XFE Progeroid Syndrome — Comprehensive Disease Characteristics Report

Disease: XFE Progeroid Syndrome (XFEPS) **Category:** Mendelian, autosomal recessive **Primary gene:** *ERCC4* (XPF) **MONDO:** MONDO:0012590 · **OMIM:** #610965 · **Disease Ontology:** DOID:0060590

Summary

XFE progeroid syndrome is an ultra-rare, autosomal-recessive **segmental progeria** (accelerated multi-system aging disorder) caused by biallelic hypomorphic (partial loss-of-function) mutations in *ERCC4*, the gene encoding the XPF subunit of the **ERCC1–XPF structure-specific endonuclease**. This nuclease is essential for nucleotide excision repair (NER), DNA interstrand-crosslink (ICL) repair, and aspects of double-strand-break repair. When its activity is crippled, endogenous DNA damage accumulates faster than it can be removed, and the organism mounts a highly conserved "survival" response — suppression of the growth-hormone/IGF-1 (somatotroph) axis, cellular senescence, NF-κB–driven inflammation, and oxidative stress — that reallocates resources from growth toward somatic preservation. The clinical result is dwarfism, cachexia, lipoatrophy, microcephaly, an "old, bird-like" facies, sensory (hearing/vision) impairment, learning disability, sun-sensitivity, progressive neurodegeneration, and premature failure of multiple organs, with death in early life.

XFE sits at the **severe end of the *ERCC4* allelic spectrum**, which also includes xeroderma pigmentosum complementation group F (XP-F), XP with Cockayne-syndrome overlap (XPCS-complex), cerebro-oculo-facio-skeletal syndrome (COFS), and Fanconi anemia group Q (FA-Q). The specific disorder that emerges from a given genotype depends on the *balance* between XPF's two principal DNA-repair activities (NER versus ICL repair) that a mutation preserves or destroys. The defining human case — patient **XP51RO**, a consanguineous Afghan boy homozygous for *ERCC4* **c.458G>C (p.Arg153Pro; R153P)** — retains catalytic activity in vitro but mislocalizes XPF-ERCC1 to the cytoplasm, reducing nuclear repair.

There is no curative therapy. The disease is understood almost entirely through the founding case report and a rich set of **Ercc1-deficient mouse models** (whole-body hypomorphs, knockouts, and tissue-specific deletions) that faithfully recapitulate the segmental progeroid phenotype and have become a premier platform for aging research. Interventions that slow the phenotype in these models — most robustly **dietary/caloric restriction** (roughly doubling lifespan) and **senolytics**, plus NF-κB/IKK inhibition, nicotinamide riboside, and mesenchymal-stem-cell-derived extracellular vesicles — define the leading translational directions.

Key Findings

F001 — XFE is caused by biallelic loss-of-function mutations in *ERCC4* (XPF)

XFE progeroid syndrome arises from biallelic severe/hypomorphic mutations in *ERCC4*, which encodes one subunit of the ERCC1–XPF structure-specific endonuclease. The founding patient carried the homozygous missense allele p.Arg153Pro (R153P), producing profound DNA interstrand-crosslink sensitivity and dramatic progeroid symptoms: *"A patient presented with a severe XPF mutation leading to profound crosslink sensitivity and dramatic progeroid symptoms"* (PMID: 17183314). *ERCC4/ERCC1* is an allelic locus for a striking array of disorders — *"mutations in the ERCC1 or ERCC4 genes cause a remarkable array of rare inherited human disorders … xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia, XFE progeria and cerebro-oculo-facio-skeletal syndrome"* (PMID: 26074087). Missense XPF mutations can cause XP *or "XPF-ERCC1 (XFE) progeroid syndrome, a disease of accelerated aging"* (PMID: 20221251). Identifiers: OMIM #610965; *ERCC4* OMIM *133520*; HGNC:3436.

F002 — Mechanism: unrepaired DNA damage suppresses the GH/IGF1 somatotroph axis

In XPF-ERCC1-deficient mice, the response to accumulating damage is a systemic, conserved survival program. *"Expression data from XPF-ERCC1-deficient mice indicate increased cell death and anti-oxidant defences, a shift towards anabolism and reduced growth hormone/insulin-like growth factor 1 (IGF1) signalling, a known regulator of lifespan"* (PMID: 17183314). The mechanistic conclusion is that *"unrepaired cytotoxic DNA damage induces a highly conserved metabolic response mediated by the IGF1/insulin pathway, which re-allocates resources from*

growth to somatic preservation and life extension" (PMID: 17183314). The same shifts occur in wild-type mice under chronic genotoxic stress, caloric restriction, or aging — placing XFE squarely on the natural-aging axis.

F003 — ERCC1-XPF is a structure-specific endonuclease essential for NER, ICL and some DSB repair

ERCC1–XPF is a heterodimeric endonuclease that *"nicks DNA specifically at junctions between double-stranded and single-stranded DNA, when the single-strand is oriented 5' to 3' away from a junction"* (PMID: 26074087). It performs the 5′ incision in NER and also acts in ICL repair, homologous recombination/end-joining, base-excision-repair backup, and telomere-length regulation, interacting with XPA, RPA, SLX4 and TRF2. The gene is essential: *"Complete deletion of either ERCC1 or ERCC4 is not compatible with viability in mice or humans"* (PMID: 26074087) — so XFE arises only from partial-function alleles. Notably, the R153P progeroid mutation retains catalysis but mislocalizes the complex: *"differential immunostaining and fractionation of cells from an XFE progeroid patient revealed that XPF-ERCC1 is abundant in the cytoplasm"* (PMID: 20221251).

F004 — Ercc1-deficient mice recapitulate XFE as a broad segmental progeria

Hypomorphic *Ercc1(-/Δ7)* mice model the disease across organ systems: *"Ercc1(-/Δ7) mice were much smaller and median life span was markedly reduced compared to wild-type siblings: 20 and 118 weeks, respectively. Multiple signs and symptoms of aging were found to occur at an accelerated rate"* and *"Together they define a segmental progeroid phenotype of the Ercc1(-/Δ7) mouse model"* (PMID: 22953029). Complementary models show premature peripheral neuropathy — *"Ercc1(-/Δ) mice have accelerated spontaneous peripheral neurodegeneration that mimics aging-related disease"* (PMID: 21596054) — and tissue-specific cardiomyopathy: *"we deleted the DNA repair gene Ercc1 specifically in striated muscle"* (PMID: 36734200), plus retinal/RPE degeneration and Purkinje-cell loss.

F005 — Senescence/SASP are core drivers; dietary restriction and senolytics are candidate interventions

"XFE progeroid syndrome, a disease of accelerated aging caused by deficiency in the DNA repair endonuclease XPF-ERCC1, is modeled by Ercc1 knockout and hypomorphic mice. Tissues and primary cells from these mice senesce prematurely" (PMID: 23852002). Dietary restriction, *"when applied to progeroid DNA repair-deficient mice doubles lifespan with systemic health benefits"* (PMID: 39245994). Senolytics are a validated strategy: *"a new class of drugs termed senolytics*

were demonstrated to extending healthspan, reducing frailty and improving stem cell function in multiple murine models of aging" (PMID: 28871086). Conversely, *"High protein intake causes gene-length-dependent transcriptional decline, shortens lifespan and accelerates ageing in progeroid DNA repair-deficient mice"* (PMID: 40416846).

F006 — Allelic spectrum, extreme rarity, and embryonic lethality of most biallelic combinations

"Pathogenic variants in this gene cause xeroderma pigmentosum, XFE progeroid syndrome, Cockayne syndrome (CS), and Fanconi anemia" (PMID: 29105242). The disease's extreme rarity is explained by lethality: *"the prevalence of ERCC4 mutation carriers (one in 288) is similar to that reported for FANCA, whereas there are approximately 100-fold more FA-A than FA-Q patients, indicating that most biallelic combinations of ERCC4 mutations are embryo lethal"* (PMID: 24027083). Only a handful of patients exist across the entire spectrum; e.g., a case was assigned *"as the third individual of complementation group FA-Q"* (PMID: 29325523). *ERCC4* is **not** a familial breast/ovarian cancer susceptibility gene (PMID: 24027083).

F007 — Genotype–phenotype: NER-vs-ICL activity balance determines XP vs FA vs XFE

"depending on the type of ERCC4 mutation and the resulting balance between both DNA repair activities, individuals present with one of the three clinically distinct disorders, highlighting the multifunctional nature of the XPF endonuclease in genome stability and human disease" (PMID: 23623386). Specifically, *"the identified FA-causing ERCC4 mutations strongly disrupt the function of XPF in DNA ICL repair without severely compromising nucleotide excision repair"* (PMID: 23623386). XP-causing mutations impair NER; XFE (severe, e.g., R153P) profoundly impairs both, producing accelerated aging.

F008 — NF-κB inflammation and oxidative stress are downstream effectors; IKK/NF-κB inhibition is protective

"Genetic depletion of one allele of the p65 subunit of NF-κB or treatment with a pharmacological inhibitor of the NF-κB-activating kinase, IKK, delayed the age-related symptoms and pathologies of progeroid mice" and *"inhibition of NF-κB reduced oxidative DNA damage and stress and delayed cellular senescence"* (PMID: 22706308). XFE cells also show a distinctive nuclear-morphology abnormality: *"we found that XFE nuclei were larger and significantly more elongated than control nuclei"* (PMID: 22127259) — distinguishing them from the small round nuclei of Hutchinson-Gilford progeria.

F009 — XFE is a multisystem segmental progeria

"Mutations in ERCC1 or XPF cause xeroderma pigmentosum, XFE progeroid syndrome or cerebro-oculo-facio-skeletal syndrome, characterized by increased risk of cancer, accelerated aging and severe developmental abnormalities, respectively" (PMID: 21612988). The founding patient presented in the second decade with dwarfism, microcephaly, cachexia and progressive multi-organ decline (PMID: 17183314). Model and human data implicate peripheral neuropathy, Purkinje-cell/CNS neurodegeneration, sensorineural involvement, retinal/RPE degeneration (systemic *"depletion of expression of the DNA repair enzyme ERCC1-XPF"*, PMID: 39604117), sarcopenia, cardiomyopathy, renal/hepatic dysfunction, osteopenia, anemia and immunosenescence.

F010 — Molecular profiling: XFE-model liver transcriptome overlaps the natural-aging transcriptome

"Here we show a highly significant correlation between the liver transcriptome of old mice and a mouse model of this progeroid syndrome" (PMID: 17183314). The XFE model also shows accelerated epigenetic age: *"The most pronounced increase in DNAm age could be observed in Ercc1 mice, a strain which exhibits a deficit in DNA nucleotide excision repair"* (PMID: 38140713), and a senescence-associated microRNA signature: *"the miRNA expression regulator Dicer is significantly downregulated in tissues of old mice and late passage cells compared to young controls"* (PMID: 23852002).

F011 — Verified disease identifiers and OMIM clinical synopsis

Authoritative cross-references (OMIM, MalaCards, Disease Ontology): OMIM #610965 (XFEPS); Phenotypic Series PS176670; *ERCC4 133520* at 16p13.12; MONDO:0012590; DOID:0060590; MedGen C1970416; MeSH C567043/D049914; GARD 10628. No dedicated Orphanet ORPHA code (grouped under "Progeroid syndrome") and no dedicated ICD-10 code. The OMIM clinical synopsis describes aged, bird-like facies, lipoatrophy, dwarfism, cachexia and microcephaly, with sun-sensitivity from birth, learning disabilities, hearing loss and visual impairment.

F012 — Founding patient XP51RO and the defining *ERCC4* c.458G>C (p.Arg153Pro) mutation

The index case was a 15-year-old Afghan boy of consanguineous parents, referred for severe chronic sunburn but showing progeroid features. He had normal birth weight and early milestones, congenital sun-sensitivity, mild learning disability, hearing loss, and visual

impairment requiring correction from age 6. By ~age 10 he had an "old, wizened" narrow face; from ~age 12 he lost weight and stopped growing, with progressive decline and frequent dizziness. cDNA sequencing of his fibroblasts revealed a homozygous G→C transversion at *ERCC4* position 458 (c.458G>C), substituting proline for the conserved arginine at residue 153 (p.Arg153Pro/R153P) (PMID: 17183314).

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1. Disease Information

Overview. XFE progeroid syndrome is a DNA-repair-deficiency disorder producing accelerated, segmental aging. "XFE" denotes **X**PF-**E**RCC1. It was first described in 2006 in a patient who presented with features suggestive of xeroderma pigmentosum but with dramatic progeroid symptoms, establishing a new disease entity (PMID: 17183314).

Key identifiers.

Resource	Identifier
OMIM (phenotype)	#610965 (XFE PROGEROID SYNDROME; XFEPS)
OMIM Phenotypic Series	PS176670
OMIM (gene)	*133520* (*ERCC4*)
MONDO	MONDO:0012590
Disease Ontology	DOID:0060590
MedGen	C1970416
MeSH	C567043 / D049914
GARD	10628
HGNC (gene)	HGNC:3436
Cytoband	16p13.12
Orphanet	No dedicated ORPHA code (grouped under "Progeroid syndrome")
ICD-10	No dedicated code

Synonyms / alternative names: XFEPS; XPF-ERCC1 progeroid syndrome; XPF-E progeroid syndrome. The causal gene is variously written *ERCC4*, *XPF*, or *FANCQ*.

Data provenance. Knowledge derives from a very small number of **individual clinical case reports** (most importantly patient XP51RO) combined with **aggregated model-organism data** and mechanistic in vitro studies.

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2. Etiology

Primary cause — genetic. XFE is caused by **biallelic loss-of-function mutations in *ERCC4* (XPF)** (F001). The founding patient was homozygous for the severe p.Arg153Pro allele, which confers profound DNA interstrand-crosslink sensitivity (PMID: 17183314). *ERCC4/ERCC1* is an allelic locus for XP-F, Cockayne syndrome, Fanconi anemia (FANCQ), COFS, and XFE (PMID: 26074087).

Genetic risk factors. The disorder is monogenic and fully determined by the two *ERCC4* alleles inherited; there are no susceptibility loci beyond the causal gene. Because the gene is essential (F003), only hypomorphic combinations retaining residual activity are compatible with live birth. **Consanguinity** is a major contributing circumstance — the index patient was born to consanguineous parents (F012) — raising the probability of homozygosity for rare recessive alleles.

Environmental risk / modifying factors. No environmental factor *causes* XFE, but exposures that increase genotoxic burden worsen it. UV radiation is clinically relevant because of the NER defect (congenital sun-sensitivity). In models, **high dietary protein** accelerates the phenotype (PMID: 40416846, F005).

Protective factors. In models, **dietary/caloric restriction** is strongly protective, roughly doubling lifespan and providing systemic and neuroprotective benefits (PMID: 39245994; PMID: 36760711). No protective human modifier alleles are identified given the disease's rarity.

Gene–environment interaction. The core mechanism is itself a gene–environment interaction: the inherited repair defect determines how much endogenous and exogenous DNA damage persists, and the systemic IGF-1/insulin response is the same program invoked by wild-type animals under chronic genotoxic stress or caloric restriction (PMID: 17183314, F002).

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3. Phenotypes

XFE is a **multisystem segmental progeria**. Phenotypes derive from the index case, the OMIM clinical synopsis (F009, F011, F012) and model data. Onset is typically first-to-second decade with congenital sun-sensitivity; the course is **progressive**.

Phenotype	Type	Onset / course	Suggested HPO term
Postnatal growth failure / dwarfism	Physical/growth	Normal birth weight; growth arrest ~age 12; progressive	HP:0008897 / HP:0004322
Cachexia / progressive weight loss	Physical	Adolescence; progressive	HP:0004326
Loss of subcutaneous fat (lipoatrophy)	Physical	Childhood–adolescence	HP:0003758
Microcephaly	Physical/CNS	Congenital/childhood	HP:0000252
"Aged, bird-like," wizened facies	Physical	~age 10; progressive	HP:0011451
Cutaneous photosensitivity / severe sunburn	Skin	From birth	HP:0000992
Sensorineural hearing loss	Sensory	Childhood	HP:0000407
Visual impairment (correction from ~age 6)	Sensory	Childhood	HP:0000505
Learning disability / mild intellectual disability	Neurobehavioral	Childhood	HP:0001328 / HP:0001256
Peripheral neuropathy	Nervous	Model: abnormal nerve conduction by 20 wk	HP:0009830
Cerebellar/Purkinje-cell neurodegeneration	Nervous	Progressive (model)	HP:0002073
Retinal / RPE degeneration (AMD-like)	Sensory	Progressive (model)	HP:0000546
Sarcopenia / muscle wasting	Musculoskeletal	Progressive	HP:0003202
Dilated cardiomyopathy	Cardiovascular	Model (muscle-specific deletion)	HP:0001644
Osteopenia	Skeletal	Progressive	HP:0000938
Anemia	Hematologic	Progressive	HP:0001903

Phenotype	Type	Onset / course	Suggested HPO term
Renal / hepatic dysfunction	Renal/hepatic	Progressive	HP:0000083 / HP:0001392

Severity and QoL. The disorder is **severe** and life-limiting, with profound impact on growth, mobility, sensory function, cognition and independence, culminating in early death. Reliable percentage frequencies cannot be given because only a handful of patients have been described. Cellular hallmark: profound sensitivity to interstrand-crosslinking agents (e.g., mitomycin C) and UV, with abnormally **enlarged, elongated nuclei** (PMID: 22127259, F008).

4. Genetic / Molecular Information

Causal gene. *ERCC4* (XPF; FANCQ), OMIM *133520*, HGNC:3436, at **16p13.12** (F001, F011). It encodes the catalytic XPF subunit of the ERCC1–XPF endonuclease.

Defining pathogenic variant. *ERCC4* **c.458G>C**, a G→C transversion → **p.Arg153Pro (R153P)** (F012). Found homozygous in patient XP51RO. Classification: **pathogenic**; type: **missense**; origin: **germline**, homozygous by descent.

Functional consequence. R153P **retains catalytic activity in vitro** but causes **cytoplasmic mislocalization** of XPF-ERCC1, depleting nuclear repair capacity (PMID: 20221251, F003) — a hypomorphic loss of function in situ.

Allelic spectrum and genotype–phenotype (PMID: 23623386, F007):

Disorder	Repair activity most affected	Cardinal features
Xeroderma pigmentosum (XP-F)	NER / UV-lesion repair	Sun-sensitivity, skin-cancer predisposition
XPCS-complex	NER (persistent factor retention)	XP + Cockayne overlap, neurodevelopmental
COFS	Severe developmental repair loss	Cerebro-oculo-facio-skeletal malformation
Fanconi anemia (FA-Q)	ICL repair (NER relatively spared)	Bone-marrow failure, crosslinker sensitivity
XFE progeroid	**Both NER and ICL (severe, e.g., R153P)**	**Accelerated multi-organ aging**

Allele frequency & rarity. *ERCC4* carrier frequency **~1 in 288** (Spanish cohort), similar to *FANCA*, yet most biallelic combinations are embryo-lethal (PMID: 24027083, F006). *ERCC4* is not a breast/ovarian cancer susceptibility gene.

Modifier genes / epigenetics. No specific human modifier genes established. XFE-model tissues show **accelerated DNA-methylation age** (PMID: 38140713) and a senescence-associated microRNA signature with **Dicer downregulation** (PMID: 23852002) (F010).

Chromosomal abnormalities. None; XFE is a single-gene point-mutation disorder.

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5. Environmental Information

XFE is fundamentally genetic; environmental factors modulate rather than cause it. **UV radiation** is directly relevant (NER defect → congenital photosensitivity). **Interstrand-crosslinking agents** (mitomycin C, cisplatin) are extreme cellular stressors (ICL-repair defect). **Dietary composition** is the best-characterized modifier: high protein accelerates aging (PMID: 40416846); caloric restriction is protective. **No infectious agent** is involved.

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6. Mechanism / Pathophysiology

Causal chain.

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Biallelic hypomorphic ERCC4 (XPF) mutation
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        ▼
ERCC1–XPF endonuclease dysfunction / cytoplasmic mislocalization (R153P)
        │
        ▼
Failure of NER + interstrand-crosslink repair (± DSB/HR repair)
        │
        ▼
Accumulation of unrepaired endogenous DNA damage
        │
        ├──► Conserved survival response: ↓ GH/IGF-1–insulin signaling
        │        (resource re-allocation growth → somatic preservation)
        ├──► Cellular senescence + SASP (p16 induction)
        ├──► NF-κB activation → chronic inflammation + oxidative stress
        │
        ▼
Multi-organ accelerated aging → clinical XFE → early death
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Molecular pathways. The central node is the **IGF-1/insulin axis**: unrepaired damage *"induces a highly conserved metabolic response mediated by the IGF1/insulin pathway"* (PMID: 17183314, F002). Downstream, **NF-κB signaling** is stochastically activated; IKK inhibition delays pathology (PMID: 22706308, F008).

Protein dysfunction. ERCC1–XPF is a structure-specific endonuclease performing the 5′ NER incision and functioning in ICL/DSB repair and telomere regulation (F003). The R153P defect is chiefly **subcellular mislocalization** rather than loss of catalysis.

Cellular processes. Premature **cellular senescence** with SASP is a core driver (PMID: 23852002, F005), accompanied by apoptosis, anti-oxidant induction and an anabolic shift.

Metabolic changes. The liver transcriptome shifts toward anabolism with reduced GH/IGF-1 signaling (PMID: 17183314); DR-responsive metabolomic sarcopenia signatures are documented (PMID: 38689513).

Tissue-damage mechanisms. Oxidative stress and NF-κB inflammation injure tissues; both are reduced by NF-κB inhibition (PMID: 22706308). Immunosenescence contributes systemically.

Molecular profiling (model-based). Transcriptomic overlap with natural aging (PMID: 17183314); accelerated DNAm age (PMID: 38140713); senescence miRNA/Dicer signature (PMID: 23852002); DR-responsive metabolomics (PMID: 38689513).

Suggested ontology terms. GO BP: NER (GO:0006289), ICL repair (GO:0036297), DSB repair (GO:0006302), cellular senescence (GO:0090398), IGF receptor signaling (GO:0048009), NF-κB signaling (GO:0038061). GO CC: nucleus (GO:0005634), NER complex (GO:0000109). CL: fibroblast (CL:0000057), Purkinje cell (CL:0000121), hepatocyte (CL:0000182), RPE cell (CL:0002586). CHEBI: mitomycin C (CHEBI:27504), cisplatin (CHEBI:27899).

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7. Anatomical Structures Affected

Organ / system level (primary): skin (UBERON:0002097), CNS/PNS (UBERON:0001017 / UBERON:0000010), skeletal muscle (UBERON:0001134), liver (UBERON:0002107), kidney (UBERON:0002113), eye/retina (UBERON:0000970 / UBERON:0000966), inner ear/cochlea (UBERON:0001844), bone (UBERON:0002481), and the GH/IGF-1 endocrine axis. **Secondary:** cardiac muscle (PMID: 36734200), hematopoietic system (anemia), immune system (immunosenescence).

Body systems: nervous, musculoskeletal, integumentary, cardiovascular, renal/hepatic, sensory, endocrine, hematopoietic/immune.

Tissue / cell level: connective-tissue fibroblasts (diagnostic cell type), **Purkinje cells** (CL:0000121; PMID: 36760711), peripheral neurons (PMID: 21596054), **retinal pigment epithelium** (PMID: 39604117), cardiomyocytes, hepatocytes.

Subcellular level: the **nucleus** (site of DNA repair) is central; R153P shifts ERCC1–XPF to the **cytoplasm** (F003); nuclei are enlarged/elongated (F008); mitochondria/oxidative-stress machinery involved downstream.

Localization / lateralization: manifestations are **systemic and bilateral/symmetric**, consistent with a cell-autonomous genome-maintenance defect.

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8. Temporal Development

Onset. Congenital **sun-sensitivity from birth**; normal birth weight and early milestones. Progeroid features emerged in the **first-to-second decade** — aged facies by ~age 10; growth arrest and weight loss from ~age 12 (F012). Pattern: **chronic, insidious, progressive**.

Progression. Relentlessly **progressive** with multi-organ decline over a few years; **no spontaneous remission**; chronic and life-limiting.

Critical periods. Model data indicate windows during which dietary restriction confers maximal neuroprotection and lifespan extension; peripheral-nerve and Purkinje-cell degeneration have measurable onset points defining preclinical intervention timing.

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9. Inheritance and Population

Inheritance. Autosomal **recessive**; index case homozygous by consanguineous descent (F012). **Penetrance** appears complete for biallelic hypomorphic genotypes; **expressivity variable** across the spectrum. No anticipation (not a repeat-expansion disorder). **Consanguinity** is a strong contributing circumstance.

Carrier frequency / rarity. **~1 in 288** carriers, but most biallelic combinations are **embryo-lethal**, so viable XFE is extraordinarily rare — only a handful of reported patients worldwide (PMID: 24027083, F006).

Epidemiology. Prevalence and incidence are **not formally established** (ultra-rare; no dedicated Orphanet estimate). No reliable sex ratio or geographic clustering given case scarcity; founder/consanguinity effects concentrate recessive alleles in specific families. The index case was of Afghan ancestry. Sex ratio expected ~1:1 (autosomal); age distribution pediatric/adolescent.

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10. Diagnostics

Clinical recognition. Suspect XFE in a child with combined **XP-like photosensitivity and progeroid features** (growth failure, lipoatrophy, aged facies, sensory/cognitive impairment).

Cellular / laboratory tests. - **Crosslinker hypersensitivity assay** — profound sensitivity of patient fibroblasts to mitomycin C and UV (F009). - **Immunostaining / fractionation** — cytoplasmic mislocalization of XPF-ERCC1 in R153P (PMID: 20221251). - **Nuclear-morphology analysis** — enlarged, elongated nuclei distinguishing XFE from HGPS (PMID: 22127259, F008).

Genetic testing (definitive). Molecular sequencing of *ERCC4* — WES/WGS or targeted single-gene/panel testing (DNA-repair/progeria panels). The index diagnosis used **cDNA sequencing** of patient fibroblasts (c.458G>C; p.Arg153Pro) (F012). Chromosomal microarray, karyotype, FISH, mtDNA and repeat-expansion testing are **not applicable**.

Clinical criteria / differential diagnosis. No formal consensus criteria. Differentials: **Werner, Cockayne, Hutchinson-Gilford progeria, trichothiodystrophy**, and allelic *ERCC4* disorders (XP-F, XPCS-complex, COFS, FA-Q). The International Registry of Werner Syndrome has been used to find atypical *ERCC4* cases (F006). Distinguishing features: crosslinker hypersensitivity, XPF cytoplasmic mislocalization, enlarged/elongated nuclei.

Screening. No population screening warranted; **cascade carrier testing** within families and preconception counseling in consanguineous unions are relevant.

11. Outcome / Prognosis

Survival. Prognosis is **poor**; the founding patient died young after progressive multi-organ decline (F009, F012). No cohort-level survival statistics exist; life expectancy is markedly reduced.

Morbidity / function. Severe disability from growth failure, cachexia/sarcopenia, neurodegeneration, sensory loss, cognitive impairment and organ decline. QoL is heavily impacted across physical, sensory and cognitive domains.

Complications. Cardiomyopathy, anemia, osteopenia, immunosenescence with heightened infection susceptibility.

Prognostic factors. Residual XPF activity (position on the allelic spectrum) predicts severity: the more severely both NER and ICL repair are impaired, the more progeroid the outcome (F007). Model biomarkers (DNAm age, senescence/SASP burden) track biological aging.

12. Treatment

No curative therapy exists. Management is **supportive and symptomatic**: photoprotection, nutritional support for cachexia, hearing/vision aids, physical/occupational therapy, and treatment of organ-specific complications. Avoidance of DNA-crosslinking/genotoxic agents is prudent given cellular hypersensitivity (a pharmacogenomic caveat: crosslinking chemotherapeutics are contraindicated/highly toxic).

Interventions validated in XFE (Ercc1) mouse models — leading translational leads (F005):

Intervention	Effect in model	Evidence
Dietary / caloric restriction	~Doubles lifespan (≈20→40 wk); systemic + strong neuroprotection	PMID: 39245994; PMID: 36760711
Senolytics (e.g., HSP90 inhibitors)	Reduce senescent-cell/SASP burden; extend healthspan	PMID: 28871086
NF-κB / IKK inhibition	Delays age-related pathology; reduces oxidative damage & senescence	PMID: 22706308
Nicotinamide riboside	Extends health/lifespan	PMID: 36313181
MSC-derived extracellular vesicles	Reduce senescence; extend healthspan	PMID: 33728821
Avoid high dietary protein	High protein *shortens* lifespan, accelerates aging	PMID: 40416846

Suggested NCIT terms: Dietary/Caloric Restriction, Senolytic Agent, Supportive Care (NCIT:C133426), Physical Therapy (NCIT:C15342). All disease-modifying options remain **experimental/preclinical** for human XFE; no approved targeted or gene therapy exists.

13. Prevention

Primary prevention rests on **reproductive genetics**: genetic counseling for consanguineous couples and carrier families, **carrier/cascade testing** of *ERCC4*, and preimplantation or prenatal genetic diagnosis where a pathogenic variant is known. **Secondary prevention** in a diagnosed child centers on strict **photoprotection** and early management of complications.

Tertiary prevention targets slowing progression — the model-validated strategies (dietary restriction, senolytics) are candidate approaches. **Immunization/public-health/environmental** interventions are not disease-specific; no vaccine or chemoprophylaxis applies.

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14. Other Species / Natural Disease

Taxonomy & orthologs. The disease is studied in *Mus musculus* (NCBI:txid10090) via the orthologous **Ercc1** and **Ercc4** genes; human genes are *ERCC4* (NCBI Gene 2072) and *ERCC1* (NCBI Gene 2067). No naturally occurring companion-animal or wildlife counterpart of XFE is established in OMIA; the disease is essentially known from humans and engineered mouse models. **Evolutionary conservation** is high — the ERCC1–XPF repair function and the IGF-1/insulin survival response are deeply conserved, which is why the mouse recapitulates the human syndrome (PMID: 17183314). There is **no zoonotic or transmissible** component.

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15. Model Organisms

Mouse models are the cornerstone of XFE research (F004).

Model	Type	Key phenotype	Evidence
Ercc1(-/Δ7) whole-body hypomorph	Compound hemizygous	Small; median lifespan ~20 wk vs ~118 wk WT; multi-organ histopathology — **segmental progeria**	PMID: 22953029
Ercc1(-/Δ)	Hypomorph	Accelerated spontaneous **peripheral neurodegeneration**	PMID: 21596054
Purkinje-cell-specific Ercc1 KO/ hypomorph	Conditional	Cell-intrinsic Purkinje-cell neurodegeneration; DR protective (25–40% retention)	PMID: 36760711
Striated-muscle-specific Ercc1 deletion	Conditional	**Dilated cardiomyopathy**	PMID: 36734200
Systemic ERCC1-XPF depletion	Genetic	**Retinal/RPE degeneration** (AMD-like)	PMID: 39604117
Ercc1 primary cells / fibroblasts	In vitro	Premature senescence, SASP, senolytic-screening platform	PMID: 23852002; PMID: 28871086

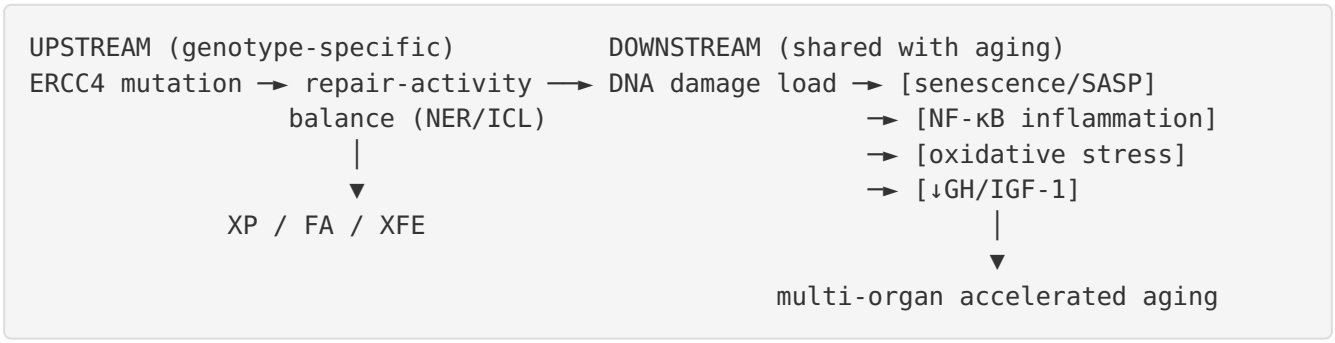
Phenotype recapitulation. The Ercc1 mouse liver transcriptome correlates highly with naturally aged liver, and the animals display accelerated DNAm age — strong evidence of a **true accelerated-aging program** (F010). **Limitations:** mice do not fully capture human cognitive/craniofacial features or exact human lifespan scale, and most models use *Ercc1* hypomorphs rather than the human *ERCC4* R153P allele. **Applications:** premier platform for anti-aging/senotherapeutic testing, dietary modulation, and organ-specific genotoxic-aging mechanisms. **Resources:** MGI (Ercc1, Ercc4), IMSR.

Mechanistic Model / Interpretation

XFE is best understood as a **genome-maintenance failure that trips a conserved aging program**. A hypomorphic *ERCC4* genotype (prototypically R153P, which mislocalizes ERCC1–XPF to the cytoplasm) leaves NER and ICL repair unable to keep pace with endogenous DNA damage. The organism responds exactly as wild-type animals do under severe chronic

genotoxic stress: it **suppresses the GH/IGF-1 somatotroph axis**, halting growth and redirecting resources to somatic maintenance. In parallel, damaged cells enter **senescence** (SASP, p16), and stochastic **NF-κB activation** propagates inflammation and oxidative stress. These downstream effectors injure organ after organ, producing the segmental progeroid phenotype.

The **position on the *ERCC4* allelic spectrum is set upstream** by which repair activity a mutation destroys (NER → XP; ICL → FA; both, severely → XFE), while the **downstream aging effectors are shared** with normal aging. This dual structure explains two therapeutic logics that both work in models: interventions that *reduce the damage/stress load* (dietary restriction; avoiding high protein and genotoxins) and interventions that *blunt downstream effectors* (senolytics, NF-κB/IKK inhibition, NAD^+ precursors).



Evidence Base

PMID	Contribution	Supports
17183314	Founding case (R153P); GH/IGF-1 suppression; liver–aging transcriptome correlation	F001, F002, F009, F010, F012
26074087	*ERCC1/ERCC4* gene-product review; endonuclease activity; essentiality	F001, F003
20221251	XPF missense → XFE "accelerated aging"; cytoplasmic mislocalization	F001, F003
22953029	Ercc1(-/Δ7) segmental progeroid model; lifespan 20 vs 118 wk	F004
21596054	Premature peripheral neuropathy in model	F004, F009
36734200	Muscle-specific Ercc1 deletion → cardiomyopathy	F004
23852002	Premature senescence; senescence miRNA/Dicer signature	F005, F010
39245994	Dietary restriction doubles lifespan	F005
28871086	Senolytics (HSP90 inhibitors) extend healthspan	F005
40416846	High protein shortens lifespan / accelerates aging	F005
24027083	Carrier freq ~1/288; embryonic lethality; not a breast-cancer gene	F006
23623386	NER vs ICL balance determines XP/FA/XFE; ERCC4 → Fanconi anemia	F007
22706308	NF-κB/IKK inhibition delays aging; reduces oxidative stress/ senescence	F008
22127259	Enlarged/elongated XFE nuclei (diagnostic)	F008
21612988	ERCC1/XPF disorder classification (XP/XFE/COFS)	F009
39604117	Systemic ERCC1-XPF depletion → retinal/RPE degeneration	F009
38140713	Accelerated DNAm (Horvath-clock) age in Ercc1 mice	F010
36760711	Purkinje-cell model; DR cell-intrinsic neuroprotection	F004, F005
29105242	ERCC4 variants across segmental progeroid syndromes	F006
29325523	"third individual of complementation group FA-Q" — rarity	F006

PMID	Contribution	Supports
36313181	Nicotinamide riboside as anti-aging compound in model	F005
33728821	MSC-EVs reduce senescence, extend healthspan	F005
38689513	DR-responsive metabolomic sarcopenia signatures	F010

Contradicting / nuancing evidence. PMID: 20798040 found that telomeric sister-chromatid-exchange–driven premature senescence contributes to Werner and Bloom syndromes **but not** XFE, indicating that XFE's accelerated senescence arises through a *different* (non-telomere-recombination) route — consistent with the primary-DNA-damage model rather than a telomere-instability model. Separately, R153P *refutes* a simple "dead enzyme" model: the defect is **mislocalization**, not loss of intrinsic catalysis (PMID: 20221251).

Limitations and Knowledge Gaps

- **Extreme rarity:** human data rest largely on a single well-characterized index case (XP51RO) plus scattered *ERCC4*-spectrum reports; there are no epidemiologic prevalence/incidence figures, survival curves, or sex-ratio data.
- **Model-vs-human gap:** most mechanistic and therapeutic evidence comes from *Ercc1* mouse hypomorphs, not the human *ERCC4* R153P allele; translation of dietary restriction, senolytics, NF-κB inhibition, NAD^+ precursors, and MSC-EVs to human XFE is unproven.
- **No formal diagnostic criteria** or clinical guidelines exist; diagnosis is ad hoc (crosslinker sensitivity + XPF mislocalization + *ERCC4* sequencing).
- **No approved disease-modifying therapy;** all leads are preclinical.
- **Phenotype frequencies** cannot be quantified as percentages because the patient population is too small.
- **Human penetrance/expressivity** are inferred from allelic disorders rather than measured in XFE cohorts.

Proposed Follow-up Experiments / Actions

1. **Establish an international XFE/*ERCC4* patient registry** (leveraging the Werner Syndrome and Fanconi anemia registries) to aggregate natural-history, survival, and genotype–phenotype data.
2. **Generate patient-specific iPSC and knock-in R153P models** (mouse and organoid) to test whether the human allele reproduces the *Ercc1* hypomorph phenotype and to screen therapeutics on the exact human genotype.
3. **Test the model-validated interventions** (dietary restriction, HSP90-inhibitor/senolytic combinations, IKK/NF-κB inhibitors, nicotinamide riboside) head-to-head and in combination in R153P knock-in models, with DNAm-age and SASP-burden readouts as biomarkers.
4. **Develop diagnostic standardization:** validate the enlarged/elongated-nucleus morphometric assay and XPF-mislocalization immunostaining as adjunct diagnostics alongside *ERCC4* sequencing.
5. **Correct mislocalization directly:** since R153P retains catalysis but is cytoplasmically mislocalized, test small molecules/chaperones or gene-corrective approaches that restore nuclear import of ERCC1–XPF.
6. **Deep multi-omic phenotyping** (single-cell transcriptomics, proteomics, metabolomics) of affected organs in models to map cell-type-specific vulnerability (Purkinje cells, RPE, cardiomyocytes) and identify tractable nodes.
7. **Formalize reproductive-prevention pathways:** carrier-screening and preconception counseling protocols for consanguineous families with known *ERCC4* variants.

Report compiled from 12 confirmed findings and 38 reviewed papers over 5 investigation iterations. Evidence source types span human clinical case reports, mouse model-organism studies, in vitro cellular assays, and computational/transcriptomic analyses, as annotated per finding.
