

Letter to the Editor

Clinical characteristics and genotype-phenotype correlations in C3 deficiency

To the Editor:

The complement system comprises 3 initiation pathways: the classical, lectin, and alternative pathways. Although each pathway is activated individually, they converge at the C3 step and subsequently follow a common pathway, indicating that C3 is a pivotal complement factor. A single-chain precursor (Pro-C3) of approximately 200 kDa is produced intracellularly, and subsequently proteolytically cleaved into 2 subunits, α (115 kDa) and β (70 kDa) subunits. Both α and β subunits assemble by a disulfide bond yielding the mature C3 protein. The C3 protein consists of 13 domains¹: 8 macroglobulin domains (MG1-8); anaphylatoxin (ANA); linker (LNK); complement C1r/C1s, Uegf, Bmp1 (CUB); thioester-containing domain (TED); and C345 C domains.

C3 deficiency is a rare autosomal-recessive inherited disorder that is characterized by susceptibility to recurrent bacterial infections, although some cases are associated with autoimmune diseases.² However, no definite genotype-phenotype correlations have been established to date, possibly because of the extremely low prevalence of the disorder. In the present study, we investigated the clinical features of our 4 cases³⁻⁶ of C3 deficiency and reviewed previously reported cases to clarify the genotype-phenotype correlations in this disorder. We searched for English and Japanese articles describing C3 deficiency in PubMed, Ovid, and Google Scholar from 1972 (first reported year of C3 deficiency) to December 2014. From 511 articles, we selected 43 articles reporting biochemically diagnosed C3 deficiency regardless of confirmation by molecular analysis, and collected their genetic and clinical information.

Thirty-seven cases (29 families) of various races have been identified from different regions in the world (Table 1). Clinical features could be divided into 3 groups: severe infections, rheumatic diseases, and renal diseases. We arbitrarily defined the criteria for severe infections in this study as follows: infections of normally sterile sites (blood, cerebrospinal fluid, peritoneal fluid, joint fluid, or bone marrow) or recurrent bacterial infections (≥ 3) before the age of 3 years regardless of the site of infection. Both rheumatic and renal diseases are possibly caused by immune complex (IC)-associated mechanisms and are grouped here as IC-related diseases.

Thirty cases (81%) developed severe infections. Fifteen cases had histories of septic meningitis, 9 (60%) of which suffered from recurrent meningitis. Among a total of 34 episodes of meningitis, *Streptococcus pneumoniae* and *Neisseria meningitidis* were detected from cerebrospinal fluids in 14 and 6 episodes, respectively. Eight cases had histories of bacteremia or sepsis, 4 (50%) of which suffered from 2 or more episodes of bacteremia. Among a total of 15 episodes of bacteremia or sepsis, *S pneumoniae* was identified in 12 episodes (80%) and the remaining microorganisms were *N meningitidis*, *Staphylococcus aureus*, and *Streptococcus milleri*. Twenty-four cases had recurrent respiratory tract infections and/or otitis media caused by *S pneumoniae*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *S aureus*, and *Streptococcus pyogenes*.

Rheumatic diseases were observed in 8 cases (22%): 6 cases from 5 families displayed systemic lupus erythematosus

(SLE)-like illness, 1 case had subacute cutaneous lupus erythematosus, and 1 case had synovitis.⁶ Six cases were positive for antinuclear antibody at low titers (1:40~1:320). Three of the 8 cases with rheumatic diseases (38%) had no history of severe infections.

Renal diseases (hematuria and/or proteinuria) were observed in 8 cases (22%). Renal biopsies were performed in 5 cases, showing membranoproliferative glomerulonephritis type 1 (2 cases), mesangiopathic glomerulonephritis (1 case), IgA nephropathy (1 case), and membranous nephropathy (1 case). Two patients with SLE-like illness who were grouped as suffering from rheumatic diseases had focal segmental glomerulonephritis and membranous glomerulonephritis, respectively, despite normal urinary analysis. Three of the 8 cases with renal diseases (38%) had no history of severe infections.

The median age of onset of any symptoms related to C3 deficiency was 2.0 years (range, 3 weeks-19 years): severe infections at 1.5 years ranging from 3 weeks to 10 years and IC-related diseases at 7.5 years ranging from 1 to 25 years. The overall mean age of diagnosis was 9.2 ± 6.5 years (range, 10 months-26 years). The patients with severe infections were diagnosed at a younger age than were those with only IC-related diseases (8.3 ± 6.3 years vs 13.8 ± 6.4 years; $P = .061$).

Genetic analyses had been carried out in only 18 cases (16 families) including the present 4 cases (4 families). Among these cases, complete analyses of both alleles were performed in 14 cases (13 families). Three cases (21%) had compound heterozygous mutations, whereas the remainder (79%) had homozygous mutations. We found 15 mutations: 6 splicing abnormalities, 4 nonsense mutations, 2 with 1 or 2 base deletion, 1 large deletion, 1 with 1 base insertion, and 1 missense mutation. We analyzed the genotype-phenotype correlation in 14 cases (13 families) with completely defined C3 mutations. Fig 1 illustrates the domains of C3 and mutations of genetically confirmed patients. In patients with severe infections, C3 mutations were located in the β -chain and upstream of the TED domain in the α -chain. However, patients without severe infections had C3 mutations that were concentrated in and downstream of the TED domain (Nos. 26-1, 26-2, 28, and 29). Given that all mutations except 1 missense mutation (No. 18) were predicted to result in frame-shift or premature termination of protein translation, the mutations of the N-terminal half of the gene may cause large truncations and, possibly, lack of C3 protein. Although the small number of genetically confirmed cases is a limitation in our study, our results raise the possibility that mutations of the nucleotides encoding the TED domain or downstream of it causes production of mutant C3, which is able to control infections but not IC-related diseases, despite being undetectable by the conventional assay system. To address this possibility, it is necessary to develop a novel quantitative and functional assay system of mutant C3 molecules.

In conclusion, the clinical features of C3 deficiency were a combination of severe infections mainly caused by *S pneumoniae* and *N meningitidis* and/or IC-related diseases such as SLE-like illness or renal diseases. Patients with C3 mutations in the N-terminal half of the gene tend to be more susceptible to severe infections. The biological functions of the mutant C3 molecule remain to be elucidated.

TABLE I. Clinical features, C3 values, C3 mutations, and sibling history in 37 patients with C3 deficiency from 29 families

Patient no.	Published year	Ethnicity	C	Age at diagnosis/ sex	C3 (mg/dL)	C3 molecular analysis	Clinical features	Sibling history	Reference
Severe infections									
1.	1972 1976 1989 1992	White South African	+	15 y/F	<0.25	800-bp deletion (homo)	Meningitis × 2, pneumonia × 14, recurrent otitis media, paronychia, impetigo, Sweet syndrome		E1-E4
2.	1976	White South African	—	4 y/M	0	NA	Meningitis × 6, recurrent tonsillitis, pneumonia × 2, deceased	Deceased, meningitis	E5
3.	1977	Unknown	+	2 y/M	<3	NA	Otitis media × 2, persistent fever (52 d), maculopapular rash, arthralgia	Deceased, encephalitis	E6
4.	1977	Unknown	—	5 y/F	<2.5~5	NA	Pneumonia, septic arthritis, recurrent otitis media, and pharyngitis		E7
5.	1981 1994	Taiwanese Aborigines	—	10 y/F	0	IVS10 +1 g>t (homo)	Pneumonia × 12, otitis media × 5, septic arthritis, buttock abscess	Deceased, meningitis	E8,E9
6-1.	1983 1992	Dutch	?	26 y/F	ND	NA	Meningitis × 3, sepsis, recurrent otitis media, skin infections	Deceased, meningitis	E10,E11
6-3.				16 y/F	ND	NA	Septic osteomyelitis, recurrent otitis media, maculopapular rash during infectious episodes		
7.	1988 2002	Brazilian	+	6 y/M	ND	G1655A (K552X) (homo)	Meningitis × 3, pneumonia × 4, otitis media × 4, osteomyelitis × 2, skin infection, UTI, arthritis, giardiasis, fever of unknown origin × 5	Deceased, meningitis, pneumonia, prolonged diarrhea	E12,E13
8.	1990	Unknown	+	10 y/M	ND	IVS18 +1g>a (homo)	Recurrent otitis media, >20 episodes of erythematous plaques during upper respiratory tract infections		E14
9-1.	1992 1994 1995	New Zealander	—	19 y/M	ND	G1645A (D549N) (hetero s/o)*	Bacteremia at age 19 y, purpura		E15-E17
10.	1992	Unknown	+	4 y/F	0.8% of normal	NA	Meningitis × 4, recurrent otitis media	Deceased (2 brothers)	E18
11.	2001 2004	Brazilian	+	8 y/M	0.015	C2542T (R848X) (homo)	Lymphadenitis, sinusitis × 2, pneumonia, tonsillitis × 2, giardiasis	Deceased (4 siblings)	E19,E20
12.	2002	Turkish	+	4 y/F	4	NA	Meningitis × 2, recurrent otitis media	Immuno- compromised	E21
13.	2004	Unknown	—	4 y/M	<10	NA	Bacteremia, iliopsoas abscess, pneumonia × 2, recurrent otitis media, tonsillitis, pharyngitis, accidental death		E22
14-1.	2006	Unknown	?	7 y/F	6	NA	Meningitis × 2, otitis media × 2, UTI × 1	Deceased, meningitis	E23
14-2				10 mo/M	6	NA	Meningitis, pneumonia, recurrent otitis media		
15.	2008	Unknown	—	2 y/M	<4.3	T1648C (S550P) (hetero s/o)*	Meningitis, pneumonia, otitis media, sinusitis	Deceased, meningitis	E24
16.	2009	Unknown	?	5 y/F	11.2	NA	Meningitis × 4		E25
17.	2011	Arab	+	4 y/M	<10	3997delA (homo)	Pneumonia × 2, bacteremia × 3		E26
18.	2013	Turkish	+	16 y/M	8–19	C4554G (C1518W) (homo)	Recurrent pneumonia, otitis media, bronchiectasis, IgA deficiency	Deceased (2 siblings)	E27
Severe infections and IC-related diseases									
6-2.				19 y/F	ND	NA	Meningitis, recurrent otitis media, maculopapular rash during infectious episodes, subacute cutaneous lupus erythematosus		

(Continued)

TABLE I. (Continued)

Patient no.	Published year	Ethnicity	C	Age at diagnosis/ sex	C3 (mg/dL)	C3 molecular analysis	Clinical features	Sibling history	Reference
19.	1975 1983	White	?	4 y/F	ND	NA	Protracted diarrhea, recurrent otitis media, bacteremia × 2, recurrent UTI, sinusitis, type 1 MPGN		E28,E29
20-2.	1980	Lebanese	?	7 y/F	0	NA	Peritonitis, proteinuria, microhematuria	Nephrotic syndrome	E30
20-3.				5 y/M	0	NA	Peritonitis, proteinuria, left atrophic kidney due to renal artery stenosis		
21.	1985 1988 1996	Laotian	—	7 y/M	0.4	Reduced C3 mRNA	Meningitis × 2, pneumonia × 6, mesangiopathic glomerulonephritis		E31-E33
22-1.	1981	Japanese	+	16 y/M	<1	NA	Meningitis, IgA nephropathy	Deceased, butterfly rash, renal failure	E34,E35
22-2.	1991			14 y/F	ND	NA	Meningitis, SLE-like illness		
23.†	2008	Japanese	—	2 y/M	<2	3176dupT and C3243G (Y1081X) (hetero)	Meningitis, bacteremia × 4, pneumonia × 2, otitis media, focal segmental glomerulonephritis, SLE-like illness		E36
24.†	2011 2012	Japanese	—	4y/M	0.3	IVS9 -2a>t and C1432T (R478X) (hetero)	Bacteremia × 2, pneumonia × 2, otitis media, synovitis		E37,E38
25.†	Unpublished	Japanese	—	4 y/M	0	IVS11 +5 g>a and IVS12 -1 g>t (hetero)	Bacteremia, otitis media, sinusitis, membranous nephropathy, SLE-like illness		
IC-related diseases									
20-1.	1980	Lebanese	?	13 y/F	0	NA	Frequent earache, sore throat, abdominal pains, proteinuria, microhematuria/no severe infections	Nephrotic syndrome	E30
26-1.	1981 2001	Japanese	+	19 y/F	ND	C3243G (Y1081X) (homo)	SLE-like illness/no severe infections		E39,E40
26-2.				14 y/F	ND	C3243G (Y1081X) (homo)	SLE-like illness/no severe infections		
27.	1987	Unknown	+	7 y/F	ND	NA	Type 1 MPGN (renal transplantation)/no severe infections		E41
28.	2005	Japanese	+	23 y/M	<2	IVS38 -2a>g (homo)	Tonsillitis and recurrent pneumonia in his late teens, SLE-like illness/mild infections		E42
29.†	2005	Japanese	+	7 y/M	<0.5	3736_3737delTT (homo)	Bronchitis, otitis media, membranous nephropathy/no severe infections		E43
Neither severe infections nor IC-related diseases									
9-2.	1992 1994 1995	New Zealand	—	7 y/F	<5% of normal	G1645A (D549N) (hetero s/o)*	Asthma, rhinitis/no severe infections		E15-E17

Siblings are indicated by the same patient (pt) number with added hyphenated numbers in order of age. (Only No. 22-1 and 22-2 were cousins.)

C, Consanguinity; F, female; M, male; MPGN, membranoproliferative glomerulonephritis; NA, not available; ND, not detected; UTI, urinary tract infection.

*Incomplete analysis.

†Our case.

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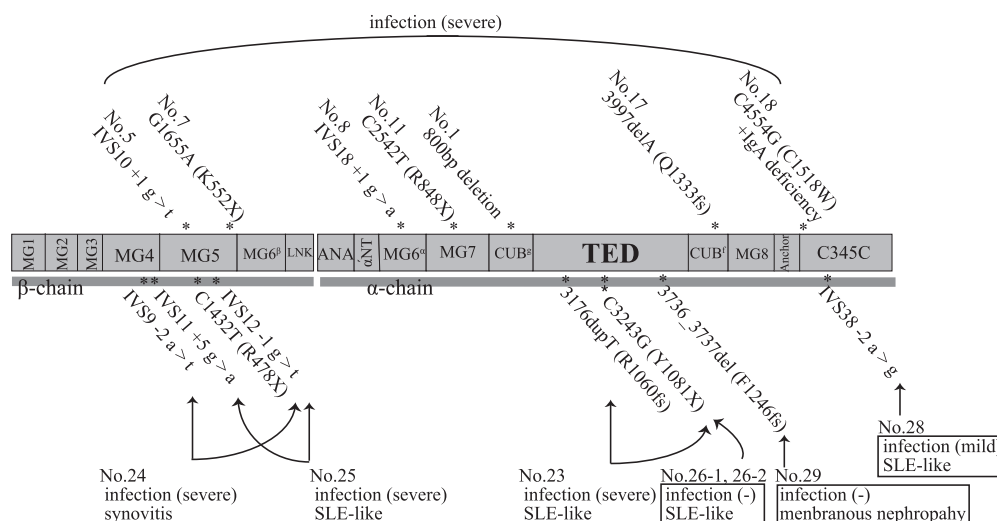


FIG 1. Severe infections preferentially develop in patients with C3 mutations in the N-terminal end of the TED domain. Domain arrangement of the C3 gene is shown. Both MG6 and CUB domains are formed by 2 separated parts, respectively. C3 mutations are indicated by asterisk marks. The mutations in Japanese and other ethnicities are shown in the lower and upper rows, respectively. The patient numbering follows that used in Table I.

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