

# Defects in the CD19 complex predispose to glomerulonephritis, as well as IgG1 subclass deficiency

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5	Defects in the CD19 complex predispose to glomerulonephritis as well as IgG1 subclass
6	deficiency.
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# 47 Capsule Summary

- 48 We identified two novel mutations in CD19. These cases add to the clinical and biological
- 49 phenotype of CD19 deficiency and point to CD19 possible role in IgG1 switching and control

50 of autoimmunity.

- 51
- 52 Key words
- 53 CVID, IgG1 subclass deficiency, glomerulonephritis, auto-immunity, CD19 deficiency

#### 54 **To the Editor:**

55 Common variable immunodeficiency (CVID) and selective IgG1 deficiency are primary 56 immunodeficiencies characterized by defective antibody production leading to recurrent 57 infections of the respiratory tract <sup>1-3</sup>. Recent studies have identified *CD19* and *CD81* biallelic 58 mutations as underlying CVID in humans. On mature B cells, CD19 functions in a complex 59 with CD21, CD81, and CD225 and acts synergistically with the B cell antigen receptor to 50 induce activation and maturation of the activated B cells into the memory compartment <sup>4</sup>.

61 Only five patients with bi-allelic deleterious mutations in *CD19* have been described to date <sup>5-</sup> 62 <sup>7</sup>. Despite variability in CD19 expression, these patients display a remarkable similar 63 phenotype characterized by moderately severe hypogammaglobulinemia, impaired antibody 64 responses upon vaccination and impaired memory B cell formation. We report on two 65 additional patients with CD19 deficiency from two different families.

66 Out of 400 patients from the French national DEFI cohort with primary 67 hypogammaglobulinemia, 18 had CD19+ cells<1% but a percentage of T, NK and CD19 B 68 cells that didn't add up to 100%. Double CD19/CD20 staining performed in these 18 patients 69 demonstrated a CD19 defect in two patients (Figure E1).

Patient A, a girl of Kurdish descent was referred at 11 years of age with pneumococcal 70 71 meningitis. She also had a history of recurrent upper respiratory tract infections and giardiasis 72 starting in early childhood. She was found to have hypogammaglobulinemia and impaired antibody response to vaccination (Table E1). Patient B, a girl of Moroccan descent and the 73 second child of consanguineous parents was first referred at 13 years of age with failure to 74 75 thrive. Urinalysis revealed microscopic hematuria and proteinuria without renal failure. Tests for antinuclear antibodies were positive (titer=1/640) in the absence of anti-DNA and anti-76 77 ENA antibodies. The complement levels were normal. At 27 years of age, she had surgery for chronic sinusitis and at 29 years of age she developed pneumococcal pneumonia. She was 78

found to have selective IgG1 deficiency (Table E1). Antibodies to polio and tetanus toxin were detected at protective levels and antibodies to pertussis toxin were detectable albeit at a low level. Isohemaglutinins were present. At 31 years of age, she was referred with nephrotic syndrome and end stage renal disease. A renal biopsy revealed endo-capillary proliferative glomerulonephritis with intense mesangial IgA deposits associated with diffuse interstitial fibrosis consistent with a diagnosis of IgA nephropathy.

85 CD19 genomic sequencing showed homozygous deletion (1464delC) causing a premature 86 stop codon (P488PfsX15) in patient A. Patient A's parents and brother were heterozygous for 87 the mutated allele. Patient B, born to consanguineous parents, was found to have an insertion 88 (1653 1671+9del28pbins23pb), assumed to be homozygous and disrupting the wild type stop 89 codon (G551GfsX25). Her two children were heterozygous for the mutated allele. Both 90 mutations were frameshift mutations located in the intracytoplasmic domain of CD19, as seen in previously reported patients <sup>5, 6</sup> (Figure 1). Normal levels of CD19 transcripts were found 91 92 by quantitative RT-PCR in patients EBV transformed cell lines (data not shown). Absence of 93 CD19 protein has been confirmed by western blot on these cell lines (Figure E2). However, 94 Western blotting on EBV lines may not be sufficient to prove that the mutation is null in all B cells. Actually, a minority of B cells from patient B expressed CD19, but these cells are not 95 96 present in EBV transformed cells (Figure E1). One could guess that there are a small number 97 of cells in which alternative stop codons are used and we cannot rule out that this could 98 account for the distinct phenotype.

99 Patient A had normal B cell count but a sharp reduction in IgD-CD27+ switched memory B 100 cells while IgD+CD27- naive B cells were increased (both in percentage and absolute count). 101 Patient B displayed a slight reduction of B cell population. Within the B cell compartment, 102 the relative frequency of IgD-CD27+ switched memory and IgD+D27- naive B cells was 103 normal (Table E2 and Figure E1). Flow-cytometric immunophenotyping revealed low CD19 expression in all five carriers. Levels of CD21 were decreased whereas levels of CD81 were normal on B cells from both patients and carriers (Figure E1). Proliferation of purified total and naive B cells from both patients was studied after stimulation with anti-IgM antibody, anti-CD40+IL10 or CpG and showed proliferation comparable to controls (Figure 2a). In vitro Ig production showed very low IgG production by purified total and naive B cells after stimulation with anti-CD40+IL10 or CpG, whereas IgM production was similar to a control for both patients (Figure 2b).

111 Considering the high similarity among patients exhibiting a monogenic defect in CD19 or CD81, it has been proposed to regard CD19 complex deficiencies as a separate disease within 112 the group of antibody deficiency syndromes <sup>7</sup>. The present study reveals the wide variance 113 114 among patients with similar CD19 deficiency. Patient B is the first patient with CD19 115 deficiency, selective IgG1 deficiency, conserved antibody response against protein antigens 116 upon vaccination and a normal IgD-CD27+ switched memory B cell compartment. Her 117 immunological phenotype points to a possible role of CD19 in IgG1 switching in humans. 118 Although clinical immune deficiency was present, the major complication in patient B was a 119 severe IgA nephropathy. Interestingly, glomerulonephritis has been observed in two other 120 patients with CD19 complex deficiency (CD19, CD81)<sup>6,7</sup>. The high frequency of 121 nephropathy in 3 out of 8 patients with CD19 complex deficiency is striking. It has been 122 recently reported that CD19<sup>-/-</sup> lupus prone NZB/W mice lack a potent splenic regulatory B 123 cell subset (B10 cells) producing IL10, which could account for the significantly earlier onset 124 of nephritis in these knock-out mice when compared with wild type NZB/W controls<sup>8</sup>.

In conclusion, we describe 2 new cases of CD19 deficiency in patients with antibody production defect. In such patients, lymphocyte phenotyping with an anti-CD19 antibody can lead to a false diagnosis of B cell alymphocytosis. In order to avoid misdiagnosis in that context, immunophenotypes using CD19 staining should be carefully examined to detect a

- 129 gap due to unstained B lymphocytes in all patients with immunoglobulin production defect,
- 130 including IgG sub-class deficiencies.
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## 214 Figure Legends

Figure 1. (a) Schematic representation of the *CD19* coding region (14 exons, 1671 nucleotides). The new mutations are shown on the top, the known mutations on the bottom.
(TM: transmembrane domain). (b) Pedigrees of patients A and B (homozygous are in black, heterozygous are in half black)

Figure 2. Proliferation (a) and immunoglobulin production (b) of B cells from both patients and one control, these experiments were also performed on naive B cells and provided comparable results (Data not shown). These results are expressed as the mean of triplicate experiments.

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226 Figure 1



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228 Figure 2