

## **CD21 deficiency in two siblings with recurrent respiratory infections and hypogammaglobulinemia**

Jeremie Rosain, Charline Miot, Nathalie Lambert, Marie-Christine Rousselet, Isabelle Pellier, Capucine Picard

► **To cite this version:**

Jeremie Rosain, Charline Miot, Nathalie Lambert, Marie-Christine Rousselet, Isabelle Pellier, et al.. CD21 deficiency in two siblings with recurrent respiratory infections and hypogammaglobulinemia . Journal of Allergy and Clinical Immunology, Elsevier, 2017, Epub ahead of print. 10.1016/j.jaip.2017.04.011 . inserm-01525046

**HAL Id: inserm-01525046**

**<https://www.hal.inserm.fr/inserm-01525046>**

Submitted on 19 May 2017

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1                    **CD21 deficiency in two siblings with recurrent respiratory infections and**  
2                    **hypogammaglobulinemia**

3  
4        Jeremie Rosain<sup>1,2</sup> PharmD,MSci, Charline Miot<sup>3,4,5</sup> MD,PhD, Nathalie Lambert<sup>1</sup>, MSci,  
5        Marie-Christine Rousselet<sup>5,6</sup> MD,PhD, Isabelle Pellier<sup>3,4,5</sup> MD,PhD, Capucine Picard<sup>1,7</sup>  
6                    MD,PhD

- 7  
8    1. Study Center for Primary Immunodeficiencies, Necker-Enfants Malades Hospital,  
9        Assistance Publique Hôpitaux de Paris (APHP), Necker Medical School, Paris, France,  
10        EU.  
11    2. Paris Descartes University, Paris, France, EU.  
12    3. Pediatric Immuno-Hemato-Oncology Unit, Angers University Hospital, France, EU.  
13    4. Inserm UMR 892, Angers, France, CNRS UMR 6299, Angers, France, EU.  
14    5. Angers University, Angers, France, EU.  
15    6. Department of Cellular and Tissue Pathology, Angers University Hospital, France, EU.  
16    7. INSERM UMR1163, Imagine Institute, Paris Descartes University, Paris, France, EU.  
17

18    **Corresponding author:**

19    Capucine Picard, Study Center for Primary Immunodeficiencies, Necker – Enfants Malades  
20    Hospital, 149 rue de Sèvres, 75015 Paris, France, EU. Phone number +33 (1) 44 49 50 88; fax  
21    number +33 (1) 42 73 06 40; capucine.picard@inserm.fr

22  
23    **Short summary**

24    We report the clinical history, immunological phenotype and causal mutation for two patients  
25    with CD21 deficiency.  
26

27    **Keywords**

28    Primary antibody deficiency, CD21, respiratory infections  
29

30    **Abbreviations**

31    **CVID:** common variable immunodeficiency  
32

33 *To the Editor,*

34

35         The complement system plays a major role in humoral immunity via activation of the  
36 classical pathway and the development of adaptive responses. This function is ensured  
37 principally by CD21 (or CR2), a receptor that recognizes C3 cleavage fractions containing a  
38 C3d moiety bound to an antigen<sup>1</sup>. CD21 is primarily expressed by follicular dendritic cells  
39 (FDC) and B cells. The CD21 on FDCs traps soluble C3d-bound antigens for their  
40 presentation to B cells in the lymphoid tissues. The CD21 on B cells forms part of the CD19  
41 complex, along with CD81, CD225 and CD19, and acts as a coreceptor for the B-cell receptor  
42 (BCR)-Iga $\beta$ . The coligation of a C3d-bound antigen to the BCR and CD21 increases the  
43 strength of the activating signal delivered to B cells<sup>1</sup>. Only two patients with a common  
44 variable immunodeficiency syndrome (CVID) phenotype caused by autosomal recessive  
45 CD21 deficiency have been reported to date<sup>2,3</sup>. We report here the first multiplex kindred with  
46 CD21 deficiency.

47         The two siblings were born to consanguineous French parents (**Figure E1**). The proband (P1),  
48 a 14-year-old girl, was first referred at the age of seven years, for recurrent otitis media and  
49 bronchitis, which persisted despite three adenoidectomies and multiple grommet insertions.  
50 She also had undocumented lobar pneumonia at the age of 12 years. Immunological tests  
51 performed at the age of seven years revealed low levels of immunoglobulin (Ig) G1, resulting  
52 in low levels of IgG. IgG and IgG1 levels were normal at the age of 10 years. IgG to tetanus  
53 and diphtheria were reduced despite routine immunization (**Table E1**). This patient developed  
54 partial conductive deafness, despite the systematic treatment of otitis media with antibiotics.  
55 Histological analysis of an adenoid sample showed a hypertrophic mucosa with florid  
56 hyperplasia of the secondary lymphoid follicles. Germinal centers contained large numbers of  
57 macrophages, the cell bodies of which were readily stained. Interfollicular areas contained

58 lymphocytes, marginal cells, immunoblasts and plasmocytes, with no cellular atypia (**Figure**  
59 **E2**). P1's 11-year-old brother (P2) was first referred at the age of five years, for recurrent  
60 otitis media, rhinopharyngitis and bronchitis, which have begun at the age of four months. He  
61 underwent one adenoidectomy and two grommet insertions. Initial immunological  
62 explorations showed normal levels of IgG but slightly low levels of IgG1. P2 then developed  
63 mild hypogammaglobulinemia between the ages of 7 and 11 years. IgG to tetanus and  
64 diphtheria were reduced despite routine immunization. After booster injections, the titers of  
65 antibodies specific for tetanus toxoid reached protective levels in the two patients, whereas  
66 those for anti-diphtheria toxoid antibodies remained low (**Table E1** and **Figure E2**). None of  
67 the two patients received immunoglobulin substitution. P1 received prophylaxis by  
68 cotrimoxazole during one winter season at the age of 7 which reduced the frequency of  
69 infections. A flow-cytometry study of B cells from the two patients showed a decrease in  
70 class-switched memory B cells and a complete loss of CD21 cell surface expression (**Figure**  
71 **E1**). CD21 immunohistochemistry of the adenoid tissue of P1 revealed a complete absence of  
72 staining (**Figure E2**). Genomic sequencing of *CR2*, the gene encoding CD21, revealed a  
73 homozygous one-base pair deletion (c.234delC) predicted to lead to a frameshift and the  
74 insertion of a premature stop codon (p.T209HfsX10) (**Figure E1**). Both parents were  
75 heterozygous for this mutation. The father was asymptomatic and had a normal  
76 immunophenotype, with slightly lower levels of CD21 expression on B cells than observed in  
77 the healthy control (**Figure E1**). The mother was asymptomatic but had had recurrent otitis  
78 media during childhood. Laboratory assessments revealed profound B lymphopenia (0.9%;  
79  $3/\text{mm}^3$ ), but normal levels of immunoglobulins and a protective titer of antibodies against  
80 toxoid tetanus in the mother at the age of 35 years.

81 We report here complete CD21 deficiency due to a new homozygous *CR2* mutation in two  
82 siblings. Both patients were referred for recurrent upper respiratory tract infections beginning

83 in early childhood. Both have mild hypogammaglobulinemia and low levels of memory class-  
84 switched B cells, with impaired production of antibodies specific for certain protein antigens.  
85 The adenoid tissue of P1 had hyperplastic germinal centers with a normal architecture but no  
86 CD21-positive FDCs. The number and size of germinal centers within splenic follicles are  
87 smaller after immunization in *cr2*<sup>-/-</sup> mice than in wild-type mice<sup>4</sup>, probably because *cr2*<sup>-/-</sup> mice  
88 are also CD35-deficient<sup>1</sup>. CD35 is another receptor of cleaved complement fractions<sup>4</sup>. Only  
89 two other CD21-deficient patients have been described to date<sup>2,3</sup>. Both have mild  
90 hypogammaglobulinemia associated with low levels of memory B cells, but they have a  
91 normal antibody response to protein antigens<sup>2,3</sup> (**Table 1**). The first patient reported was  
92 diagnosed at the age of 26 years. He had recurrent upper respiratory tract infections before the  
93 age of six years and remained asymptomatic for 20 years following adenoidectomy<sup>2</sup>. At the  
94 age of 26 years, he developed symptoms suggestive of COVID. The second reported case was a  
95 16 year old boy with a history of autoimmune disease with no history of recurrent infection<sup>3</sup>.  
96 The two patients reported here had more severe clinical and immunological phenotypes than  
97 the first two patients to be described<sup>2,3</sup> (**Table 1**). As our patients were born to  
98 consanguineous parents, we cannot rule out the existence of other pathogenic variants in their  
99 genomes, although laboratory investigations detected no other immunological abnormality.  
100 Low levels of calcium flux have been reported in CD21-deficient B cells exposed to a  
101 suboptimal quantity of C3d-bound antigen<sup>2</sup>. This finding suggests that the impaired B-cell  
102 response in CD21-deficient patients is due to decreased stimulation of B cells from the  
103 germinal center in the absence of positive signals mediated via the CD21 coreceptor<sup>1</sup>. The  
104 absence of CD21 expression on FDCs may also be responsible for impaired antigen retention  
105 in lymphoid follicles. Taken together, these data suggest that the absence of CD21 expression  
106 on B cells and FDCs could lead to an inability to sustain specific humoral responses after  
107 antigen challenge. This finding highlights the importance of CD21 for the development of

108 humoral adaptive immunity and the induction of memory B cells in humans. CD21 deficiency  
109 may however be surmountable in case of high concentration or repeated antigen exposure<sup>2</sup>.  
110 Other deficiencies in components of the CD19 complex (CD19 and CD81 deficiencies) are  
111 also associated with an impaired response to protein antigens, albeit with a more severe  
112 clinical and immunological phenotype than in CD21 deficiency<sup>3,5-9</sup>. This underlie that CD21  
113 may be more redundant than CD19 and CD81. Additional clinical reports for CD21-deficient  
114 patients and their long term follow-up are now required to improve our understanding of the  
115 natural course of this deficiency. The defect observed in these patients could easily be  
116 screened by flow cytometry panel for CVID, which should be offered to patients with an  
117 impairment of humoral immunity.

118

119

120 **Acknowledgment:** We would like to thank Mirjam van der Burg, Jacinta Bustamante,  
121 Véronique Frémeaux-Bacchi and Ludovic Lhermitte for helpful discussions. We also thank  
122 Aminata Diabate, Barik Konte, Stéphanie Ndaga and Corinne Jacques for excellent technical  
123 assistance.

124 **References**

- 125 1. Carroll MC, Isenman DE. Regulation of humoral immunity by complement. *Immunity*  
126 2012; 37:199-207.
- 127 2. Thiel J, Kimmig L, Salzer U, Grudzien M, Lebrecht D, Hagen T, et al. Genetic CD21  
128 deficiency is associated with hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;  
129 129:801-10 e6.
- 130 3. Wentink MW, Lambeck AJ, van Zelm MC, Simons E, van Dongen JJ, H IJ, et al.  
131 CD21 and CD19 deficiency: Two defects in the same complex leading to different disease  
132 modalities. *Clin Immunol* 2015; 161:120-7.
- 133 4. Ahearn JM, Fischer MB, Croix D, Goerg S, Ma M, Xia J, et al. Disruption of the Cr2  
134 locus results in a reduction in B-1a cells and in an impaired B cell response to T-dependent  
135 antigen. *Immunity* 1996; 4:251-62.
- 136 5. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, et al.  
137 An antibody-deficiency syndrome due to mutations in the CD19 gene. *N Engl J Med* 2006;  
138 354:1901-12.
- 139 6. Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, et al. Novel  
140 mutations in a Japanese patient with CD19 deficiency. *Genes Immun* 2007; 8:663-70.
- 141 7. van Zelm MC, Smet J, Adams B, Mascart F, Schandene L, Janssen F, et al. CD81  
142 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. *J*  
143 *Clin Invest* 2010; 120:1265-74.
- 144 8. Vince N, Boutboul D, Mouillot G, Just N, Peralta M, Casanova JL, et al. Defects in  
145 the CD19 complex predispose to glomerulonephritis, as well as IgG1 subclass deficiency. *J*  
146 *Allergy Clin Immunol* 2011; 127:538-41 e1-5.
- 147 9. van Zelm MC, Smet J, van der Burg M, Ferster A, Le PQ, Schandene L, et al.  
148 Antibody deficiency due to a missense mutation in CD19 demonstrates the importance of the  
149 conserved tryptophan 41 in immunoglobulin superfamily domain formation. *Hum Mol Genet*  
150 2011; 20:1854-63.

**Table 1 – Clinical, immunological and genetic characteristics of CD21-deficient patients**

	<b>Thiel <i>et al.</i>, 2012<sup>2</sup></b>	<b>Wentink <i>et al.</i>, 2015<sup>3</sup></b>	<b>P1</b>	<b>P2</b>
<b>Age at diagnosis</b>	26 y	13 y	14 y	11 y
<b>Sex</b>	M	M	F	M
<b>Country of residence</b>	Germany	The Netherlands	France	France
<b>Consanguinity</b>	No	No	Yes	Yes
<b>Clinical history</b>	< 6 y: URT infections 6 – 26 y: asymptomatic 26 y: URT and LRT infections, SMG, diarrhea, fever	No recurrent infection Possible autoimmune disease	Recurrent URT and LRT infections since early childhood	Recurrent URT infections since early childhood
<b>CR2 mutations</b>	c.1225+1G>C/ p.W766X	p.R142X/ p.I926SfsX14	p.T209HfsX10/ p.T209HfsX10	p.T209HfsX10/ p.T209HfsX10
<b>Immunophenotyping</b>				
CD21 expression	Absent	Absent	Absent	Absent
Class-switched memory B cells	Decreased	Decreased	Decreased	Decreased
<b>Immunoglobulin</b>				
IgG	Low	Low	Low to normal	Low to normal
IgA	Low	Low	Normal	Normal
IgM	Normal	Low	Normal	Subnormal
<b>Serology</b>				
Protein antigens	Normal	Normal	Low	Low
Polysaccharide antigen	Low	Normal	Normal*	Low*

\*assessed by blood group isohemagglutinin production; URT: upper respiratory tract; LRT: lower respiratory tract; SMG: splenomegaly