

Role of tumour necrosis factor (TNF)- α and *TNFRSF1A* R92Q mutation in the pathogenesis of TNF receptor-associated periodic syndrome and multiple sclerosis

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Summary

It has long been known that tumour necrosis factor (TNF)/*TNFRSF1A* signalling is involved in the pathophysiology of multiple sclerosis (MS). Different genetic and clinical findings over the last few years have generated renewed interest in this relationship. This paper provides an update on these recent findings. Genome-wide association studies have identified the R92Q mutation in the *TNFRSF1A* gene as a genetic risk factor for MS (odds ratio 1.6). This allele, which is also common in the general population and in other inflammatory conditions, therefore only implies a modest risk for MS and provides yet another piece of the puzzle that defines the multiple genetic risk factors for this disease. *TNFRSF1A* mutations have been associated with an autoinflammatory disease known as TNF receptor-associated periodic syndrome (TRAPS). Clinical observations have identified a group of MS patients carrying the R92Q mutation who have additional TRAPS symptoms. Hypothetically, the co-existence of MS and TRAPS or a co-morbidity relationship between the two could be mediated by this mutation. The *TNFRSF1A* R92Q mutation behaves as a genetic risk factor for MS and other inflammatory diseases, including TRAPS. Nevertheless, this mutation does not appear to be a severity marker of the disease, neither modifying the clinical progression of MS nor its therapeutic response. An alteration in TNF/*TNFRSF1A* signalling may increase proinflammatory signals; the final clinical phenotype may possibly be determined by other genetic or environmental modifying factors that have not yet been identified.

Keywords: genetic factors, multiple sclerosis, TNF, TNFR1, *TNFRSF1A* R92Q mutation

A brief introduction to the genetics of MS

Multiple sclerosis (MS) is a chronic recurrent inflammatory and neurodegenerative disorder. The genetic determinants of susceptibility to this disease are highly complex. For many years, the major histocompatibility complex (MHC) has been the only region of the genome found to be associated consistently with the disease. In particular, the DR15 haplotype (DRB1*1501-DQB1*0602) is a constant finding in northern European populations [1,2], with an odds ratio of 2.75 [3].

In recent years, genome-wide association (GWA) studies have identified other loci outside the MHC showing solid associations with MS, albeit with reduced genetic effects. These loci act as genetic markers, regardless of whether or not they have functional effects themselves [4] and include, among others, genes encoding cytokine receptors such as the

interleukin (IL)-2 receptor (IL-2RA) and the IL-7 receptor (IL-7R) [5]. In a recent meta-analysis of three large MS cohorts, the combined analysis led to the identification of three new loci associated with MS genetic risk, *TNFRSF1A* (tumour necrosis factor receptor superfamily 1A), *IRF8* (interferon regulatory factor 8) and *CD6* [3].

The association between MS and the *TNFRSF1A* gene (chromosome 12p13) encoding the type 1 tumour necrosis factor (TNF)- α receptor (TNFR1) is particularly intriguing, as the TNF- α signalling pathway has major implications in the pathophysiology of MS. It could be speculated that allelic variant-mediated alterations in *TNFRSF1A* function might have an impact on the TNF- α signalling pathways, and increase proinflammatory signals.

Two polymorphisms have been detected in this gene that are associated with MS: rs1899693, located in intron 6 of the

gene, which is highly frequent but of a little effect, and rs4149584, positioned in exon 4 of the gene. The latter polymorphism is associated with an arginine-to-glutamine substitution at position 92 (R92Q), with a lower frequency than the first one, but with greater genetic effect [3]. Although more in-depth research is needed to characterize the effects of this polymorphism and others in the *TNFRSF1A* gene in MS, this meta-analysis provides the first definitive evidence that *TNFRSF1A* is an MS susceptibility locus [3].

Objective and method

The aim of this paper is to address the issue related to the potential involvement of TNF/*TNFRSF1A* signalling mechanisms in the pathophysiology of MS, its relationship to the TNF receptor-associated periodic syndrome (TRAPS) and the possibility of a genetic link between both disorders through the R92Q mutation.

To this purpose we will review the biology of this cytokine, the data that provide evidence of the implication of TNF–TNFR1 signalling in MS, and will make a brief description of the diseases associated with the R92Q mutation, mainly TRAPS. We will also comment on the scarce studies to date that address the clinical relationship between MS and TRAPS, and some questions that remain unsolved. All relevant original articles and reviews in English were taken into account to complete this paper.

Biology and functions of TNF- α

TNF- α is a proinflammatory cytokine produced by immune cells, mainly macrophages and lymphocytes, in response to a great variety of stimuli. It exerts pleiotropic effects on immunity, inflammation, cell proliferation, differentiation and apoptosis, and also acts as an endogenous pyrogen [6–9]. Two forms of TNF- α are biologically active: transmembrane TNF (tmTNF) and soluble TNF (sTNF) [9].

TNF interacts with two receptors (TNFR), TNFR1 and TNFR2, in a wide range of cell types. TNFRs are transmembrane glycoproteins characterized by four cysteine-rich extracellular domains (CRDs), which can be cleaved proteolytically to generate soluble receptor fragments that may function as natural TNF- α antagonists [10,11].

TNFR1 is expressed constitutively in all cell types except erythrocytes, while TNFR2 is inducible and expressed preferentially by endothelial and immune cells. sTNF binds preferentially to TNFR1 *versus* TNFR2 [12].

TNFRs lack their own enzyme activity and their signalling depends on the association of adaptor proteins that bind to the cytoplasmic domains of the receptors. The cytoplasmic tail of TNFR1 contains a death domain that couples this receptor to one of two distinct signalling pathways. One pathway leads to activation of nuclear factor kappa-B (NF- κ B) and subsequently transcription of proinflammatory and anti-apoptotic genes, whereas a different pathway leads to

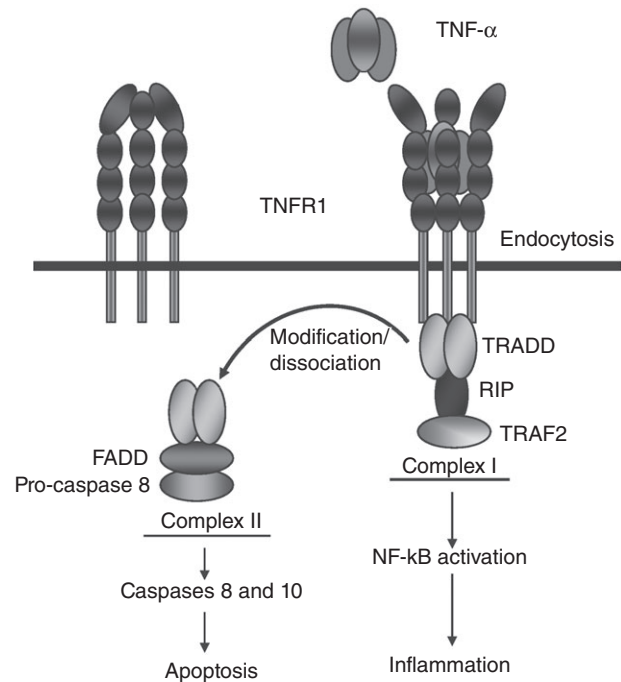


Fig. 1. Tumour necrosis factor receptor 1 (TNFR1) and its signalling pathways. TNFR1 has four extracellular cysteine-rich domains (CRDs). Signalling via TNFR1 occurs by TNF-induced recruitment of monomeric membrane-bound TNFR1 molecules to form a homotrimer configuration which, when bound to ligand, causes a three-dimensional conformational change in the extracellular domain that is then transduced intracellularly to activate signalling pathways. The cytoplasmic tail of TNFR1 contains a TNF receptor type 1-associated death domain (TRADD) that couples this receptor to one of two distinct signalling pathways. The default pathway activates nuclear factor kappa-B (NF- κ B) and other non-apoptotic pathways (not shown). This is mediated by the formation of complex I, comprising TNFR1 and NF- κ B activating signalling components such as receptor interacting protein (RIP) and TNF receptor-associated factor 2 (TRAF2). Formation of complex I is transient and TNFR1 can be internalized after TNF binding leading to dissociation of the TRADD/TRAF2/RIP complex and association of FADD, recruitment of pro-caspase 8 and formation of complex II, which then recruits the apoptotic machinery. If NF- κ B activation triggered by complex I is successful, cellular FLIP_L levels (see below) are sufficiently elevated to block apoptosis and cells survive. The ovals in the figure represent different activating signalling components. FADD: FAS-associated death domain. FLIP_L: FLICE-like inhibitory protein long, the long form of caspase 8 inhibitor.

apoptosis via activation of caspases 8 and 10. Therefore, TNFR1 will activate proinflammatory or apoptotic signals depending mainly on the cell type and the state of the cell [13] (Fig. 1).

TNFR2-mediated signalling produces far fewer biological effects than TNFR1 signalling. Such signals lead to the activation of NF- κ B, promoting tissue survival, although in some cases the receptor could also collaborate with its counterpart, contributing to cell death [14]. Although the activa-

tion of this receptor is also important in mediating TNF- α functions in different pathological conditions, such as MS, a description of TNFR2 signalling and its implications in MS falls outside the scope of the present review.

TNF- α and *TNFRSF1A* in MS

TNF- α signalling is implicated in the immunopathogenesis of MS [15]. Autopsy studies in MS patients have revealed high levels of TNF- α in active MS lesion sites [16]. The TNF- α levels in cerebrospinal fluid (CSF) are increased in MS patients *versus* controls, and these levels in turn are correlated with the severity of the lesions, the severity of the disease, the rate of neurological deterioration and a poorer prognosis after 24 months of follow-up [17]. In peripheral blood, the mononuclear cells of patients with MS secrete large amounts of TNF- α prior to the exacerbation of symptoms, compared with the cells of the same patients during periods of disease remission [18].

TNF- α involvement in the pathogenesis of MS has also been suggested in the experimental allergic encephalitis (EAE) animal model [19], as well as in the cuprizone model of toxic demyelination [20]. Most biological responses attributed to TNF- α are due to its action on TNFR1, because signalling through this receptor plays an important role in the onset of inflammation and the extension of demyelination in the acute phases of the disease [21]. TNF has also shown immunosuppressive properties during the later phases of the disease and, for instance, in the absence of TNF, autoreactive T cells fail to revert and expansion of activated T cells appears to be abnormally prolonged [22,23]. These immunosuppressive properties were shown to be independent of TNFR1 signalling and probably mediated through TNFR2 [22–24]. Therefore, it is believed that divergent roles exist between the two receptors in CNS autoimmunity, with TNFR1 playing roles in CNS inflammation and demyelination and TNFR2 apparently acting to limit pathology, possibly by elimination of autoreactive CD4⁺ T cells and macrophages and/or by playing roles in remyelination.

TRAPS: a genetically defined heterogeneous entity

TRAPS is an autosomal-dominant (AD) autoinflammatory disorder caused by heterozygous mutations in the *TNFRSF1A* gene [25,26]. It belongs to the group of 'hereditary recurrent fever syndromes' [25]. It is characterized by recurrent, unprovoked, self-limiting attacks of fever, abdominal pain, myalgia, rash, arthralgia/arthritis, rhinopharyngolaryngeal involvement and conjunctivitis/periorbital oedema. The severest complication of TRAPS is renal amyloidosis. TRAPS episodes can last from a few days to weeks (mean 21 days), and on average they recur every 5–6 weeks. Clinical symptoms can vary greatly from one individual to another and even from one episode to another. Mean age of onset is 10 years, but ranges from 22 weeks of

Table 1. Diagnostic indicators of traps (modified from Hull KM *et al.* [25]).

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| 1. Recurrent episodes of inflammatory symptoms spanning a period longer than 6 months (several symptoms will generally occur simultaneously) |
| 1.1 Fever |
| 1.2 Gastrointestinal involvement (diarrhoea, abdominal pain, etc.) |
| 1.3 Myalgia (migratory) |
| 1.4 Rash (erythematous macular rash occurs with myalgia) |
| 1.5 Conjunctivitis/periorbital oedema |
| 1.6 Chest pain |
| 1.7 Arthralgia or monoarticular synovitis |
| 1.8 Lymphadenopathy |
| 2. Episodes last more than 5 days on average (variable) |
| 3. Responsive to glucocorticosteroids but not colchicine |
| 4. Affected family members (may not always be present) |
| 5. Any ethnicity may be affected |

life to age 53 years [25]. Table 1 shows the diagnostic indicators of TRAPS as proposed by Hull *et al.* [25]. Many other symptoms may be part of the clinical phenotype of TRAPS, although less often (vasculitis, sacroileitis, splenomegaly, neurological manifestations, etc.) [26–28].

During TRAPS exacerbations, acute-phase reactants are elevated [25,26]. Autoantibodies are either not detected or are found at very low levels [25,26].

Inflammation responds to glucocorticoids but not to colchicine. The response to anti-TNF- α drugs is variable, and there are reports of response to anakinra (a recombinant IL-1 receptor antagonist) [25,29].

Genetics

To date, more than 60 mutations have been reported in association with TRAPS in coding and non-coding regions of the *TNFRSF1A* gene (for details, refer to the INFEVERS database <http://fmf.igh.cnrs.fr/ISSAID/infevers>) [30]. The majority of these mutations affect the extracellular domain of the receptor (Fig. 2), leading to modifications in ligand binding (CRD2) or alterations in ligand-independent receptor assembly and activation (CRD1) [11,31–33].

Two other rare variants in the gene coding sequence have been described that alter single amino acids and do not affect cysteine residues, P46L and R92Q. These variants have also been identified in asymptomatic relatives of an index case, in patients without family history (sporadic forms), in other inflammatory conditions and also infrequently in healthy populations (1–5% in the general population; P46L substitution is found in up to 10% of the West African population) [34–36]. The increased frequencies of these two substitutions in patients with TRAPS, as well as functional studies of *TNFRSF1A in vitro*, suggest that these are low-penetrance mutations rather than benign polymorphisms [34]. It is therefore possible that they could synergize with other

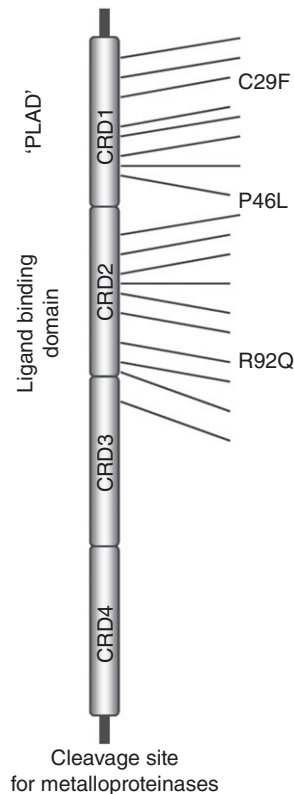


Fig. 2. Tumour necrosis factor receptor 1 (TNFR1) mutations in TNF receptor-associated periodic syndrome (TRAPS) [32]. The figure illustrates the ectodomain of the TNFR1 with the location of the TRAPS mutations, clustered mainly in cysteine-rich domains (CRD1 and CRD2). There are more than 60 known mutations. Only a few are shown in this diagram. R92Q is located at CRD2. PLAD: preligand assembly domain.

genetic-immune defects to cause a milder form of TRAPS with low penetrance [37].

Nevertheless, not all familial or sporadic cases of patients with clinical symptoms compatible with TRAPS have *TNFRSF1A* gene mutations, so there is still much to be learned about the genetics of these diseases.

There are no phenotype–genotype correlations [25], with two exceptions: (i) mutations in cysteine residues have a higher clinical penetrance than non-cysteine residues substitutions (93% *versus* 82%) and they increase the probability of developing amyloidosis (24% *versus* 2%) [25,34,38,39]; and (ii) patients with R92Q and P46L mutations have more heterogeneous and benign manifestations of the condition. *R92Q mutation and TRAPS.* This substitution is located in the CRD2 (Fig. 2). It is considered to be a low-penetrance mutation [34] and the most frequent genetic defect observed in TRAPS patients. Onset occurs at a later age and presentation in adulthood is fairly common. Episodes are shorter-lasting, the rash is less typical, abdominal pain is less common, and in general these individuals require less steroid or immunosuppressive therapy. The majority of patients

with this mutation are sporadic cases [34,35,40]. This mutation was observed in 3.3% of 274 independent chromosomes in individuals with clinical symptoms suggestive of TRAPS (1% in control chromosomes in an Irish and North American population of European ancestry) [34].

From genetics to pathogenesis

Altered receptor cleavage ('shedding hypothesis') was considered initially to be a key process in this disease [31], allowing repeated stimulation of membrane receptors and a diminished pool of potentially inhibitory soluble receptors. However, defective shedding has not been demonstrated in many *TNFRSF1A* mutations associated with TRAPS, including the R92Q mutation [34].

The mutations affecting cysteine residues (structural mutations) [41] cause changes in the three-dimensional structure of the TNFR1 ectodomain, leading to accumulation of the mutated receptor in the endoplasmic reticulum [42]. The mutant receptors self-interact and trigger an inflammatory response [38,41,43]. They are also unable to activate the TNF- α -induced NF- κ B transcription pathway, which leads to a reduction in apoptosis [44] and prolonged survival of the activated inflammatory cells, contributing to the inflammatory phenotype of the disease [45,46].

Conversely, the so-called non-structural variants, with fairly conservative amino acid substitutions – including the R92Q mutation – have shown normal behaviour in terms of receptor trafficking and TNF- α binding ability on the cell surface [38,43]. It has been observed that neutrophils of patients carrying this mutation are resistant to TNF- α -induced apoptosis [44]; defective shedding is not found in all cases, and only subtle abnormalities have been described in surface receptor expression in the endothelial cell line [26,34]. Much work is under way to try to understand the pathophysiology of the disease in patients with this substitution. It has been suggested that the R92Q mutation does not cause the disease directly, but acts in synergy with other genetic or environmental factors, triggering the auto-inflammatory phenotype [44].

R92Q mutation and diseases other than TRAPS

The R92Q mutation has also been associated with clinical phenotypes other than TRAPS, such as early arthritis [34], Behçet's disease with extracranial deep vein thrombosis [47], atherosclerosis [48] or recurrent pericarditis [49]. These findings support the known fact that different inflammatory diseases share genetic susceptibility loci.

Thus, unlike the causal effect of high-penetrance mutations that behave like specific monogenic disorders, there are other milder, lower-penetrance mutations, such as the R92Q mutation, which may have a broader influence on susceptibility to inflammation or may contribute to amplifying inflammatory responses in multi-factorial diseases [25].

Considering the hypothesis that complex genetic diseases arise from a combination of mutations or common low-penetrance polymorphisms [50], R92Q mutation carriers would be more likely to develop a wide range of inflammatory and autoimmune diseases, and the final phenotypic expression may depend possibly on other genetic or environmental modifying factors, as yet unidentified [51].

TRAPS and neurological disease

There are reports of patients with TRAPS who have CNS involvement (CNS-TRAPS) in the form of headache, meningitis, encephalitis, psychosis, memory impairment, behavioural changes and inflammatory symptoms (optic neuritis/papillitis, posterior fossa involvement, etc.) [31,40,52–57]. In three of these cases abnormalities were found in neuroimaging studies with brain magnetic resonance imaging (MRI) [54–57], and in two of them they were also found through brain biopsy [54,55,57]. A 38-year-old male with clinical symptoms of TRAPS and the *TNFRSF1A* C55R mutation presented with posterior fossa symptoms and had a single gadolinium-enhancing lesion in the cerebellum that contained inflammatory cells, but showed no demyelination on histopathological examination. Furthermore, oligoclonal bands were not found in CSF. The patient improved with an anti-TNF agent (etanercept) [54,55]. In two other patients, one with the T50K mutation [56] and the other with the R92Q substitution [57], disease progression, brain MRI and CSF findings were consistent with MS. A brain biopsy performed in one case showed both inflammation and demyelination [57].

It is not known how many TRAPS patients have symptoms suggestive of CNS inflammatory disease. There is some debate as to whether the CNS disease in these cases is, in fact, CNS-TRAPS (neurological inflammatory symptoms that form part of the clinical phenotype of TRAPS) or whether TRAPS and MS co-exist in some patients, either by coincidence or because there is some genetic or pathophysiological connection between both diseases [57–59]. From a pathogenic viewpoint, increased TNF signalling through the TNFR1 receptor – which is typical in TRAPS – may also be involved in the CNS inflammatory symptoms in these patients.

Inflammatory CNS disease has also been reported in other autoinflammatory syndromes, such as familial Mediterranean fever (FMF). In a recent study conducted in an Israeli population, the frequency of MS in FMF patients was reported to be two times higher than expected in the general population [60]. However, the opposite situation has also been reported and Akman-Demir *et al.*, for instance, observed a fourfold higher prevalence of FMF among patients with definite MS compared with the general Turkish population [61]. Distinguishing between CNS-TRAPS and MS plus TRAPS is not only important from a nosological standpoint, but also because the therapeutic approach differs

and is actually contradictory. The clinical presentation of MS and TRAPS may be similar, both disorders manifesting with variable and episodic symptoms. MS is usually defined according to the McDonald criteria (2010 revisions) [62], which require dissemination in time and space clinically and on MRI, and exclusion of other possible causes of CNS disease; typical clinical episodes involve the optic nerve, brainstem and/or spinal cord, and it is often difficult to make the diagnosis in the first event, despite the use of paraclinical tests. Regarding CNS-TRAPS, the diagnosis is not so well established due to the small number of patients published to date, their short-term follow-up and the inherent difficulty in obtaining brain biopsies/autopsies. Therefore, a careful investigation, including disease course, laboratory and CSF examinations, evoked potentials and cerebral and spinal MRI, are the main tools to help us distinguish between these two entities. In fact, many R92Q mutation carriers with different neuropsychiatric manifestations did not fulfil the diagnostic criteria for MS.

In the case where CNS involvement is part of TRAPS, anti-TNF agents may be a therapeutic option [54], but if an individual has TRAPS and MS, these drugs would be contraindicated for treating TRAPS symptoms because they can worsen MS clinical progression [63,64].

TRAPS, R92Q and MS

In two cohorts of unselected samples of patients with MS or clinically isolated syndromes, the R92Q mutation was observed in 4.66% [65] and 5.5% [66] of patients *versus* 2.95% and 1.5%, respectively, in Caucasian control populations. Differences were not statistically significant, although a trend towards association was observed in both studies [65,66].

The carrier frequency of the R92Q mutation in a selected group of MS patients with additional TRAPS-like symptoms was 13%, a frequency higher than those reported for other groups of patients [67] (the incidence of the R92Q mutation was found to be approximately 5% in patients with early arthritis [34] and also in patients with a clinically suspected inherited autoinflammatory syndrome [26]). This high frequency in a selected group of MS patients could be explained partially because the selection of patients for the genetic study was based on family history and on a clinical picture, which only required the presence of recurrent attacks with at least two autoinflammatory symptoms of those listed in Table 1 (sections 1.1–1.8), fever not being essential.

The majority of patients with MS, TRAPS and the R92Q mutation developed oligosymptomatic and late forms of TRAPS, with combinations of the following symptoms: arthralgia/arthritis, myalgias, urticarial rashes, pharyngitis and fatigue; however, fever and acute-phase reactants were not always present [66,67]. Therefore, if we use less rigid diagnostic criteria, it is possible that the prevalence of TRAPS is higher than considered hitherto. Nevertheless, and

although the R92Q mutation is the most common mutation associated with TRAPS, other mutations in the *TNFRSF1A* gene or mutations in different genes may be responsible for TRAPS or TRAPS-like symptoms in any population group. In almost all these patients, the start of the systemic symptoms of inflammation preceded the symptoms of MS, thus contributing to the diagnostic difficulty of a first inflammatory process of the CNS in a patient with TRAPS (CNS-TRAPS versus TRAPS plus MS) and to the choice of a suitable treatment which does not cause adverse reactions.

In a German cohort [67], the patients with MS, clinical TRAPS and the R92Q mutation presented adverse reactions to the use of disease-modifying drugs (interferons, glatiramer acetate, natalizumab or mitoxantrone) with great frequency; in addition, the reactions were more severe than normal, in many cases forcing the withdrawal of treatment. In contrast, this was not seen in an Argentine cohort [66].

The clinical course of MS in these patients with TRAPS and the R92Q mutation was otherwise considered normal [66,67], except for the presence of intense fatigue [67] and for the greater frequency of clinical brainstem symptoms (frequently with facial palsy) as the starting point of the MS (15% compared to 5% in other small case series of MS patients [66,68]). These data, together with the results of a recent GWA study [69], have allowed us to reach the conclusion that the R92Q mutation does not have an influence on the general clinical characteristics of the disease [66], nor on its severity [measured by the Multiple Sclerosis Severity Scale (MSSS)] [69] or on the therapeutic response [66].

Conversely, the penetrance of TRAPS in patients with MS and the R92Q mutation is similar to that found for patients without MS in the general population (approximately 82%) [33,35,36]. In the Argentine cohort, this penetrance was 80% [68]. In the German cohort it was somewhat higher, and 88% of family members of patients with MS and clinical TRAPS who were carriers of the mutation had clinical symptoms of TRAPS [67].

It is not known how the R92Q mutation can cause disease and how it can fit into the pathogenesis of MS. Further studies are required to define the functionally relevant variants in the identified region and to investigate their effects at molecular and cellular level.

Conclusions

MS has a strong genetic component. Most of its risk variants are located at or near genes with central immunological functions also associated with other autoimmune diseases [3]. Many of the immunological effects of TNF in MS are thought to be delivered through the TNFR1. Thus, there is a biological plausibility for this association.

Variants within previously confirmed MS susceptibility loci do not appear to influence severity as measured by the MSSS [69], and this is also the case for the R92Q mutation; nor have clinical studies made it possible to demonstrate that

this mutation modifies the clinical course or therapeutic response in MS [67].

The R92Q substitution is the most frequent mutation identified in patients suffering from TRAPS. Some clinical observations have identified MS patients carrying the R92Q mutation who have additional late onset and milder forms of TRAPS [65–67]. Thus, this disorder should be considered in MS patients who report symptoms such as arthralgias/arthritis, myalgias, urticarial rash and severe fatigue [65]. Nevertheless, the clinical course and severity of the MS were no different from those of patients without clinical TRAPS.

The TRAPS phenotype is associated with multiple mutations in *TNFRSF1A* gene and different clinical phenotypes have been associated with the presence of the R92Q mutation. Given the rare nature, autosomal-dominant mode of inheritance and the varied clinical presentation of TRAPS, it is difficult to conclude that TRAPS itself is involved directly in the great majority of MS cases. The co-existence of TRAPS and MS is possible, but is likely to be a rare occurrence.

As things stand today, we do not know the clinical and/or therapeutic implications that the presence of this mutation may have on patients with MS. Further studies are warranted to clarify its importance and its usefulness as a marker of some aspect of this complex disease.

Disclosure

The authors have no disclosures in relation to the article.

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