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REVIEW

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TNF-receptor-associated periodic syndrome (TRAPS): an autosomal dominant multisystem disorder

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Abstract The TNF-receptor-associated periodic sydrome (TRAPS) is an autosomal dominant auto-inflammatory disorder, characterized by recurrent febrile attacks and localized inflammation. TRAPS is caused by mutations in the gene encoding the TNF Receptor Super Family 1A (TNFRSF1A) on chromosome 12p13. However, the incomplete penetrance and genetic heterogeneity have been reported in this syndrome. Although the ethnic diversity and clinical heterogeneity may propose the role of other genes in the pathogenesis of TRAPS, some low-penetrance TNFRSF1A variants contribute to atypical inflammatory responses in other autoimmune diseases. Furthermore, molecular studies on TRAPS and other auto-inflammatory disorders could be suggested to identify additional genes coding the molecules in the TNF signalling process.

Keywords Hereditary periodic fever syndromes · Mutation · Penetrance · TNFRSF1A (Tumor necrosis factor receptor superfamily, member 1A)

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Introduction

The hereditary periodic fever syndromes are a group of auto-inflammatory disorders characterized by recurrent episodes of fever and localized sites of inflammation in the absence of high titre autoantibodies [1–3]. These syndromes, categorized into three groups, include familial Mediterranean fever, hyper-IgD with periodic fever syndrome, and tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS) [1, 2].

TRAPS (OMIM: 142680) is a new subset of auto-inflammatory disorders characterized by periodic febrile attack and inflammation in different sites [1, 4–6]. It was first termed as familial Hibernian fever by Williamson et al. in 1982. They described this syndrome in an Irish-Scottish family with recurrent fever, abdominal pain, localized myalgia, and erythematous skin lesions [7]. Afterwards, several studies were performed on these patients to describe the detailed clinical manifestations, pathogenesis, inheritance, and genetics of this syndrome [5, 8–10].

In this review, the genetic inheritance of TRAPS and its mutations have been purposed. To achieve these aims, the review of this syndrome including the clinical features, pathogenesis, inheritance, the underlying mutations, and genotype–phenotype correlations have been described.

Clinical feature

TRAPS is a multisystem auto-inflammatory disorder with recurring and remitting feature [1, 4, 11]. Although the clinical manifestations of TRAPS are variable, approximately all patients experience the periodic episodes of fever, pain, and inflammation [1, 3, 5, 12]. Different organs could be involved by this syndrome, including joints, muscles, abdomen, skin, eyes, lungs, and testes [1, 3, 4, 7, 12].

Recurrent fever, abdominal pain, myalgia, and arthralgia are the most common manifestations of TRAPS, followed by tender erythematous skin lesion, chest pain, conjunctivitis, periorbital edema, testicular pain, headaches, lymphadenopathy, and amyloidosis [1, 4, 7, 12].

Inheritance of TRAPS

TRAPS has been described in many different ethnic backgrounds [1, 11, 13–15]. Moreover, the genetic mode of inheritance, as a first step to determine the responsible gene and mutations, has been reported in some articles [11, 13–15]. Analysis of pedigrees helps us to understand the mode

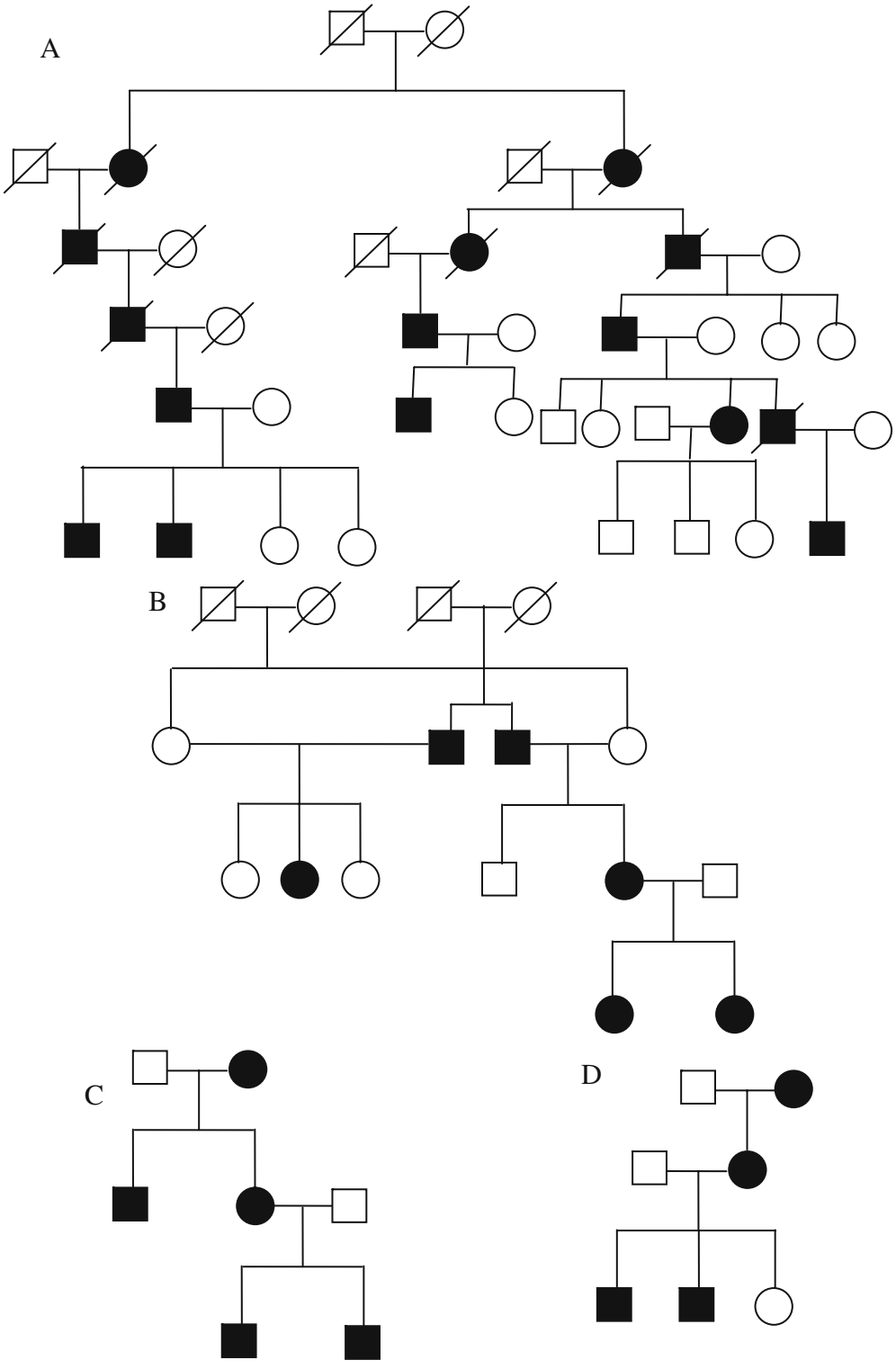

Fig. 1 The pedigrees of four families with TNF-receptor-associated periodic syndrome. **a** The Australian family of Scottish Ancestry [15]; **b** the Irish family [11]; **c** the family of French origin [14]; **d** the family, referred to National Institutes of Health, USA [13]; (*Open shapes* represent healthy individuals, *filled shapes* represent affected with syndrome, and *shapes with slashes* represent deceased individuals. *Boxes*: males, *circles*: females)

of inheritance in TRAPS (Fig. 1). The pedigrees of TRAPS patients indicate that all children of affected parents have an equal chance to be affected with this syndrome, and there is no gender-specific influence. Moreover, this syndrome can be transmitted by either the mother or the father, and there is a direct transmission without any skip generation from affected parents to affected children. These findings characterize an autosomal dominant mode of inheritance in TRAPS [1, 4, 5, 8, 11–15].

Genetics of TRAPS

The genome-wide searches in the affected families mapped the susceptibility locus to the distal short arm of chromosome 12. Linkage analysis and recombination indicated that the gene is located in an ~11 cM interval between D12S77 and D12S93 [15]. Other studies on these patients also confirm the linkage to this chromosomal region and indicate that the mutations in the same locus on chromosome 12p13 may cause this syndrome [5]. Although there are several plausible candidate genes in the abovementioned interval [5, 6], the *TNFR1* gene encoding the Tumor Necrosis Factor Receptor Super Family 1A (TNFRSF1A) was particularly interesting as TNF is a proinflammatory cytokine. In addition, there was an evidence of reduced levels of soluble TNFR1 in the serum of affected patients [5]; therefore, the recent studies have been focused to sequence TNFRSF1A [1]. The *TNFRSF1A* gene consists of ten exons situated on chromosome 12p13. According to the internet periodic fevers (INFEVERS) database (http://fmf.igh.cnrs.fr/infevers), at least 50 different TNFRSF1A mutations have been identified to date [16]. The majority of mutations are single-nucleotide missense mutations in exons 2, 3, 4, and 6 [16]. These mutations are found in the families from diverse ethnic backgrounds [1, 2, 11, 13–15].

Pathogenesis of TRAPS

TNF as a key mediator in the inflammatory response has pleiotropic activities, including increased expression of adhesion molecules, induction of cytokine secretion, activation of leukocytes, and host defence against intracellular pathogens [4, 5]. So, any defect, either in production or signaling of TNF, causes auto-inflammatory disorders and infectious complications [4]. There are two kinds of receptor for TNF: TNFRSF1A (p55, TNFR1, CD120a) that is expressed in the vast majority of cells and encoded on chromosome 12p; and TNFRSF1B (p75, TNFR2, CD 120b) that is found on the cells of immune system and encoded on chromosome 1p [1, 4]. TNFRSF1A as the main component in TNF signalling contains the extracellular region, transmembrane region, and an intracellular death domain. The extracellular regions consist of four cysteine-rich domains that bind to TNF, while intracellular regions use different signalling molecules to initiate cell death and survival [4] (Fig. 2).

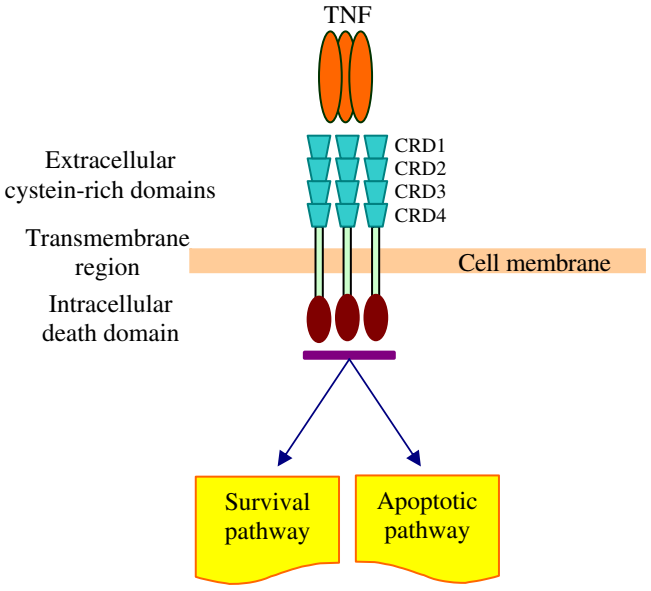

Fig. 2 Schematic structure and function of TNF receptor super family 1A [4]. (*CRD*: Cysteine-rich romain)

The extracellular domain of TNFRSF1A can be cleaved from the cell membrane after the receptor activation. This shedding mechanism produces a pool of soluble receptors into the plasma, which may attenuate the inflammatory response; therefore, in the patients with mutations in TN FRSF1A, shedding of receptors into the plasma would be decreased [1, 4, 8, 9]. In addition to shedding defects, other mechanisms could be involved in the pathogenesis of this syndrome, including impaired intracellular TNFRSF1A trafficking and TNF-binding, defective TNF-induced apoptosis, and TNF-independent NFκB activation [4].

Penetrance of mutations

The studies on the pedigrees of the affected patients demonstrate that the clinical features of TRAPS are present in part of the population. In fact, some of the family members who had the mutation gene do not express the genetic trait [14]. Thus, there is an incomplete penetrance in TRAPS. The pedigrees in Fig. 3 illustrate the incomplete penetrance in two families with TRAPS. In the pedigree on Fig. 3a, TRAPS is passed from the mother I-2 to the girl II-1; however, I-3 does not express TRAPS. He must have inherited the mutant allele because he passed it on to the boy II-2. Moreover, in the pedigree on Fig. 3b, although the father I-2 does not express the syndrome, TRAPS is passed on to the boy II-2. These cases (I-3 in Fig. 3a and I-2 in Fig. 3b) are the examples of incomplete penetrance in TRAPS.

Several studies emphasized that the penetrance of the clinical features in individuals with cysteine-containing mutations is much higher than the group with noncysteine-containing mutations [1, 13]. Haplotype analysis of mutations indicated that the P46L, R92Q, and T61I variants are

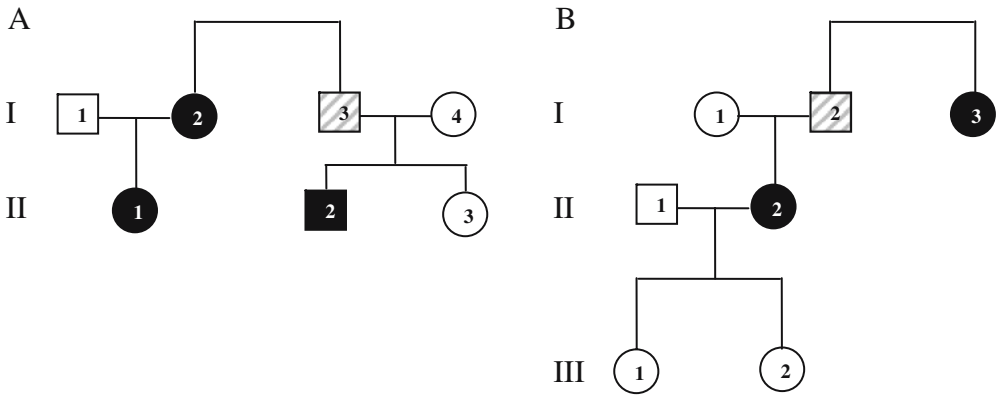

Fig. 3 The incomplete penetrance of mutations in the pedigrees of two families with TNF-receptor-associated periodic syndrome [14]. (*Open shapes* represent healthy individuals, *filled shapes* represent affected with syndrome, and *shaded shapes* represent asymptomatic carriers of the mutation. *Boxes*: males, *circles*: females)

low-penetrance TNFRSF1A mutations [1, 4, 13], and they may also accompany shedding defect and reduced level of soluble TNFRSF1A in plasma [4].

Genotype–phenotype correlation

Although the exact correlation between genotype and phenotype has not been described till now, there are a few reports demonstrating the correlation between cysteine-containing mutations and increased risk of development of systemic amyloidosis, type AA. Noncysteine-containing mutations may also lead to amyloidosis; however, the significant difference between two groups makes it a prognostic indicator for this serious long-term systemic complication [1, 4, 13]. Moreover, the low-penetrance variants of TNFRSF1A may be involved in the chronic inflammatory disease condition via the pro-inflammatory effects. Among them, patients with the R92Q mutation present less typically and have milder clinical manifestations than other TRAPS patients [1, 4].

Genetic heterogeneity

As it has been mentioned earlier, a number of patients with mutations do not express the TRAPS phenotype in spite of mutations [1, 4, 13]. In contrast, there are several studies reporting a number of patients with TRAPS without any mutations in the coding region of TNFRSF1A [11, 13, 14]. It indicates the genetic heterogeneity in TRAPS. In a recent study, the mutations of TRAPS have been detected in only half of the familial cases; meanwhile, the study on other patients without mutation demonstrated the shedding defect in half of them [11]. Furthermore, the clinical variations and diverse ethnicity could suggest existence of other responsible loci or mutations of several genes in the pathogenesis of TRAPS [1, 2, 4]. However, we should keep in mind that incomplete penetrance and genetic heterogeneity are two specific phenomena in the autosomal dominant diseases and environmental factor could also play an important role in clinical heterogeneity. Thus, as the reasons noted before, *TNFRSF1A* is still the most important gene in TRAPS, and its mutations are certainly involved in the pathogenesis of this syndrome [1, 2, 4–6, 11, 13–15].

Conclusions

TRAPS is an autosomal dominant multisystem disorder caused by mutations in the gene encoding the TNFRSF1A on chromosome 12p13 [1, 2, 4, 5, 8, 9, 15]. The several investigations on TRAPS patients lead to the identification of more than 50 different TNFRSF1A mutations to date [16]. They help find the new pathogenesis of this syndrome and, consequently, develope new medications for controlling the progress of this syndrome [2, 4]. Moreover, identification of TNFRSF1A mutations in this syndrome helps physicians to confirm the diagnosis in suspected cases before complications [4].

The clinical differences among the patients with this syndrome, variation in ethnic background, and the presence of TRAPS patients without any mutation in TNFRSFA1 has created doubtfulness about the responsible genetic factors [1, 2, 4, 5]. So, studying the molecules involved in the inflammatory response helps the identification of new genes [2]. The usage of the proteomics technology, including protein chip technology and mass spectrometry, may help scientists in this process [4].

After the discovery of TNFRSF1A, several studies have been done to find the genetics and pathogenesis of other auto-inflammatory disorders as well. Some of them indicated that the low-penetrance TNFRSF1A variants might contribute to atypical inflammatory responses in TRAPS, including: pericarditis, myocarditis, sacroiliitis, panniculitis, arthritis, aphthous stomatitis, pharyngitis, and adenitis. Thus, it seems that the TNFRSF1A mutations may play a role in the pathogenesis of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematous, and Behcet's disease [1, 4, 5]. Further studies should confirm the potential role of TNFRSF1A mutations in these disorders and investigate it in other inflammatory diseases. Moreover, the TNF signaling in the inflammatory process should be investigated by further studies on transgenic and knockout mice [2, 5]. Thus, additional genes coding the

molecules in this process may be identified as responsible genes in the inflammatory diseases in the near future.

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