Mammalian And Yeast NER Genes

FUNCTION	MAMMALIAN	YEAST	COMMENTS
Recognition (bulk repair)	XP-A	RAD14 (1)	binds damaged DNA
	XP-E (Chu, Linn)		=DNA pol ε, Ku?
Recognition (TCR)	TFSII		Transcript cleavage (2)
	CS-B/ERCC6 (3)	RAD26	
	CS-A		
Unwinding	XP-B/CS-C/ TTD6VI/ERCC3	RAD25 = SSL2	helicase; in TFIIH/BTF2 (4)
	XP-D/ERCC2	RAD3	helicase; in TFIIH/BTF2 (5-7)
	p44	SSL1	in TFIIH/BTF2
	p62	TFB1	in TFIIH/BTF2
	TTD1BR		in TFIIH/BTF2
3' Incision	XP-C	RAD4?	part of single-strand nuclease complex (8)
	hRAD23	RAD23	associated with XP-C
	XP-G/ERCC5 (9)	RAD2	single-strand nuclease; CS in some patients
5' Incision	XP-F/ERCC4	RAD1	XP-F/ERCC4, ERCC1 and ERCC11 form a single-strand nuclease complex (10, 11)
	ERCC1	RAD10	
	ERCC11		
Excision, synthesis	DNA polymerase δ		
	DNA polymerase ε		= XP-E? Ku? bind + repair double strand breaks
	PCNA	PCNA	part of sliding clamp
	RPA		
	RFC1	CDC44	RFC large subunit
Ligation	DNA ligase I	CDC9	

RAD's <-> ERCC's <-> XP (CS)'s

RAD Locus	ERCC	XP / CS	Enz.Activity	Few Facts	Ref.#
Rad1	ERCC -4	XP-F	endonucl. (w/10)		
Rad2	ERCC -5	XP-G		<-> Tfb1(75K),SSL2; (has TX-AD)	
Rad3	ERCC-2	XP-D		ε TfbI; =85K; <-> SSL1(50K),SSL2	
Rad4		XP-C			
Rad5			helicase	~Zn^{++}(~18), ε Rad6, err.-free (18)	
Rad6			ubiquitin, ~E2(?)		
Rad7					
Rad10	ERCC-1		endonucl. (w/1)		
Rad11					
Rad14		XP-A			
Rad18				Cys ~Zn^{++}; ~RAG1/Rad5	
Rad25 (SSL2)	ERCC-3	XP-B	helicase	haywire/BTF2(TFIIH), opp. polar? <-> Rad2 & Rad3 & Tbf1(75K);	

ERCC	RAD Locus	XP / CS	Enz.Activity	Few Facts	Ref.#
ERCC-1	Rad10		endonucl. (w/1)		
ERCC-2	Rad3	XP-D		ε TfbI; =85K; <-> SSL1(50K),SSL2	
ERCC-3	Rad25 (SSL2)	XP-B	helicase	haywire/BTF2(TFIIH), opp. polar? <-> Rad2 & Rad3 & Tbf1(75K);	
ERCC -4	Rad1	XP-F	endonucl. (w/10)		
ERCC -5	Rad2	XP-G		<-> Tfb1(75K),SSL2; (has TX-AD)	
ERCC -6					
ERCC -7 ?					

XP / CS	RAD Locus	ERCC	Enz.Activity	Few Facts	Ref.#
XP-A	Rad14				
XP-B	Rad25 (SSL2)	ERCC-3	helicase	haywire/BTF2(TFIIH), opp. polar? <-> Rad2 & Rad3 & Tbf1(75K);	
XP-C	Rad4				
XP-D	Rad3	ERCC-2		ε TfbI; =85K; <-> SSL1(50K),SSL2	
XP-E					
XP-F	Rad1	ERCC -4	endonucl. (w/10)		
XP-G	Rad2	ERCC -5		<-> Tfb1(75K),SSL2; (has TX-AD)	
XP-H ?					

Mammalian nucleotide excision repair genes 7/10/93 RW

human gene	rodent group	human map position	S. cerevisiae homolog	S. pombe homolog	predicted MW no. of aa (kDa)	comments
XPA ✓	(not 1 to 6)	9q34.1	RAD14		273 aa 31 kDa (40/42 on gels)	binds damaged DNA
XPB/CSC/ ERCC3 ✓	3	2q21	SSL2 = RAD25		782 aa 89 kDa	helicase / transcription; part of yeast factor b, & TFHIIH/BTF2
XPC ✓	(not 1 to 6)	3	RAD4		125 kDa	assoc. with trans. facts.
hRAD23b ✓			RAD23		58 kDa	associated with XP-C
XPD / ERCC2 ✓	2	19q13.2	RAD3	rad15	760 aa 87 kDa	DNA helicase; part of TF IIH/BTF2
XPG / ERCC5 ✓	5	13q33	RAD2	rad13	mRNA ~ 4 kb (human) protein 133 kDa	CS in some affected individuals
XPE ✓		11			127 kDa protein	binds damaged DNA
ERCC4 ✓ XPF (?)	4/11?	16p13.13 (ERCC4)	RAD1	rad16	126 (S. cerevisiae)	component of ss DNA nuclease?
ERCC1 ✓	1	19q13.2	RAD10	swi10	31 (human) (39 on gels)	component of ss DNA nuclease?
	7					
	8					
ERCC9 ✓	9	7				
	10					
	11					
TTD1BR						in BTFII/TFIIH
TTD6VI						in BTFII/TFIIH
			SSL1		50 kDa in yeast	in transcription factor b
			TFB1		70-73 kDa in yeast	in transcription factor b
			RAD18		55 kDa in yeast	in transcription factor b
CS-A						
CS-B / ERCC6 ✓	6	10q11.2			168 kDa	DNA helicase? transcription coupling?
RP-A p70 ✓		17	RFA1		70 kDa	ss DNA binding
RP-A p32 ✓		1	RFA2		34 kDa	"
RP-A p14 ✓		7	RFA3		13 kDa	"
DNA ligase I		19q13.2-3	CDC9	CDC17	98	ligase
RFC1			CDC44		140 kDa	RFC large subunit
PCNA ✓		20	PCNA	PCNA	36	part of sliding clamp

10/9/93 Update. Make copies for distribution to all

1 p

Human Hereditary DNA Repair Defects

XP = xeroderma pigmentosum
CS = Cockayne's syndrome

	Skin cancer	CS	Frequency	UDS	Comments	Gene
XP-A	+	-	high	< 5%	not CHO grp. 1-6	XP-AC
XP-B = CS	+/?	+	only 3	< 8%	vital gene	ERCC 3
XP-C more mild than A	+	-	high	15-30%	(XP-I) global repair def.	XP-CC
XP-D	+	+/-	int.	20-50%	(XP-H), TTD	ERCC 2
XP-E	-	-	rare	< 50%	damage recognition def.	
XP-F	-	-	rare	15-30%	slow repair	ERCC 4?
XP-G	+	+/?	rare	5-15%	vital gene?	ERCC5
XP-variant	+	-	high	~ 100%	post repl. repair defect	
CS-A	-	+	rare	~ 100%	active gene repair def.	
CS-B	-	+	high	~ 100%	active gene repair def.	ERCC 6

Not assigned: ERCC 1

(April 1992)

Cockayne
- aging
- hearing loss
- dwarfism
- cataracts

Ataxia Telang...
- extremely sensitive to X-Rays
- muscle problems
- dilated capillaries in eyes
- neurological deterioration
- radioresistant DNA synt
- hypomutable by X-Rays

Blooms
- Growth retardation
- High cancer
- Sunlight sensitive
- high level of sister chromatid exchanges after irradiation
- appears to be ligase defect but not in sequence.

Fanconis Anemia
- defective in X-linking repair

Human Genes involved in Nucleotide Excision Repair

Gene	Corrected human comp. gp	Chromosomal location	~ Gene size (kb)	Encoded protein	*S. cerevisiae* homolog	Other homologies & possible functional domains
ERCC1	none	19q13.2	15	297 aa	RAD10 large region has 35% similarity	parts of UvrA & C, DNA binding
ERCC2	XP-D (CS)	19q13.2	19	760 aa	RAD3 52% identity 73 % similarity	UvrA & B, helicase, nuclear localization, DNA & nucleotide binding, essential
ERCC3 **(TFIIH)**	XP-B/CS-C	2q21	45	782 aa	SSL2 (RAD25) 54% identity 80% similarity	haywire (drosophila); nuclear localization; DNA, chromatin & nucleotide binding; helicase; essential
ERCC4	XP-F?					
ERCC5	XP-G (CS)	13q32-33	32		RAD2 70% sim at c-term	acidic, no helicase domains
ERCC6	CS-B	10q11-21	100	1493 aa		nuclear localization, chromatin & nucleotide binding, helicase, not essential
XPAC	XP-A	9q34.1	25	273 aa	RAD14 27% identity 54% similarity	nuclear localization, zinc-finger, DNA binding
XPAC-2	XP-A	8				
XPCC	XP-C			823 aa	RAD4 23% identity 44% similarity	hydrophobic, acidic and basic domains; nuclear localization

complied by Lori Lommel 4/93

Table 4 Properties of XP, CS and TTD complementation groups

Complementation group	UV sens.	residual UDS[1)]	Affected NER TCR[2)]	Affected NER GGR[3)]	relative frequency	skin cancer	neurologic abnormalities	remarks
XP-A	+++	<5%	-	-	high	+	++	
XP-B	++	10-40%	-	-	3 families	+/-	++/+	XP/CS and TTD
XP-C	+	15-30%	+	-	high	+	-	
XP-D	++	15-50%	-	-	intermediate	+/-	++/±	XP,XP/CS and TTD
XP-E	±	≥50%	?	?	rare	+/-	-	
XP-F	+	15-30%	-	-	rare	+/-	-/±	
XP-G	++	<5-25%	-	-	rare	+/-	++/+	XP and XP/CS
TTD-A	+	10%	-	-	1 family	-	+	
CS-A	+	normal range	-	+	intermediate	-	++	
CS-B	+	normal range	-	+	high	-	++	
XP-V[4)]	+/±	normal range	+	+	high	+/-	±	

1) Unscheduled DNA Synthesis, expressed as percentage of repair synthesis in normal cells. 2) transcription coupled repair.
3) global genome repair. 4) XP-variant, defect in post replication repair, proficient NER.

Table 5 Properties of Rodent NER Complementation Groups

Group	Representative mutant	Parental strain	Sensitivity[1)] UV	MMC	Incision deficiency	Correcting human gene	XP/CS equivalent
1	UV20, 43-3B	CHO	++	+++	yes	yes	not existing
2	UV5, VH-1	CHO/V79	++	+	yes	yes	XP-D
3	UV24, 27-1	CHO	++	+	yes	yes	XP-B
4	UV41	CHO	++	+++	yes	yes	XP-F
5	UV135, Q31	CHO, mouse lymphoma	+(+)	±	yes	yes	XP-G
6	UV61, US46	CHO, mouse lymphoma	+	+	partial	yes	CS-B
7	VB11	V79	+	±	partial	-	?
8	US31	mouse lymphoma	+	+	?	yes	CS-A
9	CHO4PV	CHO	+	+	partial	-	?
10	CHO7PV	CHO	+	+	partial	-	?
11	UVS1	CHO	+/++	+	yes	yes	XP-F

1) +: 2-5x; ++: 5-10x; +++: >10x wt sensitivity.