News Release

Identification of a novel xeroderma pigmentosum complementation group, XP-J - Discovery of the first XP-associated gene (*GTF2H4* / *XPJ*) in half a century -

Key Points

・We identified a novel XP complementation group, XP-J, and its causative gene, *GTF2H4*/*XPJ*, responsible for XP, a hereditary disorder characterised by skin cancer predisposition and neurological abnormalities.

・The prevalence of XP in Japan is estimated to be approximately 1 in 20,000-30,000 individuals (about 500 patients nationwide).

・We identified an XP-J patient carrying mutations in the *GTF2H4*/*XPJ* gene.

・*GTF2H4*/*XPJ* encodes the p52 protein, a subunit of the TFIIH complex involved in nucleotide excision repair (NER). This finding is expected to provide new insights into the pathogenesis of XP and related disorders.

Summary

A team of researchers at Nagoya University has identified a novel complementation group XP-J and the responsible gene *GTF2H4*/*XPJ* in xeroderma pigmentosum (XP), one of the designated intractable diseases. XP is caused by congenital defects in a DNA repair mechanism known as nucleotide excision repair (NER), leading to the persistence of DNA damage induced by ultraviolet radiation (UV) or endogenous chemicals. As a result, affected individuals are highly predisposed to skin cancer in sun-exposed areas and frequently develop progressive neurological impairments.

Until now, eight complementation groups, XP-A to -G and XP-variant (XP-V), have been recognised. Our findings establish XP-J as the ninth complementation group. Case analyses revealed that XP-J is caused by mutations in the *GTF2H4*/*XPJ* gene, which encodes the p52 subunit, a structural component of the TFIIH complex involved in NER. Congenital defects in TFIIH complex components are also implicated in other disorders, such as Cockayne syndrome (CS), characterised by premature aging, and trichothiodystrophy (TTD), associated with developmental abnormalities. The present study is expected to advance our understanding of the molecular pathogenesis underlying these conditions.

Research Background

Our group investigates genome instability disorders caused by defects in DNA repair and DNA damage response systems. Specifically, we focus on identifying

pathogenic variants, analysing disease mechanisms, and performing functional studies of DNA repair-related genes. Through these efforts, we aim to advance our understanding of DNA repair pathways and the molecular basis of the associated disorders.

XP is a genetic disorder caused by impaired DNA repair capacity, resulting in a high risk of skin cancer in sun-exposed regions. Its prevalence is particularly high in Japan, Europe, and the United States. To date, mutations in eight genes have been reported as causative, classified into complementation groups XP-A to -G and XP-V.

Research Results

The present case exhibited marked photosensitivity, pigmentation abnormalities, and mild developmental delay, suggesting typical XP; however, the responsible gene mutations were unknown.

Patient-derived cells exhibited reduced repair activity against UV-induced DNA damage. We measured global genome NER (GG-NER) and transcription-coupled NER (TC-NER) activities, both of which were reduced in the patient-derived cells. Virus complementation assays with known NER-related genes excluded previously identified causative genes. Whole-genome sequencing revealed pathogenic variants in the *GTF2H4* gene, encoding p52, a subunit of the TFIIH complex. Ectopic expression of *GTF2H4* cDNA in patient cells fully restored NER activity, indicating that the identified mutations in *GTF2H4* are causative. Protein analyses showed that although a truncated p52 protein derived from the frameshift allele was expressed at low levels, other TFIIH subunits were destabilised. Taken together, these results demonstrate that mutations in the *GTF2H4* gene cause XP, constituting the ninth complementation group XP-J. We therefore designated the gene as *XPJ*.

Research Summary and Future Perspective

Congenital defects in TFIIH complex subunits are known to cause not only XP, but also CS, characterised by premature aging and neurodegeneration, and TTD, associated with developmental and hair abnormalities. Our study identified *GTF2H4*/*XPJ* mutations as causative for XP, while not producing CS- or TTD-like features. Further functional analyses of *GTF2H4*/*XPJ* and evaluation of disease models will contribute to elucidating the pathogenic mechanisms of XP, CS, and TTD, and to advancing our molecular understanding of these disorders.

Publication

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