CD55-deficiency in Jews of Bukharan descent is caused by the Cromer blood type Dr(a−) variant

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Received: 31 October 2021 / Accepted: 27 December 2021 / Published online: 21 March 2022
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Abstract
The complement system regulator CD55 was initially found to carry the Cromer blood group system antigens, and its complete loss of function was subsequently revealed to cause a severe monogenic gastrointestinal syndrome characterized by protein-losing enteropathy and susceptibility to venous thrombosis. Here we present homozygosity to the CD55 c.596C>T; p.Ser199Leu variant, which was previously described as the Cromer Dr(a−) genotype, in two Bukharan Jewish CD55-deficiency patients with variable disease severity. We confirm that this missense variant causes aberrant splicing and deletion of 44 bp in exon 5, leading to premature termination and low expression of the CD55 protein. Furthermore, Patient 1 exhibited a mildly abnormal B cell immunophenotyping profile. By population screening we established that this variant is highly prevalent in the Bukharan Jewish population, with a carrier frequency of 1:17, suggesting that many similar patients are un- or mis-diagnosed. The phenotypic variability, ranging from abdominal pain when eating a high-fat diet to the full CD55-deficiency phenotype, is likely related to modifiers affecting the proportion of the variant that is able to escape aberrant splicing. Establishing the diagnosis of CD55-deficiency in a timely manner, even in patients with milder symptoms, may have a critical effect on their management and quality-of-life since treatment with the complement inhibitor eculizumab is highly effective in ameliorating disease manifestations. Awareness of founder mutations within certain populations can further guide genetic testing and prevent a diagnostic odyssey, by placing this CD55 variant high on the differential diagnosis.

Introduction
CD55 [OMIM *125240], also known as decay-accelerating factor (DAF), is a glycosylphosphatidylinositol (GPI)-anchored membrane-bound complement regulator, with a key role in restricting complement-induced damage on autologous tissues (Lublin 2005; Kim and Song 2006; Zipfel and Skerka 2009). CD55 is widely expressed on epithelial, endothelial and hematopoietic cells, and was initially found to carry the Cromer blood group system antigens, which result from different genetic variants [OMIM #613793] (Lublin et al. 1991; Lublin 2005; Storry et al. 2010). Loss of all Cromer antigens, deemed ‘Cromer Inab’, was previously linked to gastrointestinal manifestations in some patients (Yazer et al. 2006; Storry et al. 2010), but no direct clinical association has been recognized until recently.

In 2017, bi-allelic loss-of-function variants in CD55 were established as the cause of a hereditary syndrome involving protein-losing enteropathy (PLE), primary intestinal lymphangiectasia (PIL), diarrhea, hypoalbuminemia and increased risk for venous thrombosis [OMIM #226300:
complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy, CHAPLE] (Ozen et al. 2017; Kurolap et al. 2017). This severe phenotype results from complement system dysregulation, marked by membrane attack complex (MAC) deposition on patient cells. Moreover, the complement C5-inhibitor eculizumab (Soliris, Alexion Pharmaceuticals, Boston, MA, USA), which is a gold-standard treatment for other complementopathies, is also highly successful in ameliorating CD55-deficiency symptoms (Kurolap et al. 2017, 2018; Hagin et al. 2020; Ozen et al. 2021). Therefore, to provide life-saving treatment, it is essential to recognize and quickly diagnose CD55-deficiency patients. This can be suspected clinically when a history of PLE and thrombosis is observed, and confirmed via a rapid flow cytometry assay exhibiting absent CD55 protein expression coupled with identification of disease-causing variants in the CD55 gene. Uncovering founder mutations, which show high prevalence in certain populations, can accelerate the diagnostic process, especially in cases where the clinical presentation may not be classical.

In this study, we provide evidence that the CD55 (NM_001114752.3): c.596C>T; p.Ser199Leu variant, previously described as the Cromer Dr(a−) genotype, is highly prevalent in the Bukharan Jewish population. We demonstrate that homozygosity for this hypomorphic variant leads to the well-established CD55-deficiency syndrome with variable expressivity due to the variant’s unique molecular characteristics.

Methods

Participants

Patient 1 was referred for immunological and genetic evaluation due to suspicion of CD55-deficiency following clinical assessment at the gastroenterology unit. Patient 2 was diagnosed following an incidental finding on clinical whole-exome sequencing (WES), which was performed for an unrelated indication (fetal mild ventriculomegaly). Following written informed consent by both patients, Patient 1 agreed to provide blood samples for flow cytometry and RNA analyses.

For the variant population screen, we utilized anonymized DNA samples of Bukharan descent individuals available at the Tel Aviv Sourasky Medical Center and Sheba Medical Center Genetics Institutes.

CD55 protein analysis and variant identification

Flow cytometry-based analysis of CD55 expression was performed as an initial screen for Patient 1. For this purpose, a fresh blood sample was collected and CD55 surface staining was performed on whole blood using FITC-conjugated anti-CD55 antibody (Clone JS11, BioLegend, CA, USA). Cells were acquired using a FACSCanto II flow cytometer (BD Biosciences, San Jose, CA, USA) and analyzed using FlowJo software (TreeStar Inc., Ashland, OR, USA).

Upon confirmation that Patient 1’s cells show reduced CD55 protein expression, we performed targeted Sanger sequencing to identify the disease-causing variant.

RNA analysis

The c.596C>T variant, which is located in exon 5 and predicted to cause a nonsynonymous substitution (p.Ser199Leu), was previously shown to cause aberrant splicing and deletion of 44 bp in exon 5 (Lublin et al. 1991, 1994; Reid et al. 1991). To observe this splicing defect, RNA was extracted from patient PBMCs using the High Pure RNA Isolation kit (Roche Applied Science, Penzberg, Germany). Reverse transcription was done using the qScript cDNA Synthesis kit (Quantbio, Gaithersburg, MD, USA). Primers encompassing CD55 exons 4–6 were used to amplify the variant region, as described previously (Reid et al. 1991). PCR products were separated on 4% agarose gel and Sanger sequenced to confirm the previously described 44 bp deletion. The relative expression of the misspliced and correctly spliced mRNA isoforms out of total CD55 mRNA for Patient 1 was calculated by semiquantitative densitometry analysis of the PCR products using NIH ImageJ software, similarly to the method previously used by Lublin et al. (1994); this allowed us to compare the findings between our patient and previously described data.

In addition, to corroborate the densitometry results, we performed quantitative real-time PCR (qRT-PCR) analysis on patient cDNA using allele-specific forward primers and the same reverse primer described above to discern between the correctly-spliced (5′-ACACAGGGT ACAATTATTTG-3′) and misspliced (5′-ATGTAA CACAGGCCAGCTGT-3′) mRNA isoforms. Results were analyzed on the StepOne v2.3 software and the relative expression of each isoform was determined in comparison to the total CD55 mRNA expression (using the primers encompassing exons 4–6). The analysis was modified from (Harvey and Cheng 2016) by comparing the 2−ΔΔCt values of both mRNA isoforms, whereby ΔΔCt=ΔCt[correct or misspliced CD55 mRNA] − ΔCt[full CD55 mRNA].

Population screen

To detect variant frequency among Jews of Bukharan descent, we utilized the restriction fragment length polymorphism (RFLP) method. The c.596C>T variant deletes a TaqI restriction site; therefore, anonymized DNA samples of Bukharan Jewish individuals (n = 268)
were amplified using the primers described above and PCR products were incubated with the TaqI restriction enzyme (New England BioLabs, Ipswich, MA, USA). Heterozygous and homozygous status was confirmed by Sanger sequencing in select samples. In addition, we queried our internal database of Israeli exome and genome sequences, which contains 43 samples of full or partial Bukharan Jewish descent (including probands and their parents) out of overall >4500 samples; only unrelated samples (e.g. both parents but not their child) that are fully or half Bukharan \( (n = 33) \) were used to determine the variant frequency.

**B-cell immunophenotyping**

B-cell immunophenotyping was performed on thawed isolated PBMCs. The following antibodies were used: CD19 PE/Cy7 (clone HIB19; BioLegend), CD27 APC/Cy7 (clone M-T271, BioLegend), CD38 PerCP/Cy5.5 (clone HIT2, BioLegend), IgM FITC (clone MHM-88, BioLegend), IgD BV510, (clone IA6-2, BioLegend), CD24 PE (clone ML5, BioLegend). Cells were acquired using a BD FACS Canto II flow cytometer and analyzed using FlowJo software (TreeStar).

**Results**

**Clinical reports**

Patient 1: A 35-year-old male of Bukharan Jewish descent was admitted to the hospital for worsening abdominal pain, diarrhea, edema and hypoalbuminemia, which appeared several weeks after recovering from mild COVID-19 infection. His medical history was significant for severe intermittent abdominal pain, diarrhea and hypoalbuminemia since he was 16 years old; between the ages 16 and 26 he carried the diagnosis of Crohn’s disease with failed attempts of high-dose steroids and anti-TNF treatment. At age 26 he suffered worsening of his symptoms with TPN-resistant hypoalbuminemia, secondary ascites and peripheral edema. Abdominal imaging demonstrated severe involvement of a defined jejunal segment, and he underwent partial small bowel resection. Pathology evaluation revealed inflammatory polyposis in the setting of multiple large mesenteric veins, as evidence for prior mesenteric thrombosis manifested by scattered intimal lesions involving mesenteric and intramural veins (Fig. 1). Although no intestinal lymphangiectasia was demonstrated, the jejunal polyps consisted of glomeruloid vascular proliferation with overlying pseudomembranous inflammation.

Following the surgical intervention, the patient fully recovered with normalization of his albumin levels (from 1.8 to 4.0 g/dL, normal range: 3.5–5.0) and resolution of
his edema and ascites. Over the next 8 years, he remained mostly symptom-free, with occasional milder symptoms of intermittent abdominal pain and weakness.

In 2020, he was diagnosed with mild COVID-19, presenting with myalgia and fever of up to 39 °C, which lasted 48 h. He was not hospitalized and required no supportive treatment. However, this prompted a flare-up of his previous symptoms with severe abdominal pain and diarrhea, and new-onset ascites and peripheral edema. Laboratory evaluation showed hypoalbuminemia of 2.3 g/dL, hypoglobulinemia of 1.47 g/dL (normal 2.30–3.50) and hypogammaglobulinemia of 538 mg/dL (normal range: 700–1600).

The combination of ascites and hypoalbuminemia, in the presence of a history of long-lasting PLE and prior pathological evidence of possible mesenteric thrombosis raised the possibility of CD55-deficiency, and flow-cytometry evaluation of CD55 expression was ordered.

Patient 2: A 36-year-old woman of Bukharan Jewish descent was diagnosed with CD55-deficiency following an incidental finding on trio WES. She was described as generally healthy, yet upon direct questioning she revealed a history of recurrent abdominal pain, sometimes with concurrent diarrhea, since the age of 18 years. These events occurred mostly after eating out or when stressed, leading her to limit her food intake to a mainly homemade and low-fat diet. There were no recent serum albumin and total protein results; however, tests done over the years revealed albumin and total protein within the normal range, thus excluding subclinical PLE. Interestingly, her mother has also been suffering from recurrent abdominal pain during the last year, which is relieved by adhering to a low-fat and low-carbohydrate diet. In addition, her paternal aunt has been suffering from an unknown gastrointestinal disease since childhood. Unfortunately, blood samples of Patient 2 and her relatives were not available for further genetic testing or staining.

**Molecular diagnosis of CD55-deficiency**

Flow cytometry-based analysis of surface CD55 staining showed significantly reduced CD55 expression on Patient 1’s leukocytes compared to healthy control (Fig. 2).

Sanger sequencing revealed that Patient 1 is homozygous for the Chr1:207,500,114C>T (GRCh37/hg19) variant, which is located in exon 5 of the CD55 gene (NM_001114752.3: c.596C>T; p.Ser199Leu). Patient 2 was found homozygous for the same variant as an incidental finding on WES for an unrelated indication.

This variant was previously linked to the Cromer Dr(a−) blood type (Lublin et al. 1991). It affects weakly conserved nucleotide (PhyloP − 1.90, phastCons 0.00) and amino acid (GERP − 5.58) (Fig. 3a), leading to mostly benign pathogenicity predictions (CADD = 21.3). However, splicing analysis tools (embedded in Alamut Visual software, Interactive Biosoftware, Rouen, France) predict disruption of a site for the pre-mRNA-splicing factor SF2/alternative splicing factor (SF2/ASF) (Fig. 3b).

**The c.596C>T variant causes abnormal alternative splicing**

PCR amplification of cDNA derived from Patient 1’s PBMCs revealed the previously observed alternative splicing defect in exon 5 (Fig. 3c). Although the patient is homozygous for the c.596C>T variant, it essentially results in two mRNA isoforms—one with the missense variant (p.Ser199Leu) and the other with a deletion of 44 bp at the 5′ of exon 5 (c.580_623del). The c.580_623del variant causes a frameshift and leads to premature termination (p.Tyr194Glnfs*7) (Fig. 3f) and subsequently reduced levels of the CD55 protein (Fig. 2). Densitometry analysis showed that 88% of Patient 1 CD55 mRNA is missspliced (44 bp deletion) compared to 12% of the correctly spliced mRNA with a nonsynonymous substitution effect (Fig. 3d). These results were confirmed by isoform-specific qRT-PCR analysis, revealing that the missspliced mRNA isoform shows 9-times higher expression than the correctly-spliced isoform (Fig. 3e).
Variant prevalence among Bukharan Jews

We performed RFLP analysis on PCR products from \( n = 268 \) anonymous Bukharan Jewish samples and observed 15 heterozygotes and one homozygote for the c.596C>T variant; genotypes of selected samples were confirmed using Sanger sequencing. Since the samples were anonymized, we were unable to contact the homozygous individual.

In addition, we queried our internal exome/genome database, which revealed three variant carriers and one homozygote among 33 unrelated individuals with full or half Bukharan Jewish background, and one carrier of Turkish/Greek Jewish descent. The variant was not observed in any of the other ~4500 individuals of different Israeli ethnicities within our internal database.

Overall, our findings reveal that in the Bukharan Jewish population, the c.596C>T carrier frequency is 1:17 (6.0%, 18/301 variant carriers, excluding the homozygous individual and the Turkish/Greek Jewish individual), and the allele frequency is 1:27 (3.7%, 22/596 Bukharan Jewish alleles).

Abnormal B cell immunophenotyping

Additional immune evaluation showed mildly abnormal B-cell development with B cells skewed toward the immature phenotype. This is reflected by a higher percentage of...
CD27$^\text{negative}$ B cells (87.9% vs. an average of 76.88% ± 6.3, $n = 10$ adult healthy controls), a higher percentage of transitional CD38$^{\text{high}}$CD24$^{\text{low}}$ B-cells (17.3% vs. an average of 3.15% ± 3.05, $n = 10$), a higher percentage of CD38$^{\text{dim}}$CD24$^{\text{low}}$ naïve mature B-cells (65.6% vs an average of 46.16% ± 13.82, $n = 10$), and a lower percentage of memory CD38$^{\text{low}}$CD24$^{\text{high}}$ B-cells (12.3% vs an average of 44.63% ± 13.82, $n = 10$), but with normal percentage of class-switched IgG$^+$ and IgA$^+$ B cells (Fig. 4).

**Discussion**

The Cromer Dr(a−) phenotype was first described in 1984 as a recessive trait in individuals from Israeli families of Bukharan Jewish descent, exhibiting low expression of Cromer blood group antigens (Levene et al. 1984). It was later identified that Cromer antigens are carried on DAF/CD55, and in 1991, the genotype of Dr(a−) was deciphered as homozygosity for the c.596C>T variant, leading to reduced CD55 protein levels (Lublin et al. 1991, 1994; Reid et al. 1991). Subsequently, this Cromer variant was also observed in a Japanese individual (Daniels et al. 1998), and in a Russian woman with a chronic intestinal disease of unknown etiology (no additional data were reported

![Abnormal B-cell immunophenotyping](image.png)

**Fig. 4** Abnormal B-cell immunophenotyping. B-cell immunophenotyping shows a skewed maturation pattern with a low percent of CD27$^+$ memory B cells, and b increased percent of transitional CD38$^{\text{high}}$CD24$^{\text{high}}$ and naïve memory CD38$^{\text{dim}}$CD24$^{\text{low}}$ B-cells, and low percent of CD38$^{\text{low}}$CD24$^{\text{high}}$ memory cells. Despite that, c CD27$^+$ B cells showed the normal percent of IgG$^+$ and IgA$^+$ class-switched B cells.
regarding her phenotype) (Reid et al. 1991; Lublin et al. 1994). To our knowledge, this is the first report of a CD55-deficiency patient exhibiting the classic disease phenotype caused by homozygosity to the c.596C>T variant.

Previous reports suggested abnormal B-cell development in cases of complement hyperactivation. As such, Richards et al. described abnormal B-cell immunophenotyping in paroxysmal nocturnal hemoglobinuria (PNH) patients, with PNH B-cells (GPI-negative B-cells) showing a low percentage of CD27 expression (Richards et al. 2000). Similarly, Ozen et al. described abnormal B-cell development in one patient, with decreased class switched IgD−CD27+ memory B-cells (Ozen et al. 2017). In accordance with these reports, we also show that Patient 1 exhibited mildly abnormal B-cell immunophenotyping with a low percentage of memory B-cells. Further evaluation of CD55-deficiency patients is required to better understand whether abnormal B-cell development is indeed a manifestation of this disorder, and whether observed abnormalities are reversible upon treatment.

The high prevalence of the c.596C>T variant we detected in the Bukharan Jewish population suggests that many patients of this ethnic origin may go undiagnosed. With a carrier rate of 1:17, the expected homozygosity incidence is 1:1156 among Bukharan couples. Considering there are approximately 150,000 Bukharan Jews in Israel and approximately 320,000 worldwide, we would expect to diagnose 130 and 277 CD55-deficiency patients, respectively, in this ethnic group.

While only one of the previously described Cromer Dr(a−) individuals was reported to have gastrointestinal symptoms (Lublin et al. 1994), this may have resulted from the authors deeming this information irrelevant at the time or the affected individuals not disclosing any phenotype. Although a link between Cromer-null phenotypes, including Inab and Dr(a−), and gastrointestinal disease has been suggested previously (Yazer et al. 2006), the CD55-deficiency phenotype of PLE and susceptibility to thrombosis has been established only in 2017 (Ozen et al. 2017; Kurolap et al. 2017). As such, these patients may have been misdiagnosed over the years with inflammatory bowel disease, irritable bowel syndrome, PLE of unknown etiology, specifically when PLE and thrombosis are observed among other symptoms.

Interestingly, although the patients are homozygous for this variant, RNA analysis reveals the co-existence of two different mRNA isoforms—one with the non-synonymous substitution leading to p.Ser199Leu, and the other resulting from missplicing and deletion of 44 bp in exon 5 (c.580_623del) (Fig. 3). While the missense variant is likely benign by itself, the splicing defect causes a frameshift and leads to premature termination (p.Tyr194Glnfs*7). The missense variant, which escapes the alternative splicing effect, could theoretically explain the residual CD55 protein expression demonstrated by flow-cytometry (Fig. 2). In the original studies describing this variant, the abundance of misspliced mRNA was 50–70% compared to 30–50% of correctly-spliced mRNA (with the missense effect) in homozygotes (Lublin et al. 1994). Here we show that Patient 1 has 90% misspliced CD55 mRNA (Fig. 3d, e), possibly explaining his severe phenotype. Potentially, Patient 2 should have lower rates of mRNA with the 44 bp deletion, and therefore also higher levels of CD55 protein, leading to a milder clinical presentation; unfortunately, she declined further testing. Different factors, whether genetic or environmental, may serve as modifiers affecting the proportion of the variant that is able to escape aberrant splicing, as well as drive the differences in phenotypic expression among patients. Therefore, the discrepancy between the observed variant frequency and the number of diagnosed affected individuals in a population group that practices endogamy, like the Bukharan Jewish community, could be in part due to CD55-deficiency being a relatively newly defined syndrome or the hypomorphic nature of this pathogenic variant.

A recent study by Snelson et al. showed that processed foods affect intestinal barrier permeability and that this process is mediated by activation of the complement system, leading to injury through the proinflammatory C5a molecule (Snelson et al. 2021). In addition, a study by Taylor et al. revealed that fructose, which is commonly used in the Western diet, promotes intestinal villus elongation, consequently increasing absorption and adiposity by expanding the intestinal surface area (Taylor et al. 2021). Moreover, it is well-recognized that a high-fat diet exacerbates PLE symptoms in the presence of lymphangiectasia (of any etiology), and such patients are often managed by a low-fat diet with medium-chain triglyceride supplementation (Vignes and Bellanger 2008; Kurolap et al. 2017). As such, patients’ nutrition may affect the severity of their phenotypic presentation. It can be assumed that similar to Patient 2 and her mother, some CD55-deficiency patients with lower rates of the misspliced c.596C>T mRNA may suffer from gastrointestinal symptoms mainly after consuming a high-fat diet, which is inappropriate for their condition, leading to avoidance of certain foods and subsequent reduction of symptoms. This may also explain the differences in age of onset among patients with different pathogenic variants, which ranges between 6 months and 25 years (Ozen et al. 2017; Hagin et al. 2020), and the fact that some patients (including the one described here) may exhibit temporary resolution of symptoms (Kurolap et al. 2017; Hagin et al. 2020). However, more patients are required to validate the above-mentioned
hypotheses and to delineate the full phenotypic and genotypic spectrum caused by this particular variant.

Establishing the diagnosis of CD55-deficiency in a timely manner, even in patients with milder symptoms, has a critical effect on their management and quality-of-life. In that regard, a flow cytometry-based assay can be used as a rapid screening tool for suspected CD55-deficiency patients followed by genetic confirmation, or to support pathogenicity of identified variants. Awareness of founder mutations within certain populations can further guide genetic testing and prevent a diagnostic odyssey, i.e. when a patient of Bukharian Jewish descent presents with gastrointestinal issues, CD55-deficiency due to homozygosity to the CD55 c.596C>T variant should be high on the differential diagnosis.

Proper understanding of the disease pathoetiology and natural history not only affects the patient’s own conduct but also offers highly effective treatment with complement inhibitors (Kurolap et al. 2017, 2018; Ozen et al. 2021). As such, Patient 1 described here was put on eculizumab treatment with rapid resolution of his symptoms. Currently, eculizumab, which is administered intravenously and requires hospital visits every 2 weeks, is the only anti-complement drug in clinical use for CD55-deficiency and other complementopathies. However, numerous other treatments are being developed, some with other modes of administration (e.g. oral and subcutaneous) (Zelek et al. 2019), which may highly affect patient well-being and adherence to treatment in the future.

**Funding** No funding was received for conducting this study.

**Data availability** Any data related to this study is available upon request.

**Declarations**

**Conflict of interest** Authors AK and HBF have a patent with Alexion Pharmaceuticals on eculizumab treatment protocol for CD55-deficiency (WO/2018/217638), which does not include any royalties. Author HBF serves on the advisory board for the C5-inhibitor Pozelimab clinical trial by Regeneron Pharmaceuticals. All other authors have nothing to declare.

**Ethical approval** The study was approved by the Tel Aviv Sourasky Medical Center Helsinki committee.

**Informed consent** The patients provided written informed consent as customary.

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