



# LUND UNIVERSITY

## Molecular basis of hereditary C1q deficiency-revisited: identification of several novel disease-causing mutations

Schejbel, L.; Melander Skattum, Lillemor; Hagelberg, S.; Ahlin, A.; Schiller, B.; Berg, S.; Genel, F.; Truedsson, Lennart; Garred, P.

*Published in:*  
Genes and Immunity

*DOI:*  
[10.1038/gene.2011.39](https://doi.org/10.1038/gene.2011.39)

2011

[Link to publication](#)

*Citation for published version (APA):*

Schejbel, L., Melander Skattum, L., Hagelberg, S., Ahlin, A., Schiller, B., Berg, S., Genel, F., Truedsson, L., & Garred, P. (2011). Molecular basis of hereditary C1q deficiency-revisited: identification of several novel disease-causing mutations. *Genes and Immunity*, 12(8), 626-634. <https://doi.org/10.1038/gene.2011.39>

*Total number of authors:*  
9

### General rights

Unless other specific re-use rights are stated the following general rights apply:  
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

# **Molecular basis of hereditary C1q deficiency – revisited:**

## **Identification of several novel disease causing mutations**

Lone Schejbel<sup>1\*</sup>, Lillemor Skattum<sup>2</sup>, Stefan Hagelberg<sup>3</sup>, Anders Åhlin<sup>4</sup>, Bodil Schiller<sup>4</sup>, Stefan Berg<sup>5</sup>, Ferah Genel<sup>6</sup>, Lennart Truedsson<sup>2</sup> and Peter Garred<sup>1</sup>

1. Laboratory of molecular medicine, Department of Clinical Immunology section 7631, Rigshospitalet, Copenhagen, Denmark
2. Department of Laboratory Medicine Lund, Section of Microbiology, Immunology and Glycobiology, Lund University, Lund, Sweden
3. Department of Pediatric Rheumatology, Astrid Lindgrens Children's Hospital, Karolinska Universitetssjukhuset, Stockholm, Sweden
4. Sachs' Children's Hospital and the Department for Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
5. Department of Pediatrics, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
6. Department of Pediatric Immunology, Dr Behcet Uz Children's Hospital, Izmir, Turkey

Running Title: C1q deficiency - revisited

\* Corresponding Author

Dr. Lone Schejbel

Department of Clinical Immunology Sect 7631, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen  
O. Telephone +45 35457631, Telefax: +45 35398766, e-mail: [l.schejbel@gmail.com](mailto:l.schejbel@gmail.com)

Keywords: Deficiency, C1q, mutation, SLE, glomerulonephritis, bacterial infection, sepsis, Arthritis, transplantation.

**Abstract**

C1q is the central pattern recognition molecule in the classical pathway of the complement system and is known to play a key role in the crossroads between adaptive and innate immunity. Hereditary C1q deficiency is a rare genetic condition strongly associated with SLE and increased susceptibility to bacterial infections. However the clinical symptoms may vary. For long, the molecular basis of C1q deficiency was ascribed to only 6 different mutations. In the present report we describe 5 new patients with C1q deficiency, present the now 12 described causative mutations and review the clinical spectrum of symptoms found in patients with C1q deficiency. With the results presented here, confirmed C1q deficiency is reported in 64 patients from at least 38 families.

**Introduction:**

The complement system is crucial in elimination of microorganisms and endogenous waste material <sup>1</sup>. Activation of the complement system depends on pattern recognition molecules and can be initiated via three different pathways: In the classical activation pathway C1q is the pattern recognition entity that recognizes IgG- or IgM-containing immune complexes; antibodies bound to foreign or self antigen; and a variety of ligands on the surface of virus and bacteria <sup>2,3</sup>. In the lectin activation pathway, mannose-binding lectin (MBL), the ficolins and also probably collectin-11 are the pattern recognition entities that recognize sugar and acetylated residues on microorganisms and dying host cells. In the alternative pathway, C3b and/or properdin bind to foreign or certain endogenous surfaces thereby initiating or amplifying the complement cascade. In all activation pathways, the key event is formation of C3-convertases, which causes the cleavage of C3 to C3a and C3b and activation of the downstream complement cascade via generation of the C5 convertase, cleavage of C5 to C5a and C5b, and formation of terminal complement complexes (TCC) involving C5b and complement factors C6-C9. This causes lysis of microorganisms, leukocyte recruitment via release of chemotactic factors, and opsonization, which facilitates phagocytosis.<sup>1</sup>

The C1q protein has a molecular weight of 460,000 kD and is present in plasma in concentrations of ~180 mg/L. It is composed of three chains; the C1qA, C1qB and C1qC chains encoded by the *C1qA* (MIM\*120550), *C1qB* (MIM\*120570), and *C1qC* (MIM\*120575) genes, which are located in the direction A, C, B on chromosome 1p36.2-p34.1<sup>4</sup>. Each chain is encoded by two exons and has a collagen-like region and a globular domain. The macromolecular structure of C1q is a tulip-like structure generated by assembly of 6 A, 6 B and 6 C chains with a collagen-like region as part of the stalk, and the C1q globular region as part of the “tulip-heads”. Every tulip-head consists of the globular domains from one A, one B, and one C chain, each with different ligand binding specificities <sup>3,5-8</sup> (Figure 1). C1q synthesis has been reported in several different cells including hepatocytes, Kupffer cells, macrophages, dendritic cells, microglial cells, fibroblasts, epithelial cells of the small intestine and newborn foreskin epidermal keratinocytes, but recent studies suggests that bone marrow derived mononuclear cells may be the major source of C1q in plasma <sup>9,10</sup>.

Besides its role as an initiator of the classical complement activation pathway C1q has several other possible functions as recently reviewed by Nayak *et al*<sup>11</sup>. It can bind to early apoptotic cells and facilitate phagocytosis, and may also participate in clearance of late apoptotic cells via IgM/C1q mediated classical pathway activation. It can induce dendritic cell maturation via C1q receptors on the immature dendritic cells, it may modulate T lymphocytes, which have been shown to express C1q receptors, and C1q is suspected to participate in the negative selection of autoreactive B-cells. In addition, C1q has been suggested to be implicated in neuronal synapse modification, and to play a part in the early stages of pregnancy.

Primary deficiency of C1q is a rare condition caused by mutations in the C1q genes, and inherited in an autosomal recessive manner. Secondary C1q deficiency may arise by generation of autoantibodies against C1q or increased loss or catabolism of C1q. However, in this paper C1q deficiency will only refer to primary inherited C1q deficiency. C1q deficiency is associated with autoimmune manifestations and systemic lupus erythematosus (SLE)-like disease as well as increased tendency for bacterial infections. Deficiency of other complement components (C1r/C1s, C4, C2) is also associated with SLE, but C1q deficient patients have the most prevalent and severe autoimmune symptoms<sup>12</sup>. This may be related to the multiple functions of C1q: The development of disease has been suggested to derive from a decreased capacity for immune complex handling; a deficient clearance of apoptotic cells, which may act as a source of auto-antigens (the waste-disposal hypothesis); a deficient regulation of B-cell tolerance and subsequent production of autoantibodies; and/or a distorted cytokine production caused by the lack of C1q<sup>13-18</sup>. Despite the strong association between C1q deficiency and SLE, the clinical presentation of hereditary C1q deficiency can be very diverse with symptoms ranging from mild recurrent infections to severe bacterial meningitis, sepsis, glomerulonephritis and/or angioedema/SLE-like skin involvement<sup>19</sup>.

### **Previously reviewed mutations in C1q deficiency**

The first molecular diagnosis of C1q deficiency was published by McAdam *et al.* in 1988 who reported a nonsense mutation in the C1qB chain (Arg177X) in a patient from Mexico, and when Petry reviewed the

molecular basis for C1q deficiency in 1998, six different mutations found in 13 unrelated families were described<sup>20,21</sup>. Four of these mutations: C1qB, Gly42Asp; C1qB, Arg177X; C1qC, Arg69X; and C1qC, Gln71fsX137 were at that time only found in one family, while the C1qC, Gly34Arg mutation was found in families from Germany, India and Saudi Arabia<sup>21,22</sup>. This mutation has since been reported in a Caucasian woman with combined C1q and C8 deficiency, and in an Arabian girl with combined C1q deficiency and Hyper IgM syndrome<sup>23,24</sup>. The most prevalent mutation is the C1qA, Gln208X mutation published in six Turkish families, in a family from the Slovak Republic, and in a family from Cyprus<sup>21,25-29</sup>. Because of the relatively high prevalence of this mutation several cohorts of SLE-patients have been screened for this mutation without identification of more homozygous individuals<sup>30,31</sup>. In these previous reports all mutations were named according to the C1q nomenclature reported by Sellar et al. based on amino acid comparisons between the C1q chains<sup>4</sup>. In this report we apply the systematic names as used by the databases for immunodeficiency-causing mutations (ID bases: [http://bioinf.uta.fi/base\\_root/index.php](http://bioinf.uta.fi/base_root/index.php)), and we propose that this nomenclature is used in the future. Both the old nomenclature and the systematic names are given in table 1

## *Results*

### **Identification of novel disease-causing mutations**

Since 2005, genetic diagnosis of C1q deficiency has been done in our laboratory in 9 patients from 6 families originating from Greenland, Sweden, Kosova, Turkey, Sudan and Iraq (Table1, Figure 2). In all patients C1q deficiency was initially suspected by lack of activation via the classical complement activation pathway and subsequently confirmed by C1q analysis by rocket immunoelectrophoresis and/or ELISA. The genetic diagnosis was done as previously described<sup>32</sup>.

The first case was an Inuit family with three C1q-deficient sisters described by Marquart *et al*<sup>32</sup>. They were homozygous for a novel Gly244Arg mutation in the glomerular C1q domain of the B chain. This amino acid is one of five strictly conserved residues in all known gC1q motifs and the adjacent amino acids are involved in the heterotrimeric hydrophobic interface of the globular heads. It was the first description of a missense

mutation that caused a lack of detectable C1q antigen in serum. All three patients had lupus-like skin involvement and two of them had episodes of pneumonia and septicaemia, none of them had renal involvement.

The second family was from Turkey. Here we identified a novel homozygous missense mutation Gly76Arg in the collagen like region of the C1q C chain in an 11-year old girl, who was the first published C1q deficient patient from Turkey without the more common C1qA, Gln208X mutation<sup>33</sup>. The parents and four healthy brothers were heterozygous carriers of the C1qC Gly76Arg mutation; a fifth brother had normal C1q alleles according to GenBank. This mutation destroys the Gly-X-X repeat, which is important for the structure of the collagen like region of the protein. The clinical symptoms of this patient were two episodes of bacterial meningitis (the first one at the age of 8 years), and no autoimmune features in a 5-year follow up period.

The third family was from Sudan. In two affected siblings aged 4 and 10 years we identified a novel homozygous nonsense mutation Trp216X in the globular domain of the C1qA chain. This mutation is in close proximity to the C1qA, Gln208X mutation described by Petry et al<sup>26</sup>. The parents and two unaffected siblings were heterozygous for the mutation; a third sibling had normal GenBank sequence. A fourth sibling with normal C1q level was not available for genetic testing. The clinical symptoms of the patients were initially cutaneous lupus, in the youngest two episodes of bacterial meningitis, the older bacterial meningitis and later bacterial keratitis. Both affected siblings now have an SLE diagnosis, but with no signs of renal involvement.

From the fourth family we only analysed a 10-year old boy from Kosova with C1q deficiency. Here we found homozygosity for the C1qC Arg69X mutation. This is the second described patient with this mutation, which was previously found in a family from the former Yugoslavia<sup>34</sup>. The parents of the patient were not known to be consanguineous and come from different cities. However, it is possible that they have an ancient common ancestor and have a distant relation to the previously described patient. The clinical symptoms of

this patient were malar rash, discoid rash and oral ulceration, which together with positivity for ANA, anti-RNP and anti-SM gave the diagnosis SLE.

In the fifth family we also identified a previously described mutation as the cause of C1q deficiency. Here an 8-year old boy from Iraq was homozygous for the C1qA Gln208X mutation initially described by Petry *et al*<sup>26</sup>. His 1-year old sister is a heterozygous carrier of the mutation. Since all the patients with this mutation identified so far come from the Mediterranean/Middle East area, it seems to be an ancestral old mutation rather than a mutational hot spot in the C1qA gene. The patient presented at the age of 1 year with rashes in the face, chest, hands and feet. He has recurrent otitis media, WHO class II glomerulonephritis, fatigue and partial hair loss.

In the sixth family we identified the first published case of C1q deficiency caused by compound heterozygosity. In a 10-year old boy from Sweden of Caucasian origin, we identified two novel mutations in the C1q A chain; a single base pair deletion in codon 53 (ggg→ gg-) causing a frameshift that changes the amino acid composition of the A-chain and a nonsense mutation Gln64X in the collagen region of the A-chain. Unfortunately, we were not able to obtain parental samples. Instead, cloning and sequencing of a PCR product covering both mutations confirmed compound heterozygosity. This patient presented at the age of 3 years with UV-sensitive malar rash and fevers and he has partial hair loss.

To our knowledge by searching the literature the only novel reported mutation apart from those described above is a homozygous single nucleotide deletion in the *C1qC* gene (Gly55Glyfs83X) found in a 24-year old female of Pakistani origin presenting with cutaneous and cerebral lupus<sup>35</sup>.

## *Discussion*

### **Clinical variability in C1q deficiency**

Even though the majority of C1q-deficient patients described so far have SLE-like symptoms there is a great variability in the clinical manifestations associated with C1q deficiency. Vassallo *et al* recently demonstrated



this in a description of a large Pakistani family with several C1q-deficient members<sup>19</sup>. The index patient debuted with bacterial meningitis at the age of three years, later he developed malar rash, mouth ulceration and had CNS vasculitis at the age of 10. However, the C1q-deficient family members had different symptoms: The index patient's father had erythematous facial rash and glomerulonephritis, a 21 year old brother had discoid lupus, a 12 year old brother had mouth ulceration and angioedema, a brother died 17 months old from bacterial meningitis, and a C1q-deficient brother remained asymptomatic at the age of 19 years except from recurrent ear infections and tonsillitis as a child. This is not the first description of asymptomatic C1q deficient family members: asymptomatic relatives have been described in a Saudi Arabian family (5 years old), in a family from Morocco (42 years old) and in a Turkish family (22 years old)<sup>36,37</sup>. Of course, these relatives may develop symptoms of C1q deficiency later in life, but since most C1q-deficient patients have their clinical onset during childhood, especially the adult relatives are noteworthy.

In the previous most updated list of clinical presentations of C1q deficiency in 42 patients, 39 patients (93%) had clinical symptoms closely related to SLE. The reports included 37 patients (88%) with rash, 16 patients (38%) with glomerulonephritis, 11 patients (26%) with bacterial infections, 8 patients (19%) with CNS disease, 6 patients (15%) with arthritis or arthralgia, 4 patients (10%) with mouth ulceration, and 4 patients (10%) with septicaemia<sup>12</sup>. Since then, 22 new confirmed cases have been presented, including the patients described here. The clinical symptoms of 21 of these patients as well as 3 suspected C1q deficient deceased relatives are included in Table 2. In one confirmed patient no clinical details except SLE-like disease were described, this patient is not included in the table. Among the 21 patients, a higher frequency of bacterial infections (62%), mouth ulceration (48%), arthritis/arthralgia (24%), and septicaemia (33%), and a lower frequency of glomerulonephritis (14%) and cutaneous disease (76%) was found than in the previous review (Figure 3). Of course, this could reflect different focuses in different publications as well as the fact that the new publications are more likely to describe patients that differ in the clinical presentation from the previously described patients. It is also important to notice, that two of the patients have multiple deficiencies with C1q deficiency combined with C8 deficiency and hyper-IgM syndrome, respectively, which is likely to influence the symptoms of the patients. However, if we only include the cohort of patients

analysed in our laboratory, who are not selected on specific clinical symptoms, and do not have other known contributing deficiencies, we still see a significantly higher frequency of septicaemia (44% versus 10%,  $P < 0.05$ ) and oral ulceration (56% versus 10%,  $P < 0.05$ ) among the patients. In the cohort of “new published cases” the portion of patients presenting without SLE or SLE-like disease based on the clinical descriptions available (18%) is higher than the in previous reviewed 42 cases. However, with few exceptions the patients reviewed here are children and more of them may develop SLE later in life. In two families suspected C1q deficient relatives died from bacterial meningitis or sepsis before the C1q diagnosis was made. Still, the initial symptoms reported in the cohort were more often cutaneous symptoms of systemic autoimmune disease than infections.

The variation in clinical manifestations of C1q deficiency, even within the same families, indicates that environmental factors or genetic variation in other genes may influence the development and progression of C1q-related disease. In the mouse, the importance of the genetic background for C1q-related disease has been clearly demonstrated<sup>38</sup>.

### **Clinical management of C1q deficiency**

The management of C1q deficient patients includes a prophylactic vaccination program, and antibiotic treatment to reduce the infection rate and standard SLE treatment. In patients with severe immunosuppression as part of the treatment for autoimmunity, gammaglobulin substitution combined with prophylactic antibiotic treatment may be indicated<sup>19</sup>. Attempts to replace C1q with administration of fresh frozen plasma have also been made in some patients with success<sup>35</sup>. A second way to replace C1q might be by haematopoietic stem cell transplantation (HSCT). It has been demonstrated that bone marrow-derived wild type cells transferred to C1qa<sup>-/-</sup> mice restores normal C1q serum levels and attenuates the autoimmune features<sup>10</sup>. This indicates that haematopoietic stem cell transplantation may be a potential treatment for C1q deficiency in humans, which has been considered but not performed yet<sup>35,39</sup>. However, before HSCT is performed, it is in our opinion essential that the C1q deficiency is confirmed by a molecular diagnosis.

## **Concluding remarks**

We initially started to sequence the C1q genes in our laboratory because none of the previously described mutations were found in the patients referred to us from Greenland. Later, it came as a surprise for us that most of the mutations we found among the patients were not described previously. Especially since no other mutations had been described until 2010 or submitted to the C1q databases (ID bases: [http://bioinf.uta.fi/base\\_root/index.php](http://bioinf.uta.fi/base_root/index.php)), since the review by Petry *et al* in 1998. This made it clear, that even though some of the previously described mutations were found in diverse ethnic groups and thus are likely to be old and more common ancestral mutations, other mutations exist with a frequency high enough to cause homozygous or compound heterozygous C1q deficiency in patients with non-consanguineous parents in different ethnic groups.

Our results emphasize the need for sequencing of the coding regions of the C1q genes in order to establish the genetic diagnosis of C1q deficiency, rather than screening for the previously described mutations. Once the genetic diagnosis has been established in the index patient, the family should be screened for the mutation in order to identify C1q deficient patients and carriers, and provide genetic counseling. With the results presented here, the total number of C1q deficient patients described is at least 64 in 38 families, and the total number of published causative mutations is 12.

## *Materials and Methods*

Patients and family members were investigated as part of the routine diagnostics for immunodeficiency. Sequencing of the C1q genes were performed by Sanger sequencing as previously described<sup>32</sup>

## **Conflict of interests**

The authors declare no conflicts of interests

## Reference List

1. Walport MJ. Complement. First of two parts. *N Engl J Med* 2001;**344**: 1058-1066.
2. Kojouharova MS, Tsacheva IG, Tchorbadjieva MI, Reid KB, Kishore U. Localization of ligand-binding sites on human C1q globular head region using recombinant globular head fragments and single-chain antibodies. *Biochim Biophys Acta* 2003;**1652**: 64-74.
3. Kishore U, Ghai R, Greenhough TJ, Shrive AK, Bonifati DM, Gadjeva MG et al. Structural and functional anatomy of the globular domain of complement protein C1q. *Immunol Lett* 2004;**95**: 113-128.
4. Sellar GC, Blake DJ, Reid KB. Characterization and organization of the genes encoding the A-, B- and C-chains of human complement subcomponent C1q. The complete derived amino acid sequence of human C1q. *Biochem J* 1991;**274 ( Pt 2)**: 481-490.
5. Kishore U Reid KB. C1q: structure, function, and receptors. *Immunopharmacology* 2000;**49**: 159-170.
6. Kishore U, Gaboriaud C, Waters P, Shrive AK, Greenhough TJ, Reid KB et al. C1q and tumor necrosis factor superfamily: modularity and versatility. *Trends Immunol* 2004;**25**: 551-561.
7. Gaboriaud C, Juanhuix J, Gruez A, Lacroix M, Darnault C, Pignol D et al. The crystal structure of the globular head of complement protein C1q provides a basis for its versatile recognition properties. *J Biol Chem* 2003;**278**: 46974-46982.
8. Gaboriaud C, Thielens NM, Gregory LA, Rossi V, Fontecilla-Camps JC, Arlaud GJ. Structure and activation of the C1 complex of complement: unraveling the puzzle. *Trends Immunol* 2004;**25**: 368-373.
9. Petry F, Botto M, Holtappels R, Walport MJ, Loos M. Reconstitution of the complement function in C1q-deficient (C1qa<sup>-/-</sup>) mice with wild-type bone marrow cells. *J Immunol* 2001;**167**: 4033-4037.
10. Cortes-Hernandez J, Fossati-Jimack L, Petry F, Loos M, Izui S, Walport MJ et al. Restoration of C1q levels by bone marrow transplantation attenuates autoimmune disease associated with C1q deficiency in mice. *Eur J Immunol* 2004;**34**: 3713-3722.
11. Nayak A, Ferluga J, Tsolaki AG, Kishore U. The non-classical functions of the classical complement pathway recognition subcomponent C1q. *Immunol Lett* 2010;**131**: 139-150.

12. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol* 2000;**76**: 227-324.
13. Botto M Walport MJ. C1q, autoimmunity and apoptosis. *Immunobiology* 2002;**205**: 395-406.
14. Korb LC Ahearn JM. C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes: complement deficiency and systemic lupus erythematosus revisited. *J Immunol* 1997;**158**: 4525-4528.
15. Lood C, Gullstrand B, Truedsson L, Olin AI, Alm GV, Rönnblom L et al. C1q inhibits immune complex-induced interferon-alpha production in plasmacytoid dendritic cells: a novel link between C1q deficiency and systemic lupus erythematosus pathogenesis. *Arthritis Rheum* 2009;**60**: 3081-3090.
16. Nauta AJ, Trouw LA, Daha MR, Tijssma O, Nieuwland R, Schwaeble WJ et al. Direct binding of C1q to apoptotic cells and cell blebs induces complement activation. *Eur J Immunol* 2002;**32**: 1726-1736.
17. Vandivier RW, Ogden CA, Fadok VA, Hoffmann PR, Brown KK, Botto M et al. Role of surfactant proteins A, D, and C1q in the clearance of apoptotic cells in vivo and in vitro: calreticulin and CD91 as a common collectin receptor complex. *J Immunol* 2002;**169**: 3978-3986.
18. Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. *Autoimmunity* 2007;**40**: 560-566.
19. Vassallo G, Newton RW, Chieng SE, Haeney MR, Shabani A, Arkwright PD. Clinical variability and characteristic autoantibody profile in primary C1q complement deficiency. *Rheumatology (Oxford)* 2007;**46**: 1612-1614.
20. McAdam RA, Goundis D, Reid KB. A homozygous point mutation results in a stop codon in the C1q B-chain of a C1q-deficient individual. *Immunogenetics* 1988;**27**: 259-264.
21. Petry F. Molecular basis of hereditary C1q deficiency. *Immunobiology* 1998;**199**: 286-294.
22. Petry F, Hauptmann G, Goetz J, Grosshans E, Loos M. Molecular basis of a new type of C1q-deficiency associated with a non-functional low molecular weight (LMW) C1q: parallels and differences to other known genetic C1q-defects. *Immunopharmacology* 1997;**38**: 189-201.
23. Pickering MC, Macor P, Fish J, Durigutto P, Bossi F, Petry F et al. Complement C1q and C8beta deficiency in an individual with recurrent bacterial meningitis and adult-onset systemic lupus erythematosus-like illness. *Rheumatology (Oxford)* 2008;**47**: 1588-1589.
24. Tsuge I, Kondo Y, Nakajima Y, Nakagawa N, Imai K, Nonoyama S et al. Hyper IgM syndrome and complement C1q deficiency in an individual with systemic lupus erythematosus-like disease. *Clin Exp Rheumatol* 2010;**28**: 558-560.

25. Hoppenreijns EP, van Dijken PJ, Kabel PJ, Th Draaisma JM. Hereditary C1q deficiency and secondary Sjogren's syndrome. *Ann Rheum Dis* 2004;**63**: 1524-1525.
26. Petry F, Le DT, Kirschfink M, Loos M. Non-sense and missense mutations in the structural genes of complement component C1q A and C chains are linked with two different types of complete selective C1q deficiencies. *J Immunol* 1995;**155**: 4734-4738.
27. Petry F, Berkel AI, Loos M. Multiple identification of a particular type of hereditary C1q deficiency in the Turkish population: review of the cases and additional genetic and functional analysis. *Hum Genet* 1997;**100**: 51-56.
28. Topaloglu R, Bakkaloglu A, Slingsby JH, Mihatsch MJ, Pascual M, Norsworthy P et al. Molecular basis of hereditary C1q deficiency associated with SLE and IgA nephropathy in a Turkish family. *Kidney Int* 1996;**50**: 635-642.
29. Sun-Tan C, Ozgur TT, Kilinc G, Topaloglu R, Gokoz O, Ersoy-Evans S et al. Hereditary C1q deficiency: a new family with C1qA deficiency. *Turk J Pediatr* 2010;**52**: 184-186.
30. Chew CH, Chua KH, Lian LH, Puah SM, Tan SY. PCR-RFLP genotyping of C1q mutations and single nucleotide polymorphisms in Malaysian patients with systemic lupus erythematosus. *Hum Biol* 2008;**80**: 83-93.
31. Topaloglu R, Bakkaloglu A, Slingsby JH, Aydintug O, Besbas N, Saatci U et al. Survey of Turkish systemic lupus erythematosus patients for a particular mutation of C1Q deficiency. *Clin Exp Rheumatol* 2000;**18**: 75-77.
32. Marquart HV, Schejbel L, Sjöholm A, Mårtensson U, Nielsen S, Koch A et al. C1q deficiency in an Inuit family: identification of a new class of C1q disease-causing mutations. *Clin Immunol* 2007;**124**: 33-40.
33. Gulez N, Genel F, Atlihan F, Gullstrand B, Skattum L, Schejbel L et al. Homozygosity for a novel mutation in the C1q C chain gene in a Turkish family with hereditary C1q deficiency. *J Investig Allergol Clin Immunol* 2010;**20**: 255-258.
34. Slingsby JH, Norsworthy P, Pearce G, Vaishnav AK, Issler H, Morley BJ et al. Homozygous hereditary C1q deficiency and systemic lupus erythematosus. A new family and the molecular basis of C1q deficiency in three families. *Arthritis Rheum* 1996;**39**: 663-670.
35. Mehta P, Norsworthy PJ, Hall AE, Kelly SJ, Walport MJ, Botto M et al. SLE with C1q deficiency treated with fresh frozen plasma: a 10-year experience. *Rheumatology (Oxford)* 2010;**49**: 823-824.
36. Berkel AI, Birben E, Oner C, Oner R, Loos M, Petry F. Molecular, genetic and epidemiologic studies on selective complete C1q deficiency in Turkey. *Immunobiology* 2000;**201**: 347-355.

37. Walport MJ, Davies KA, Botto M. C1q and systemic lupus erythematosus. *Immunobiology* 1998;**199**: 265-285.
38. Mitchell DA, Pickering MC, Warren J, Fossati-Jimack L, Cortes-Hernandez J, Cook HT et al. C1q deficiency and autoimmunity: the effects of genetic background on disease expression. *J Immunol* 2002;**168**: 2538-2543.
39. Stone NM, Williams A, Wilkinson JD, Bird G. Systemic lupus erythematosus with C1q deficiency. *Br J Dermatol* 2000;**142**: 521-524.

**Figure 1. Schematic view of the C1q chains and the heterotrimeric unit.**

(a) Each chain of the C1q molecule consists of a N-terminal region (N-term) involved in disulfide bond formation, a collagen region (CLR) involved in C1r activation, and a globular domain (gC1q) with distinct ligand binding specificities for each chain. (b) The A and B chains form heterodimers, and the C chains form homodimers. (c) Two A/B heterodimers and one C/C homodimer join in a heterotrimeric unit, and three heterotrimers combine in the final C1q-structure (not shown). Reprinted from Marquart et al<sup>32</sup> with permission from Elsevier

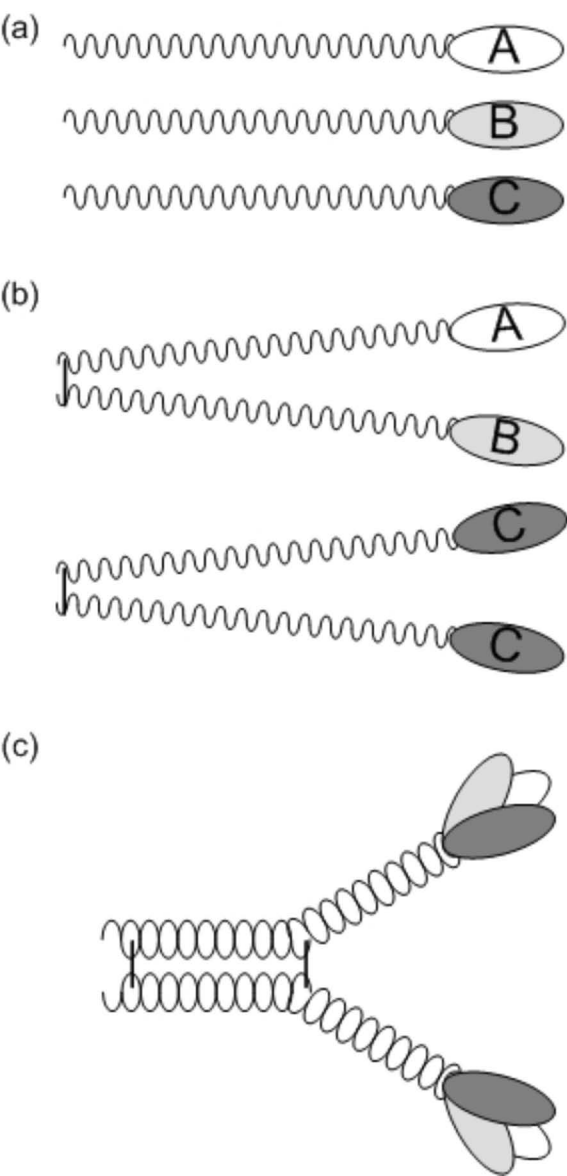


**Figure 2 Genograms for the six families with C1q deficiency identified in our laboratory, also indicated in table 2.**

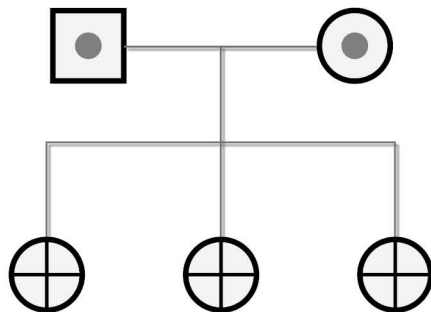
**Figure 3. Distribution of clinical symptoms in C1q-deficient patient cohorts**

The clinical manifestations reported in C1q deficiency in the previously reviewed 42 patients<sup>12</sup>, in the 21 confirmed “new cases” included in this review, in the nine patients from the cohort of patients evaluated in our lab (“Our Cohort”), and in the total number of reported C1q-deficient patients (n=63). The figure only includes patients with confirmed C1q deficiency, not deceased relatives with suspected C1q deficiency. The gray shades indicate the fractions of affected patients. Bacterial infections include meningitis of undescribed origin. SLE-like disease includes ANA-positive patients with cutaneous symptoms of autoimmune disease or patients described as SLE-like in the original publication.

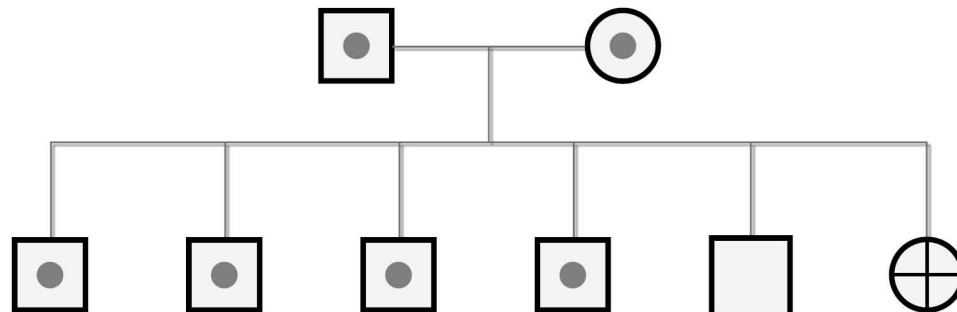
N-term                      CLR                      gC1q



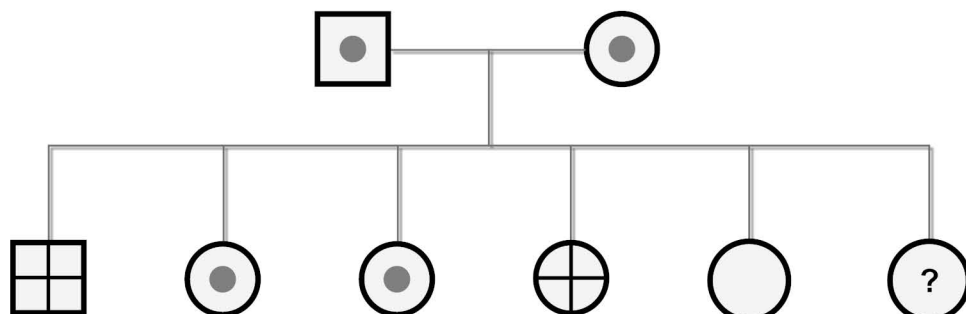
A C1QB Gly244Arg



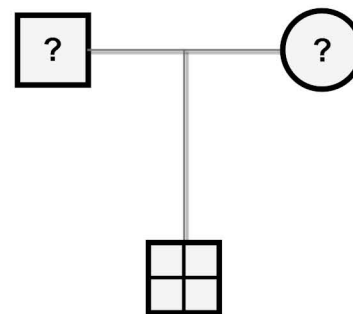
B C1QC Gly76Arg



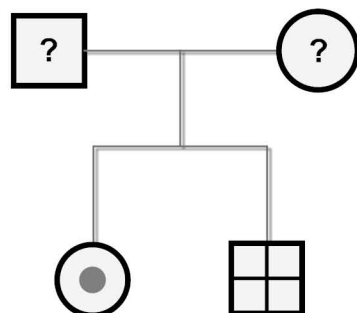
C C1QA Trp216X



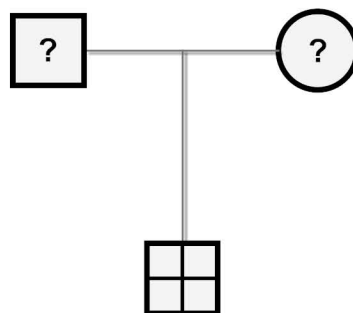
D C1QC Arg69X





E C1QA Gln208X



F C1QA Gln64X / C1QA Glu53fs





 Female, non-carrier


 Female, Carrier


 Female, Affected

 Female, Not analysed

 Male, Non-carrier

 Male, Carrier

 Male, Affected

 Male, Not analysed

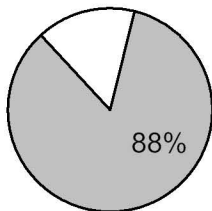
Previous Review

New Cases

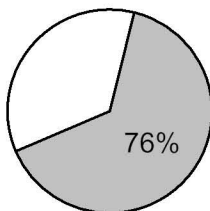
Our Cohort

Total

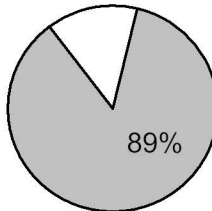
Cutaneous Disease



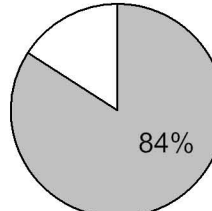
88%



76%

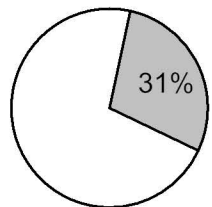


89%

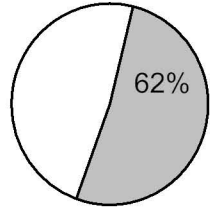


84%

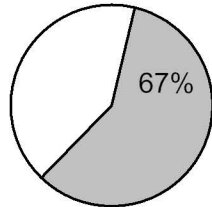
Bacterial infections



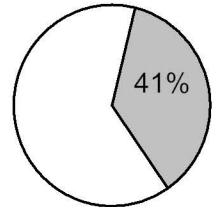
31%



62%

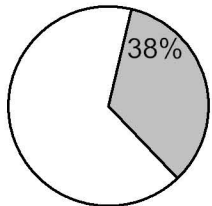


67%

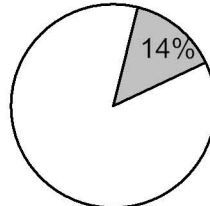


41%

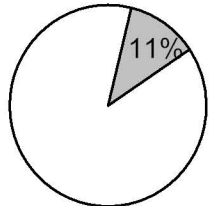
Glomerulonephritis



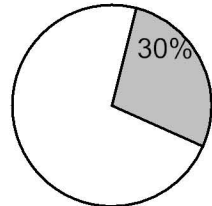
38%



14%

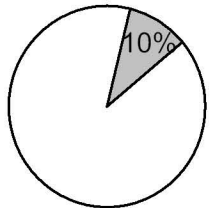


11%

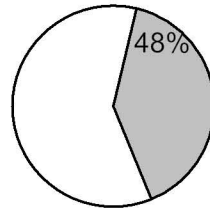


30%

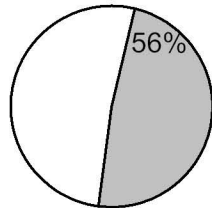
Oral Ulceration



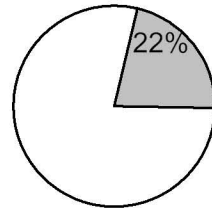
10%



48%

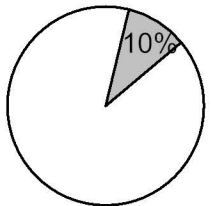


56%

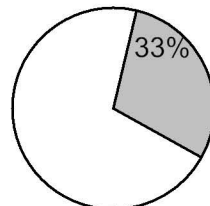


22%

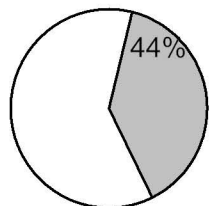
Sepsis/septicemia



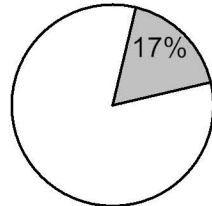
10%



33%

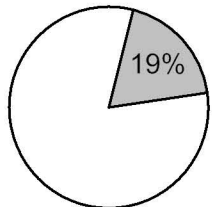


44%

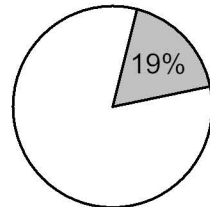


17%

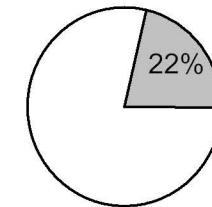
CNS involvement



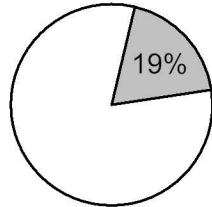
19%



19%

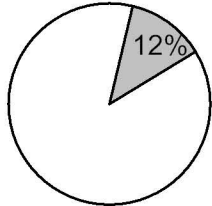


22%

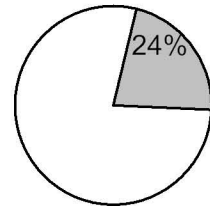


19%

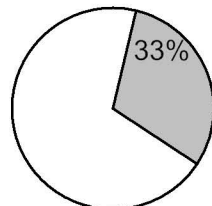
Arthritis/Arthralgia



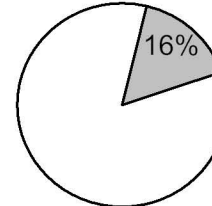
12%



24%

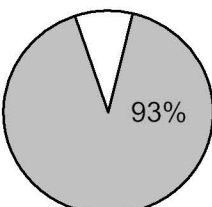


33%

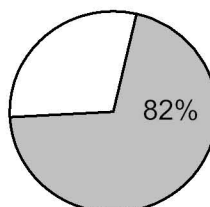


16%

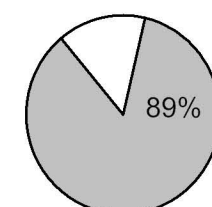
SLE/SLE-like disease



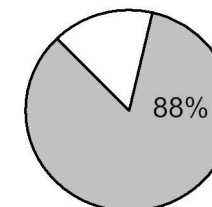
93%



82%



89%



88%

C1q chain	Mutation <sup>1</sup>	Systematic names	Old nomenclature <sup>2</sup>	Total number of families described	Origin of families
<b>C1qA</b>	<b>g.6149delG</b> <b>g.7235C&gt;T</b>	<b>Glu5335fs</b> <b>Gln64X</b>	<b>Glu12fs</b> <b>Gln42X</b>	1	<b>Sweden</b> [ <i>This paper</i> ]
<b>C1qA</b>	<b>g.7667C&gt;T</b>	<b>Gln208X</b>	<b>Gln186X</b>	8	<b>Iraq</b> [ <i>This paper</i> ] Turkey <sup>25-29</sup> Slovak Republic <sup>26</sup> Cyprus <sup>27</sup>
<b>C1qA</b>	<b>g.7693G&gt;A</b>	<b>Trp216X</b>	<b>Trp194X</b>	1	<b>Sudan</b> [ <i>This paper</i> ]
C1qB	g.11393G>A	Gly42Asp	Gly15Asp	1	Morocco <sup>22</sup>
C1qB	g.12965C>T	Arg 177X	Arg150X	1	Mexico <sup>20</sup>
<b>C1qB</b>	<b>g.13166G&gt;A</b>	<b>Gly2442Arg</b>	<b>Gly217Arg</b>	1	<b>Inuit</b> <sup>32</sup>
C1qC	g.5499G>A	Gly34Arg	Gly6Arg	5	Germany <sup>25</sup> India <sup>34</sup> Saudi Arabia <sup>21</sup> Caucasian <sup>23</sup> Arabian <sup>24</sup>
C1qC	g.5564delG	Gly55fsX83		1	Pakistan <sup>35</sup>
<b>C1qC</b>	<b>g.86265C&gt;T</b>	<b>Arg69X</b>	<b>Arg41X</b>	2	<b>Kosova</b> [ <i>This paper</i> ] Yugoslavia <sup>34</sup>
C1qC	g.8633delC	Gln71fsX137	Gln43fs→108X	1	England <sup>34</sup>
<b>C1qC</b>	<b>g.8647G&gt;A</b>	<b>Gly76Arg</b>	<b>Gly48Arg</b>	1	<b>Turkey</b> <sup>33</sup>

<sup>1</sup>According to NCBI reference sequence NG\_007282 (C1qA), NG\_007283 (C1qB) and NG\_007565 (C1QC)

<sup>2</sup>Codon numbers according to original publications or Sellar et al, 1991<sup>4</sup>.

Mutations and origin of patients identified in our laboratory are in bold.

**Table 1. Mutations reported causing C1q deficiency**

Patient age at Debut/Report <sup>1</sup> gender	Origin	Con-sanguinity	Cutaneous disease	Glomerulonephritis	Bacterial Infections	Oral ulceration	Septicemia/Sepsis	CNS involvement, non-infectious	Arthritis	Other findings	Auto-antibodies	SLE / SLE-like	Mutation	Ref.
6 mts/4 years, f (Fig. 2. C.)	Sudan	Yes	<sup>2</sup> Cutaneous Lupus and vasculitis Discoid Lupus	No	2x bact. meningitis	Yes	Yes		Hip		ANA and anti-SSA	Yes	Trp216X	This review
Brother 3/10 years			<sup>2</sup> Cutaneous Lupus and vasculitis Discoid Lupus	No	1x bact. meningitis	Yes	Yes		Poly-arthritis		ANA and anti-RNP	Yes		
10 years, m (Fig. 2. D.)	Kosova	No known relation	<sup>2</sup> Malar rash, Discoid rash	No	No	Yes	No	No	No		ANA, anti-RNP and anti-SM	Yes	Arg69X	This review
1/8 years, m (Fig. 2. E.)	Iraq		<sup>2</sup> Rash on face, chest, palmar and plantar. Hair loss (partial)	Yes. WHO Class II	Recurrent otitis media	No.	No	Fatigue	No		ANA, anti-RNP and anti-SSA	Yes	Gln208X	This review
3/10 years, m (Fig. 2. F.)	Sweden	No	<sup>2</sup> Malar rash UV-sensitivity Hair loss (partial)	No	No	Enanem on the hard palate	No	No	No	Initially fevers.	2004: ANA and anti-SM. (Negative 2007 and 2008)	Yes	Glu533fs Gln64X	This review
Infancy/10 years, f	Arabian	Yes	Mucocutaneous manifestations		<sup>2</sup> Recurrent bacterial infections since infancy			Lethargy, aphasia, multiple ischemic lesions	Hip joint pain	Hyper-IgM syndrome	ANA Anti-dsDNA Anti SSA Anti SSB	Yes	Gly34Arg	Tsuge et al 2010
1/1 year, m	NA	Yes	<sup>2</sup> Rash with desquamation		Recurrent upper respiratory tract infections						Low ANA within normal range 1/60	No		Sun-Tan et al 2010
Brother Deceased <sup>3</sup>					Pneumococcal meningitis		Yes							
Sister Deceased <sup>3</sup>							Yes							
8/16 years, f (Fig. 2. B.)	Turkish	Yes	No	No	2x <sup>2</sup> Bact. Meningitis, Pneumonia.	No	No		No		Negative for ANA and rheumatoid factor	No	Gly76Arg	Gulez et al 2010
14/14 months, f	NA	Yes	<sup>2</sup> Pyoderma gangrenosum		Skin	Yes	Yes		Knees		ANA Anti-dsDNA Anti-Cardiolipin Anti-B2-Glycoprotein	Yes	NA	Abanomi et al 2008
21/49 years, f	Caucasoid	Yes			2x <sup>2</sup> Bacterial meningitis	Yes	Yes			Hypothyroidism Autoimmune hepatitis C8 deficiency	ANA Anti-Ro antibodies Anti-thyroid microsomal antibodies	Adult onset of SLE-like disease	Gly34Arg C8B,R427X	Pickering et al 2008
2/3 years, f	Tunesian	Yes	<sup>2</sup> Photosensitive rash, Discoid Lupus.	Yes	Cutaneous					Thrombocytopenia	ANA Anti SM Anti-RNP Anti-SSA	Yes	NA	Kallel-Sellami et al 2007

3/12 years, f (Fig. 2. A.)	Inuit	No known relation	<sup>2</sup> Discoid Lupus, photosensitive malar rash, necrotic vasculitis	No	Recurrent upper and lower respiratory infections,	Yes	Yes	CNS inflammation	No	Pancreatitis	ANA Anti-ENA Anti-SM	Yes	Gly2442Arg	Marquart et al 2007
Sister ?/14 years			LE	No				No	Yes		ANA Anti-ENA Anti-SM	Yes		
Sister 2/15 years			LE, <sup>2</sup> necrotizing vasculitis	No	Pneumonia	Yes	Yes	No	No		ANA Anti-ENA Anti-SM	Yes		
3/10 years, m	Pakistani	Yes	Malar rash		<sup>2</sup> Bacterial meningitis,	Yes		CNS vasculitis at 10 years of age			ANA Anti-SM Anti-Ro	Yes	NA	Vassallo et al 2007
Father 18/38			Erythematous facial rash	Yes						Coronary vascular disease, died from acute myocardial infarct in 1998	ND	Yes		
Brother, 9/21 years			<sup>2</sup> Discoid lupus								ANA Anti-Ro	Yes		
Brother, 19 years (no symptoms <sup>4</sup> )											ANA	No		
Brother, ?/12 y						Yes				Angioedema	Low ANA 1/100	No		
Brother, Deceased <sup>3</sup>					<sup>2</sup> Bacterial meningitis						ND			
4/15 years, m <sup>5</sup>	Turkish	Yes			2x <sup>2</sup> Meningitis (1x unknown origin, 1x meningococ.), pericarditis, Pneumonia		Meningococ al Sepsis		Elbow and ankle	Parotitis; Secondary Sjögren's syndrome	ANA Anti-RNP Anti-SM Anti-SSB Rheumatoid factor	Yes	Gln208X	Hoppenreij s et al 2004
6/24 years, f	Asian	Yes	<sup>2</sup> Scaly erythematous rash, Cheeks and fingers		Recurrent urinary and respiratory infections, Proteus pyelonephritis	Yes		Cerebral vasculitis		Raynaud's <a href="#">phenomenon</a> , Alopecia	ANA	Yes	Gly55Glyfs 83X	Stone et al 2000 / Metha et al 2010



<sup>1</sup>Age of debut, defined as the first recognition of clinical symptoms, ? indicates if this information is not available. <sup>2</sup>Major symptom at debut, if this information is available. <sup>3</sup>Family members with suspected but not confirmed C1q deficiency. <sup>4</sup>Recurrent ear infections and tonsillitis as a child, but has since been very well. <sup>5</sup>This patient has a brother, who is homozygous deficient and reported to have SLE-like symptoms, but since no further details on the symptoms are available he is not included in this table.

**Table 2. Clinical characteristics of C1q deficiency cases not reported in previous review.**