# Normal IgG Antibody Deficiency

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# A diagnostic problem

- **32 year old male**
- **Recurrent bacterial pneumonia**
  - 5 hospital admissions 1993-94

- **Underlying Immunodeficiency?**
  - Low IgA during childhood and recurrent pneumonia <5 years
  - No family history of infection
  - IgA 0.1 (0.8-3.5g/L), IgM 0.3 (0.5-2g/L), **IgG 8.3 (7.0-14g/L)**

# Immunology investigations 1995

Peripheral lymphocyte subsets:

- **very few CD19+ and/or CD20+ B cells (less than 1% of lymphocytes)**
- normal T cell and NK cell populations

**Poor vaccination response** to Pneumovax 23, conjugated Haemophilus and Tetanus toxoid

- Normal full blood count and ESR
- Normal IgG subclasses
- Normal complement
- Normal serum protein electrophoresis

# What we know

- Treated as **antibody deficiency** with IV immunoglobulin
- No further serious infection or hospital admissions
- No autoimmune/ lymphoproliferative sequelae

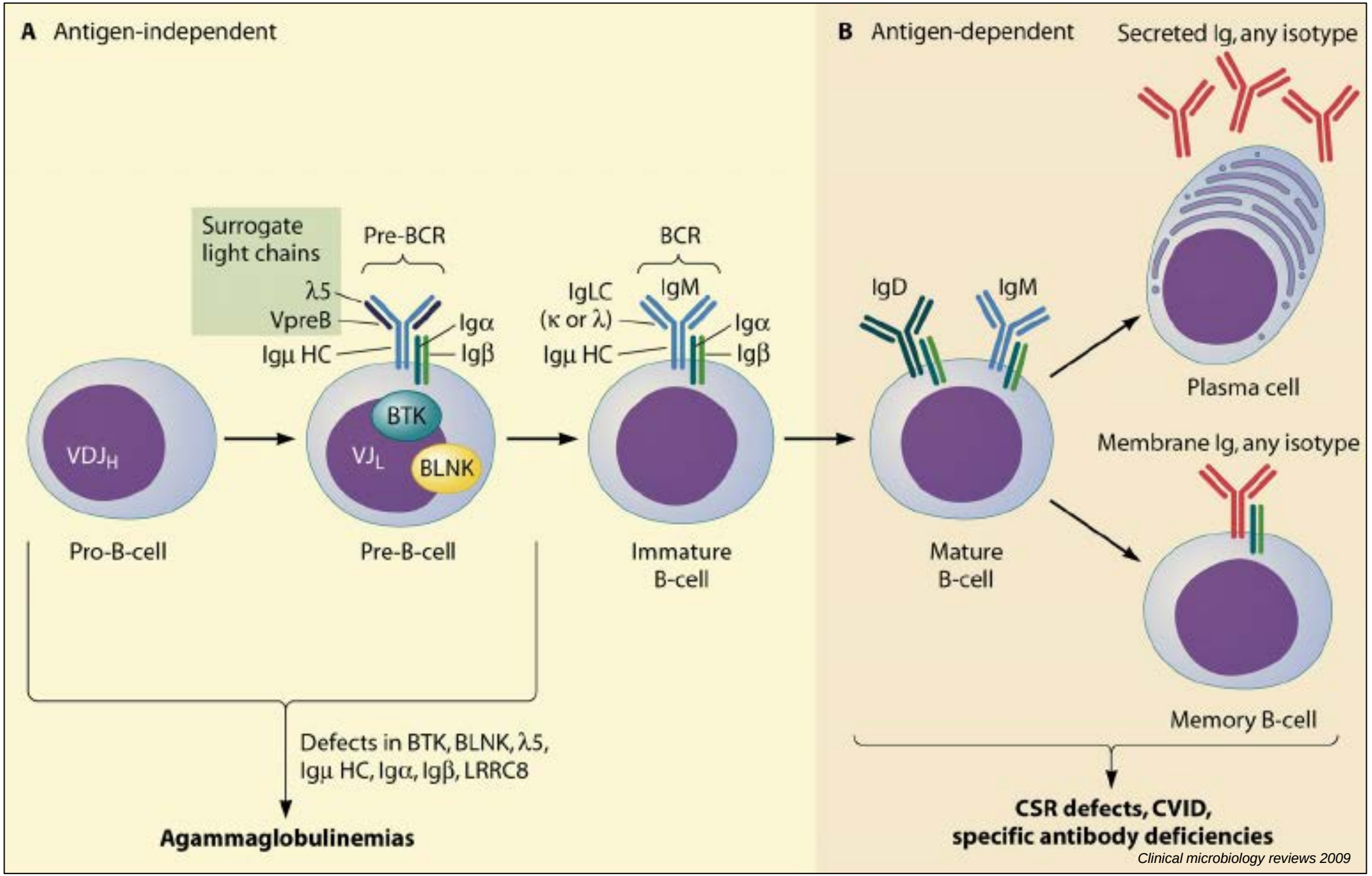
# What we don’t know

**Diagnosis?**

- Immunodeficiency phenotype
- Poor antibody response
- Clinical improvement after immunoglobulin

**Normal IgG without CD19+ B cells?**

**Normal IgG with absent/ low IgM?**




*Clinical microbiology reviews 2009*

# Possible theories

**B cell development problem?**

- Reservoir of restricted IgG secreted from plasma cells

- Abnormality arising in heavy chain isotype-switching mechanism?

# Possible theories

**Presence of an inhibitor?**

- Blocking/ Inhibiting agent
  - autoantibodies
  - cytokine milieu

# Possible theories

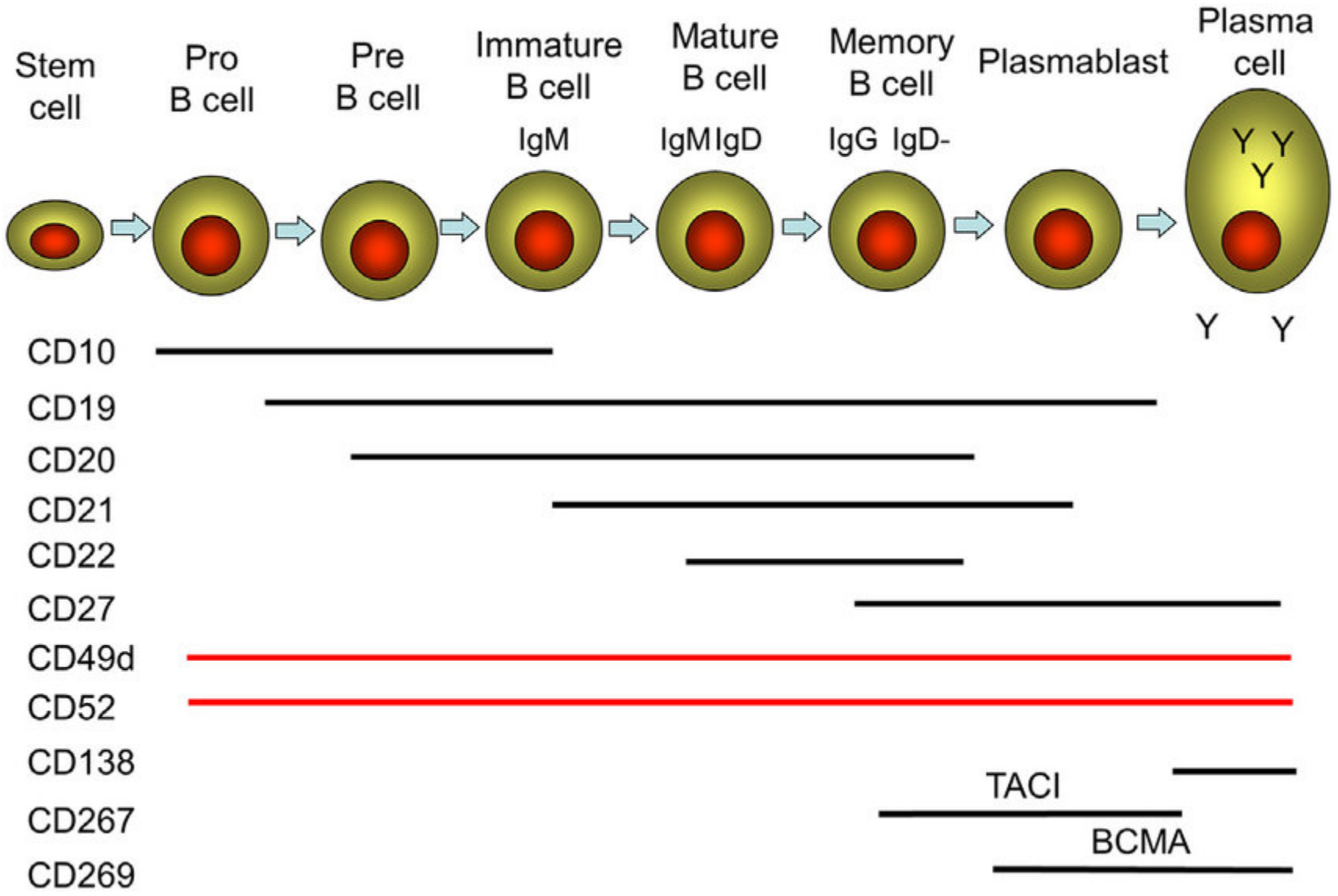
**Detection**

- Measurement error

# Bone marrow examination 1995

- Trephine: no evidence of a lymphoproliferative disorder
- Aspirate: normal active marrow, no abnormal lymphocytes
- Flow: CD19 cells 4.4%

**“majority of CD19+ cells display early B cell phenotype and less than 12% of CD19+ cells expressed mature B cell markers CD21 and CD22”**

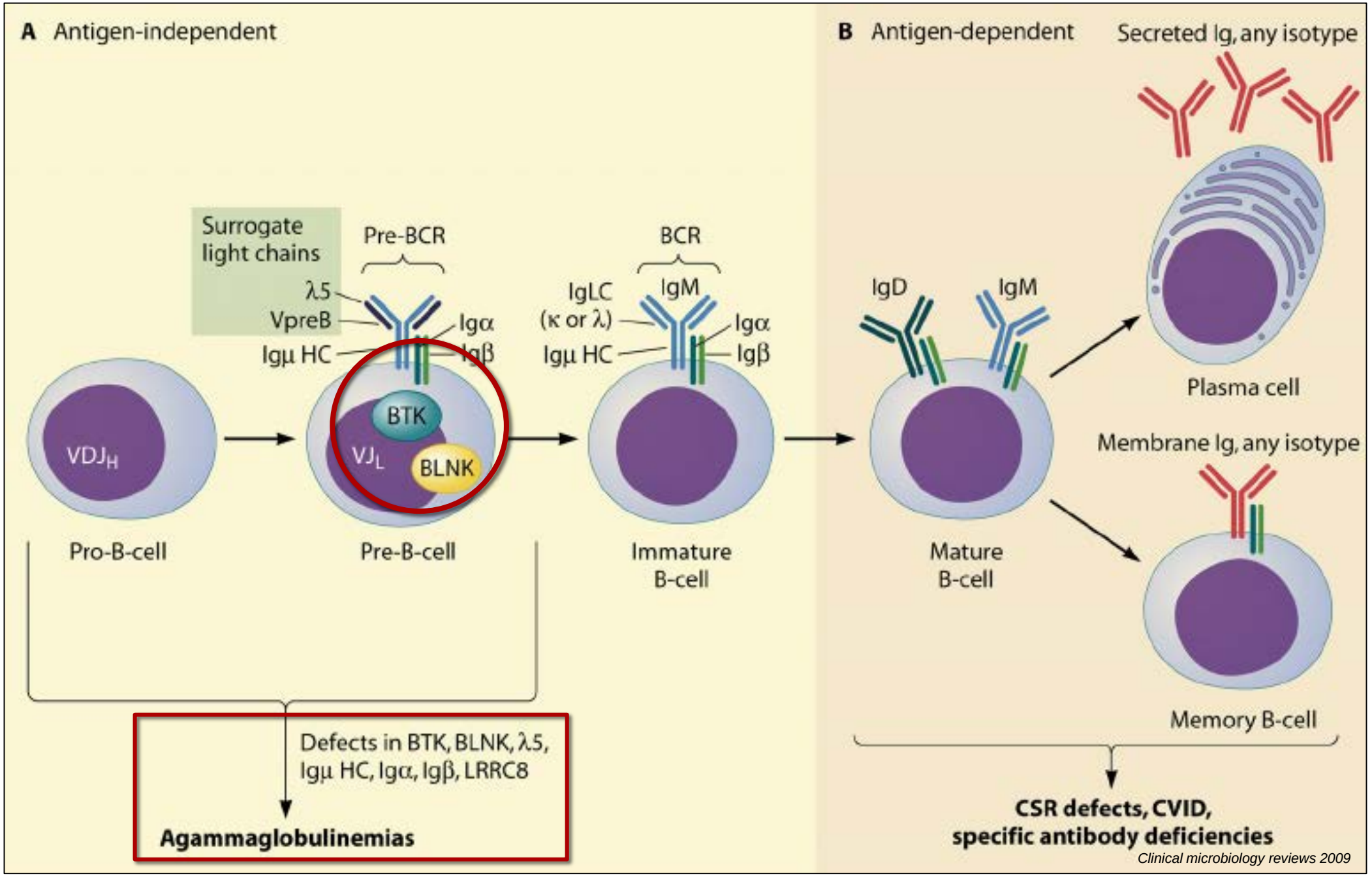



*EBioMedicine* 2017

# A defect of B cell maturation arising in the bone marrow

**Atypical presentation of CVID?**

**Pre B-cell check-point defect ?**


A Antigen-independent
B Antigen-dependent
Secreted Ig, any isotype
Surrogate light chains
Pre-BCR
λ5
VpreB
Igμ HC
Igα
Igβ
BCR
IgLC (κ or λ)
IgM
Igμ HC
Igα
Igβ
IgD
IgM
BTK
VJL
BLNK
VDJH
Plasma cell
Membrane Ig, any isotype
Pro-B-cell
Pre-B-cell
Immature B-cell
Mature B-cell
Memory B-cell
Defects in BTK, BLNK, λ5, Igμ HC, Igα, Igβ, LRRC8
Agammaglobulinemias
CSR defects, CVID, specific antibody deficiencies
Clinical microbiology reviews 2009

Clinical and Molecular Allergy

BioMed Central

Review

Open Access

# X-linked agammaglobulinemia diagnosed late in life: case report and review of the literature

Justin R Sigmon*, Ehab Kasasbeh and Guha Krishnaswamy

**Table 3: Clinical data and Btk mutations of 16 patients reported in the world literature with atypical XLA.**

| | | Serum Ig level (mg/dL)* | | | Btk Mutation | |
|---|---|---|---|---|---|---|
| **Patient no.** | **Age (yrs)ᵠ** | **IgG** | **IgA** | **IgM** | **Nucleotide Change** | **Domain** |
| P1 | 51 | 401 | <7 | 15 | 567C>A | TH |
| P2 | 26 | 169 | 8 | 7 | UD | UD |
| P3 | 25 | 773 | UD | 1 | UD | UD |
| P4 | 34 | 420 | UD | UD | UD | UD |
| P5 | 27 | 635 | <5 | 11 | Glu605stop | SH1 |
| P6 | 40 | <20 | <20 | 22 | G>Aᵠ | NA |
| P7 | 39 | 220 | UD | UD | W563L | SH1 |
| P8 | 60 | 429 | 7 | 14 | 994C>T | SH2 |
| P9 | 27 | 132 | 7 | 17 | 230C>T | PH |
| P10 | 21 | 35 | 8 | 29 | 1630A>G | SH1 |
| P11 | 32 | 462 | <8 | <7 | 227T>C | PH |
| P12 | 32 | 702 | 185 | <25 | 1706G>A | SH1 |
| P13 | 28 | 454 | 95 | 38 | UD | UD |
| P14 | 27 | 346 | 16 | 8 | 1705C>T | SH1 |
| P15 | 24 | NA | 0 | 1 | 1942-1943del AG | SH1 |
| P16 | 31 | 527 | 8 | 30 | UD | UD |

# Source of immunoglobulin production?

- “Leaky B cells”
  - Pre-B cells in bone marrow may be source of limited immunoglobulin production
- Restricted IgG from plasma cells or memory B cells

# A real problem

- Moved to UK in 2017
  - last SC immunoglobulin in Oct 2017
- Clinically well in Feb 2018
  - **IgG 10.02g/L (6-16)**, IgA <0.05g/L (0.8-4) and IgM 0.09g/L (0.5-2)
- Admitted to ICU with sepsis in June 2018
- Re-commenced on immunoglobulin therapy July 2018

# Investigations in UK

- Repeat immunoglobulin in July 2018: **IgG 7g/L (6-16g/L)**
- Lymphocyte markers:
  - **Absent CD19 cells (<1%)**
  - normal T cell and NK cell populations
- **Poor response to Pneumovax and Haemophilus vaccination**
- No paraprotein band on serum electrophoresis

# Where to from here?

- Life long immunoglobulin +/- antibiotics when required
- Molecular genetic testing