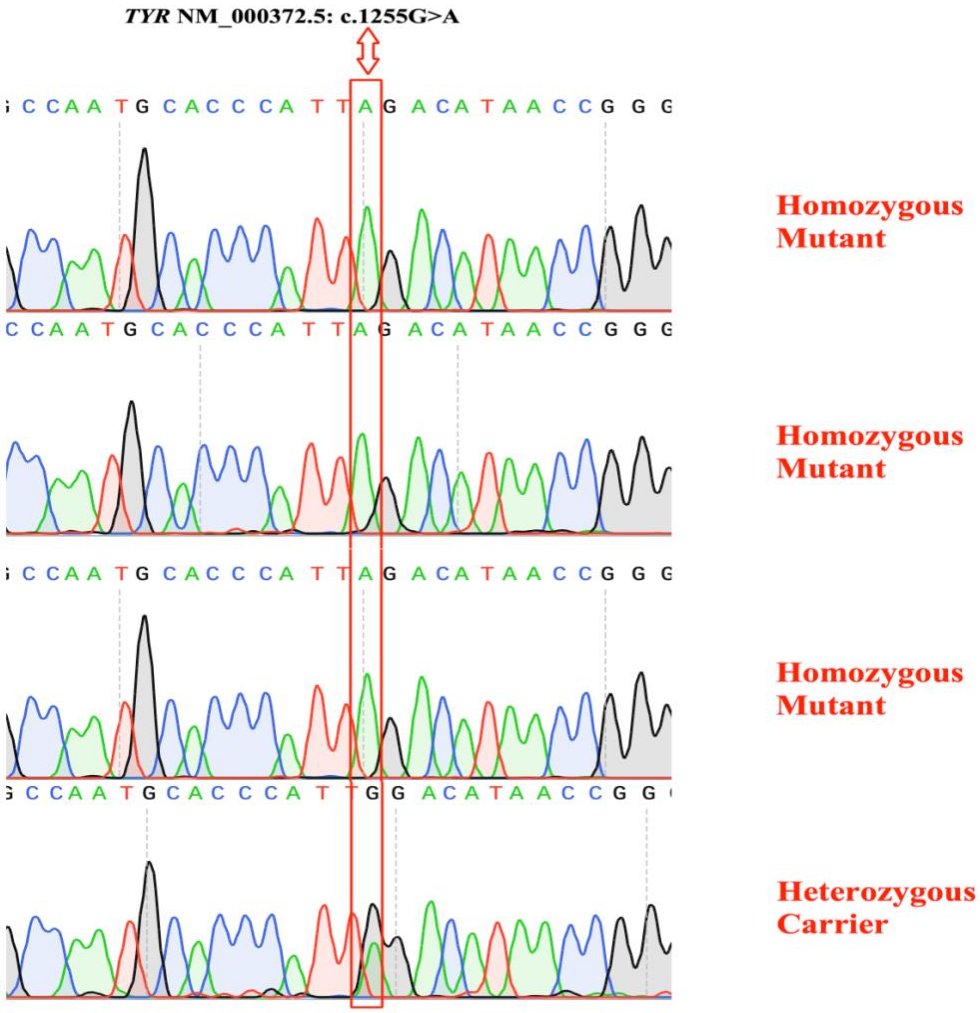


Molecular Genetic Findings

Whole exome sequencing identified a homozygous missense variant, c.1255G>A (p.Gly419Arg), in the TYR gene. Segregation analysis by Sanger sequencing confirmed that all affected individuals were homozygous for the variant, whereas both parents were heterozygous carriers. This variant has been classified as pathogenic according to the ACMG/AMP variant interpretation guidelines. (Figure 3).

Figure 3

Sanger Sequencing Chromatograms of the Affected Family



Bioinformatics Analysis

The identified TYR variant was predicted as pathogenicity using Silico analyses. The variant was predicted to be probably damaging by PolyPhen-2, and as a result of the amino acid substitution, it is predicted to cause a decline in protein stability by I-Mutant.

By multiple sequence alignment, the Gly419 residue was highly conserved among different species of vertebrates, which is indicative of the functional importance of this residue during the evolution of species (Figure 4). The variant was identified as very rare in public population databases and met ACMG/AMP criteria for pathogenicity. The molecular and segregation data, along with the computational data, were highly suggestive of a pathogenic effect for the c.1255G>A (p.Gly419Arg) variant in the affected family, consistent with the data presented in Table 2.

Table 2

Table Showing the Pathogenicity of the Identified Variant According to the ACMG Guideline

Variant	Type	ACMG Criteria Applied	Evidence Details	Final Classification
c.1255G>A (p.Gly419Arg)	Missense	PS3 (Strong), PM1 (Moderate), PM2 (Moderate), PM5 (Moderate), PP2 (Supporting), PP3 (Supporting), PP4 (Supporting)	- PS3: Functional studies (in silico modeling shows structural disruption; prior literature confirms reduced tyrosinase activity). - PM1: Located in critical catalytic domain/hotspot. - PM2: Rare in gnomAD (MAF <0.001 in South Asians). - PM5: Different pathogenic missense at same residue reported. - PP3: Deleterious predictions (SIFT: Damaging; PolyPhen-2: Probably Damaging). - PP4: Specific OCA1 phenotype match.	**Pathogenic**

DISCUSSION

Among the most frequently reported pigmentary disorders in populations with a high prevalence of consanguineous marriages is one form, Oculocutaneous albinism type 1 (OCA1). We studied a consanguineous family of Saraiki speakers from Dera Ismail Khan, Pakistan, with classical clinical features of non-syndromic OCA1. Molecular analysis revealed the variant c.1255G>A (p.Gly419Arg). Segregation analysis revealed complete co-segregation with the disease phenotype in the analyzed family, confirming the pathogenic role of the variant in the studied family. The clinical phenotype observed in the affected individuals (generalized hypopigmentation of skin and hair, photophobia, congenital nystagmus, strabismus, and decreased visual acuity) is compatible with the classic clinical features described for TYR-associated OCA1.

In families of Pakistani origin and other South Asian families with pathogenic TYR variants, identical phenotypic observations have been reported, suggesting a high degree of phenotypic uniformity among them despite the genetic diversity (Ayaz *et al*., 2023; Chaki *et al*., 2011; Kalahroudi *et al*., 2014; Muzammal, Khan, *et al*., 2022). The lack of a syndromic presentation further corroborates the diagnosis of non-syndromic OCA1 (Gul *et al*., 2021; Kalahroudi *et al*., 2014; Muzammal *et al*., 2019). The variant identified p.Gly419Arg, is a recurrent pathogenic variant in the South Asian population and has been previously reported in people affected with OCA1. They are not a new variant of the gene, but rather molecular proof of this disease-causing variant in a population that is underrepresented in the region of southern Khyber Pakhtunkhwa (Diallo *et al*., 2025; Hashmi *et al*., 2026; Muzammal, Ali, *et al*., 2022; Muzammal, Di Cerbo, *et al*., 2022). The absence of the variant in other relatives within the family, the evolutionary conservation, and bioinformatics prediction further support pathogenicity *(Centurion & Schwartz, 2003; Kamaraj & Purohit, 2014; Muzammal, Khan, et al.*, 2025). The prevalence of autosomal recessive disorders like OCA1 is high in Pakistan due to one of the highest rates of consanguineous marriages. Although there have been several molecular studies carried out in various parts of the country, the genetic information available for Dera Ismail Khan is still scarce (Ali *et al*., 2022; Ma *et al*., 2023; Neveu *et al*., 2022).

Thus, the current study provides useful local genetic information and highlights the significance of molecular diagnosis, carrier screening, and genetic counselling for families living in high-risk populations. Early genetic diagnosis can help facilitate appropriate clinical management, family counseling, and informed reproductive decision-making (Galli *et al*., 2023; Hussain *et al*., 2022; Kromberg *et al*., 2023; Pennamen *et al*., 2021). There are some limitations in the present study. It was based on a single consanguineous family with a small number of affected individuals, and functional validation of the identified variant was not done (Khan *et al*., 2025; Peixoto *et al*., 2024; Ravichandran *et al*., 2023). However, the overall clinical assessment, segregation analysis, whole-exome sequencing, and bioinformatics data strongly validate the pathogenic contribution of the TYR variant identified. Larger, multicenter studies of other ethnic groups in Pakistan will help to better characterize the regional mutation

spectrum and aid in the creation of new and useful genetic screening programs.

CONCLUSION

This study molecularly characterized Oculocutaneous Albinism Type 1 (OCA1) in a consanguineous family by integrating clinical evaluation, whole-exome sequencing, Sanger sequencing, and bioinformatics analyses. A recurrent homozygous pathogenic TYR variant, c.1255G>A (p.Gly419Arg), was identified and demonstrated complete segregation with the disease phenotype within the investigated family. The clinical and molecular findings provide strong evidence supporting the pathogenic role of this variant in OCA1. Although the identified variant has been reported previously, this study expands the molecular genetic data from an underrepresented region of Pakistan and emphasizes the importance of molecular diagnosis, carrier screening, and genetic counselling in populations with a high prevalence of consanguineous marriages.

LIMITATIONS

This study has several limitations. First, it was conducted in a single consanguineous family with a limited number of affected individuals, which restricts the generalizability of the findings. Second, functional laboratory experiments were not performed to validate the biological effect of the identified TYR variant. Finally, only one family from a single geographical region was investigated; therefore, the regional mutation spectrum cannot be fully established based on the present findings alone.

STUDY CONTRIBUTIONS

This study provides a comprehensive molecular characterization of a recurrent pathogenic TYR variant in a consanguineous family affected with Oculocutaneous Albinism Type 1. It contributes valuable genetic information from the underrepresented region of Dera Ismail Khan and expands the available mutation data for the Pakistani population. The integration of clinical evaluation, molecular diagnosis, segregation analysis, and bioinformatics strengthens the evidence supporting the pathogenicity of the identified variant.

PRACTICAL AND CLINICAL IMPLICATIONS

The findings of this study highlight the importance of integrating molecular genetic testing into the clinical diagnosis of inherited disorders such as Oculocutaneous Albinism Type 1. Early molecular diagnosis can facilitate accurate genetic counselling, carrier identification, informed reproductive decision-making, and timely clinical management. The results may also contribute to the development of future regional genetic screening strategies in populations where consanguineous marriages are common.

FUTURE RESEARCH DIRECTIONS

Future studies should include larger cohorts from different regions and ethnic groups of Pakistan to better define the national mutation spectrum of Oculocutaneous Albinism Type 1. Functional studies are also required to further investigate the biological effects of the identified TYR variant. In addition, advanced genomic approaches and multicenter collaborations may improve the understanding of genotype–phenotype relationships and support the development of more effective diagnostic and genetic counselling strategies.

DECLARATION

Ethical Considerations: This study strictly adhered to the Declaration of Helsinki and relevant national and institutional ethical guidelines. All procedures performed in this study were consistent with the ethical standards of the Declaration of Helsinki. The study was conducted according to ethical and clinical standards for research.

Conflict of Interest: The authors have no conflict of interest to declare for the publication of this study.

Consent for Publication: All participants were briefed on the aims and process of the research.

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Authors' Contributions: H.S and A.S. did research, analysis of data, and software; M.S. and S.K. helped in family recruitment and clinical analysis; I.U.R. did overall supervision.

Use of Artificial Intelligence (AI)- Assisted Technology for Manuscript Preparation: No AI tools were used for data extraction, statistical analysis, result interpretation, or the generation of original scientific content. All analyses were conducted by the authors, and they take full responsibility for the integrity and accuracy of the manuscript; however, we used AI for our questionnaire alignments, yet no AI was involved in conducting the test for the analysis.

Similarity Index/ Plagiarism: The similarity index was checked, and it is well below the threshold value of 19%, whereas each source is less > 5%.

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