

ATAXIA–TELANGIECTASIA

A multisystem disorder of DNA-damage signaling, neurodegeneration and immune dysfunction

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One inherited defect, four disease domains

Neurological

Early ataxic–dyskinetic syndrome; Progressive deficits

Vascular

Conjunctival and cutaneous telangiectasias

ATM loss of function

Immune

Variable B- and T-cell abnormalities; Infections

Neoplastic

Elevated risk of leukemias and lymphomas

Disease classification begins with inheritance

Autosomal recessive

Disease requires pathogenic alterations of both ATM copies.

Childhood-onset multisystem phenotype.

Spinocerebellar degeneration

Part of the inherited ataxia spectrum.

Neurological manifestations coexist with systemic abnormalities.

Characteristic clinical presentation evolves with age

Early childhood

Unsteady walking and an ataxic–dyskinetic syndrome

Often early

Recurrent sinopulmonary bacterial infections

Subsequently

Conjunctival and skin telangiectasias

Later evolution

Dysarthria and eye-movement abnormalities

ATM links genome maintenance to systemic disease

Inherited ATM defects

Loss of normal ATM-mediated signaling



Abnormal double-strand-break response

Defective checkpoint and repair coordination



Tissue-specific consequences

Neurodegeneration, immune dysfunction, cancer predisposition

ATM is encoded on chromosome 11

11q22–q23

The ATM gene encodes a protein kinase.

ATM as a central organizer of responses to DNA double-strand breaks.

Ataxia–telangiectasia is caused by inherited ATM defects.

ATM is a signaling kinase, not merely a repair enzyme

Principal molecular role

Recognizes/coordinates the cellular response to DNA double-strand breaks.

Relays damage signals to downstream effectors.

Important distinction

ATM deficiency disrupts a response network.

Avoid equating ATM with a single DNA-joining reaction.

Double-strand breaks require coordinated responses

DNA double-strand break

Both strands of the DNA duplex are injured



ATM-dependent signaling

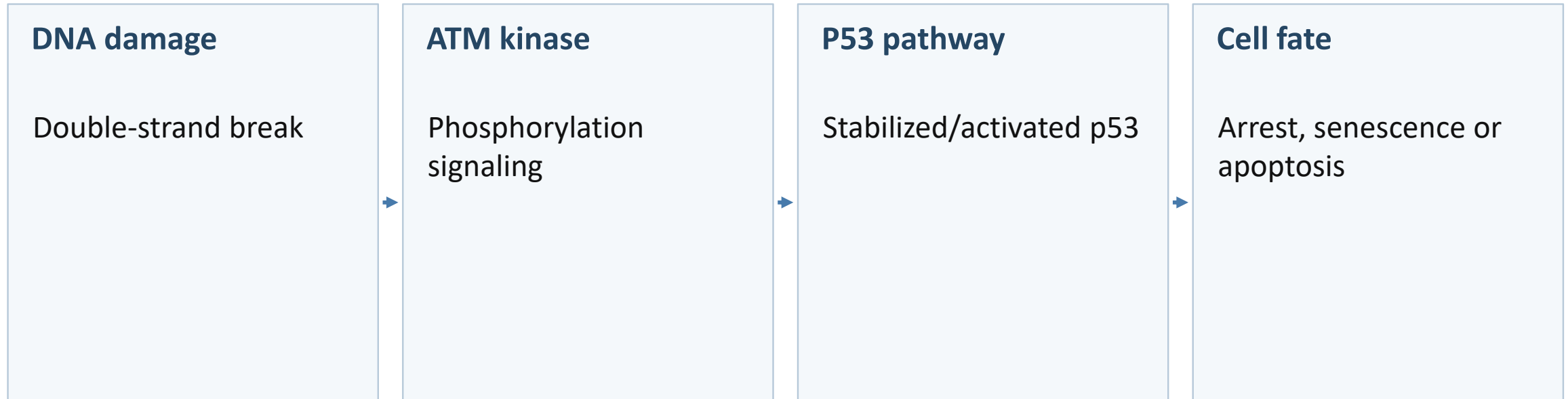
Damage signal is relayed to effector pathways



Cellular decision

Checkpoint control, repair response or apoptosis

ATM activates the p53 axis after DNA damage



Damage signaling normally restrains cell proliferation

Cell-cycle checkpoint

Provides time to respond to damaged DNA.

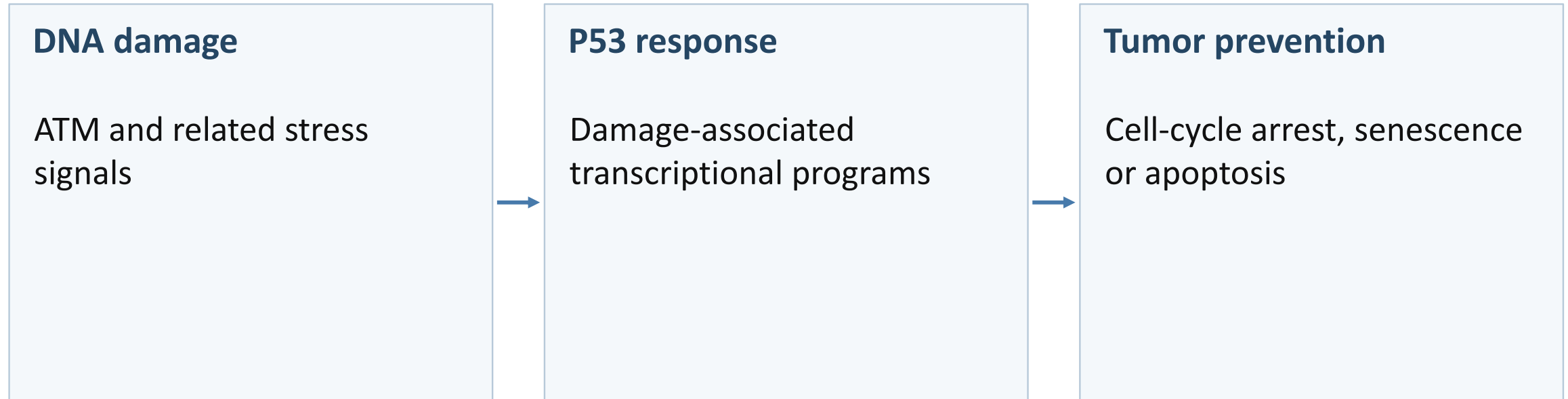
Limits propagation of genomic lesions.

Programmed cell death

Removes severely damaged cells.

Part of the ATM → p53 response network.

P53 acts downstream of ATM as a tumor suppressor



DNA damage can lead to distinct cellular outcomes

Temporary arrest

Pause cell-cycle progression

Senescence

Durable withdrawal from division

Activated p53

Apoptosis

Eliminate the injured cell

Context dependent

The outcome depends on cellular stress and signaling

ATM signaling extends beyond canonical DNA repair

Telomere maintenance

Genome-end homeostasis

Mitochondria

Mitochondrial homeostasis

ATM signaling

Oxidative stress

Stress-response regulation

Proteostasis

Ubiquitin–proteasomal degradation

Defective genome surveillance causes chromosomal instability

ATM deficiency

Impaired response to double-strand breaks



Persistence of damage

Genomic instability can accumulate



Pathological impact

Predisposition to malignant transformation

Radiation hypersensitivity reflects defective break repair

DNA double-strand breaks

Robbins explicitly links ATM deficiency to radiation hypersensitivity.

The relevant mechanism is inadequate repair of radiation-associated double-strand DNA injury.

Radiosensitivity belongs to the molecular phenotype, even though it is not the presenting neurological feature.

Cerebellar degeneration is a central tissue phenotype

Neurological localization

Neurodegeneration particularly affects the cerebellum.

This explains prominence of ataxia in the syndrome.

Limits of present source

The relevant Robbins excerpt does not detail a diagnostic histological pattern.

A cellular pathogenesis beyond ATM loss is not established there.

The mechanism of neuronal death is not settled

Mechanistic uncertainty

ATM influences apoptosis, telomeres, mitochondria, oxidative stress and proteostasis.

Robbins does not identify which dysfunction(s) cause the neuronal degenerative phenotype.

The existence of plausible pathways is not proof that any one is dominant.

Single-strand repair disorders offer a mechanistic parallel

Ataxia–telangiectasia

Defective double-strand-break response associated with cerebellar neurodegeneration.

Other inherited ataxias

Comparable neurodegeneration when single-strand-break repair is disrupted.

DNA maintenance matters in postmitotic neurons

Established by Robbins

Loss of ATM is associated with progressive neuronal dysfunction and degeneration.

Not established by the excerpt

The relative contributions of oxidative stress, mitochondria, telomeres and proteostasis to neuronal loss.

Different tissues produce different clinical consequences

Tissue / system	Relevant ATM-linked process	Recognized consequence
Cerebellum / CNS	DNA-damage response; Other ATM-regulated functions	Ataxia and neurological decline
Lymphocyte lineages	Recombination and antibody maturation	Immune dysfunction
Dividing tissues	Genome surveillance and p53 response	Cancer predisposition

Ataxia is an early neurological clue

Unsteadiness in walking

Gait abnormality commonly appears early in childhood.

The disorder is described as an ataxic–dyskinetic syndrome.

Early neurological symptoms can precede later visible telangiectasias.

Ataxia and dyskinesia are distinct components

Ataxia

Impaired coordination and stability.

Clinically evident as an unsteady gait.

Dyskinesia

Abnormal involuntary movement component.

Part of the syndrome.

Speech changes emerge as degeneration progresses

Dysarthria

Speech becomes dysarthric later in the clinical course.

Dysarthria is a neurological manifestation rather than a primary language disorder.

Its emergence adds evidence of progressive motor-system involvement.

Eye-movement abnormalities join the later phenotype

Oculomotor dysfunction

Eye-movement abnormalities develop during progression.

These are distinct from the visible conjunctival telangiectasias.

The combination of gait, speech and eye findings supports a neurological syndrome.

Neurological progression is sustained, not episodic

Onset

Early childhood unsteadiness

Evolution

An ataxic–dyskinetic syndrome

Further progression

Dysarthria and eye-movement problems

Long-term course

Relentless neurological decline

Telangiectasias are characteristic vascular findings

Conjunctival lesions

Visible dilated surface vessels are a recognized feature.

They often arise after neurological onset.

Cutaneous lesions

Telangiectasias also develop in the skin.

Vascular findings coexist with, rather than explain, the ataxia.

Vascular and neurological eye findings should not be conflated

Conjunctival telangiectasia

Superficial vascular abnormality.

A characteristic systemic sign.

Abnormal eye movements

Motor-system dysfunction.

Reflects progressive neurological involvement.

An early neurological case: Localize and integrate

Clinical vignette

A young child develops progressive unsteadiness in walking. Recurrent respiratory infections are also reported, but no skin vascular lesions are yet evident.

Reasoning question

Which disease mechanism can plausibly unify neurological and immunological abnormalities?

The absence of early telangiectasia is not exclusionary

Chronological fact

Early ataxic–dyskinetic symptoms with later conjunctival and skin telangiectasias.

Clinical reasoning implication

Do not require all hallmark domains to appear simultaneously in early childhood.

Neurological findings anchor the CNS differential

Feature	Ataxia–telangiectasia	Interpretive role
Onset	Early childhood	Raises suspicion of inherited disease
Movement	Ataxic–dyskinetic syndrome	Multicomponent motor phenotype
Progression	Dysarthria and abnormal eye movements	Evolving neurological deficit
Systemic clues	Telangiectasias and immunodeficiency	Distinguishes it from isolated cerebellar syndromes

The immune deficit affects adaptive immunity

B-cell-related abnormalities

Defective production of selected isotype-switched antibodies.

May include reduced IgA and IgG2 production.

T-cell-related abnormalities

Variable defects in cellular immunity.

Associated with thymic hypoplasia.

Immune severity varies among affected individuals

Variable B- and T-cell dysfunction

Immune defects of variable severity.

Both humoral and cellular immunity may be affected.

T-cell dysfunction is often less pronounced than humoral abnormalities.

Failure of antibody isotype switching is prominent

B-cell response

Antigen-specific
humoral response



Ig class switching

DNA recombination
changes the antibody
isotype



ATM deficiency

Switching-related DNA
damage is poorly
handled



Humoral phenotype

Defective IgA and IgG2
production

IgA deficiency is part of the characteristic profile

Impaired IgA production

IgA is specifically identified among impaired switched isotypes.

The problem is a humoral immune defect within a broader ATM syndrome.

Do not mistake this multisystem disorder for an isolated antibody deficiency.

IgG2 deficiency provides an additional humoral clue

Impaired IgG2 production

IgG2 among the prominent switched-antibody defects.

The abnormality is consistent with defective recombination during isotype switching.

The humoral phenotype does not imply that all immunoglobulin classes are uniformly absent.

Thymic hypoplasia accompanies T-cell dysfunction

ATM deficiency

Broad effects on lymphocyte biology



Thymic hypoplasia

Associated with T-cell abnormalities



Cellular immunity

Defects are generally less marked than humoral defects

Antigen-receptor assembly requires controlled DNA breaks

V(D)J recombination

Rearrangement of
antigen-receptor gene
segments



Double-strand-break intermediates

DNA ends require
controlled stabilization



ATM-dependent contribution

Stability of break
complexes during
recombination



Possible consequence

Impaired receptor
generation

Class switching and V(D)J recombination are not identical

V(D)J recombination

Builds antigen-receptor gene diversity.

ATM helps maintain double-strand break complexes.

Isotype switching

Changes antibody constant-region class.

ATM-associated repair defects can disturb this DNA recombination process.

ATM links DNA repair to lymphocyte maturation

DNA-level process

Programmed recombination produces DNA intermediates that require controlled handling.

Clinical consequence

Impaired receptor formation and switching contribute to immune incompetence.

Sinopulmonary bacterial infections are common

Immunodeficiency

Variable defects in antibody and T-cell compartments



Clinical infection pattern

Recurrent upper and lower respiratory bacterial infections



Presentation

Infections may accompany early unsteady gait

Autoimmune manifestations can coexist with infection

Dysregulated immunity

Multiple autoimmune phenomena in affected patients.

Immune dysfunction is not confined to insufficient antimicrobial defense.

The combination underscores disordered immune regulation.

The respiratory and neurological axes are independent clues

Recurrent respiratory infection

Prominent clinical consequence of adaptive immune defects.

Progressive gait ataxia

Consequence of neurodegeneration affecting the cerebellum.

ATM deficiency increases lymphoid cancer susceptibility

Genome instability

Defective responses to DNA breaks



Lymphoid vulnerability

Antigen-receptor gene recombination involves DNA breaks



Neoplastic risk

Increased leukemia and lymphoma incidence

T-cell leukemia is a highlighted malignancy

Lymphoid neoplasia

Robbins Chapter 28 emphasizes that many patients develop lymphoid neoplasms.

T-cell leukemias are particularly noted in the neurological chapter.

Chapter 7 also identifies a marked increase in lymphomas.

Cancer predisposition and immunodeficiency share a genomic basis

V(D)J recombination

May compromise antigen-receptor generation

Isotype switching

May compromise switched antibody output

**ATM-dependent DNA-break
response**

Damage checkpoints

Can fail to suppress damaged cells

Clinical endpoint

Immune deficiency and increased malignancy risk

Germline ATM disease differs from somatic ATM mutation

Germline ATM defects

Inherited autosomal recessive syndrome.

Neurological, immune, vascular and cancer phenotype.

Somatic ATM driver mutations

Acquired variants within tumor clones.

Reported in certain lymphoid neoplasms;
Not equivalent to inherited syndrome.

A second clinical case: Expanding phenotype

Clinical vignette

A patient with childhood-onset ataxia and conjunctival telangiectasias has recurrent bacterial respiratory infections. Later, a lymphoid malignancy is identified.

Reasoning question

Which cellular defect connects antibody dysfunction with cancer susceptibility?

Friedreich ataxia differs in its molecular mechanism

Characteristic	Ataxia–telangiectasia	Friedreich ataxia
Gene	ATM	FXN
Molecular lesion	DNA-break response kinase defect	GAA repeat expansion with reduced frataxin
Characteristic systemic clue	Immunodeficiency; Telangiectasias	Cardiomyopathy; Sensory neuropathy
Shared phenotype	Progressive ataxia	Progressive ataxia

Dominant spinocerebellar ataxias have different genetic patterns

Ataxia–telangiectasia

Autosomal recessive ATM disease.

Systemic immune and vascular manifestations.

Spinocerebellar ataxias

Often autosomal dominant.

May involve CAG/polyglutamine, noncoding-repeat or conventional mutations.

Bloom syndrome and ATM disease share instability, not phenotype

Feature	Ataxia–telangiectasia	Bloom syndrome
Inheritance	Autosomal recessive	Autosomal recessive
Defective factor	ATM kinase response	Homologous-recombination helicase
Neuroimmune phenotype	Ataxia and immunodeficiency emphasized	Developmental anomalies emphasized
Cancer risk	Increased	Increased

Fanconi anemia is another repair-defect cancer syndrome

Feature	Ataxia–telangiectasia	Fanconi anemia
Principal issue	Double-strand DNA break signaling	DNA cross-link repair pathway
Dominant clinical axis	Ataxia plus immune dysfunction	Developmental changes; Bone marrow failure
DNA-damage sensitivity	Radiation hypersensitivity	Cross-linking chemotherapy hypersensitivity
Cancer predisposition	Leukemia / lymphoma	Leukemia

X-linked hyper-IgM and ATM disease share a switching defect

Ataxia–telangiectasia

ATM-dependent DNA repair and recombination defect.

Immune phenotype occurs with ataxia, telangiectasias and cancer susceptibility.

X-linked hyper-IgM

Defective CD40L-related T–B interaction impairs isotype switching.

No ATM-based neurodegenerative syndrome is implied.

Use phenotype and mechanism together in the differential

Candidate disorder	Discriminating mechanism	Anchor phenotype
Ataxia–telangiectasia	ATM / double-strand-break response	Ataxia + telangiectasia + immunity defect
Friedreich ataxia	FXN / frataxin deficiency	Ataxia + cardiomyopathy
Autosomal dominant SCA	Repeat or other dominant variants	Inherited cerebellar syndrome
Fanconi anemia	DNA cross-link pathway	Marrow failure / developmental anomalies

Neurological findings alone do not capture disease burden

Motor

Gait, speech and ocular motor changes

Vascular

Conjunctival and skin findings

Full clinical assessment

Immune

Respiratory infection pattern and humoral defects

Oncology

Awareness of lymphoid neoplasia

The disorder is progressive and life-limiting

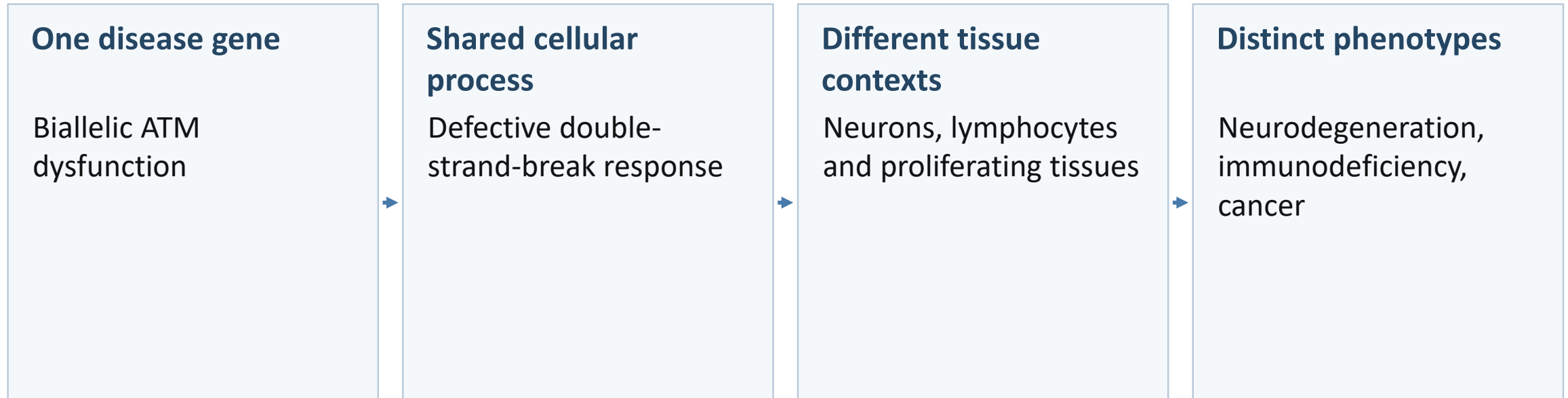
Long-term clinical course

Relentless progression of neurological disease.

Death is reported as typically occurring in early adulthood.

Clinical burden includes recurrent infections and lymphoid malignancy, in addition to neurological deterioration.

Ataxia–telangiectasia exemplifies pleiotropy



A pathogenesis question: What remains unresolved?

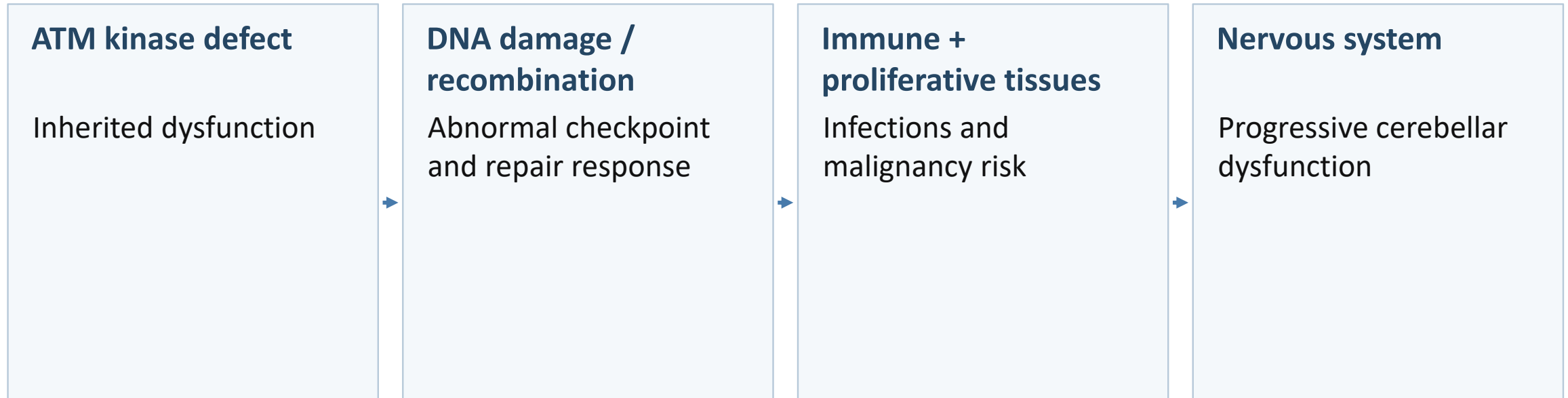
Clinical vignette

A researcher proposes that mitochondrial dysfunction is the unique proven cause of neuronal degeneration in ataxia–telangiectasia.

Reasoning question

How should this statement be evaluated against Robbins?

Pathology synthesis: A four-part causal map



Five findings to retain

- Early-onset, progressive ataxic–dyskinetic syndrome.
- Later conjunctival and cutaneous telangiectasias.
- Variable B- and T-cell immunodeficiency; IgA and IgG2 defects are prominent.
- ATM orchestrates responses to DNA double-strand breaks.
- Radiation sensitivity and lymphoid malignancy risk reflect genome-maintenance failure.

Primary textbook references

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 28: The Central Nervous System; Spinocerebellar Degenerations—Ataxia-Telangiectasia (pp. 1171–1172).

Same textbook, Chapter 7: Primary (Inherited) Immunodeficiencies—Ataxia Telangiectasia; p53 signaling; Homologous Recombination Repair Factors.

Same textbook, Chapter 1: DNA Damage; Chapter 25: Familial Cancer Syndromes With Cutaneous Manifestations (supporting context).