Introduction to chronic lymphocytic leukaemia (CLL)

Definition, epidemiology, aetiology and pathogenesis

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Contents

Types of leukaemia

How types of leukaemia are distinguished

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Types of leukaemia

- **Haematopoiesis** is the formation of blood cells.[1]
- Leukaemias are a group of **haematologic malignancies** that result from abnormal haematopoiesis and the accumulation of malignant blood cells.[1]
  - Different types of leukaemia are distinguished based on:[1]
    - Haematopoietic cell lineage – myeloid or lymphoid
    - Clinical course – acute or chronic

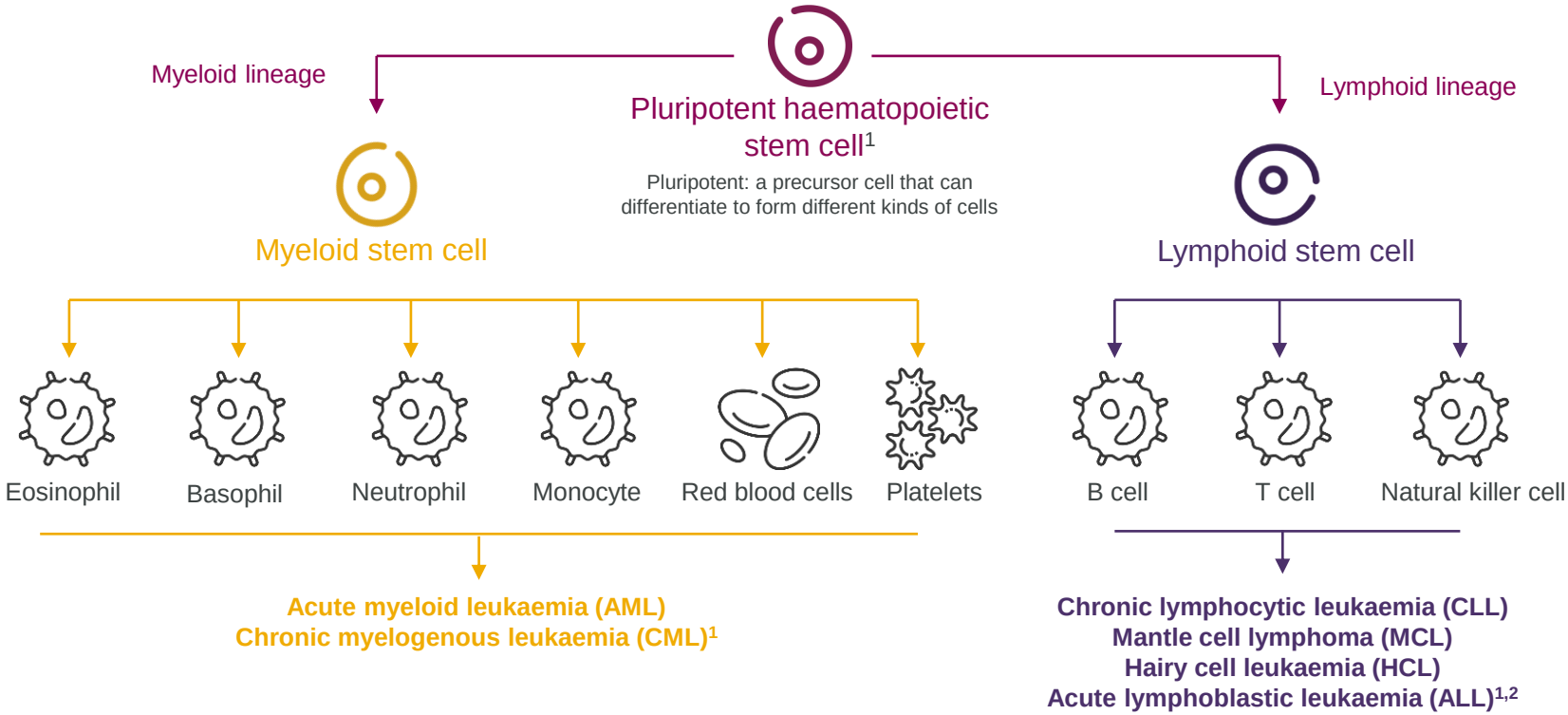

Figure adapted from Tortora GJ 2017 [1]

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CLL definition

How the CLL disease state is defined

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Definition of CLL

- **CLL** is characterised by the accumulation of **abnormal lymphocytes**[3]
  - Lymphocytes are a type of white blood cell that have several functions in the immune system[4]
  - Lymphocytes include T cells, B cells, and natural killer cells[1]
- **CLL** and **small lymphocytic lymphoma (SLL)** are different manifestations of the same disease.[5]
  - The WHO classifies them as **one disease**[6]

- The main difference between **CLL** and **SLL** is where the cancer cells are found[5]:

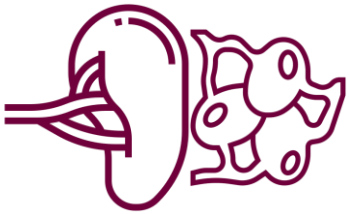
In CLL, cancer cells are mainly found in the blood[5]

Blood

Bone marrow

Lymph nodes and other lymphoid tissues

In SLL, cancer cells are mainly found in the lymph nodes and lymphoid tissues[5]



Lymph nodes and other lymphoid tissues

Bone marrow

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CLL epidemiology

Key epidemiologic statistics for CLL

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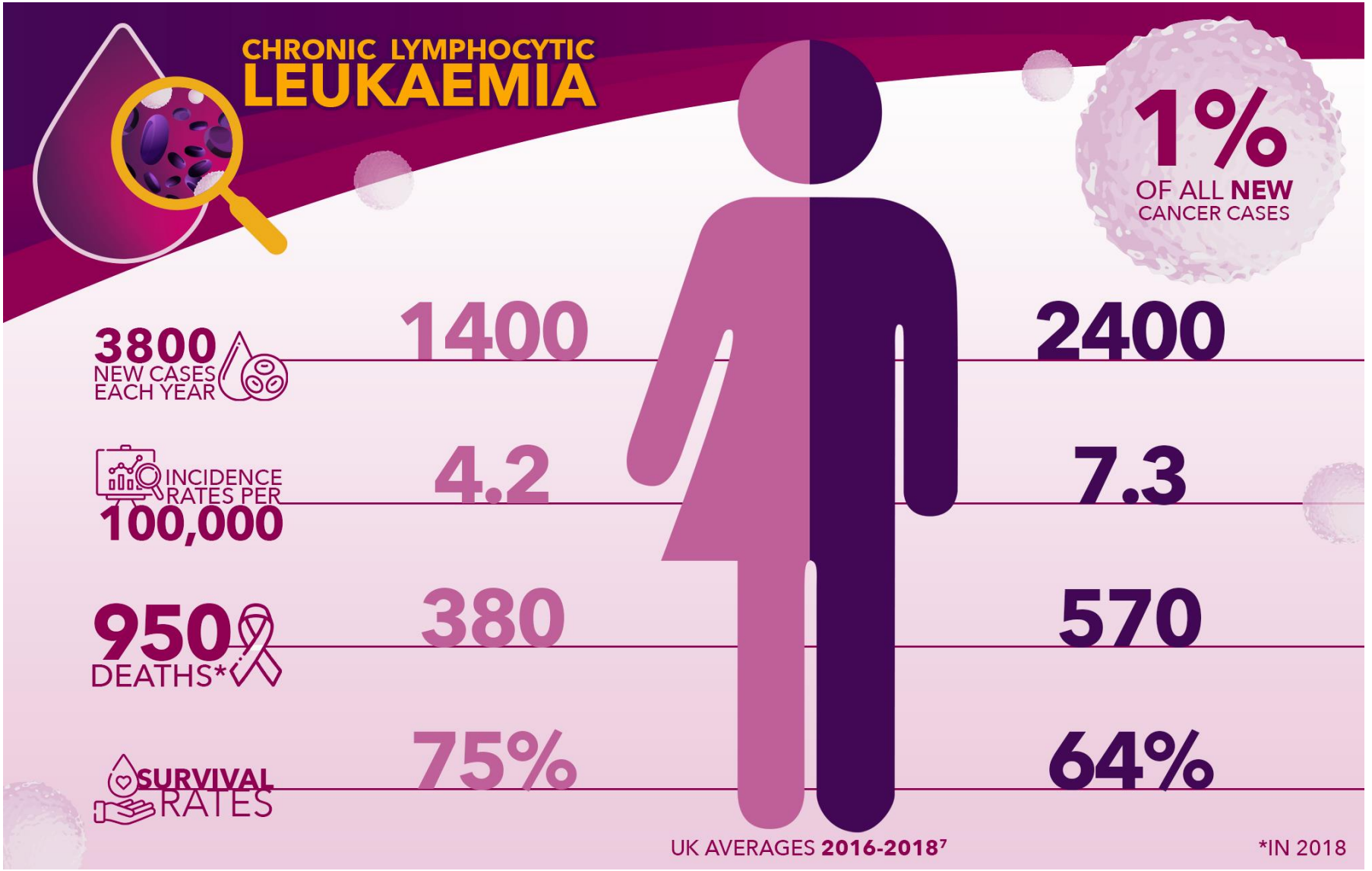
UK CLL epidemiology



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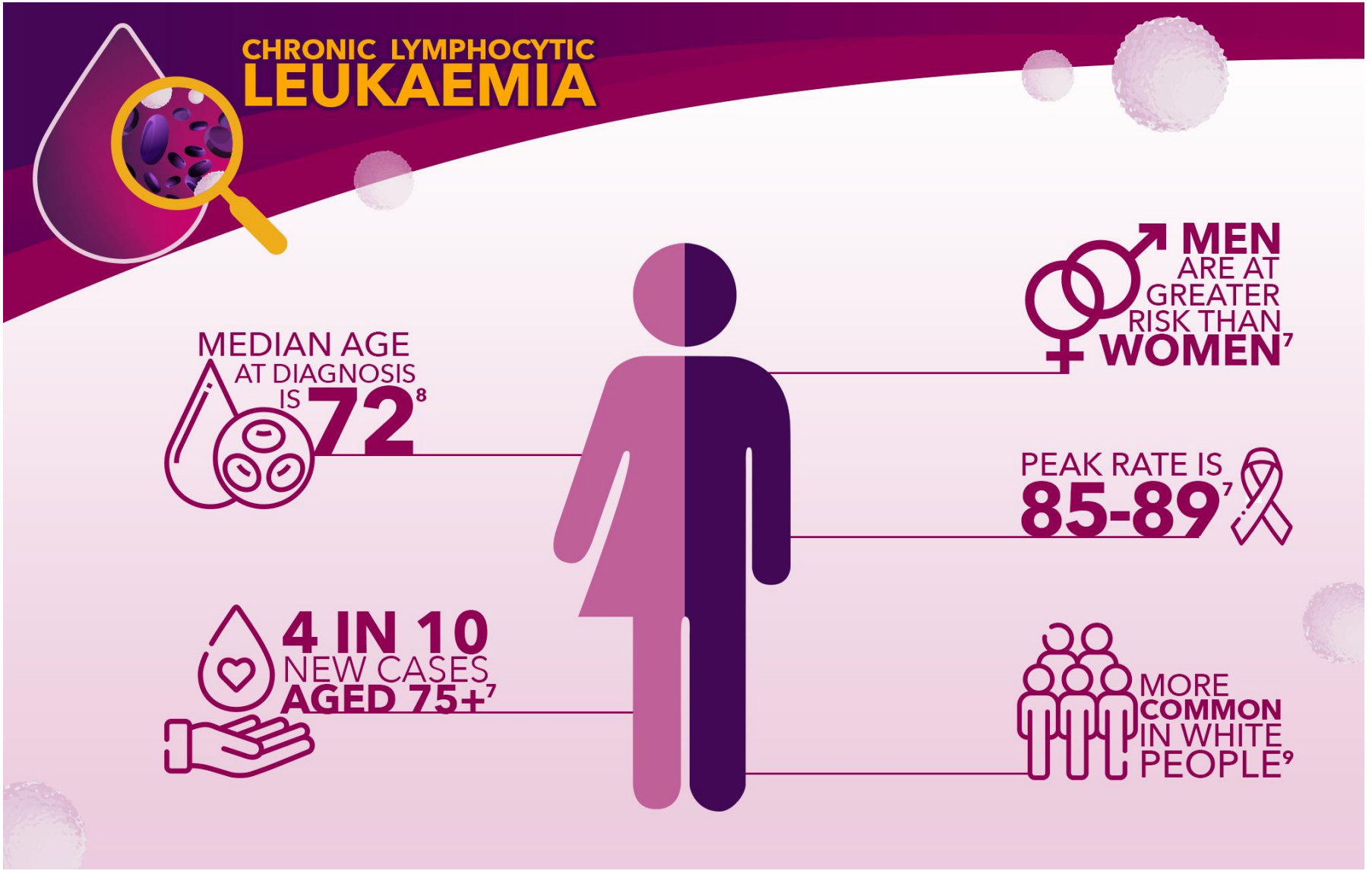
CLL patient demographics



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CLL aetiology

The underlying causes of CLL

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Aetiology overview

- While evidence suggests that CLL cells are **derived from memory B cells**, genetic changes are likely to begin much earlier, at the level of the **haematopoietic stem cell (HSC)**[10]
- It is likely that **CLL** is the result of the progressive accumulation of **mutations during B-cell development**[10]

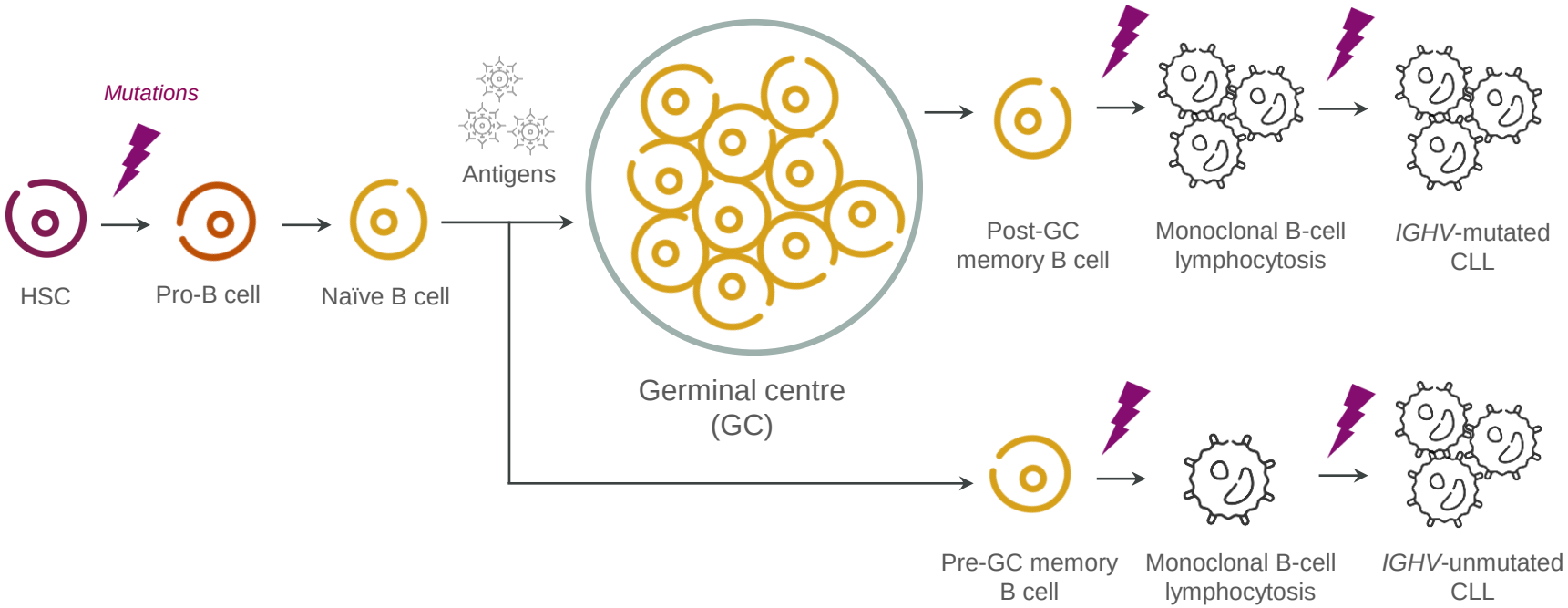

Figure adapted from Fabbri 2016[10]

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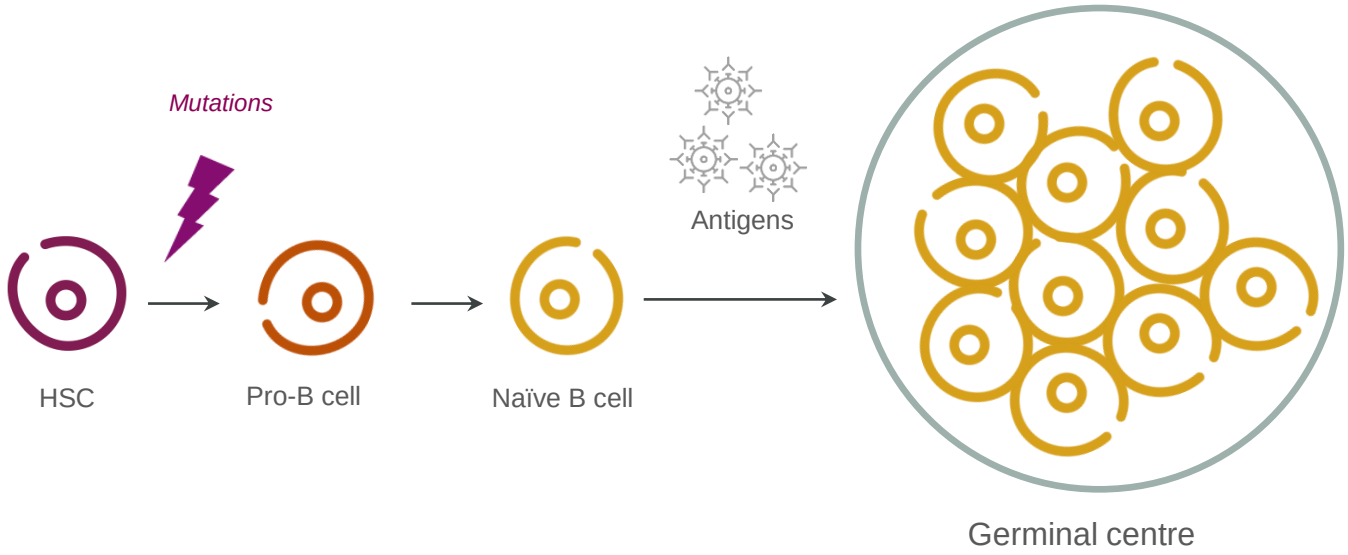
Aetiology – in detail



1 **HSCs** acquire mutations as they differentiate into **B cells.**[10]

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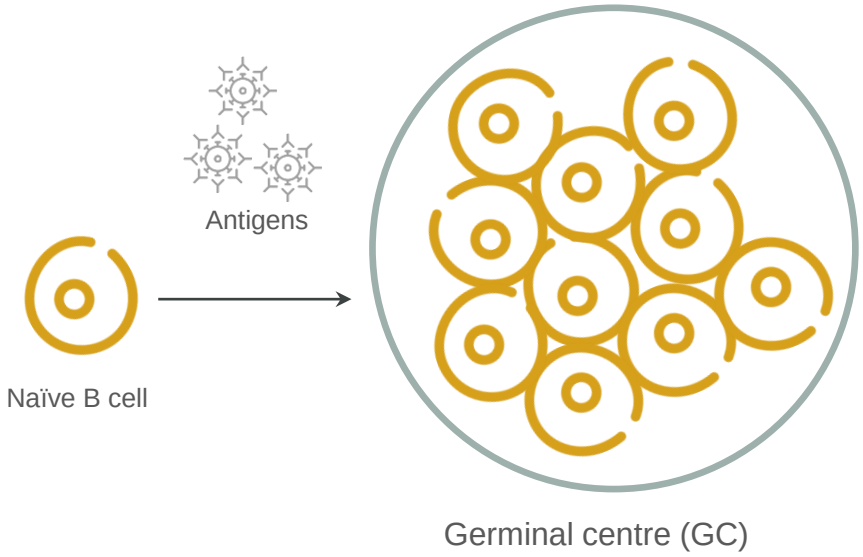
Aetiology – in detail



2

Naïve B cells encounter antigens in a peripheral lymphoid tissue. Some **B cells** then enter a primary lymphoid follicle and continually proliferate to form a **germinal centre.**[11]

A germinal centre is an area within a lymphoid follicle where B cells proliferate and differentiate after binding to an **antigen.**

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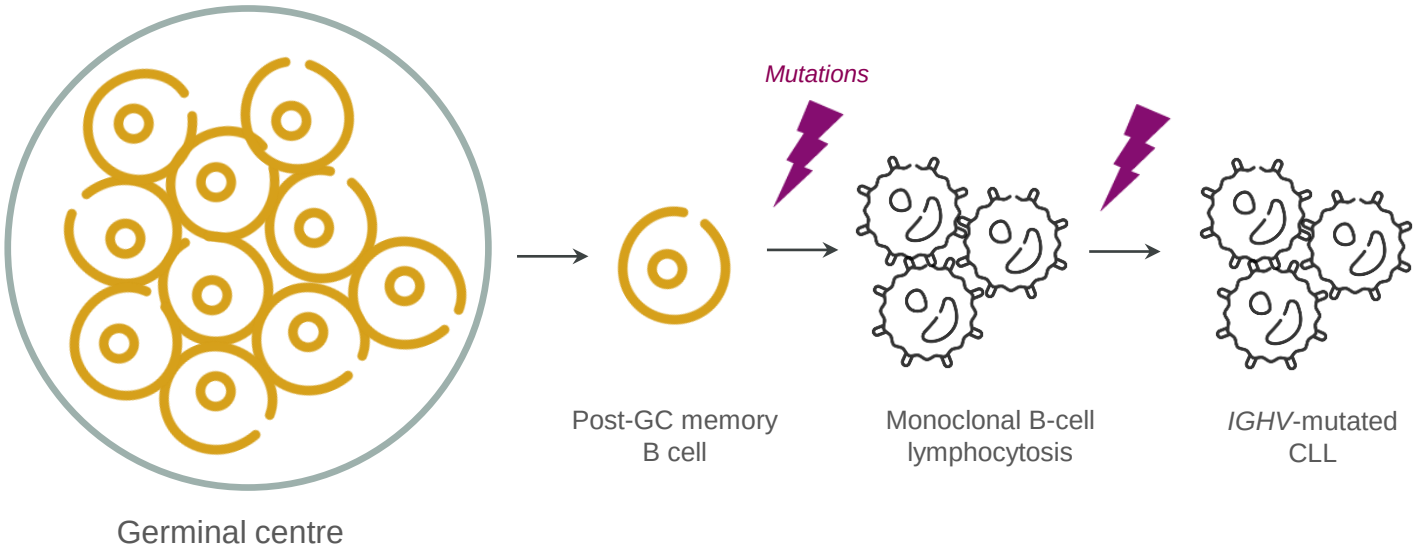
Aetiology – in detail



3

Activated B cells can then differentiate into **memory B cells**. It is thought that ***IGHV*-mutated CLL** develops from memory B cells that have traversed the germinal centre and acquired additional mutations to progress from **monoclonal B-cell lymphocytosis** (MBL) to CLL.[10]

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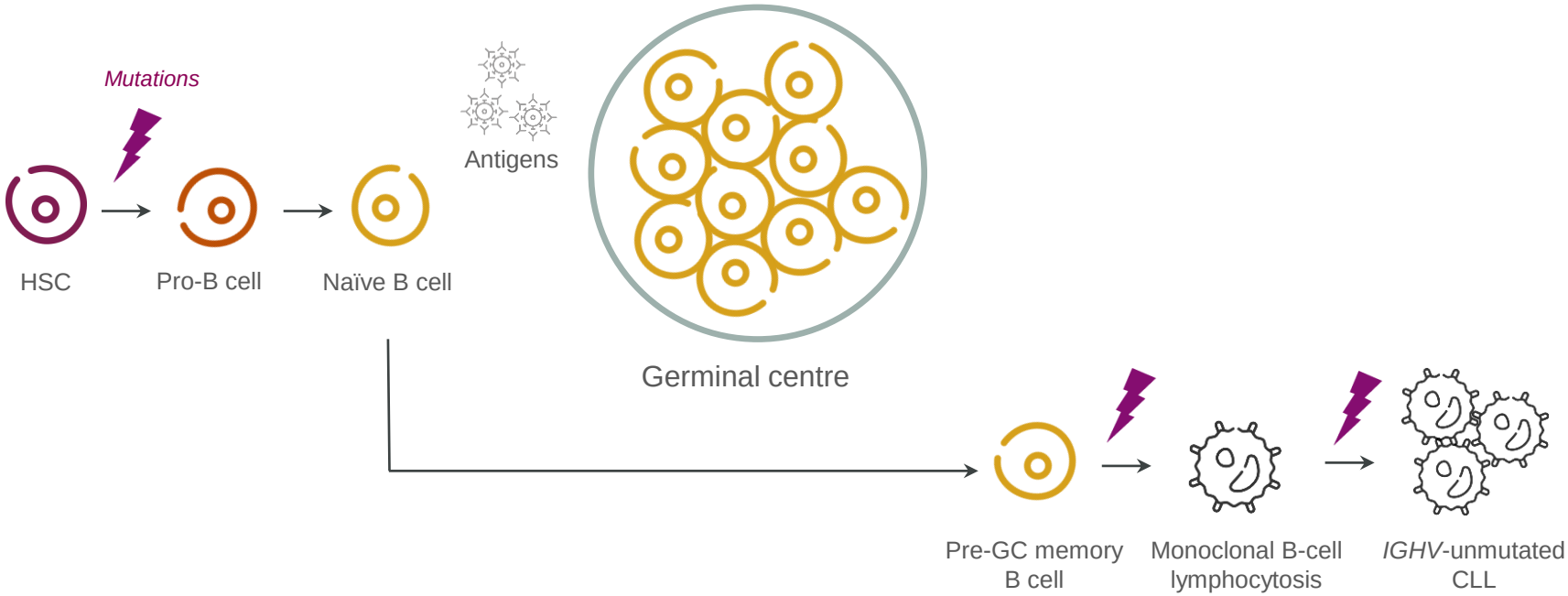
Aetiology – in detail



4

It is thought that ***IGHV*-unmutated** CLL develops from a small fraction of **memory B cells** that have not proliferated within the **germinal centre**.[10]

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CLL pathogenesis

The underlying mechanisms of CLL

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Pathogenesis

Several mutations that promote cell proliferation and survival drive the pathogenesis of CLL. No single, common genetic event has been identified in all cases:[11]

13q14 chromosomal deletion

The most common mutation in CLL is the deletion of the 13q14 chromosomal region[10]

Deleted genes include a gene encoding an inhibitor of a pro-survival protein, and tumour suppressor genes that regulate the cell cycle[10]

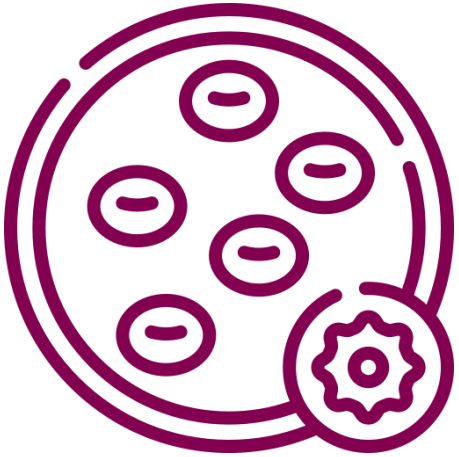
NOTCH1 mutations

Mutations in the *NOTCH1* gene promote the activation of the NOTCH1 signaling pathway. This leads to pro-survival and anti-apoptotic signals[10]

17p13 deletion and *TP53* mutation

The 17p13 chromosomal deletion includes the *TP53* tumour suppressor gene[10]

TP53 normally blocks cell cycle progression in response to DNA damage[13]



Tumour suppressor gene: a gene that suppresses cancer development. Its inactivation can lead to malignancy.[14]

NF-κB activation

A number of mutations associated with CLL activate nuclear factor-kappa B (NF-κB)

They do this by activating positive regulators and inhibiting negative regulators[10]

NF-κB may also be stimulated by extracellular signals, such as the B-cell receptor (BCR – see next slide)[10]

NF-κB activates many genes that promote B-cell survival and proliferation[12]

IGHV mutation status

CLL is often classified into 2 main subtypes, defined by the mutational status of the immunoglobulin heavy chain variable region (*IGHV*) genes[10]

Go to the next slide for more information on *IGHV*

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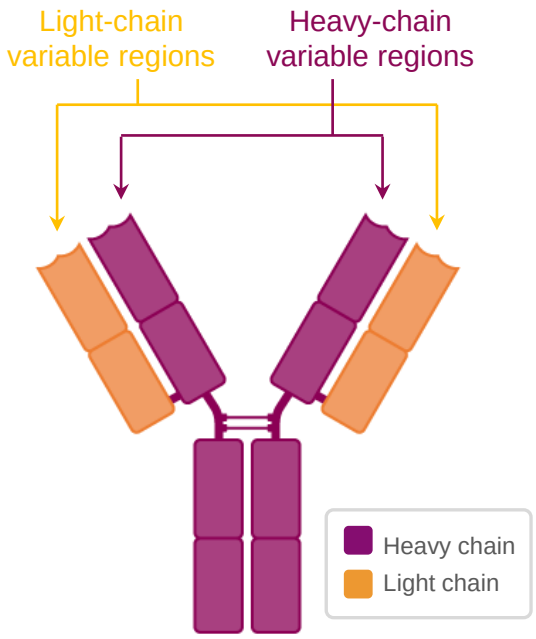
B-cell receptor (BCR) and *IGHV*-mutated CLL

The BCR

- The BCR is an **antigen-binding receptor** on the surface of B cells[11]
- Upon antigen binding, BCR signals through Bruton tyrosine kinase (BTK) to promote B-cell proliferation, activation and differentiation[13]
- In the form of an **antibody**, each BCR comprises a combination of **heavy chains and light chains**[14]
- The variable regions of the heavy and light chains form the **antigen-binding sites** of the antibody[14]



IGHV

- *IGHV* encodes the heavy-chain variable region[11,15]
- During B-cell development, a process called **somatic hypermutation** occurs, in which mutations are introduced into the variable region to produce antibodies that will bind more strongly to antigens[15]
- **IGHV-mutated CLL** accounts for approximately **60% of cases**
- **IGHV-unmutated CLL** accounts for approximately **40% of cases**[14]
- **IGHV-unmutated CLL** is associated with a **less-favourable prognosis**[11]

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Summary

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Summary

Types of leukaemia	Different types of leukaemia are distinguished based on: • Haematopoietic cell lineage – myeloid or lymphoid • Clinical course – acute or chronic
Definition	• CLL is characterised by the accumulation of abnormal lymphocytes • CLL and SLL are different manifestations of the same disease
Epidemiology	• Men are more at risk than women • Median age at diagnosis is 72 • More common in white people
Aetiology	• While evidence suggests that CLL cells are derived from memory B cells, genetic changes likely begin much earlier, at the HSC level • CLL is the result of progressive accumulation of mutations during B-cell development
Pathogenesis	• Several mutations that promote cell proliferation and survival drive the pathogenesis of CLL • No single, common genetic event has been identified in all cases

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Knowledge check

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Knowledge check

1. Fill in the blanks: In CLL, malignant cells are concentrated in the _____, bone marrow and lymphoid tissues. In SLL, malignant cells are concentrated in the _____, bone marrow, and other lymphoid tissues.

A. Blood, lymph nodes
B. Blood, spleen
C. Lymph nodes, blood
D. Lymph nodes, spleen

2. Fill in the blanks: CLL is most common in _____, with a median age at diagnosis of _____ years.

A. Men, 62
B. Men, 72
C. Women, 62
D. Women, 70

3. CLL cells are derived from which of the following types of cells?

A. Memory B cells
B. Naïve B cells
C. Pro-B cells
D. T cells

4. Which of the following are frequently observed mutations that may contribute to the pathogenesis of CLL?

A. 13q14 deletion, BTK activating mutation, BCR deletion, and NOTCH1 mutations
B. 13q14 deletion, 17p13 deletion, BTK activating mutation, and TP53 mutation
C. 13q14 deletion, 17p13 deletion/TP53 mutation, NOTCH1 mutations, and NF-κB activation
D. NF-κB activation, BCR deletion, 17p13 deletion, and BTK activating mutation

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Answers

1. **A**: In CLL, malignant cells are concentrated in the blood, bone marrow, and lymphoid tissues. In SLL, malignant cells are concentrated in the lymph nodes, bone marrow, and other lymphoid tissues.

2. **B**: CLL is most common in men, with a median age at diagnosis of 72 years.

3. **A**: CLL cells are derived from memory B cells.

4. **C**: Frequently observed mutations that may contribute to the pathogenesis of CLL include the 13q14 deletion, 17p13 deletion/*TP53* mutation, *NOTCH1* mutations, and NF-κB activation.

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