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Research Article

Significant Effects of *CCR5delta32* Polymorphism on Alzheimer'S Disease, Neurological Disorders, Cancer, Diabetes and Viral Infection in the Worldwide Population

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Abstract

The *CCR5delta32* allele is a mutation in the sequence encoding CCR5 that leads to a loss of expression of this chemokine receptor, normally expressed on immune cells. The *CCR5delta32* allele is known to provide protection against HIV and is involved in numerous diseases, including Alzheimer's disease. This study explored CCR5 involvement in different diseases by comparing *CCR5delta32* allele frequency to the overall number of registered deaths attributed to Alzheimer's disease and neurological disorders, cancer, diabetes and viral infection in the worldwide population. Accordingly, we revealed significant positive correlations between *CCR5delta32* allele frequency and Alzheimer's disease, numerous neurologic diseases and cancers but negative correlations between *CCR5delta32* allele frequency and diabetes and viral infection. Our results thus highlight the differential involvement of the CCR5 receptor in various diseases and its importance as a potential therapeutic target. Moreover, this study emphasizes the importance of delineating the involvement of CCR5 in complex diseases and deciphering the mechanism of its actions.

Introduction

C-C chemokine receptor 5 (CCR5), a seven transmembrane G protein-coupled receptor (GPCRs), is a cell surface protein belonging to the β-chemokine receptor family that binds chemokines [1]. It is the natural receptor of the C-C chemokine macrophage inflammatory proteins (MIP)-1 alpha (CCL3), MIP-1 beta (CCL4) and RANTES (regulated on activation, normal T cell expressed and secreted; CCL5) [2]. CCR5 is located on chromosome 3 and is presented on immune cells, as well as on microglia, astrocytes and neurons [3]. CCR5 mediates the transport of immune cells to inflammatory sites, including peripheral monocyte migration into the inflamed central nervous system, traversing the blood brain barrier (BBB) [4].

The *CCR5delta32* allele is a 32 bp deletion in the CCR5 gene which results in the loss of a post-translational phosphorylation site. As a result, CCR5 biogenesis is prematurely terminated in the endoplasmic reticulum, such that the protein is not expressed on the cell surface [5]. Individuals carrying the *CCR5delta32* allele were found to be less sensitive to HIV infection, with *CCR5delta32* homozygosity having been shown to protect against HIV due to its role in cell penetration as a co-receptor [6]. Strong selective pressure is thought to have applied in favor of the *CCR5delta32* allele [7]. Therefore, we hypothesized that this mutation might also play an important role in other viral infections. Accordingly, in late 2018, Jiankui He described genetically editing babies in whom CCR5 had been deleted for the purpose of protecting them from HIV infection [8]. In the present study, we examined the association between CCR5 and a variety of diseases, seeking to define the effects of CCR5 mutation from a broad perspective and highlight the implications of such mutation.

As CCR5 had been previously studied in the context of Alzheimer's disease (AD), with no clear conclusion been set,

depending on the studied model [9], we analyzed the correlation between *CCR5delta32* and AD and expanded this analysis to other neurological disorders. AD is a polygenic disease defined by the presence of amyloid plaques and neurofibrillary tangles (NFT) in neurons. Plaques are extracellular deposits of fibrils and amorphous aggregates of amyloid β-peptide (Aβ), while NFTs are intracellular fibrillar aggregates of the microtubule-associated protein tau, which exhibits hyperphosphorylation and oxidative modifications [10]. Loss of memory and impairment of related cognitive functions are the main features of AD, with neuronal damage eventually affecting basic bodily functions, leading to death [11]. Glial cells and neurons express CCR5 ligands, while CCR5 is up-regulated on reactive microglia associated with Aβ deposits in AD patients [12]. CCR5 and its ligands can contribute to the recruitment of microglia to Aβ deposits and are somehow involved in AD pathogenesis [4,12].

Various studies have suggested connections between AD and cancer [13,14] and have also identified diabetes as a risk factor for developing AD [15]. Taking these considerations together, we decided to examine the relationship of *CCR5delta32* and AD to cancer and diabetes. As such, we compared *CCR5delta32* allele frequency to the percent of deaths resulting from various diseases and found positive Spearman correlation coefficients (SCC) between *CCR5delta32* allele frequency and AD and many neurologic disorders and cancers. However, negative SCCs between *CCR5delta32* allele frequency and AD and viral infection and diabetes were found. Our results thus highlight CCR5 being differently involved in various diseases, in turn, suggesting new research directions.

Results

We hypothesized that the *CCR5delta32* allele is related to AD and they both are related to neurological disorders, cancer, diabetes and viral infection. As our data do not present normal distribution, we decided to perform SCC analysis to find correlations between the groups. When we explored differences in *CCR5delta32* allele frequency relative to the percent of registered deaths from AD worldwide in 2017, we found positive correlation between *CCR5delta32* allele frequency and AD (r=0.4839, p-value <0.0001;) (Table 1 & Figure 1). These results indicate that the presence of the *CCR5delta32* allele is correlated with a high risk for AD and that CCR5 may be involved in resistance to AD.

Table 1: *CCR5delta32* allele frequency and AD SCC correlation. Stars ("*") represents a p-value 330 summary, with the higher the number of stars, the higher the correlation.

Disease	CCR5 (Δ32) Percent				AD & dementias			
	SCC, r	P (two-tailed)	P value summary	Significant (alpha = 0.05)	SCC, r	P (two-tailed)	P value summary	Significant (alpha = 0.05)
CCR5 allele (Δ32) percent	-	-	-	-	0.4839	<0.0001	****	Yes
Neurological disorders								
AD & dementias	0.4839	<0.0001	****	Yes	-	-	-	-
Epilepsy	-0.2984	0.0195	*	Yes	-0.138	0.289	ns	No
Mental disorders	0.5693	<0.0001	****	Yes	0.6184	<0.0001	****	Yes
Motor neuron disease	0.7098	<0.0001	****	Yes	0.7095	<0.0001	****	Yes
Multiple sclerosis	0.7915	<0.0001	****	Yes	0.4591	0.0002	***	Yes
Neurological disorders	0.7421	<0.0001	****	Yes	0.8191	<0.0001	****	Yes
Parkinson's disease	0.7529	<0.0001	****	Yes	0.737	<0.0001	****	Yes
Cancer								
All cancers	0.7406	<0.0001	****	Yes	0.6863	<0.0001	****	Yes
Acute lymphoid leukemia	-0.2065	0.1104	ns	No	0.08604	0.5097	ns	No
Acute myeloid								
leukemia	0.7319	<0.0001	****	Yes	0.5744	<0.0001	****	Yes
Bladder cancer	0.6323	<0.0001	****	Yes	0.5304	<0.0001	****	Yes
Brain and nervous system cancer	0.5745	<0.0001	****	Yes	0.4334	0.0005	***	Yes
Breast cancer	0.7063	<0.0001	****	Yes	0.476	0.0001	***	Yes
Cervical cancer	-0.2231	0.084	ns	No	-0.3609	0.0043	**	Yes
Chronic lymphoid	0.8534	<0.0001	****	Yes	0.4667	0.0001	***	Yes
leukemia								
Chronic myeloid	0.6181	<0.0001	****	Yes	0.4304	0.0005	***	Yes

leukemia								
Colon and rectal	0.7412	<0.0001	****	Yes	0.5673	<0.0001	****	Yes
cancer								
Hodgkin lymphoma	-0.1393	0.2844	ns	No	-0.257	0.0456	*	Yes
Kidney cancer	0.8365	<0.0001	****	Yes	0.5851	<0.0001	****	Yes
Larynx cancer	0.0771	0.5548	ns	No	-0.1508	0.2461	ns	No
Leukemia	0.5569	<0.0001	****	Yes	0.6935	<0.0001	****	Yes
Lip and oral cavity cancer	0.3995	0.0014	**	Yes	0.1153	0.3761	ns	No
Liver cancer	0.1861	0.1511	ns	No	0.3447	0.0065	**	Yes
Malignant skin	0.8247	<0.0001	****	Yes	0.4908	<0.0001	****	Yes
melanoma								
Multiple myeloma	0.7405	<0.0001	****	Yes	0.7368	<0.0001	****	Yes
Nasopharynx cancer	-0.06759	0.6048	ns	No	0.08969	0.4918	ns	No
Neoplasms	0.7255	<0.0001	****	Yes	0.6764	<0.0001	****	Yes
Non-Hodgkin lymphoma	0.5169	<0.0001	****	Yes	0.6821	<0.0001	****	Yes
Non-melanoma skin cancer	0.5649	<0.0001	****	Yes	0.4094	0.0011	**	Yes
Ovarian cancer	0.781	<0.0001	****	Yes	0.5318	<0.0001	****	Yes
Pancreatic cancer	0.7806	<0.0001	****	Yes	0.6891	<0.0001	****	Yes
Prostate cancer	0.7824	<0.0001	****	Yes	0.6341	<0.0001	****	Yes
Stomach cancer	0.3852	0.0022	**	Yes	0.5161	<0.0001	****	Yes
Thyroid cancer	0.2452	0.0568	ns	No	0.5439	<0.0001	****	Yes
Tracheal, bronchus, and lung cancer	0.6391	<0.0001	****	Yes	0.5522	<0.0001	****	Yes
Uterine cancer	0.7006	<0.0001	****	Yes	0.4147	0.0009	***	Yes
Viral and bacrerial infections								
Acute hepatitis A	-0.6438	<0.0001	****	Yes	-0.3634	0.004	**	Yes
Acute hepatitis B	-0.8055	<0.0001	****	Yes	-0.4302	0.0005	***	Yes
Acute hepatitis C	-0.6705	<0.0001	****	Yes	-0.383	0.0023	**	Yes
Acute hepatitis E	-0.6036	<0.0001	****	Yes	-0.3412	0.0071	**	Yes
Bacterial skin	0.07951	0.5424	ns	No	0.249	0.053	ns	No
diseases								
HIV/AIDS	-0.4652	0.0002	***	Yes	-0.192	0.1382	ns	No
Leishmaniasis	-0.4743	0.0001	***	Yes	-0.338	0.0077	**	Yes
Neglected tropical diseases and malaria	-0.7854	<0.0001	****	Yes	-0.4443	0.0003	***	Yes
Varicella and herpes zoster	-0.4261	0.0006	***	Yes	-0.1566	0.2282	ns	No
Diabetes mellitus type 1	-0.6309	<0.0001	****	Yes	-0.6159	<0.0001	****	Yes
Diabetes mellitus type 2	-0.3122	0.0143	*	Yes	-	0.8432	ns	No

We next examined *CCR5delta32* allele and AD involvement in other disorders affecting the nervous system. Accordingly, we found positive SCC correlations between *CCR5delta32* allele frequency or AD and different mental disorders and motor neuron diseases, multiple sclerosis, certain neurological disorders, and Parkinson's disease. Surprisingly, we found negative SCC correlations between *CCR5delta32* allele frequency (but not AD) and epilepsy (r=-0.2984, p-value<0.05; (Table 1 & Figure 1). These results indicate that CCR5 might contribute to preventing specific nervous system disorders and that these disorders might be a risk factor for AD. As such, we suggest further investigating these putative links.

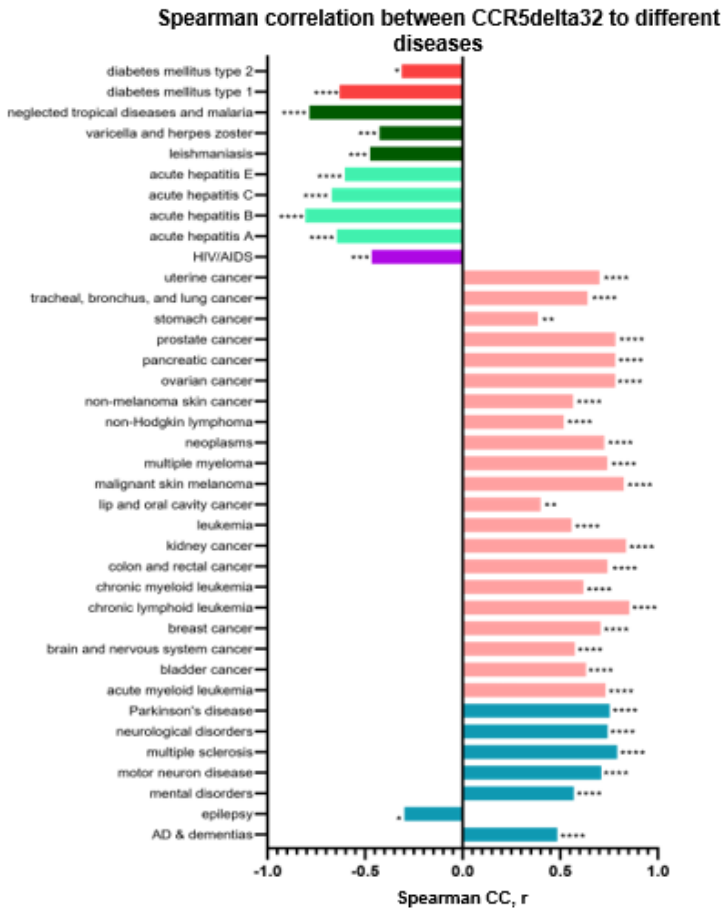

Figure 1: SCC correlations between *CCR5delta* 32 allele frequency and different diseases in the worldwide population. Significantly positive correlations were found between *CCR5delta32* allele frequency and registered deaths from Alzheimer's disease and neurological disorders, different cancers, and rheumatoid arthritis. Negative correlations were found between *CCR5delta32* allele frequency and registered deaths from epilepsy, HIV, diabetes, hepatitis, leishmaniasis, varicella and herpes zoster, and malaria.

Having proposed a link between *CCR5delta32* allele frequency and AD, we next addressed the relationship of *CCR5delta32* allele frequency or AD and different cancers. We accordingly found positive SCC correlation with acute myeloid leukemia, bladder cancer, brain and nervous system cancers, breast cancer, chronic lymphoid and chronic myeloid leukemia, colon and rectal cancers, kidney cancer, leukemia, malignant skin melanoma, multiple myeloma, neoplasms, non-Hodgkin's lymphoma, non-melanoma skin cancer, ovarian cancer, pancreatic cancer, prostate cancer, stomach cancer, tracheal bronchus and lung cancers and uterine cancer. Positive SCCs were found between *CCR5delta32* allele frequency and lip and oral cavity cancers, but not with AD, and between AD and liver and thyroid cancers, but not with *CCR5delta32*. Negative SCC correlations were found between AD and cervical cancer and Hodgkin's lymphoma (Table 1 & Figure 1). According to these results, CCR5 might act as a protective agent in many cancers that may be suspected as risk factors for AD.

Having established a relationship between *CCR5delta32* allele frequency with AD and considering studies linking AD and diabetes on the basis of shared molecular and cellular features [16], we checked for an AD and *CCR5delta32* allele relationship with diabetes by SCC. We found negative SCC correlations between *CCR5delta32* allele frequency and diabetes mellitus types 1 and 2 but negative correlation only for AD and diabetes mellitus type 1 (Table 1 & Figure 2). We thus concluded that diabetes mellitus type 1 is not likely to be a risk factor for AD and suggest that CCR5 serves a possible role in protection against diabetes.

Comparing *CCR5delta32* allele frequency with viral infection, we found negative SCC correlation between *CCR5delta32* allele frequency or AD and acute hepatitis A, B, C, and E, leishmaniasis, neglected tropical diseases, malaria and between *CCR5delta32* allele frequency and HIV/AIDS and varicella and herpes zoster (Table 1 & Figure 1). It can thus be assumed that many viral infections present inverse relationships with *CCR5delta32* allele frequency. Hence, people presenting the *CCR5delta32* allele would be expected to have some immune resistance to these diseases, as in the case of HIV. This also implies that some viruses might offer a protective effect against AD.

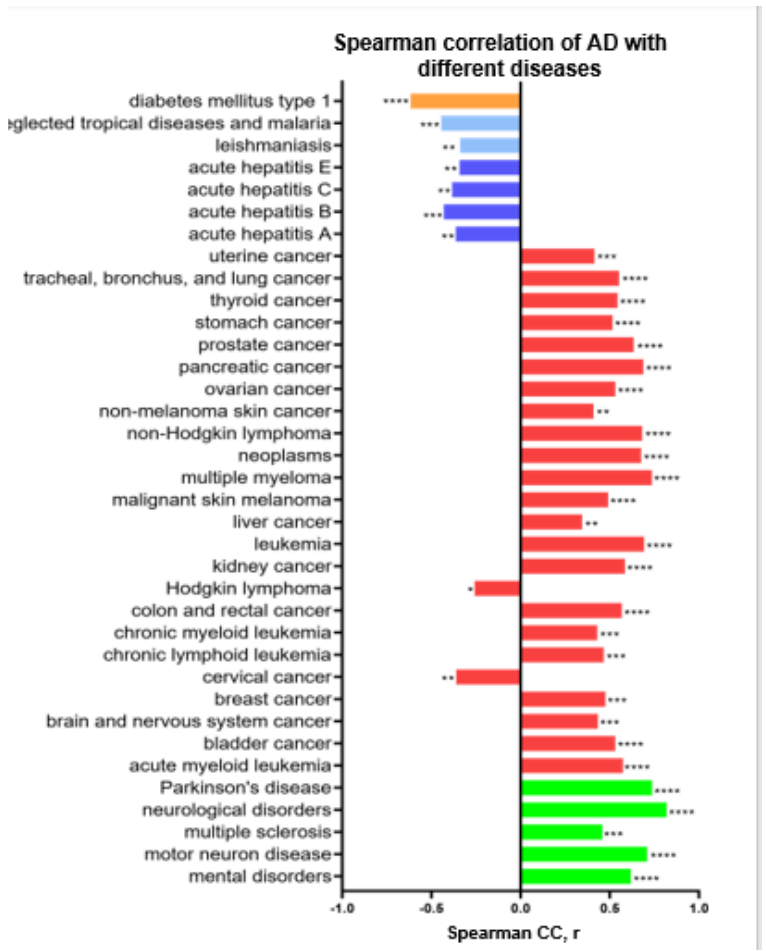

Figure 2: SCC correlations between Alzheimer's disease and other diseases in the worldwide population. Significantly positive correlations were found between registered deaths from Alzheimer's disease and neurological disorders, different cancers, and rheumatoid arthritis. Negative correlations were found between registered deaths from Alzheimer's disease and registered death cases from Hodgkin's lymphoma, cervical cancer, diabetes type 1, hepatitis, leishmaniasis, and malaria.

Discussion

The role of CCR5 in AD and other neurological disorders

In this project, we considered the involvement of CCR5 gene deletion in the form of *CCR5delta32* allele frequency in various diseases by exploring the spread of this deletion among 61 countries versus the percent of recorded deaths attributed to different diseases in the same locations. Results were analysed using SCC and revealed positive correlation between *CCR5delta32* allele frequency and AD. We expanded our analysis to various disorders related to the nervous system and found positively correlations with *CCR5delta32* allele frequency and AD.

The numerous studies that have tried to link *CCR5delta32* to AD [9,17,18] included small cohorts of patients and focused solely on subjects from a single country. As far as we know, the current study is the first worldwide analysis addressing this link. Brain inflammation is a pathological hallmark of AD. For decades, it was accepted that AD is the outcome of losing immune system balance, such that blocking immune responses was seen as a route to treat AD [19,20]. In contrast, others claimed that the immune system protein CCR5 improves memory in AD patients. The Schwartz group was one of the first to propose that the immune system can combat AD [21]. Over time, support for this concept has accumulated. Growing evidence also links neuroinflammation with AD, with emphasis on the role of CCR5 in this process [22]. Chronic activation of an inflammatory feedback loop by amyloid plaques and neurofibrillary tangles induces the expression and release of proinflammatory cytokines by activated microglial cells that are found in amyloid plaques during the early and late phases of AD [23]. It has been shown that chemokines and their receptors, particularly CCR5, are involved in recruiting microglia and monocytes into the brain and activate these cells to uptake amyloid beta [24]. Amyloid beta plaques stimulate activation of microglial and glial cells that induce the production of pro-inflammatory cytokines and chemokines [25-27]. Chemokines and their receptors were found to be upregulated in AD brain cells. Increased CCR5

and CCL5 levels in the brain of a mouse AD model were also found [28]. In vitro studies have demonstrated the ability of amyloid beta to stimulate production of the CCR5 ligands CCL3 and CCL4. Furthermore, in reactive astrocytes, CCL3 was detected in nearby sites of plaque-associated inflammation and neurodegeneration [29,30]. Hwang et al. reported that CCR5 knockout mice produced amyloid beta deposits and showed impaired memory function, in contrast to wild type mice [31]. Other studies have shown that amyloid beta up-regulates CCR5 expression, leading to T cell infiltration of the brain via the BBB [32]. CCR5 also chemotactically attracts microglia to the brain [33]. Keren-Shaul et al. found up-regulation of unique microglial cells in mouse AD brain [34]. At the same time, consideration of the immune system as a therapeutic target for treating neurodegenerative diseases other than AD is lacking. In these disorders, the immune system can also be considered to be part of the problem and not part of the solution. Still, Wojta et al. recently detected *CCR5delta32* carriers in early age of onset neurodegenerative disease patients [35]. Choi et al. found that CCR5 might be important for dopaminergic neuron survival in Parkinson's disease [36].

The multiple sclerosis disability status scale score is significantly expanded in *CCR5delta32*-presenting individuals [37]. Our results highlight CCR5 involvement in AD and other neurological disorders and support the importance of the immune system for therapy, with emphasis on the contribution of CCR5 in fighting AD and additional neurological disorders.

Surprisingly, whereas most neurological disorders show positive correlation with AD and *CCR5delta32* allele frequency, negative *CCR5delta32* allele correlation was found with epilepsy (no significant correlation was found for AD with epilepsy). In studies on epilepsy using rat models, blocking CCR5 function led to protection from seizures, neuroinflammation, BBB damage, and neuron loss [38]. However, none of the studies specifically examined CCR5 involvement in the disease. As such, we suggest examining CCR5 inhibition as epilepsy therapy.

CCR5, AD and cancer

It has been previously suggested that negative correlation exists between patients with AD and those with cancer. The inverse pathway of these two diseases, namely that cancer is mostly identified with proliferation while AD involves degeneration [13,39,40], supports this relation. Therefore, we sought correlation between AD or presence of the *CCR5delta32* allele and different cancers (Figure 1 & 2). While numerous such positive correlations were detected, no significant correlation of AD or the *CCR5delta32* allele and acute lymphoid leukemia, larynx cancer, nasopharynx cancer, or between the *CCR5delta32* allele and liver cancer, Hodgkin's lymphoma, thyroid cancer, and cervical cancer were seen. Indeed, we only found negative correlation between AD and cervical cancer and Hodgkin's lymphoma. According to these results, it can be assumed that AD and most cancers have direct connection (Figure 1 & 2).

In cancer, as well as in AD, the conventional therapeutic approach advocates the use of CCR5 blockers [41,42]. As early as 1986, Dvorak compared the wound-healing process and cancer, claiming that immune system cells are present in the tumor and can be recruited for its elimination [43]. Correlation between the *CCR5delta32* allele and breast cancer was also previously suspected, although no significance was found, perhaps due to the low number of research cohorts considered [44]. Our detailed analysis, however, found that despite the different pathways involved, cancers and neurodegenerative diseases share common factors, as previously reported [45,46]. For instance, it was shown that amyloid precursor protein (APP) is over-expressed in breast cancer and other cancers, is related to tumorigenicity [47] and its expression is associated with neurodegenerative diseases and cancer [48,49]. In addition, APP cleavage via the non-amyloidogenic APP pathway is related to a series of malignancies [50,51]. A GWAS study revealed positive correlation between AD and colon, breast, prostate, ovarian, and lung cancers, indicative of shared genetic variants [52].

The therapeutic strategy of CCR5 inhibition as tumor therapy in colon cancer did not, however, show success [53]. Recently, Okereke and Meadows [54] indicated flaws in studies of the relationship between AD and cancer. In our opinion, this is relevant for most studies indicating an inverse relationship between AD and other neurodegenerative diseases and cancer. One of the most significant problems in such efforts is the breadth of research data and its geographical spread, reflective of the complexity in collecting big and heterogeneous data for research. Another challenge to such studies involves extrapolation to different cancers and most importantly, the inability to define treatments. According to our results, there is direct relationship between most neurodegenerative diseases and the majority of cancers, such that cancer treatment may have therapeutic effects on neurodegenerative disorders in parallel.

While there is support for the concept of a relationship between the immune system and cancer, the mechanisms involved remain unclear [55]. Inflammatory responses play important roles at different stages of cancer and can affect immune surveillance and response to therapy [56]. One of the mechanisms tumors use to avoid immune system recognition and elimination involves cytokine production that inhibits normal pathways of the immune response [57]. During the first stage of tumor development, immunogenic cancer cells are eliminated by T cells [58]. Recently, Crowther et al. reported that a unique T cell lineage recognizes the MHC-I-related protein MR1 on cancer cells and kills such cells via a T cell receptor-mediated mechanism [59]. These T cells were found to identify a wide range of cancer cell types, including primary cancer

cells. We assume that as CCR5 recruits T cells to inflammatory sites, the *CCR5delta32* allele would prevent such recruitment, thereby enabling tumor proliferation.

CCR5, AD and viral infection

We also examined the relationship of AD and *CCR5delta32* allele frequency with viral infection. We found negative correlation with acute hepatitis A, acute hepatitis B, acute hepatitis C, acute hepatitis E, leishmaniasis and other neglected tropical diseases, and malaria. In addition, we noted negative correlation between *CCR5delta32* allele frequency (but no significant correlation for AD) and HIV/AIDS, varicella and herpes zoster (Figure 1 & 2). It is well known that the *CCR5delta32* allele provides protection against HIV [60] due to the role of CCR5 in HIV entry into cells [61]. The CCR5-CCL5 axis is known to be important in the context of hepatitis, with the *CCR5delta32* allele having been found to have a protective effect against hepatitis B [62,63]. Later, it was found that hepatitis C virus replication can be inhibited by blocking CCR5 [64]. CCR5 has also been tied to varicella and herpes zoster infection [65,66], leishmaniasis [67] and malaria [68]. As these findings support the concept of the *CCR5delta32* allele providing a protective effect against viral infection, we suggest examining CCR5 inhibition as therapy for different viral infections, in addition to HIV.

CCR5, AD and diabetes

Several studies have identified diabetes as an AD risk factor [15]. Given the relationship of the *CCR5delta32* allele with AD, we examined the relation of AD and the *CCR5delta32* allele with diabetes. We found negative SCC correlation between *CCR5delta32* allele frequency and diabetes mellitus types 1 and 2 but significant negative correlation only between AD and diabetes mellitus type 1 (Figure 1 & 2). Diabetes type 2 has significantly lower prevalence rates in Europe, relative to the rest of the world [69]. CCR5 and its ligand CCL5 were found to be up-regulated in diabetes type 2 patients [70]. It was, moreover, found that the *CCR5delta32* allele has a protective effect against type 1 diabetes [71]. CCR5 inhibition in non-obese mice inhibited beta cell destruction and diabetes [72]. In humans carrying the *CCR5delta32* allele, the age of diabetes type 1 onset was delayed and morbidity due to diabetes type 2 was reduced [73]. In Australian and New Zealand populations, partial protection from diabetes type 1 was observed in individuals homozygous for the *CCR5delta32* allele [74]. At the same time, CCR5 down-regulation in cell cultures promoted a protective mechanism against cellular destruction in diabetes type 1 [75]. In diabetes type 2, the *CCR5delta32* allele is associated with better survival and a protective effect [76]. Diabetes is associated with viruses, such as hepatitis B and C [25,77],

Epstein-Barr virus, human papillomavirus, cytomegalovirus, and herpes simplex virus type 1 [78]. While studies have indicated impaired cognitive performance in diabetics with or without insulin-dependence, post-mortem diabetic brains showed no evidence of AD pathology, implying that diabetes is not a risk factor for AD. Our study revealed that CCR5 might play an important role in diabetes pathogenesis and that diabetes may be a disease associated with viral infection, as CCR5 correlates these two in the same manner.

CCR5 is involved in various diseases in different manners

The pioneering aspect of the present study was its analysis of large data cohorts comparing *CCR5delta32* allele frequency to AD and other neurodegenerative disorders, different cancers, viral diseases and diabetes across the global population. Our results indicate positive correlation of CCR5 and AD and other neurodegenerative disorders and cancers but show an inverse relationship with viral infection and diabetes. We, therefore, suggest using CCR5 inhibition to treat viral infection, as well as diabetes, yet propose recruiting CCR5 to fight AD, neurologic disorders and various cancers. Our data are thus relevant in the context of the impact of CCR5 and immune system activity in these diseases and could open new research directions for treatment options.

Methods

2017 data for *CCR5delta32* allele frequency in different countries were taken from Solloch et al. Data for deaths due to different diseases in different countries in 2017 were obtained from the Global Health Data Exchange (GHDx) (http://ghdx.healthdata.org/). Using the GBD Results Tool, worldwide locations were chosen according to *CCR5delta32* allele frequency. Context cause was selected for all ages and both sexes, using percent as the metric. Deaths were tabulated according to measure and cause for the diseases listed below. Analysis was performed and graphs were drawn using GraphPad Prism 8, version

Data for the following diseases were compared: Alzheimer's disease and dementia, neurological disorders, motor neuron disease, epilepsy, mental disorders, Parkinson's disease, multiple sclerosis, HIV/AIDS, breast cancer, brain and nervous system cancer, acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, colon and rectal cancer, bladder cancer, kidney cancer, larynx cancer, leukemia, lip and oral cavity cancer, liver cancer, malignant skin melanoma, nasopharynx cancer, Hodgkin's and non-Hodgkin's lymphoma, non-melanoma skin cancer, uterine cancer, tracheal, bronchus, and lung cancer, thyroid cancer, stomach cancer, ovarian cancer, prostate cancer, multiple myeloma, other leukemia, pancreatic cancer, cervical cancer, neoplasms, acute hepatitis A, acute hepatitis B, acute hepatitis C, acute hepatitis E, diabetes mellitus type 1, diabetes mellitus type 2, bacterial skin diseases, leishmaniasis, neglected tropical diseases and malaria, varicella and herpes zoster.

Data from the following countries were compared: Albania, Algeria, Austria, Azerbaijan, Bangladesh, Belgium, Bosnia and Herzegovina, Brazil, Cameroon, Canada, Colombia, Congo, Croatia, Cuba, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Eritrea, Estonia, Finland, France, Georgia, Germany, Ghana,

Greece, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Japan, Jordan, Kenya, Lebanon, Luxembourg, Macedonia, Mexico, Morocco, Netherlands, Nigeria, Norway, Pakistan, Peru, Philippines, Portugal, Serbia, Slovakia, Slovenia, Somalia, South Korea, Spain, Sri Lanka, Switzerland, Tunisia, Turkey, United Kingdom.

Competing Interests

The authors must declare that there are any competing interests in relation to the work described.

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