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Clinical laboratory standard capillary protein electrophoresis alerted of a low C3 state and lead to the identification of a Factor I deficiency due to a novel homozygous mutation

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ABSTRACT

Complement factor I (CFI) deficiency is typically associated to recurrent infections with encapsulated microorganisms and, less commonly, to autoimmunity. We report a 53-years old male who, in a routine control for non-alcoholic fatty liver disease, presented a flat beta-2 fraction at the capillary protein electropherogram. Patient's clinical records included multiple oropharyngeal infections since infancy and an episode of invasive meningococcal infection. Complement studies revealed reduced C3, low classical pathway activation and undetectable Factor I. *CFI* gene sequencing showed a novel inherited homozygous deletion of 5 nucleotides in exon 12, causing a frameshift leading to a truncated protein. This study points out that capillary protein electrophoresis can alert of possible states of low C3, which, once confirmed and common causes ruled out, can lead to CFI and other complement deficiency diagnosis. This is important since they constitute a still underestimated risk of invasive meningococcemia that can be greatly reduced by vaccination.

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1. Introduction

The complement system is an important arm of the immune system. It participates in the host defense against pathogens both in the natural immunity and the adaptive response, in the removal of immune complex and apoptotic cells and in maintaining immune system homeostasis [1]. It comprises more than 30 soluble and membrane-bound proteins that upon recognition of different molecules are proteolytically activated following one of the three amplification pathways described; classical, alternative and lectins. Activation of C3 by any of the pathways will lead to the common terminal pathway, in which C5 is activated and the membrane attack complex (MAC) is assembled. Classical (CP) and lectins' pathway (LP) converge in the activation of C4, which acquires then proteolytic functions and together with C2 constitutes the C3 convertase of these two pathways. On the other hand, the alternative pathway (AP) is initiated at a low rate by spontaneous C3 hydrolysis but only when is stabilized by the binding of Factor B, results in the assembling of the C3 convertase of the AP. This constitutes an amplification loop that must be tightly regulated in order to prevent a massive consumption of C3 [2].

One of the most important regulators is the serine protease Factor I. Since this factor has no endogenous inhibitor neither circulates as an uncleaved proenzyme, it is regulated by the presence of its cofactors. Factor I needs the presence of Factor H/MCP/CR1 in order to cleave C3b into the inactive form iC3b. However, it is also capable of disrupting C4b using C4BP as cofactor. The Factor I gene (*CFI*, OMIM*217030), located in chromosome 4q25, consists of 13 exons which encode a protein of 583 amino acids and 66 kDa. Factor I mature protein is heavily N-glycosylated and circulated as a zymogen at a concentration of 30–40 μg/mL [3]. The protein consists of two polypeptide chains linked by a single disulfide bond. The

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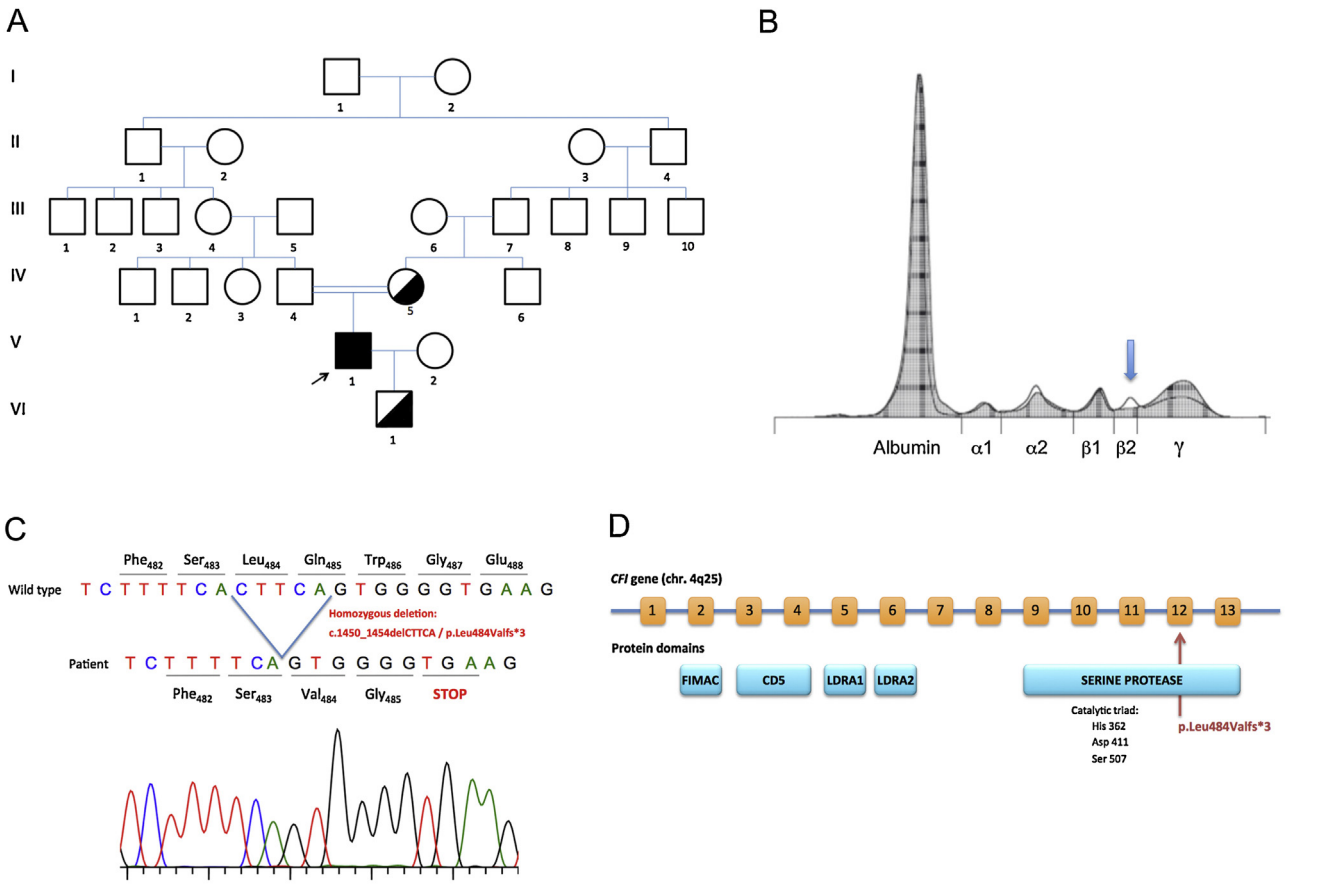

Fig. 1. A. Patient's serum proteins analysis by capillary electrophoresis. Patient (grey) and control (white) profiles are shown. Blue arrow indicates the flat β2 zone of the patient. B. Sequencing the *CFI* gene from the patient. Patient's CFI sequence is compared with the wild type one and the homozygous deletion of five nucleotides is indicated. C. Schematic model of the *CFI* gene and the main protein domains. The mutation found in our patient is depicted (red arrow). D. Pedigree of the patient family. Index patient is denoted with an arrow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

heavy chain (50 kDa) contains the N-terminal region, a Factor I MAC domain, a scavenger receptor domain, two low-density lipoprotein receptor domains and a C-terminal region that presents a high variability across species [4]. The light chain (38 kDa) contains a serine protease domain with a conserved catalytic residue.

The absence of Factor I leads to a continuous consumption of C3 due to an uncontrolled amplification of C3 cleavage, resulting in an acquired C3-deficiency state [5]. Complete Factor I deficiency (OMIM#610984) is a rare immunodeficiency inherited in an autosomal recessive manner and, so far, around 40 cases have been described, with 16 mutations being described [6–10]. The clinical presentation is remarkably variable among the different patients studied. Like in primary C3 deficiency, these patients are more susceptible to infections by encapsulated bacteria, such as *Haemophilus influenzae*, *Streptococcus pneumonia* or *Neisseria meningitidis*. Defective opsonization in these patients makes them susceptible to recurrent pyogenic infections as well as to aseptic meningitis. Moreover, the deregulation of the cascades can lead to autoimmune diseases, glomerulonephritis or vasculitis [11]. Monoallelic mutations in Factor I have also been identified in atypical hemolytic uremic syndrome (aHUS, OMIM#612923) patients, resulting in only partial deficiency and with a very different clinical presentation comprising the clinical triad of thrombocytopenia, microangiopathic hemolytic anaemia, and acute renal failure [12,13].

In this paper, we describe an adult patient with a complete Factor I deficiency that was detected because of a minor abnormality in the capillary protein electrophoresis (CPE) profile. The clinical record revealed a number of infection episodes that lead to a full investigation of the complement system and the detection of a novel homozygous mutation causing Factor I deficiency.

2. Material and methods

2.1. Plasma analysis

Proteins profile was assessed by CPE (Capillarys2. Sebia, Evry Cedex, France). Complement C3 and C4 levels were measured by nephelometry (BNII. Siemens, Erlangen, Germany) and classical activation pathway, CH50, was measured using a liposome based assay (Wako. Neuss, Germany). Complement factor I was measured by radial immune diffusion (The Binding Site. Birmingham, UK).

2.2. Sequencing of the CFI gene

CFI gene (all exons and flanking regions) was sequenced in the patient. In the rest of the family only exon 12 was sequenced. Genomic DNA was extracted from EDTA-containing whole blood samples using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Polymerase chain reaction (PCR) to amplify the 13 exons of *CFI* and their flanking regions was carried out (primers and PCR conditions are available upon request) and purified PCR products were sequenced on an ABI 3100 DNA Sequencer using the BigDye Terminator sequencing kit 3.1 (Applied Biosystems, Foster, VA, USA).

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