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Xeroderma Pigmentosum Complementation Group G Associated with Cockayne Syndrome

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Summary

Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) are two rare inherited disorders with a clinical and cellular hypersensitivity to the UV component of the sunlight spectrum. Although the two traits are generally considered as clinically and genetically distinct entities, on the biochemical level a defect in the nucleotide excision-repair (NER) pathway is involved in both. Classical CS patients are primarily deficient in the preferential repair of DNA damage in actively transcribed genes, whereas in most XP patients the genetic defect affects both "preferential" and "overall" NER modalities. Here we report a genetic study of two unrelated, severely affected patients with the clinical characteristics of CS but with a biochemical defect typical of XP. By complementation analysis, using somatic cell fusion and nuclear microinjection of cloned repair genes, we assign these two patients to XP complementation group G, which previously was not associated with CS. This observation extends the earlier identification of two patients with a rare combined XP/CS phenotype within XP complementation groups B and D, respectively. It indicates that some mutations in at least three of the seven genes known to be involved in XP also can result in a picture of partial or even full-blown CS. We conclude that the syndromes XP and CS are biochemically closely related and may be part of a broader clinical disease spectrum. We suggest, as a possible molecular mechanism underlying this relation, that the XPGC repair gene has an additional vital function, as shown for some other NER genes.

Introduction

Accumulation of DNA damage, caused by chemical or physical agents, can hamper transcription as well as replication and can induce mutations. To prevent these deleterious consequences, all living organisms are equipped with a network of DNA repair systems (for an extensive review, see Friedberg 1985). One of the best-understood and universal DNA repair mechanisms is the nucleotide excision-repair (NER) pathway. This is a multistep process that recognizes and removes lesions from the DNA by a dual incision around the lesion in the damaged strand and excision of some flanking nucleotides (Huang et al. 1992), followed by repair synthesis (also referred to as "unscheduled DNA synthesis" [UDS]), using the nondamaged strand as template, and ligation. In this way the system eliminates a wide variety of structurally unrelated lesions. Detailed studies on the repair of unique genes have led to the differentiation of NER into two subpathways: preferential repair of the transcribed strand of active genes to a slower and less efficient "overall genome" repair (Bohr 1991; Hanawalt 1991).

The importance of the NER system is reflected by the existence of two rare, human, hereditary diseases caused by a defective excision repair: xeroderma pigmentosum (XP) (Cleaver 1968) and Cockayne syndrome (CS) (Venema et al. 1990*a*). Cells from most excision-defective XP patients are impaired in both NER subpathways, and some are impaired in the "overall" pathway alone (Venema et al. 1990*b*). In CS patients, however, the repair deficiency seems to be restricted to the preferential subpathway (Venema et al. 1990*a*). Since nontranscribed sequences represent the bulk of the genome, measurement of repair synthesis (i.e., UDS) in whole cells primarily reflects the rate of the "overall"

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NER modality. As a consequence, CS cells display normal rates of UV-induced UDS, whereas XP cells have UDS levels reduced to a varying extent. Since UV-induced DNA damage acts as a block to transcription, the rate of RNA synthesis is depressed following UV exposure, and subsequent recovery is dependent on preferential NER. CS patients' cells thus fail to recover RNA synthesis rates, as do those XP cells with defective preferential NER.

Clinically, the two autosomal recessive disorders show clear differences as well as similarities. They share an extreme sun sensitivity of the skin. XP patients exhibit, in addition, other pronounced cutaneous abnormalities: atrophic skin with hyper- and hypopigmented spots in sun-exposed areas, in most cases combined with skin malignancies at an early age (Cleaver and Kraemer 1989). The disease is frequently associated with progressive neuronal degeneration. In CS patients, cutaneous abnormalities are less pronounced and are often restricted to sun sensitivity, whereas neurological disease is obligate and of a different type than that in XP (Nance and Berry 1992). Neurological dysfunctioning is predominantly due to demyelination in the cases of CS, while the neurological abnormalities of XP are believed to be based on primary neuronal degeneration (Robbins et al. 1991). In addition, retinal degeneration (salt-and-pepper pigmentation) together with retinal artery narrowing are characteristically associated with CS. Often intracranial calcifications are observed in CS patients but not in XP. Although different in origin, some neurological features, such as microcephaly, sensorineural deafness, and psychomotor retardation are shared by the two syndromes. A striking difference between XP and CS is the absence of cancer predisposition in CS patients, compared with a 2000-fold increased risk of developing cutaneous malignancies in XP individuals (Cleaver and Kraemer 1989). Within both DNA repair syndromes the clinical manifestations are rather heterogeneous. At the genetic level this heterogeneity is partly reflected by the existence of seven distinct genetic complementation groups in XP (XP-A to XP-G) (Vermeulen et al. 1991) and at least two complementation groups within classical CS (CS-A and CS-B) (Tanaka et al. 1981; Lehmann 1982). But even within some groups the clinical picture may vary considerably.

In only two cases a combination of clinical hallmarks of XP and CS has been reported, and these have been assigned to XP groups B (Robbins et al. 1974) and D, respectively (Lafforet and Dupuy 1978; Johnson et al. 1989; Vermeulen et al. 1991). Robbins (1988) has proposed to consider this XP/CS combination a distinct clinical entity, called "XP-CS complex." On the other hand, the exceptional conjunction could also fall within the extreme clinical heterogeneity encountered in some of the XP complementation groups, which could imply that the distinction between XP and CS is smaller than originally thought.

Here we report a genetic study of two unrelated patients combining very severe CS symptoms with a strongly reduced level of UDS typical of XP cells. Both are assigned to the rare XP complementation group G, which previously was not associated with CS. This finding demonstrates that the overlap between XP and CS is more extensive than believed thus far and that it involves at least three of the seven excision-deficient XP complementation groups.

Material and Methods

Cell Strains, Culture Conditions, and Cell Hybridization

All primary fibroblast cultures (table 1) were grown on Ham's F10 medium (Gibco) supplemented with 11% FCS (Biological Industries), 100 IU penicillin/ml, and 100 μg streptomycin/ml. Prior to Sendai virus–mediated cell hybridization, the cytoplasm of each fusion partner was labeled by culturing for 2–3 d in the presence of latex beads of different sizes (Jaspers and Bootsma 1982; Vermeulen et al. 1991); the cells were trypsinized, mixed in a 1:1 ratio, and extensively washed with PBS to remove free beads. Fused cells were seeded on coverslips and were cultured under standard conditions for 2 d prior to assays of UV-induced UDS or RNA synthesis recovery. Homopolykaryons, to be used for the microinjection experiments, were generated in the same way, except that the addition of latex beads was omitted and only one cell strain was used for the fusion.

Microneedle Injection

Nuclear microinjection of cDNA was performed according to a method described elsewhere (van Duin et al. 1989). In short, *XPBC/ERCC3* cDNA was cloned into the mammalian expression vector pSVL, yielding the plasmid pSV3H (Weeda et al. 1990) dissolved in PBS at a concentration of 100 μg/ml and, with the aid of a glass microneedle, injected into one of the nuclei of XP homopolykaryons. Coverslips with injected and uninjected cells were cultivated for 24 h to permit expression of the introduced cDNA before they were assayed for their repair capacity.

UV-induced UDS

The UDS assay (Vermeulen et al. 1986) was performed 2 d after fusion and 1 d after microinjection.

Table 1

Repair Activity of Cell Strains Used

Cell Strain	UDS (% of normal)	Source
CS-TK	80–100	Jaeken et al. 1989
XPCS1LV	5	Jaeken et al. 1989
XPCS2LV	5	Jaeken et al. 1989
CS3BE (CS-A)	80–100	Lehmann 1982
CS1BE (CS-B)	80–100	Lehmann 1982
XP25RO (XP-A)	2	
XPCS1BA (XP-B)	8	W. Vermeulen et al., unpublished data
XP2BI (XP-G)	5	Keijzer et al. 1979
C5RO (normal control)	100	

Cells were washed with PBS, irradiated with 15 J/m^2 UV-C light (Philips TUV lamp), incubated for 2 h in 10 μCi [methyl-^{3}H]-thymidine (50 Ci/mmol; Amersham)/ml containing culture medium, were washed with PBS, and were fixed and dipped in a photo-sensitive emulsion (Ilford K2). Repair capacity was quantitated by grain counting after autoradiography.

RNA Synthesis Recovery

RNA synthesis recovery after UV irradiation (Lehmann 1982; Mayne and Lehmann 1982) was determined 2 d after fusion. Cells were UV irradiated (10 J/m^2), cultivated for 16 h to recover, then incubated for 1 h in medium containing 10% dialysed FCS and 10 μCi [5,6-^{3}H]-uridine (50 Ci/mmol; Amersham)/ml, and finally were processed for autoradiography as described above. The relative rate of RNA synthesis was expressed as the number of autoradiographic grains over the UV-exposed nuclei (G_{UV}) divided by the number of grains over the nuclei of nonirradiated cells on parallel slides (G_0) (RNA synthesis; G_{UV}/G_0).

Results

Summary of Clinical Symptoms of Patients

Patients NF and BT have been described in detail elsewhere (Jaeken et al. 1989). These unrelated patients are designated here as "XPCS1LV" and "XPCS2LV," respectively. The most important clinical symptoms are briefly recapitulated here.

XPCS1LV.—Psychomotor retardation and microcephaly of this girl were noted at the age of 9 mo. She attained a maximal level of development of 8–10 mo. Her skin was very sensitive to sunlight, and she had several small pigmented spots on face, trunk, and limbs. Nerve conduction velocity was normal. Salt-and-pepper retinal pigmentation and retinal artery narrowing were noted. She died from bronchopneumonia at age 6.5 years.

XPCS2LV.—This boy did not reach a level of psychomotor development above 2 mo and exhibited extreme microcephaly. Dysplastic ears and large extremities were apparent at age 6 wk. His sun-sensitive skin exhibited pigmented spots on trunk and limbs. Nerve conduction velocity was decreased, and visual and auditory-evoked potentials were absent. Salt-and-pepper retinal pigmentation but no intracranial calcification were observed. He died from a pulmonary infection at age 20 mo.

At the cellular level, both patients showed pronounced UV sensitivity and a reduced rate of overall thymidine-dimer removal, as measured in a radioimmunoassay.

Determination of UV-induced UDS

To further characterize the repair phenotype of these patients, the level of UV-induced UDS was determined and compared with the levels of UDS found in repair-competent and reference XP and CS cell strains. Table 1 shows that XPCS1LV and XPCS2LV cells exhibit a strongly reduced UDS (≤5% of repair-proficient cells; C5RO). This level is in the same range as is usually found for representatives of XP complementation groups A, B, and G and is significantly lower than the residual UV-induced UDS of XP groups C, D, E, and F (≥15% of repair-proficient cells), whereas the UDS in CS cells is in the wild-type range (CS1BE, CS3BE, CS-TK, and C5RO; table 1).

Microinjection with the Cloned XPBC/ERCC3 cDNA

The combination of clinical symptoms and the biochemical features of XPCS1LV and XPCS2LV resem-

Table 2

Microinjection of the *XPBC/ERCC3* cDNA

Injected Cells	DNA[a]	UV Irradiation	UDS (% of normal)
XPCS1BA	pSV3H	+	80–100
XPCS1BA	...	+	8
XPCS1BA	pSV3H	...	0
XPCS1LV	pSV3H	+	5
XPCS1LV	...	+	5
XPCS2LV	pSV3H	+	5
XPCS2LV	...	+	5

[a] Vector pSV3H contains the human *XPBC/ERCC3* gene cloned into the mammalian expression vector pSVL.

ble most closely those of the exceptional XP group B: a low residual UDS and combined XP/CS clinical symptoms. To investigate whether the XP-like CS patients indeed belong to this complementation group, nuclei were microinjected with cDNA from the recently cloned human excision-repair gene *XPBC/ERCC3*, which specifically corrects the repair defect of XP-B (Weeda et al. 1990). As shown in table 2, the introduction of this gene failed to enhance UV-UDS, in both cell strains, whereas, in a parallel experiment, fibroblasts of XP-B (XPCS1BA; W. Vermeulen, unpublished data) were corrected, by the *XPBC/ERCC3* cDNA, to the level seen in normal cells. The microinjection results indicate that patients XPCS1LV and XPCS2LV are not members of XP group B.

Complementation with XP-A and XP-G

In light of the low level of UDS, only two other candidate XP complementation groups exist: A and G. Therefore XPCS1LV and XPCS2LV fibroblasts were hybridized to representative cell strains of these groups. Both XP/CS cell strains were fully complemented by XP-A cells (XP25RO; table 3), as is evident from the approximately normal UDS in the heterokaryons. An XP-G representative (XP2BI; table 3) caused no such complementation. Consistent with this observation, XPCS1LV and XPCS2LV failed to complement each other. From these results we conclude that the two CS patients belong to the rare XP complementation group G.

Complementation with CS Cell Strains

To investigate the relationship between the two XP/CS patients and classical CS, additional complementation studies were performed with known CS patients' cells. In view of the normal UDS levels in CS cells, we utilized the feature of RNA synthesis recovery in these experiments, which is suitable for complementation analysis of CS (Lehmann 1982).

A significant degree of recovery occurred after fusion of XPCS1LV and XPCS2LV cells with CS3BE (CS-A), CS1BE (CS-B), and XPCS1BA (XP-B) (table 4). Consistent with the absence of UDS complementation observed between XPCS1LV and XPCS2LV cells, no complementation also was found between these lines with RNA synthesis recovery as a repair parameter. As regularly observed in correction of RNA synthesis recovery (Lehmann 1982), the RNA synthesis rates in complementing heterokaryons did not reach the level observed in normal control cells (i.e., C5RO). This phenomenon can be explained by several possible mechanisms (discussed by Troelstra et al. 1992), but which of these possibilities is correct has remained unresolved so far. The significant correction exerted by all CS strains tested, however, clearly excludes assignment of XPCS1LV and XPCS2LV to any of the known classical CS groups.

Discussion

Several clinical hallmarks exhibited by the two severely affected patients analyzed here categorize them as CS, as opposed to classical XP. These include the retinal abnormalities, the decreased physical and mental development, and the conduction abnormalities in some peripheral nerves. Furthermore, lateral ventricles were found to be slightly or moderately enlarged, although intracranial calcifications were not noted. It is possible that this trait, characterized as "not consistently observed in CS individuals" (Nance and Berry 1992, p. 78), would have become apparent at a more advanced age.

On the other hand, there are also some features reminiscent of XP. Small pigmented spots were observed on trunk, limbs, and (in XPCS1LV) face. It cannot be excluded that these cutaneous symptoms typical for XP would have become more prominent when the patients would have been older. Also, the absence of skin cancer may be due to their young age. In this respect it is worth noting that the occurrence of skin tumors is relatively rare in XP group G: in only one patient (of the seven) was a basal cell epithelioma reported, and this occurred at a rather late age (32 years).

Although the CS symptoms are more prominent than the XP features, the repair defect of both patients is typical of XP: UV-induced UDS is severely reduced (in

Table 3

XP Complementation-Group Analysis

Fused Cells[a]	Type of Binucleate Cell	Grains/Nucleus (Mean ± SEM)	UDS (% of normal response)	Complementation?
XPCS1LV × XP25RO(A)	XPCS1LV	2 ± 0	3	
	XP25RO	2 ± 0	3	
	Heterodikaryons	40 ± 2	63	Yes
XPCSILV × XP2BI(G)	XPCS1LV	2 ± 0	3	
	XP2BI	2 ± 0	3	
	Heterodikaryons	2 ± 0	3	No
XPCS2LV × XP25RO(A)	XPCS2LV	3 ± 0	3	
	XP25RO	2 ± 0	2	
	Heterodikaryons	60 ± 3	68	Yes
XPCS2LV × XP2BI(G)	XPCS2LV	2 ± 0	2	
	XP2BI	2 ± 0	2	
	Heterodikaryons	3 ± 0	3	No
XPCS1LV × XPCS2LV	XPCS1LV	2 ± 0	2	
	XPCS2LV	2 ± 0	2	
	Heterodikaryons	3 ± 0	3	No
XP25RO(A) × XP2BI(G)	XP25RO	2 ± 0	2	
	XP2BI	2 ± 0	2	
	Heterodikaryons	64 ± 3	73	Yes

[a] Letters in parentheses are XP complementation group.

contrast to classical CS). The failure to recover RNA synthesis rates after UV exposure is a characteristic of CS and most XP cells. This property permitted us to perform complementation analysis using both parameters. Our analysis indicates an unequivocal assignment of the NER defect to XP group G and excludes assignment to XP group A and the known classical CS complementation groups. The inability of the microinjected

Table 4

CS Complementation-Group Analysis

Fused Cells[a]	Type of Binucleate Cell	Mean ± SEM RNA Synthesis, 16 h Post UVA: G_{UV} (10 J/m²) (grains/nucleus)	Mean ± SEM RNA Synthesis, 16 h Post UVA: G_0 (0 J/m²) (grains/nucleus)	G_{UV}/G_0	Complementation?
XPCS1LV × CS3BE(A)	XPCS1LV	7 ± 1	64 ± 2	.11	
	CS3BE	13 ± 1	68 ± 3	.19	
	Heterodikaryon	39 ± 2	65 ± 2	.60	Yes
XPCS1LV × CS1BE(B)	XPCS1LV	8 ± 1	80 ± 3	.10	
	CS1BE	15 ± 1	75 ± 3	.20	
	Heterodikaryon	42 ± 2	81 ± 3	.52	Yes
XPCS1LV × XPCS1BA[b]	XPCS1LV	11 ± 1	76 ± 2	.14	
	XPCS1BA	12 ± 1	76 ± 2	.16	
	Heterodikaryon	57 ± 2	77 ± 2	.74	Yes
XPCS1LV × XPCS2LV	XPCS1LV	5 ± 1	78 ± 2	.06	
	XPCS2LV	5 ± 1	72 ± 2	.07	
	Heterodikaryon	4 ± 1	72 ± 2	.06	No
Normal cells (C5RO)	Not fused	86 ± 3	84 ± 2	1.04	

[a] Letters in parentheses are CS complementation group.
[b] New patient of XP complementation group B (W. Vermeulen, unpublished data).

Table 5

Clinical and Biochemical Features of XP-G Patients

XP-G Patient	Reference[a]	Age at Diagnosis	UV[b] Sensitivity	UDS (% of normal)	Acute Sun Sensitivity?	Pigmentation Symptoms[c]	Skin Cancer?	Retarded Growth?	Neurological Abnormalities?	Micro-cephaly?	Ocular Abnormalities?
XP2BI	1,2	16 years	8 ×	≤5	Yes	++	No	Yes	Yes	Yes	No
XP3BR	3	6 years	8 ×	≤5	Yes	++	No	Yes	Yes	Yes	Unknown
XP31KO ...	4	37 years	5 ×	25	Yes	+	Yes[d]	No	No	No	No
XP124LO ..	5	14 years	?	15	Yes	+	No	No	No	No	No
XP125LO ..	5	12 years	?	15	Yes	+	No	No	No	No	No
XPCS1LV ..	6	9 mo	9 ×	≤5	Yes	±	No	Yes	Yes	Yes	Yes
XPCS2LV ..	6	6 wk	9 ×	≤5	Yes	±	No	Yes	Yes	Yes	Yes

[a] 1 = Cheesbrough and Kinmont (1978); 2 = Keijzer et al. (1979); 3 = Arlett et al. (1980); 4 = Ichihashi et al. (1985); 5 = Norris et al. (1987); and 6 = Jaeken et al. (1989).

[b] Cellular sensitivity to UV-C irradiation of XP-G patients, compared with normal donor cells.

[c] ++ = Severe XP pigmentation; + = clear XP pigmentation but less severe; and + = mild and limited pigmentation.

[d] Basal cell epithelioma at age 37 years.

XPBC/ERCC3 gene to correct the UDS, in agreement with normal RNA synthesis recovery after hybridization to XP-B cells, ruled out XP complementation group B. The assignment of both strains to the same complementation group is consistent, since they were unable to complement each other's defect with regard to both UDS and recovery of UV-blocked transcription.

The assignment of XPCS1LV and XPCS2LV to XP group G further extends the clinical heterogeneity within this group, which is summarized in table 5. Until now the G group comprised five patients, none of whom has been reported to be associated with CS. Within XP group G the clinical symptoms vary from mild cutaneous and no neurological abnormalities (XP31KO, XP124LO, and XP125LO) to severe dermatological and neurological impairment (XP2BI and XP3BR). For most clinical manifestations, there is a reasonable correlation between the severity and the magnitude of the NER defect. The exception are the cutaneous abnormalities. The patient exhibiting the highest residual UDS (XP31KO; 25%) is the only XP-G patient who developed skin tumor, which appeared at a relatively late age.

Symptoms characteristic of CS have been reported so far in two XP cases. One is patient XP11BE, the only representative of XP group B (identical to CS group C), and the other is patient XPCS2 from XP group D. The latter group also shows extensive clinical heterogeneity (reviewed by Johnson and Squires 1992). Thus, XP groups B, D, and G resemble each other with regard to concurrence of XP and CS symptoms and (for D and G) the pronounced heterogeneity. The genes responsible for XP groups B and D, *XPBC/ERCC3* (Weeda et al. 1990) and *XPDC/ERCC2* (Fletjer et al. 1992; also see citation of Weber, in Lehmann et al. 1992), have recently been isolated and show striking parallels. Both are postulated to encode helicases, based on the basis of the presence, in the predicted amino acid sequence, of seven consecutive motifs that are associated with a superfamily of DNA- and RNA-unwinding enzymes. Furthermore, both human genes have strongly conserved yeast cognates with a distinct "as yet uncharacterized" vital function, in addition to their role in NER. It is likely that the human repair genes also participate in a process essential for viability. The rarity of XP-B and the striking heterogeneity of clinical symptoms of XP-D are certainly consistent with the hypothesis that the affected genes are vital and tolerate only a limited set of mutations disturbing the repair—but not the vital—function. Likewise, a possible explanation for the severity, heterogeneity, and rarity of XP-G could be an additional essential function for the *XPGC* gene, in analogy with XP-B and XP-D.

The findings reported here identify a third XP complementation group in which patients with CS presentations occur. In the case of XP-B and XP-D, the XP/CS patients clearly show a combination of the typical skin manifestations of XP and the characteristic neurological and other features of CS. The distinctive clinical features of the XP/CS patients in XP groups B and D have prompted Robbins et al. (1988) to define a distinct clinical entity, the "XP-CS complex." However, for the two XP-G individuals described here, the clinical traits of CS prevail, whereas those characteristic of XP are only marginally expressed. This demonstrates that the

heterogeneity, at least within group G, can range from exclusively XP to virtually only CS, and it argues against a narrowly defined "XP-CS complex" in this complementation group.

Furthermore, this observation may have important implications for a rigid distinction between XP and CS. In this respect it is relevant to note that recently three siblings were described with clinical symptoms associated with XP but with a repair defect typical of CS (Greenhaw et al. 1992). In this case, however, no (CS) complementation group assignment was performed. A clue to the resolution of the problem of heterogeneity may come from the molecular analysis of the genetic defect in clinically different patients of the same complementation group. Unfortunately, at present this is not possible for XP-G, as the *XPGC* gene has not yet been cloned. A relevant answer probably will come soon from mutation determination in the *XPDC/ERCC2* gene of various XP-D patients. Analysis of additional XP/CS patients will reveal whether specific mutations correlate with a specific phenotype and will help to link the clinical features with the molecular defects. Thus, for one XP/CS patient (XP11BE; XP group B), a single gene defect has been demonstrated (Weeda et al. 1990) to be responsible for the entire complex clinical phenotype.

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