

Novel germline *ERCC5* mutations identified in a xeroderma pigmentosum complementation group G pedigree

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Key words: *ERCC5*; Excision Repair Cross-complementing Rodent Repair Deficiency Complementation Group 5 gene; nucleotide excision repair; whole exome sequencing; xeroderma pigmentosum complementation group G.

INTRODUCTION

Xeroderma pigmentosum (XP) is an autosomal recessive genodermatosis caused by a germline loss of function in DNA repair enzymes.^{1,2} This defect impairs physiologic DNA repair after ultraviolet (UV) radiation–induced damage, which can lead to photosensitivity in about half of all patients,^{3,4} pigmentation abnormalities, and an increased risk of nonmelanoma skin cancers as well as melanoma.⁵ XP patients classically exhibit a 10,000-fold increase in the frequency of skin cancers arising in sun-exposed skin, eyes, and other mucosal areas (eg, lips and tongue), which appear at an early age.⁵ Prognosis and mortality of XP patients are mostly tightly related to the risk of metastasis of cutaneous squamous cell carcinomas and melanomas but also depend on the extent of the underlying DNA repair deficiency. The life expectancy of XP patients is reduced by 30 years.^{2,6}

Seven genetically distinct complementation groups of XP (designated XP-A through XP-G depending on the gene mutated) with germline loss of function mutations to enzymes are involved in nucleotide excision repair (NER).⁶ The degree of photosensitivity, risk of skin cancer, and risk of neurologic abnormality vary from complementation group to group.³ XP complementation group G

Abbreviations used:

CS:	Cockayne syndrome
<i>ERCC5</i> :	Excision Repair Cross-complementing Rodent Repair Deficiency Complementation Group 5 gene
NER:	Nucleotide excision repair
UV:	Ultraviolet
WES:	Whole exome sequencing
XP:	Xeroderma pigmentosum
XP-G:	Xeroderma pigmentosum complementation group G

(XP-G, OMIM 278780) represents one of the rarest subtypes of XP with mutations identified in the Excision Repair Cross-complementing Rodent Repair Deficiency Complementation Group 5 gene (*ERCC5*), which encodes an enzyme involved in the incision step during the removal of UV-damaged DNA. XP-G is one of the most clinically lethal subtypes of XP, wherein patients also exhibit clinical features of Cockayne syndrome (CS) or XP with neurologic symptoms. To date, there have been less than 20 XP-G cases reported in the literature.^{7,8} Approximately 30 noncutaneous malignancies have also been associated with this lethal XP subtype.⁹ Herein, we report a Chinese proband patient who had XP group G diagnosed, resulting

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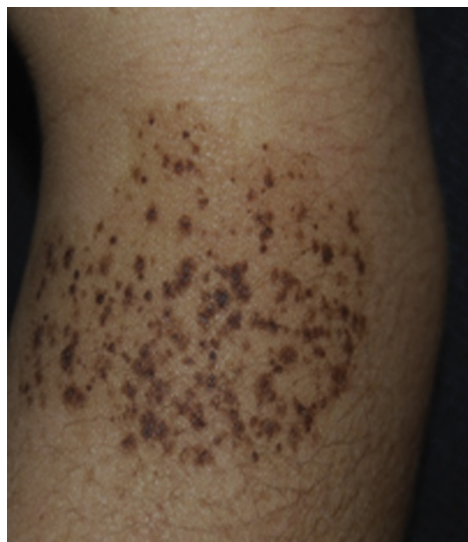


Fig 1. XP-G patient has multiple lentigines on arm.

from 2 compound heterozygous germline mutations in *ERCC5*—a nonsense mutation from the father and a missense mutation from the mother. To the best of our knowledge, this patient is the first reported XP-G case identified in the Chinese population.

CASE REPORT

Clinical history of proband patient

A 17-year-old Chinese girl, born to nonconsanguineous parents, was referred to our institution for evaluation. She had multiple pigmented lesions at the age of 3 years, which had progressively increased in size and in number. The patient lived in the northeastern part of China and received minimal to moderate amounts of sun exposure. There was no history of sun burns or sun sensitivity and no family history of skin cancers. Physical examination found a teenage girl who appeared her stated age, measuring 165 cm in height (60th percentile) and 60 kg in weight (72nd percentile), and with a head circumference of 55 cm (25th-75th percentile).¹⁰ Cutaneous examination was notable for numerous pigmented macules, consistent with solar lentigines, on the forearm (Fig 1), face, chest, and neck in a photodistributed manner (Fig 2) and hyperpigmentation of the bilateral eyelids. External eye and fundoscopic examination results were within normal limits, and she denied any history of visualizing bright or dark floaters. The patient's history was also notable for significant photophobia and failing to finish primary school due to poor memory. Furthermore, neurologic evaluation also found bilateral sensorineural deafness. Deep tendon



Fig 2. XP-G patient has areas of poikiloderma at upper chest and neck.

reflexes were present. Computed tomography scan of the brain found no evidence of significant abnormality (eg, atrophy).

Cutaneous lentigines confirmed by shave biopsy

Shave biopsies of several representative hyperpigmented macules on the face and arms found epidermal acanthosis with elongated rete ridges and hyperpigmentation of the basal layer keratinocytes (Fig 3). Superficial dermal pigment incontinence was also noted. The histologic findings were consistent with solar lentigines.

Novel mutations identified by whole-exome sequencing

Her overall clinical presentation was consistent with XP. We were not able to pursue functional studies to determine the complementation group and to assay the activities of DNA repair enzymes, because cell cultures were not available from the proband or her family members. Therefore, genetic testing with consent from the patient was performed to identify the etiology. Whole-exome sequencing (WES) was performed on the proband with analysis restricted to known XP genes to avoid secondary findings. In addition to the patient, the patient's parents also requested testing of themselves and their younger daughter.

WES identified 2 novel compound heterozygous mutations, *c.*[4G>T];[697C>T] (*p.*[Gly2Trp];[Gln233*]) in *ERCC5* (NM_000123.3) in the proband. Familial testing found that the patient inherited a nonsense point mutation *c.*697C>T(*p.*(Gln233*)) in exon 7 from her father and a missense point mutation *c.*4G>T(*p.*(Gly2Trp)) in exon 1 from her mother. Only the maternal mutation was detected in the unaffected sibling, consistent with an autosomal recessive inheritance pattern (Fig 4). Neither mutation has been seen in more than 7,800 East Asian chromosomes (exac.broadinstitute.org). The paternal nonsense mutation is predicted to lead

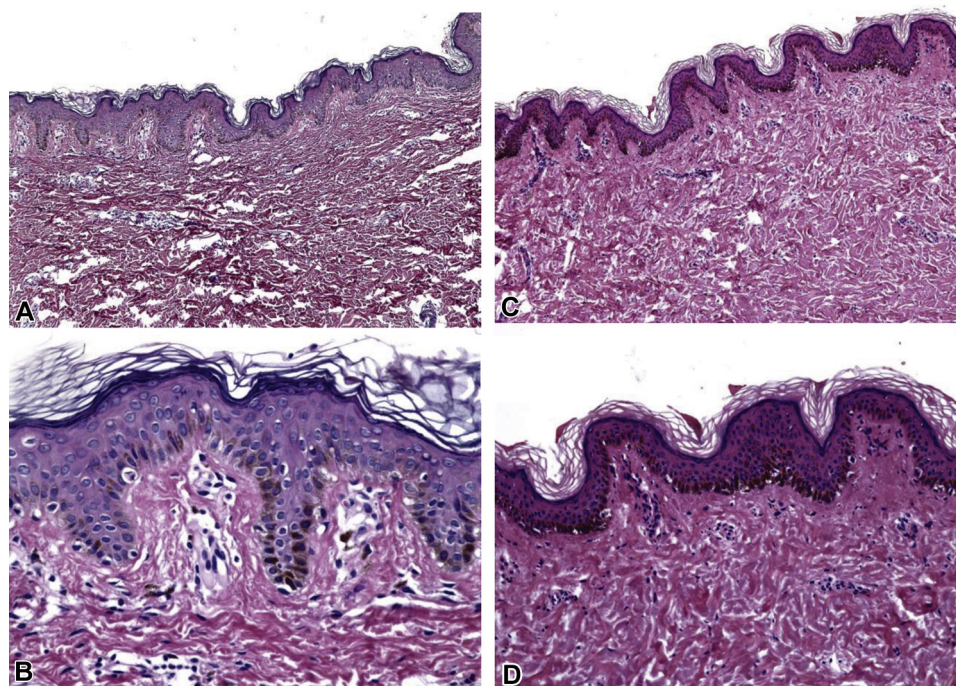


Fig 3. Hematoxylin and eosin–stained sections of face (**A** and **B**) and arm lesions (**C** and **D**). Biopsy specimen shows acanthotic epidermis with elongated rete ridge and basal hyperpigmentation consistent with lentigo.

to a truncation or absence of the protein because of nonsense-mediated decay. The maternally inherited G to T transversion at the fourth position in the cDNA is highly conserved at both DNA and amino acid levels. This variant alters the Kozak consensus sequence, which plays a major role in the initiation of the translation process.¹¹ Therefore, full-length functional protein may be absent or significantly reduced. If a residual amount of the full-length protein is produced, the resulting p.Gly2Trp change is still predicted to affect protein function by multiple computational prediction tools (MutationAssessor, MutationTaster, PolyPhen-2, and SIFT).¹²⁻¹⁵ The 2 mutations occur *in trans* in the proband; therefore, both copies of the *ERCC5* genes are affected, likely resulting in significantly reduced activity of the protein.

Management

The patient and her family were counseled regarding the patient's diagnosis and the importance of minimizing sun exposure and the use of sun-protective clothing and sun protection factor 30+ sunscreen.

DISCUSSION

XP is a rare autosomal recessive, cancer-prone genodermatosis characterized by a defective DNA

repair after UV damage, resulting in a higher risk of cutaneous malignancies, including basal cell carcinomas, squamous cell carcinomas, and melanomas in sun-exposed areas.² Clinically, patients can present with multiple, early-onset solar lentiginos with early development of senile, photoaging-related changes. The histopathologic criteria of certain XP skin lesions include hyperkeratosis, chronic inflammation in the upper dermis, and hyperpigmentation in the early stage with basophilic degeneration of dermal collagen bundles and solar elastosis in the papillary dermis in the later stage. Intensive research of XP patient skin samples has provided a critical disease model for understanding the biologic relationship between UV exposure, point mutations, and the development of skin cancers. Identifying the defective NER mechanism in UV-irradiated cutaneous fibroblasts from XP patients has also led to current understanding and classification of the distinct 7 complementation groups (A-G) of this disease.¹⁶

Although early diagnosis and treatment of XP may be rendered based on typical clinical and histopathologic features, genetic testing remains one of the most important measures in making a definitive diagnosis and managing patients affected by XP. The genetic testing in this study

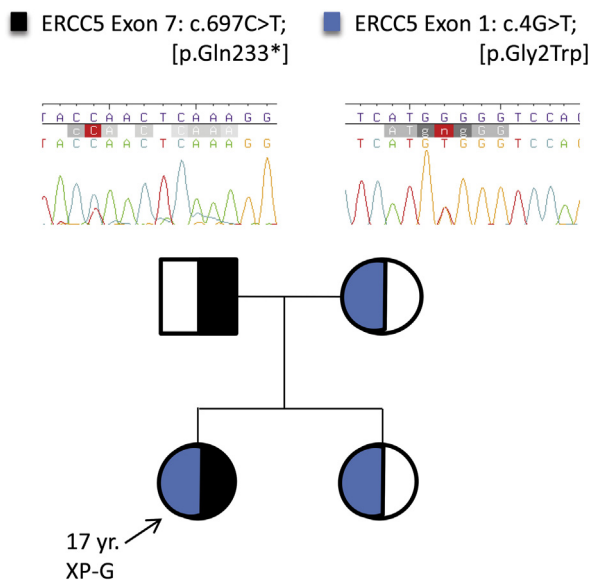


Fig 4. Pedigree chart of *ERCC5* mutations. The c. nomenclature is based on the cDNA sequence, NM_000123.3, in which the “A” in the “ATG” start codon is denoted number 1, and the p. nomenclature is based on the translated protein. The patient has 2 compound heterozygous mutations in *ERCC5*: a missense mutation in exon 1 (c.4G>T; p.Gly2Trp) inherited from her mother and a nonsense mutation in exon 7 (c.697C>T; p.Gln233*) inherited from her father. The patient’s unaffected parents and younger sister are heterozygous carriers of only 1 of the mutations.

found that each of the patient’s parents contributed 1 of the 2 compound heterozygous mutations, leading to the expression of XP disease in the proband. Taken together, we made a primary diagnosis of XP based on the clinicopathologic features and confirmed the diagnosis of XP-G by genetic testing.¹⁷

The human *ERCC5* gene contains 15 exons^{2,18} and encodes the XP-G protein, which participates in the NER pathway by making incisions at the 3’ end of damaged DNA to release a 25-27 nucleotide DNA fragment containing the damaged photoproduct.¹⁸ Mutations resulting in markedly truncated, inactive XP-G proteins are found in XP/CS complex patients, whereas individuals with XP-G without neurologic disease are found to have missense mutations that retain some functional activity.^{9,19} Although our patient does not meet the diagnostic criteria for the XP/CS complex, her overall clinical presentation is strongly suggestive of some neurologic involvement. We hypothesize that her unique phenotype may be caused by residual functional activity resulting from the missense variant, which may also impact protein translation at the cDNA level.

Although we determined the patient’s and her familial genotypes, the biochemical functional studies could not be pursued because the patient’s parents refused further biopsy and blood sampling. The relationship between the identified two mutations, the predicting amino acid changes, and their functional relevance in UV damage repair and neurologic function deserve further investigation. In summary, we report the first XP-G patient of Chinese extraction with 2 novel germline mutations in the *ERCC5* gene identified by WES.

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