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Review

Defining the genetics of thrombotic microangiopathies

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ABSTRACT

The spectrum of the thrombotic microangiopathies (TMA) encompasses a heterogeneous group of disorders with hereditary and acquired forms. Endothelial cell injury in the microvasculature is common to all TMAs, whatever the pathophysiological process. In this review we describe genetic mutations characteristic of certain TMAs and review their contributions to disease. Recent identification of novel pathologic mutations has been enabled by exome studies. The monogenic forms of TMA are more frequently caused by recessive alterations in von Willebrand factor cleaving protease ADAMST13, leading to congenital thrombotic thrombocytopenic purpura, or cobalamine C and DGKE genes, leading to an atypical hemolytic-uremic syndrome (aHUS)-like TMA. aHUS, whether idiopathic or linked to a known complement amplifying condition, is a TMA that primarily affects kidney function. It often results from a combination of an underlying genetic susceptibility with environmental factors activating the alternative complement pathway. Pathogenic variants in at least five complement genes coding for complement factor H (CFH) complement factor I (CFI), MCP (CD46), C3 and complement factor B (CFB) have been demonstrated to increase the risk of developing aHUS, but several more genes have been implicated. A new challenge is to separate disease-associated genetic variants from the broader background of variants or polymorphisms present in all human genomes that are rare, potentially functional, but may or may not be pathogenic.

Contents

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Introduction

The term thrombotic microangiopathy (TMA) refers to the pathological features resulting from microvascular endothelial cell injury with resultant thrombocytopenia, hemolytic anemia, and thrombosis with tissue ischemia [1]. The pathophysiology of the TMAs is complex. It includes hemolytic uremic syndrome (HUS) associated with Shiga toxin producing *E. coli* (STEC) or invasive pneumococcal infections, atypical HUS (aHUS), and thrombotic thrombocytopenic purpura (TTP), as well as secondary forms of aHUS which may be linked to a variety of complement amplifying conditions (other infections, cancer, drugs, autoimmune disease, pregnancy, organ and tissue transplantation) [2–5]. Congenital mutations leading to a TMA can be caused by pathogenic variants in one gene (monogenic disorder) or by a combination of inherited variants in multiple genes, often acting in concert with environmental factors [6]. Of particular interest to this special topic issue is the subgroup commonly referred to as aHUS, caused by genetic abnormalities of regulation of the alternative pathway of complement [7,8]. Here we summarize the contributions of novel and rare gene variants to the pathology of TMA, with a focus on aHUS.

1.1. Monogenic inheritance of a thrombotic microangiopathy (TMA)

Monogenic diseases are caused by alterations in a single gene. If characterized by complete penetrance they segregate in families according to traditional Mendelian patterns of inheritance.

1.1.1. Autosomal recessive TTP and biallelic pathogenic variants in ADAMTS 13 (reviewed in Ref. 9)

Upshaw–Schulman syndrome is the recessively inherited form of TTP, caused by the absence of the von Willebrand cleaving protease ADAMTS13, resulting in the persistence of ultra-large von Willebrand factor multimers (ULVWF). These patients are extremely rare, constituting less than 5% of all TTP cases. More than 130 distinct ADAMTS13 mutations have been found in a homozygous or compound heterozygous state. Nearly 60% are missense variants. Patients with Upshaw–Schulman syndrome respond to periodic fresh frozen plasma (FFP) infusions and do not require plasma exchange (PEx) or immune suppressive therapies as in acquired TTP.

1.1.2. Cobalamin C defect (cblC)-associated HUS

Methylmalonic aciduria with homocystinuria is the most common inborn error of vitamin B12 metabolism. It is caused by mutations in the MMACHC gene [10]. This disorder of cobalamin metabolism is characterized by elevated levels of plasma homocysteine and plasma and urine levels of methylmalonic acid. To date, around 70 different mutations have been identified; duplication of an A at the C271 position (c.271dupA or p.R91KfsX14) is the most frequent reported mutation [11–13]. HUS is a rare but well-described complication of a Cblc defect, although its mechanism remains unclear. Clinical onset usually occurs during infancy but recently cases of late-onset disease have been reported [14–17]. Supplementation with hydroxocobalamin and betaine is the main therapy.

1.1.3. DGKe deficiency-associated HUS

Recessive mutations in the gene coding for Diacylglycerol Kinase Epsilon (DGKE) were established as a novel cause of pediatric-onset aHUS [18]. The *DGKE* gene encodes diacylglycerol kinase-epsilon, an intracellular lipid kinase that phosphorylates diacylglycerol (DAG) to phosphatidic acid. Loss of DGKE in endothelial cells induces cell death, impairs angiogenic responses, and leads to an activated and prothrombotic phenotype [19]. Fourteen disease causing nucleotide changes have been identified, including one located in the intronic region [18,20,21]. One recurrent nonsense variant (p.Trp322*) was previously seen among 8,475 subjects of European descent, and in several unrelated aHUS subjects (homozygous and heterozygous traits). Affected individuals present with aHUS before one year of age have persistent hypertension, hematuria and proteinuria (sometimes in the nephrotic range), and develop chronic kidney disease.

1.1.4. aHUS with bi-allelic pathogenic variants in complement genes

aHUS can be classified as sporadic or familial. Familial aHUS is defined as the presence of aHUS in at least two members of the same family. Approximately 50% of familial forms have an autosomal recessive pattern of disease inheritance.

1.1.4.1. CFH deficiency-associated HUS. CFH is the most important negative regulator of the alternative complement pathway [22]. The CFH gene is approximately 100 kb long and comprises 23 exons. The association between a clinical diagnosis of aHUS and low plasma C3 was first reported in pediatric patients more than 25 years ago [23]. A few years later, CFH deficiencies were documented in recessive forms of pediatric onset aHUS [reviewed in Ref. 1]. The homozygous deletion of 4 nucleotides located at the end of *CFH*, leading to the deletion of the stop codon (c.3693delATAG), accounts for more than 50% of reported cases [8,24,25]. One case of complete CFH deficiency was explained by a chromosome 1 uniparental isodisomy [26]. The penetrance of CFH-linked disease is nearly complete as all patients were diagnosed with aHUS or C3 glomerulopathy [27].