Inflammation, Vol. 36, No. 3, June 2013 (© 2012)
DOI: 10.1007/s10753-012-9585-8

Is the CCR5 Δ 32 Mutation Associated with Immune System-Related Diseases?

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Abstract—Hypersensitivity and autoimmunity are the main features of immune system-related diseases such as type 2 diabetes (T2D), multiple sclerosis (MS), and asthma. It has been established that chemokines play key roles in the activation and regulation of immune cell migration which is important in the pathogenesis of the diseases mentioned. CC chemokines receptor 5 or CCR5 is a receptor for RANTES, MIP-1α, and MIP-1β and is expressed by several immune cells including NK cells, T lymphocytes, and macrophages. It plays key roles in the regulation of migration and activation of the immune cells during immune responses against microbe and self-antigens during autoimmunity and hypersensitivity disorders. Therefore, any alteration in the sequence of CCR5 gene or in its expression could be associated with immune system-related diseases. Previous studies revealed that a 32-base pair deletion (Δ 32) in exon 1 of the CCR5 gene led to downregulation of the gene. Previous studies demonstrated that not only CCR5 expression was altered in autoimmune and hypersensitivity disorders, but also that the mutation is associated with the diseases. This review addresses the recent information regarding the association of the CCR5 Δ 32 mutation in immune-related diseases including T2D with and without nephropathy, MS, and asthma. Based on the collected data, it seems that the CCR5 Δ 32 mutation can be considered as a risk factor for MS, but not asthma and T2D with and without nephropathy.

KEY WORDS: CCR5 Δ 32 mutation; type 2 diabetes; nephropathy; multiple sclerosis; asthma.

INTRODUCTION

Immune responses are the main defense against tumors and infectious diseases [1, 2]. Uncontrolled immune responses against self and foreign antigens are described as autoimmunity and hypersensitivity, respectively [3]. It has been shown that chemokines play key roles in the regulation of immune responses which are important in the pathogenesis of both autoimmunity- and hypersensitivity-based diseases [4]. Chemokine receptor 5 (CCR5) is located on the short arm of chromosome 3 (3p21.31), which is a locus for multiple chemokine receptor genes [5]. CCR5 is a receptor for the MIP-1α/CCL3, MIP-1β/CCL4, and RANTES/CCL5 chemokines and is expressed by several immune cells including NK cells, T lymphocytes, macrophages, and immature dendritic cells and is upregulated by proinflammatory cytokines [6, 7] as well as nuclear factor kappa-light-chain-enhancer (NF-κB) [8]. It can also be regulated by the cAMP response element-binding protein pathway [9]. CCR5 belongs to the heterotrimeric G protein family and can inhibit cAMP production, while stimulating Ca^{2+} release and promote activation of the PI3-kinase, mitogen-activated protein (MAP) kinases, and other

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tyrosine kinase cascades including FAK and Pyk2, which play important roles in cell movement and migration [10]. CCL3, 4, and 5 also activate the three main members of the MAP kinase family (ERK1/2, p38, and SAPK/JNK), Rho GTPase, and protein kinase B (PKB) *via* CCR5, which are proposed to be crucial for T cell proliferation and expression of inflammatory cytokines [11]. Activation of JAK/STAT pathways by CCL5/CCR5 interactions was also reported by Wong *et al.* [12]. Therefore, it appears that CCR5 plays a key role in immune responses ranging from infiltration to activation of immune cells (Fig. 1) [13]. It has been established that the deletion of 32 nucleotides in exon 1 of the CCR5 gene (known as the Δ 32 mutation) leads to decreased expression and dysfunction of CCR5 receptor [13-16]. Interestingly, recent evidence demonstrated that this mutation is polymorphic in different ethnic and geographical populations [17, 18]. Furthermore, it has been documented that CCR5 acts as a co-receptor for HIV-1 and is critical for its transmission [19]. Interestingly, previous studies demonstrated that the CCR5 Δ 32 mutation can affect infection of T lymphocytes by HIV-1 [20]. In contrast to HIV infection, CCR5 and its known mutation play different roles in different immune-related diseases, including multiple sclerosis (MS), type 2 diabetes (T2D), and asthma [21-23].

Furthermore, the exact role of the Δ 32 mutation is confounded by factors such as a patient's immunological status and genetic and epigenetic factors. Individually or combined, all these factors can alter the response by a patient to the different immune system-related diseases. This is further confounded by ethnic and geographical populations which may carry polymorphisms in the genes that interact with CCR Δ 32, thereby subtly changing the biological activity of the protein. Evaluating the association of the CCR5 Δ 32 mutation to immunological disorders or disease, within a specific population, may avail us to the first clues that will unravel the function of the gene and its mutation. It has been documented that the CCR5 Δ 32 mutation leads to a much greater change in expression of the receptor in the homozygotic form when it is compared to the heterozygotic form. The immune cells of affected CCR5 individuals (carrying the CCR5 Δ 32 mutation) are unable to elicit a complete response to CCL3, 4, and 5. Therefore, it seems that CCR5 Δ 32 mutation may affect an individual's immune responses; hence, evaluation of the mutation can be rationalized to better understand immune-related disease mechanisms.

It has also been demonstrated that there is a positive correlation between asthma [24, 25], MS [26-28], T2D without nephropathy [29-32], and T2D with nephropathy [32, 33] with immune system factors. Therefore, it is plausible that genetic variations within CCR5 may be correlated to T2D with and without nephropathy, MS, and asthma. On the other hand, previous studies demonstrated that the epidemiology of the CCR5 Δ 32 mutation is different among ethnic populations. The rate of CCR5 Δ 32 mutations is high among the northern European population, while its value is low among the southeastern Asian population; hence, evaluation of the relation between the CCR5 Δ 32 mutation and immune-related diseases may be more important in some ethnic populations and less in others. Therefore, the aim of this review was to collate the current information regarding the correlation between the CCR5 Δ 32 mutation with these diseases. Demographic data and supporting information regarding the reported studies are summarized in Table 1.

THE STATUS OF THE CCR5 Δ 32 MUTATION IN TYPE 2 DIABETES

It has been well documented that parameters that influence or regulate the immune system can be associated with T2D and its complications [32-36]. Previous studies have revealed that adiponectin can upregulate expression of CCL3, 4, and 5, while down-regulating surface CCR5 expression [37]. In addition, previous studies demonstrated that T2D alters CCR5 expression on the immune cells [38, 39]. The expression of adiponectin is changed in T2D pathology, and the data suggest that the expression of CCR5 is suboptimal in these patients. The presence of the CCR5 Δ 32 mutation may exacerbate disease progression in T2D patients carrying this mutation. Additionally, infiltration of immune cells within the pancreas has been documented in T2D [37]. Some studies proposed that CCR5 can be involved in the recruitment of immune cells to the pancreas; hence, it seems that the genetic and epigenetic factors that alter CCR5 expression, including the CCR5 Δ 32 mutation, can be considered as an important risk factor in the pathogenesis of T2D and its complications including nephropathy. Our previous findings demonstrated that the CCR5 Δ 32 mutation was not prevalent in either southeast Iranian T2D patients without nephropathy or T2D patients with nephropathy [36]. The control group in our study also carried a very low prevalence of this mutation (0.66 %) [36]. In agreement with our previous results, Kalev and

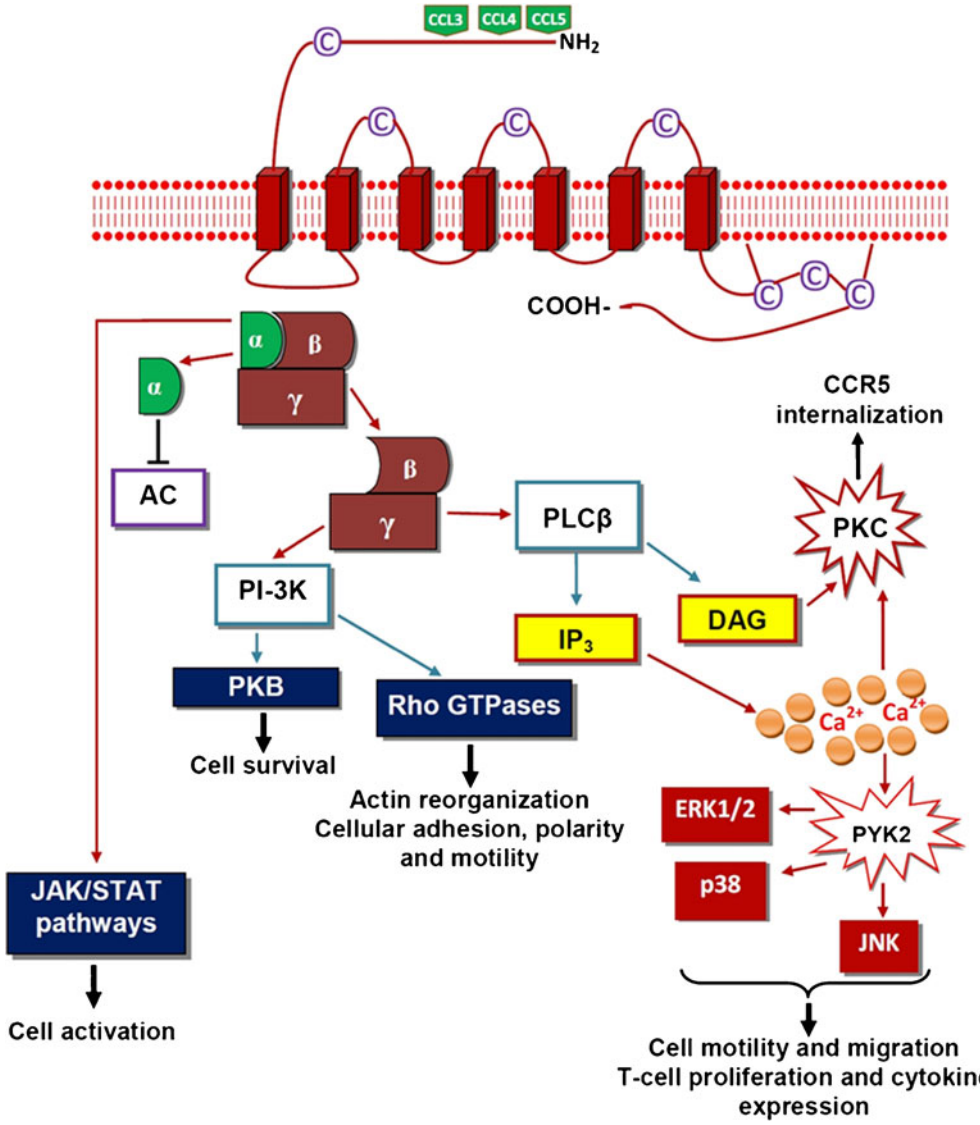

Fig. 1. The figure illustrates the CCR5 receptor structure and its signaling pathways. CCR5 is shown as cellular receptor with seven transmembrane domains. CCL3, 4, and 5 bind to the extracellular domain of CCR5 and lead to the activation of intracellular pathways. The conserved amino acids (DRYLAVHA) within the first intracellular loop are essential for interactions with G proteins (α, β, and γ). The CCR5/ligand interaction induces G protein dissociation and consequently the activation of intracellular pathways including JAK/STATs, phospholipase Cβ (*PLCβ*), phosphoinositide 3-kinase (*PI-3K*), diacylglycerol (*DAG*), triphosphoinositol (IP_3), calcium ions (Ca^{2+}), protein kinase C (*PKC*), proline-rich tyrosine kinase 2 (*PYK2*), extracellular signal-regulated kinase (*ERK1/2*), p38 and c-Jun N-terminal kinase (*JNK*), protein kinase B (*PKB*), Rho GTPase, and adenylyl cyclase (*AC*). Adapted from Sorce *et al.* [11].

colleagues reported that there was no association between the CCR5 Δ 32 mutation and native Estonian T2D patients [40]. Interestingly, Muntinghe *et al.* reported that the CCR5 Δ 32 mutation is associated with better survival in T2D patients [21]. They concluded that the protective potential of pharmacological blockage of CCR5 can be considered as a therapeutic method in type 2 diabetic patients [21]. Ahluvalia *et al.* revealed that homozygotic CCR5 Δ 32 mutations (Δ32/Δ32) were more prevalent in a North Indian nephropathic T2D group [41]. These results are in contrast with the Bogdanski *et al.* study [39] who demonstrated that CCR5 expression is increased on immune cells in T2D [39]. Due to the fact that CCR5 Δ 32 mutation leads to

Table 1. A summary of the literature reviewed in relation to the reported immune-related diseases

Diseases	Country	Racial information	Sample size	Sex M/F	CCR5 Δ 32 genotype	Ref
Type 2 diabetes	Iran	Fars	200 patients and 300 controls	Female, 301; male, 199	Δ32/Δ32; 0 % in patients and 0 % in healthy controls Δ32/wt; 0 % in patients and 0.66 % in healthy controls	[36]
	Estonia	Estonian	111 patients and 504 healthy controls	ND	Δ32/Δ32; 0 % in patients and 3.2 % in healthy controls Δ32/wt; 21.6 % in patients and 23.2 % in healthy controls	[40]
	USA	American	798 total sample	ND	Δ32/Δ32; 0.8 % in patients Δ32/wt; 18.1 % in patients	[21]
	India	Indian	Type 2 diabetes without nephropathy (n=255) and type 2 diabetes with nephropathy (n=240)	Males to females 94/146 with nephropathy. Males to females 105/150 without nephropathy	Δ32/Δ32; 37 % in type 2 diabetes without nephropathy and 21 % in type 2 diabetes with nephropathy	[41]
Multiple sclerosis	Iran	Fars	100 patients and 300 healthy controls	Female, 180; male, 120	Δ32/Δ32; 0 % in patients and 0 % in healthy controls Δ32/wt; 0 % in patients and 0.66 % in healthy controls	[47]
	Australia	Australian	120 patients and 168 healthy controls	ND	Δ32/Δ32; 0.1125 % in patients and 0.0921 % in healthy controls	[48]
	USA	American	221 total sample	Female, 157; male, 64	Δ32/Δ32; 0.9 % in patients Δ32/wt; 23.5 % in patients	[49]
	Russia	Russian	219 patients and 354 healthy controls	Female, 344; male, 229	Δ32 positive patients carrying DR4, 34.7 %[a] Δ32 positive controls carrying DR4, 2.1 %	[56]
	Germany	German	243 patients	Female, 164; male, 79	Δ32/Δ32; 14 % in patients Δ32/wt; 67 % in patients.	[51]
	USA	American	132	Female, 85; male, 47	Δ32/Δ32; 19.7 % in patients and 17.1 % in controls 90.5 % of patients with Δ32/wt genotype survived more than 21 years, while its value for Δ32/Δ32 genotype was 9.5 %	[55]
	Iran	Fars	254 patients and 380 healthy controls	ND	Δ32/Δ32; 15 % in patients and 8 % in healthy controls Δ32/wt; 6 % in patients and 13 % in healthy controls	[54]
	Denmark	Danish	80 total sample	Females, 54; males, 26	Δ32/Δ32; 1.5 % in patients with possible onset symptoms of multiple sclerosis and 0 % in patients with clinically definite multiple sclerosis and 1.3 % in controls Δ32/wt; 22 % in patients with possible	[22]

					onset symptoms of multiple sclerosis and 21 % in patients with clinically definite multiple sclerosis and 26 % in controls	
	Finland	Finish	208 total sample	ND	Δ32/Δ32; 6.7 % in patients and 0.8 % in controls Δ32/wt; 13.4 % in patients and 25.2 % in controls	[58]
	Denmark	Danish	109 patient and 105 healthy control	ND	Δ32/Δ32; 1 % in patients and 2 % in controls Δ32/wt; 19 % in patients and 22 % in controls	[52]
	Italy	Italian	180 patients and 213 in healthy control	Females, 49; males, 131	Δ32/Δ32; 6 % in patients and 6 % in controls	[57]
	Hungry	Hungrian	118 total sample	ND	Δ32/Δ32; 3.4 % in patients and 1.7 % in controls Δ32/wt; 16.1 % in patients and 19.1 % in controls	[65]
Asthma	Canada	British Columbia	294 total sample	ND	Δ32/Δ32; 1 % in patients with mild-to-moderate asthma and 3 % in fatal or near-fatal asthmatic patients Δ32/wt; 24 % in patients with mild-to-moderate asthma and 24 % in fatal or near-fatal asthmatic patients	[59]
	United Kingdom	British	77 total sample	ND	Δ32/wt; 9.1 % in patients Δ32/Δ32; 0 % in patients	[67]
	Hungary	Hungarian	416 total sample	ND	Δ32/Δ32; 1.7 % in patients and 1.4 % in controls Δ32/wt; 15.7 % in patients and 19.3 % in controls	[64]
	Iran	Fars	162 patients and 200 healthy controls	ND	Δ32/Δ32; 0 % in asthmatic patients and 0 % in controls Δ32/wt; 0 % in patients and 1.5 % in controls	[62]
	Australia and UK	Australian and England	413 total sample	ND	Δ32/Δ32; 1.2 % in total population Δ32/wt; 24.4 % in total population	[63]
	English	British	46 patients and 109 healthy controls	ND	Δ32/Δ32; 0 % in asthma and 3 % in controls Δ32/wt; 17 % in asthma 35 % in controls	[66]
	Germany	German	39 patients and 167 healthy controls	ND	Δ32/Δ32; 0 % in asthma and 1 % in controls Δ32/wt; 13 % in asthma and 17 % in controls	[66]
	UK	Nottingham	415 total sample	ND	Δ32/Δ32; 0 % in patients and 1.9 % in healthy controls Δ32/wt; 11.2 % in patients and 24.3 % in healthy controls	[68]

[a] DR4 is the HLA-DR4 [56]

decrease expression of CCR5, it could be assumed that the patients that were evaluated in the Bogdanski *et al.* study did not carry the CCR5 Δ 32 mutation. To the best of our knowledge, there are only a limited number of studies regarding other polymorphisms within the CCR5 gene among T2D patients; however, several studies have demonstrated that polymorphisms within other regions of the CCR5 gene are significantly associated with T2D [5, 8, 9]. In summary, an increased expression of CCR5 on immune cells of T2D patients with and without nephropathy was reported by several researchers [38, 39]. It seems that the CCR5 Δ 32 mutation cannot be considered as a potential risk factor for initiating T2D in select populations, but there may be a relation between other polymorphisms with T2D in patients with and without nephropathy; however, this can only be validated by more studies. It should also be noted that the discrepancy between reports may be related to the different ethnicity and geographical backgrounds of the studied populations.

THE STATUS OF THE CCR5 Δ 32 MUTATION IN MULTIPLE SCLEROSIS

Multiple sclerosis is considered a complex immune system-related disorder [28, 42] and the most prevalent symptoms of MS are the loss of myelin and inflammation of the central nervous system [43], but the mechanisms of its pathology have yet to be completely clarified [44]. It has been established that immune cells, including T lymphocytes, NK cells, and dendritic cells, infiltrate and cause inflammation of the central nervous system (CNS) in MS patients [27, 45]. CCL3, 4, and 5 chemokines are the main chemotactic agents that induce recruitment of the immune cells to the CNS *via* interaction with their corresponded receptor (CCR5) [46]. Based on the important role of CCR5 in recruitment of the immune cells to the CNS in MS patients, we have collected reports regarding the prevalence of CCR5 Δ 32 mutations among MS patients. Our research team evaluated the CCR5 Δ 32 mutation in Iranian patients previously and found that this mutation was not prevalent among southeast Iranian MS patients [47]. Similar results were reported by Bennets *et al.* [48]. They revealed that the CCR5 Δ 32 mutation is not associated with MS in an Australian population [48]. Additionally, investigators from the USA and Ireland also demonstrated that CCR5 Δ 32 mutations are not related to MS [49, 50]. In parallel with these results, Haase *et al.* reported that CCR5 Δ 32 mutations are not associated with MS in Germany [51]. Sellebjerg *et al.* revealed that 22 and 1.5 % of cases with possible onset symptoms of multiple sclerosis carried CCR5 Δ 32 mutations in heterozygotic (wild-type (wt)/Δ32) and homozygotic (Δ32/Δ32) forms, respectively [22]. Interestingly, they have shown that in cases with clinically definite multiple sclerosis, the frequencies of heterozygotic and homozygotic (Δ32/Δ32) forms were 21 and 0 %, respectively. They also revealed that the CCR5 Δ 32 mutation is not related to MS in DRB1 1501-negative and DRB1 1501-positive cases [22]. In a subsequent paper, Sellebjerg *et al.* also revealed that 1 % of MS patients and 2 % of controls carried CCR5 Δ 32 mutation in the homozygotic (Δ32/Δ32) state and that 19 % of MS patients and 22 % of controls carry heterozygotic alleles while 80 % of patients and 76 % of controls carried wild-type CCR5 [52]. Their original results from 2000 demonstrated that the differences were not significant between the study groups [22] and the authors reconfirmed their results by repeating their study in 2002 [53]. However, some publications have demonstrated that the CCR5 Δ 32 mutation may affect MS. For instance, a conflicting report by Shahbazi *et al.* indicated high a prevalence of this mutation in MS patients from northeast of Iran [54]. Although Shahbazi and his colleagues evaluated patients from the Iranian population, the ethnic background of the subjects differed from our previous studied population. Our study group focused on Fars, while the patients studied by Shahbazi *et al.* were Turk; hence, the discrepancy may be related to different population genetics. The association of the CCR5 Δ 32 mutation with short patient survival was also reported by Gade and colleagues [55]. A study on HLA-DR4-positive Russian populations revealed that the CCR5 Δ 32 mutation could be associated with MS [56]. D'Angelo *et al.* reported that the presence of the CCR5 Δ 32 mutation is significantly frequent in MS patients with an expanded disability status scale score [57]. Pulkkinen *et al.* compared the frequencies of CCR5 genotypes and its relation to CCR5 mRNA in peripheral blood mononuclear cells [58]. In all MS patients, the Δ32/Δ32 genotype was found in 6.7 % of patients, while it was present in only 0.8 % of the controls [58]. Interestingly, they reported that the Δ32/Δ32 genotype was increased among primary progressive MS patients, in comparison to other MS subtypes and controls [58].

Therefore, it seems that there is no consensus regarding the association of the CCR5 Δ 32 mutation with MS. Once again, the discrepancy in the reports may

reflect the differences in the studied populations in terms of genetic background as well as their exposure to environmental factors. Although it has been revealed that CCR5 expression is significantly increased in MS patients [46] it would appear that, in addition to the CCR5 Δ 32 mutation, there are other polymorphisms or haplotypes as well as other genetic and epigenetic factors that may be important for CCR5 expression in MS patients.

THE STATUS OF THE CCR5 Δ 32 MUTATION IN ASTHMA

Asthma is an airway obstructive respiratory disease caused by acute and chronic bronchial inflammation [59]. The main characteristics that are associated with the asthma phenotype are bronchial hyperresponsiveness, increased total serum IgE levels, and infiltration of eosinophils and Th2 lymphocytes [60]. Due to the fact that a hyperactive immune response is seen in asthma [61], it is reasonable to assess the factors that regulate the immune system to determine if they can influence asthma pathogenesis [62]. Previous studies revealed that Th2 lymphocytes infiltrate the inflamed bronchus *via* responses initiated by CCR5 and its ligands (CCL3, 4, and 5) [23]. Interestingly, increased expression of the chemokines has been reported by our research team (unpublished data); hence, it seems that CCR5 and its related Δ 32 mutation can be associated with asthma. Similar to MS and T2D, our previous studies demonstrated that CCR5 Δ 32 mutations are rare in southeast Iranian asthmatic patients and, interestingly, none of the asthmatic patients that we studied carried the CCR5 Δ 32 mutation [62]. Based on these results, it appears that CCR5 Δ 32 mutations are not related to asthma in the southeastern Iranian population [62].

Similar to these findings, Mitchell and colleagues demonstrated that there were no associations between the CCR5 Δ 32 mutations in atopy or asthma [63]. Szalai *et al.* were also unable to find the mutation in asthmatic patients [64]. Sandford *et al.* also reported that the CCR5 Δ 32 mutation was not significantly related to asthma and its severity in the UK population [59]. They revealed that of 87 mild-to-moderate asthma patients, 75 % carried homozygous wild-type, 24 % heterozygous, and 1 % homozygous CCR5 Δ 32 mutations. They also showed that 73 % of fatal or near-fatal asthmatic patients carried homozygous wild-type, 24 % heterozygous, and 3 % homozygous CCR5 Δ 32 mutations [59]. Nagy *et al.* showed that among 118 asthmatic children, 80.5 % carried the wt allele, 16.1 % heterozygous (Δ32/wt), and 3.4 % were homozygous for the CCR5 Δ 32 mutation [65]. They also showed that of 145 non-asthmatic children with atopy, 80.0 % carried CCR5 wt, 17.9 % heterozygous (Δ32/wt), and 2.1 % homozygous alleles [65]. Additionally, they have shown that 79.2, 19.1, and 1.7 % of children without atopy or asthma carried CCR5 wt, heterozygous (Δ32/wt), and homozygous alleles, respectively [65]. Therefore, it is likely that, similar to our study population, the CCR5 Δ 32 mutation was not associated with atopy and asthma in UK population [65]. Similarly, McGinnis *et al.* showed that in English patients diagnosed as asthma, 46 (83 %) had CCR5 wt, 17 % carried the heterozygous genotype (Δ32/wt), and no patients were homozygous for CCR5 Δ 32 mutations [66]. They also reported that the non-asthmatic group (n=109) carried 62, 35, and 3 % CCR5 wt, heterozygous (Δ32/wt), and homozygous CCR5 Δ 32 mutations, respectively [66]. The authors also revealed that the CCR5 Δ 32 mutation was not associated with asthma in the Germany population [66]. These results were confirmed in a study by Srivastava *et al.*, which was carried out on the British population [67]. They reported that among 77 children asthmatic samples, 70 cases (90.9 %) carried CCR5 wt/wt, 7 (9.1 %) Δ32/wt, and 0 (0 %) were homozygous for the CCR5 Δ 32 mutation [67]. Their study on adult patients emerged with similar results [67]. In contrast to the mentioned studies, Hall *et al.* identified that there was a negative correlation between the CCR5 Δ 32 mutation and the development of asthma [68]. They proposed that CCR5 Δ 32 mutations are protective against asthma due to the reduced responsiveness to CCL3, CCL4, and CCL5, as a result of decreased CCR5 expression [68].

According to the studies surveyed here, it seems that there is no association between CCR5 Δ 32 mutations with asthma and it cannot be considered as a risk factor in all populations. It may be a candidate for some populations carrying specific genetic backgrounds such as those patients from Northern Europe, an endemic region for the CCR5 Δ 32 mutation.

CONCLUSION

The CCR5 Δ 32 mutation was not associated with MS patients in our studies and those of several other groups. However, there are a few reports regarding its

correlation with MS; therefore, it may be concluded that this mutation could be associated with MS, but this needs to be evaluated with more studies in endemic regions, especially the northern region of Europe. From the data of the combined reports on T2D (with and without nephropathy) as well as asthma, it can be concluded that CCR5 Δ 32 mutations cannot be considered as a risk factor for these diseases. Potentially, other genetic and epigenetic factors may lead to an increase in CCR5 expression on the immune cells of T2D patients (both with and without nephropathy) as well as asthma. However, there is a lack of information regarding the presence of other polymorphisms and their roles in regulating CCR5 expression. The discrepancies between the reported studies may be due to differences in the evaluated populations that originated from varying ethnic groups with different genetic backgrounds. CCR5/ligand interactions lead to immune cell survival, activation, cellular adhesion, and motility [11] (Fig. 1). Therefore, it is difficult to reconcile a model in which CCR5 Δ 32 mutations, which appear to downregulate CCR5 expression, could give rise to asthma and T2D which are inflammatory diseases. On the other hand, it seems that MS, which is an autoimmune disease, may be associated with the CCR5 Δ 32 mutation, especially in the populations where the mutation is prevalent (*i.e.*, Northern Europe). In these populations, the expression of chemokines may be perturbed as a result of the mutation and the subsequent downregulation of CCR5. Previous studies revealed that when expression of CCR5 is decreased, the expression levels of CCL3, 4, and 5 will be increased. Based on the fact that CCL3, 4, and 5 can use other receptors, including CCR1 and CCR3, it is possible that overexpression of the chemokines may lead to immune cell activation and migration leading to inflamed CNS in MS patients. Therefore, it seems that evaluating the expression of CXCR1 and CXCR3 as well as CCL3, 4, and 5 should be considered in future studies of MS patients. Finally, due to the fact that chemokines and their receptors form a complex regulatory network, it will be important to study the presence of polymorphisms within the regulatory regions of genes of the inflammatory and anti-inflammatory chemokines and their related receptors before the complicated multigenic aspects of these diseases can be resolved.

ACKNOWLEDGMENTS

This project was supported by a grant from the Rafsanjan University of Medical Sciences.

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