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Molecular basis of hereditary C1q deficiency – revisited:
Identification of several novel disease causing mutations

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Running Title: C1q deficiency - revisited

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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. 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 vira and bacteria. 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.

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. 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. 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.
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. 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. 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. 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.

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 \(^{20,21}\). 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 \(^{21,22}\). 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 \(^{23,24}\). 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 \(^{21,25-29}\). 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 \(^{30,31}\). 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 \(^4\). 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), 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 \(^{32}\).

The first case was an Inuit family with three C1q-deficient sisters described by Marquart et al \(^{32}\). 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. 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. 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. 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. 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.

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. Vassalo et al recently demonstrated
this in a description of a large Pakistani family with several C1q-deficient members\textsuperscript{19}. 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)\textsuperscript{36,37}. 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 septicemia\textsuperscript{12}. 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 septicemia (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 septic aemia (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.38

**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 19. Attempts to replace C1q with administration of fresh frozen plasma have also been made in some patients with success 35. 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−/− mice restores normal C1q serum levels and attenuates the autoimmune features10. 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 35,39. 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), 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

Conflict of interests
The authors declare no conflicts of interests
Reference List


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.


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 heterotrimeres combine in the final C1q-structure (not shown). Reprinted from Marquart et al\textsuperscript{32} 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\(^1^2\), 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 undescibed origin. SLE-like disease includes ANA-positive patients with cutaneous symptoms of autoimmune disease or patients described as SLE-like in the original publication.
According to NCBI reference sequence NG_007282 (C1qA), NG_007283 (C1qB) and NG_007565 (C1QC) Codon numbers according to original publications or Sellar et al, 1991.

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

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<th>C1q chain</th>
<th>Mutation(^1)</th>
<th>Systematic names</th>
<th>Old nomenclature(^2)</th>
<th>Total number of families described</th>
<th>Origin of families</th>
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\(^1\)According to NCBI reference sequence NG_007282 (C1qA), NG_007283 (C1qB) and NG_007565 (C1QC) \(^2\)Codon numbers according to original publications or Sellar et al, 1991.

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

Table 1. Mutations reported causing C1q deficiency
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<td>Yes</td>
<td>Cutaneous Lupus and vasculitis Discoid Lupus</td>
<td>No</td>
<td>2x bact. meningitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Hip</td>
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<td></td>
<td></td>
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<td>Trp216X</td>
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<td>1x bact. meningitis</td>
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<td></td>
<td>Poly-arthritis</td>
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<td>Malar rash, Discoid rash</td>
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<td>No</td>
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<td>No</td>
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<td>Iraq</td>
<td>Yes</td>
<td>Rash on face, chest, palmar and plantar. Hair loss (partial)</td>
<td>Yes. WHO Class II</td>
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<td>No</td>
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<td>No</td>
<td>No</td>
<td>Initially fevers.</td>
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<td>Infancy/10 years, f</td>
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<td>Mucocutaneous manifestations</td>
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<td>Recurrent bacterial infections since infancy</td>
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<td>NA</td>
<td>Yes</td>
<td>Rash with desquamation</td>
<td>Recurrent upper respiratory tract infections</td>
<td></td>
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<td></td>
<td></td>
<td>Low ANA within normal range 1:60</td>
<td>No</td>
<td></td>
<td>Sun-Tan et al 2010</td>
</tr>
<tr>
<td>Brother Deceased</td>
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<tr>
<td>Sister Deceased</td>
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<tr>
<td>8/16 years, f (Fig. 2. B.)</td>
<td>Turkish</td>
<td>Yes</td>
<td>Malar rash</td>
<td>No</td>
<td>No</td>
<td>2x Bact. Meningitis, Pneumonia.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Negative for ANA and rheumatoid factor</td>
<td>No</td>
<td>Gly76Arg</td>
<td>Gulez et al 2010</td>
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<tr>
<td>14/14 months, f</td>
<td>NA</td>
<td>Yes</td>
<td>Pyoderma gangrenosum</td>
<td>Skin</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Knees</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>Abanomi et al 2008</td>
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<tr>
<td>21/49 years, f</td>
<td>Caucasian</td>
<td>Yes</td>
<td>Bacterial meningitis</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Hypothyroidism Autoimmune hepatitis C3 deficiency</td>
<td>ANA Anti-dsDNA Anti-Cardiolipin Anti-B2-Glycoprotein</td>
<td></td>
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<td></td>
<td>Gly34Arg C8B,R427X</td>
<td>Pickering et al 2008</td>
</tr>
<tr>
<td>2/3 years, f</td>
<td>Tunisian</td>
<td>Yes</td>
<td>Photosensitive rash, Discoid Lupus.</td>
<td>Yes</td>
<td>Cutaneous</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td>ANA Anti SM Anti-RNP Anti-SSA</td>
<td></td>
<td></td>
<td>Yes</td>
<td>NA</td>
<td>Kallel-Sellami et al 2007</td>
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<tr>
<td>Age</td>
<td>Sex</td>
<td>Ethnicity</td>
<td>Relation</td>
<td>Diagnosis</td>
<td>Recurrent lower respiratory infections</td>
<td>Photosensitive malar rash</td>
<td>Discoid Lupus, necrotizing vasculitis</td>
<td>CNS vasculitis at 10 years of age</td>
<td>Inflammation</td>
<td>Pancreatitis</td>
<td>ANA</td>
<td>Anti-ENA</td>
<td>Anti-SM</td>
<td>Anti-ENA</td>
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<tr>
<td>3/12 years, f</td>
<td>Inuit</td>
<td>No known relation</td>
<td>1Discoid Lupus, photosensitive malar rash, necrotizing vasculitis</td>
<td>Yes</td>
<td>CNS inflammation</td>
<td>No</td>
<td>Pancreatitis</td>
<td>ANA</td>
<td>Anti-ENA</td>
<td>Anti-SM</td>
<td>Yes</td>
<td>Gly24 Arg</td>
<td>Marquart et al 2007</td>
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<tr>
<td>Sister</td>
<td>7/14 years</td>
<td>LE</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Sister</td>
<td>2/15 years</td>
<td>LE, necrotizing vasculitis</td>
<td>No</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>3/10 years, m</td>
<td>Pakistani</td>
<td>Yes</td>
<td>Malar rash</td>
<td>2Bacterial meningitis</td>
<td>Yes</td>
<td>CNS vasculitis at 10 years of age</td>
<td>ANA</td>
<td>Anti-SM</td>
<td>Anti-Ro</td>
<td>Yes</td>
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<tr>
<td>Father</td>
<td>18/38</td>
<td>Erythematous facial rash</td>
<td>Yes</td>
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<tr>
<td>Brother, 9/21 years</td>
<td>2Discoid lupus</td>
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<td>Brother, 19 years (no symptoms)</td>
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<td>Brother, 7/12 y</td>
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<td>Brother, Deceased</td>
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<tr>
<td>4/15 years, m</td>
<td>Turkish</td>
<td>Yes</td>
<td>2x 2Meningitis (1x unknown origin, 1x meningococ.), pericarditis, Pneumonia</td>
<td>Meningococcal Sepsis</td>
<td>Elbow and ankle</td>
<td>Coronary vascular disease, died from acute myocardial infarct in 1998</td>
<td>ANA</td>
<td>Anti-Ro</td>
<td>Yes</td>
<td>ND</td>
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<tr>
<td>6/24 years, f</td>
<td>Asian</td>
<td>Yes</td>
<td>2Scaly erythematous rash, Cheeks and fingers</td>
<td>Recurrent urinary and respiratory infections, Proteus pyelonephritis</td>
<td>Yes</td>
<td>Cerebral vasculitis</td>
<td>Raynaud’s phenomenon, Alopecia</td>
<td>ANA</td>
<td></td>
<td>Yes</td>
<td>Gly55Glyfs 83X</td>
<td>Stone et al 2000 / Mehta et al 2010</td>
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Table 2. Clinical characteristics of C1q deficiency cases not reported in previous review.