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Genetic role in the pathogenesis of complex regional pain syndrome: a review

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Abstract

The ambiguity of complex regional pain syndrome (CRPS) posed a challenge to many medical researchers in the early days after its discovery and continues to do so till date. The establishment of the Budapest Criteria of the International Association for the Study of Pain resolved certain queries on CRPS. Many aspects of CRPS, such as pathophysiology and etiology, remain unknown. Therefore, of these aspects, we focused on the genetic basis of CRPS. In this qualitative review, we summarized the recent findings on the genetic association of CRPS and analyzed the roles of genes identified in each study and limitations of the studies. In particular, we confirmed the reliability of each study by comparing the following research, which used the following control groups or the same candidate genes. Notably, specific phenotypes of CRPS with dystonia indicate a significant association with human leukocyte antigen (HLA)-DQ8. Further, HLA-DQ8, which is associated with aberrant CD4+ T-cell reaction, could be associated with CRPS etiology since an increased CD4+ T-cell population was reported in CRPS patients. In addition, matrix metalloproteinase (MMP)-9 found in genome-wide expression profiling is noteworthy since MMP-9 is associated with neuro-inflammatory reactions. Despite these suggestions on the genetic aspects of CRPS, the pathophysiology and etiology of CRPS may be polygenic and multifactorial, influenced by multiple genes and other factors. Further, some studies have suggested that CRPS phenotypes have different etiologies. Thus, further studies with the precise classification of CRPS on a unified basis and with a significant number of case groups are required.

Keywords: complex regional pain syndromes; genes; HLA antigens; matrix metalloproteinases; genome

INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic condition with continuing regional pain, often accompanied by hyperalgesia and allodynia in severe cases. It is classified into two types: CRPS type I (proof without nerve damage) and CPRS type II (evidence with nerve damage in the affected limbs) [1]. Further, CRPS is an uncommon disease whose cause is not yet identified. Approximately 90% of CRPS patients experience injury (usually in severe cases), including crush

injury, surgery, acute myocardial infarction, stroke, or cancer. However, in approximately 10% of CRPS patients (CRPS type II), clear precipitance is not found [2]. Although the pathophysiology of CRPS is not fully proven, some theories indicated correlations between CRPS and neurogenic inflammation, autoimmune nervous system, and release of neuropeptides. The objective potential risk factors for CRPS onset remain elusive. However, some possible risk factors were identified with substantial evidence, such as female gender (particularly postmenopausal female) [3], old age (mean age of 56 years) [4], and patients with distal radius fracture [5]. Some studies proposed specific genetic and immunologic features and proteins associated with CRPS patients [6, 7].

In conclusion, CRPS is a complicated syndrome requiring further studies to determine its etiology, pathophysiology, and risk factors. Notably, identifying genetic risk factors and causes will provide more opportunities for better prevention, diagnosis, and treatment of CRPS. While some pathophysiologic mechanisms explained the signs and symptoms of CRPS (central and peripheral sensitization, ectopic discharge, central recognition of Aβ fibers, and loss of inhibitory control), a genetic role has also been proposed.

In this review, we summarized the studies that investigated the genetic factors of CRPS and genes that were closely associated with the occurrence and progression of CRPS. In addition, we analyzed several studies to determine the genetic factors that are involved in certain types of CRPS. Through our investigation, we have clarified the genetic etiology of CRPS.

Genetic association of complex regional pain syndrome (CRPS)

We provided an account of the genes associated with CRPS through a literature review (Table 1). Of those genes, we described the key genes that indicated a significant association with CRPS, such those of human leukocyte antigen (HLA)-DQ1, HLA-DR13, HLA-B62, and HLA-DQ8. We also considered the role of genome-wide expression in CRPS pathogenesis.

Human leukocyte antigen (HLA)-DQ1

HLA-DQ1 is a first genetic factor associated with CRPS [8]. This study compared the *HLA-DQ1* frequencies of 52 reflex sympathetic dystrophy (RSD) patients with those of 295 healthy control individuals using serologic HLA-typing. In conclusion, they found that the frequency of *HLA-DQ1* was significantly higher among patients with RSD than healthy controls. However, other researchers raised queries regarding the data of control individuals. Due to the significant difference in *HLA-DQ1* frequency between the more extensive Dutch group data of another study and control group data of this study, they proposed a possible cohort bias or erroneous analysis or publication of data. Furthermore, recent findings on the association between HLA family genes and CRPS indicated insignificant results regarding the involvement of *HLA-DQ1* [9]. Thus, significant evidence is required to establish an association between *HLA-DQ1* and CRPS.

Human leukocyte antigen (HLA)-DR13

A previous study investigated the association between CRPS and *HLA-DR13* [10]. This

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Table 1. Genes associated with CRPS patients

First author / publication year	Study design	Patients and controls	CRPS subtype / patients characteristic	Gene(s) serotype(s) marker(s)	Summary / conclusions / comments
Mailis A 1994 [10]	Candidate gene study; Serologic HLA typing	15 cases with RSD	Caucasian female patients were diagnosed using detailed protocols and scoring systems used in the Toronto hospital. This study used inclusion and exclusion criteria for specific patients (arbitrarily called "psychogenic RSD") with a painful and homogeneous complex of signs and symptoms arising from derangement of sudomotor, vasomotor, and trophic (superficial and deep) tissue mechanisms.	*Class I MHC Class II MHC (HLA-A3 HLA-B7 HLA-DR15 HLA-DR4)*	MHC antigens with varying frequencies compared with controls were HLA A3, B7, DR15, and DR4. None of the MHC antigen frequencies in the patient group (due to the small sample size) was statistically different when compared with the control frequencies using Fisher's exact test. Remarkably, five of six patients positive for HLA-DR15 resisted treatment, while only one of six patients with HLA-DR15 responded well to the treatment. These results did not reach statistical significance. The principal finding of this pilot study was the clustering of DR15 antigen in patients with RSD who indicated a poor outcome to treatment (high resistance to treatment).
Kemler MA 1999 [8]	Candidate gene study; Serologic HLA typing	52 unrelated Dutch CRPS patients	Patients with a definite diagnosis of RSD according to the criteria of the International Association for the Study of Pain.	*Class I MHC Class II MHC (HLA-DQ1)*	The frequency of HLA-DQ1 was found to be increased from 42% in the average population to 69% in patients with RSD (Bonferroni corrected x^2, p=0.02). All other MHC antigens did not significantly differ from control frequencies. The association with DR15 was found in a previous study on a small number of patients (Mailis A et al. 1994 [10]). The association was compatible with this study as DQ1 is closely associated with DR15.
van de Beek WJT 2000 [9]	Correspond / Letter to previous study			*Class I MHC Class II MHC (HLA-DQ1)*	The study of Kemler et al. [8] indicated an insignificant increase in DQ1 frequency compared with the frequencies in a much more extensive Dutch database. The control group they used in the study significantly differs from that in the more extensive Dutch database. Possible erroneous analysis or publication data or a cohort bias can cause this.
van Hilten JJ 2000 [11]	Candidate gene study; HLA-SSO typing	26 patients with a distinct phenotype of CRPS that progressed toward multifocal or generalized tonic dystonia. A panel of 2,355 healthy blood donors was used for comparison.	Tonic dystonia was observed in all patients. In 12 patients, dystonia occurred together with sensory and autonomic symptoms at the time of onset, although in 14 patients, dystonia developed at a later phase of the disease. In all except one patient, dystonia of the hands resulted in flexor postures of the fingers. Patients were diagnosed according to the International Association for the Study of Pain criteria.	*HLA-DRB1 HLA-DQA1 HLA-DQB1 polymorphism (HLA-DR13)*	A significant association of *HLA-DR13* and *HLA-DR13* genes with CRPS was present in 46% of the patients and 27% of the control group individuals (p<0.03). No differences between patients and control individuals reached statistical significance for any other alleles tested. Although DQ1 frequency seemed to be increased in the patients, this increase was not significant. As a result, this distinct phenotype of CRPS with progressive tonic dystonia is associated with HLA-DR13.
van de Beek WJ 2003 [13]	Subsequent candidate gene study; Typing of microsatellite loci	26 CRPS patients; Control values were obtained from a panel of 324 healthy blood donors.	26 Caucasian patients fulfilled the criteria of CRPS patients who presented with tonic dystonia in at least two of the affected extremities (van Hilten et al. 2000 [11]).	*Microsatellite markers (DS61014, D6S273, TNFα, MIB, C1_2_5, C1_3_2) (HLA-DR13)*	Significantly increased frequencies of alleles *D6S1014*134*, *D6S1014*137*, *C1_2_5*204*, *C1_3_2*342*, and *C1_3_2*354* were found in patients as compared with those of controls. Additionally, the frequency of alleles *D6S1014*140* and *C1_3_2*345* was significantly decreased in the patients. For *D6S273*, *TNFα*, and *MIB*, no differences emerged between patients and controls. The significantly higher frequencies of *D6S1014*134*, and *D6S1014*137* strengthen the previous finding of an association of *HLA-DR13* with CRPS with multifocal or generalized tonic dystonia.
de Rooij AM 2009 [14]	Candidate gene study; SSO-HLA class I, SSP-HLA class II, Both with PCR	150 cases (CRPS patients), 2440 Healthy controls (previously published group of healthy Dutch Caucasian blood donors)	CRPS-related fixed dystonia of at least one extremity. CRPS criteria of International Association for the Study of Pain. Dutch–Caucasian patients were recruited at the Leiden University Medical Center.	*MHC class I (HLA-A HLA-B) MHC class II (HLA-DRB1 HLA-DQB1) (HLA-B62, HLA-DQ8)*	Genetic associations of HLA-A, HLA-B, HLA-DR, and HLA-DQ alleles were determined in CRPS patients with fixed dystonia. Initial uncorrected association analyses revealed four HLA alleles that appeared to be associated with the disease: HLA-A23 (OR = 2.63 [95% CI 1.29–5.31], p=0.017), HLA-B62 (OR = 2.05 [95% CI 1.41–2.99] p=0.001), HLA-DR4 (1.55 [95% CI 1.11–2.18] p=0.016), and HLA-DQ8 (1.75 [95% CI 1.20–2.57] p=0.005). After correction for comparisons of multiple HLA alleles (P_c), HLA-B62 (P_c = 0.02) and HLA-DQ8 (P_c = 0.04) remained significantly associated.

Table 1. Genes associated with CRPS patients

First author / publication year	Study design	Patients and controls	CRPS subtype / patients characteristic	Gene(s) serotype(s) marker(s)	Summary / conclusions / comments
van Rooijen DE 2012 [15]	Subsequent candidate gene study; SSO-HLA class I, SSP-HLA class II, Both with PCR	131 cases; 150 cases; 5,604 healthy controls	131 Dutch–Caucasian CRPS patients without dystonia. Patients were recruited at three different medical centers. 150 Dutch–Caucasian CRPS patients with dystonia, previously published group of Dutch–Caucasian CRPS patients. The study was performed on a homogeneous group of CRPS patients, and homogenization of clinical diagnoses was done by including only CRPS patients who fulfilled the Budapest Research Criteria.	*MHC class I (HLA-A, HLA-B, HLA-C) MHC class II (HLA-DR, HLA-DQ) (HLA-B62, HLA-DQ8)*	For 131 patients without dystonia, initial (uncorrected) analysis of the two target HLA alleles revealed a significant association with HLA-DQ8 (OR = 1.65 [95% CI 1.12–2.42], p=0.014), whereas no association with HLA-B62 was found (OR = 1.22 [95% CI 0.78–1.92], p=0.458). Re-analyzed data of 150 CRPS patients with dystonia, the two alleles indicated a significant association, similar to the original study's findings (de Rooje AM et al. 2009 [14]). The study provided genetic clues that CRPS with and without dystonia are genetically different, but overlapping, phenotypes. In exploratory analysis, 6 HLA alleles indicated an association with the disease (CRPS without dystonia) when uncorrected for multiple testing: *HLA-B13*, *HLA-B37*, *HLA-Cw4*, *HLA-Cw6*, *HLA-DR4*, *HLA-DR11*. However, after correction for comparisons of various HLA alleles, according to Edwards, none of the associations remained significant.
Jin EH 2013 [6]	Candidate gene study; Genome-wide expression profiling followed by qRT-PCR	24 cases 18 controls (healthy Korean controls)	24 Korean CRPS patients diagnosed using Budapest criteria. (13 CRPS type I patients. 11 CRPS type II patients) A clinical diagnosis of CPRS was performed according to the Budapest Criteria published by the International Association for the Study of Pain (IASP) in 2007.	*80 DEGs for microarray analysis; 14 genes for qRT-PCR (HLA-DRB1, HLA-A29.1, HLA-DRB6, MMP9, PTGS2, ANPEP, HDC, G-CSF3R, STAT3, ARHGEF10)*	The microarray analysis was conducted for four (2 CRPS I and 2 CPRS II) of 24 patients and five of 18 controls. The qRT-PCR was conducted on all cases and controls. In microarray, 69 genes were up-regulated, and 11 were down-regulated among 80 DEGs. Of 80 DEGs, the researchers selected 12 specific genes through a literature review: *HLA-DRB1*, *HLA-A29.1*, *HLA-DRB6*, *MMP9*, *PTGS2*, *IL-8*, *MMP25*, *ANPEP* (*CD13*), *HDC*, *G-CSF3R*, *STAT3*, and *ARHGEF10*. All the selected genes were found to be up-regulated using microarray analysis, except ARHGEF10. They validated the microarray result using qRT-PCR; all genes indicated concordant results, except *ARHGEF10*, which was up-regulated in qRT-PCR. The most substantial finding of this study was the *MMP9* gene, which indicated significantly different levels of expression in CRPS patients compared with that in the controls, which is suggested to play an important role in the pain progression of CRPS patients.
Tan W 2017 [7]	Subsequent bioinformatics study, DEGs analysis, protein-protein interaction (PPI) analysis, and functional enrichment study	4 cases and 5 controls (healthy Korean controls)	2 CRPS type I patients, 2 CRPS type II patients (4 Korean CRPS patients); A clinical diagnosis of CRPS was performed according to the Budapest Criteria published by the International Association for the Study of Pain (IASP) in 2007.	*257 DEGs (HLA-DRB1, HLA-DQB1, HLA-DRB4) EP300, CREBBP, STAT3, STAT5*	They used GSE47603 microarray data from a previous study (Jin EH et al. 2013 [6]). In DEGs analysis, 257 DEGs were identified (243 up-regulated, 14 down-regulated); the most significantly up-regulated and down-regulated genes were *HLA-DRB1* and *HLA-DQB1*, respectively. In the functional enrichment analysis, those identified DEGs were enriched in immune response, cell motion, adhesion, and angiogenesis. Therefore, these signaling pathways were associated with CRPS. In PPI analysis, genes with a higher degree included adenovirus early region 1A binding protein p300 (EP300), CREB-binding protein (CREBBP), signal transducer and activator of transcription (STAT)3, and STAT5 of the STAT protein family. As a result, immune reactions and critical genes may have an essential role in CRPS development.
Piotr KJ 2016	Genome-wide association study	230 cases, 230 controls	Males and females > 18 years, fulfilling the criteria of Budapest Criteria published by the International Association for the Study of Pain (IASP) 2007	*83% of all common SNPs in the human genome*	In this study, the investigated common SNPs may be associated with the CRPS phenotype.
Escolano-Lozano F 2021 [16]	Specific protein expression study; ELISA of skin and serum biopsies	31 cases, 19 pain controls, 17 controls (healthy subjects)	31 CRPS patients diagnosed by Budapest Research Criteria. Some patients who visited the University Medical Center Mainz were recruited; 19 pain controls with post-traumatic or diabetic neuropathic limb pain without CRPS	Protein expression (MMP9 MMP2)	

CRPS, complex regional pain syndrome; RSD, reflex sympathetic dystrophy; qRT-PCR, quantitative real-time-polymerase chain reaction.

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gene is significantly expressed in patients with certain types of CRPS [11]. In all 26 CRPS patient case groups, tonic dystonia was observed in all patients. In this study, *HLA-DR13* was present in 46% of the patients in the case group and only 27% in the control group (p<0.03). However, the clinical significance of the association between HLA-DR13 and CRPS remains to be elucidated [12]. Although this study did not confirm the association between the case group and *HLA-DQ* [11], a previous study did [8]. Therefore, specific clinical phenotypes of CRPS were found to express specific entities. This study confirmed that CRPS with progressive tonic dystonia was associated with *HLA-DR13*.

For a follow-up study, a group of researchers studied the genetic association of *HLA-DR13* and CRPS with multifocal or generalized tonic dystonia using microsatellite loci amplification [13]. They used the dataset from a previous study [11]. This study used six microsatellite markers—*D6S1014*, *D6S273*, tumor necrosis factor α, *MIB C1_2_5*, and *C1_3_2*, which are located in the centromeric to the telomeric side of the MHC region. As a result, they found significantly increased frequencies of *D6S1014*134*, *D6S1014*137*, *C1_3_2*342*, and *C1_3_2*354* alleles and decreased frequencies of *D6S1014*140* and *C1_3_*345* alleles. This supported the previous findings from HLA-typing [11]. They suggested that *D6S1014*134*, *D6S1014*137*, *C1_3_2*342*, and *C1_3_2*354* alleles and *D6S1014*140* and *C1_3_*345* alleles are associated with genetic protection and susceptibility of CRPS with specific phenotype, respectively.

Human leukocyte antigen (HLA)-B62 and HLA-DQ8

Since the associations between the HLA system and CRPS were previously reported, further studies were conducted to determine the association between the specific subtypes of CRPS and HLA system to minimize the clinical heterogeneity of CRPS [14]. In a study, 150 CRPS patients with fixed dystonia were reported with significantly high frequencies of HLA-B62 and HLA-DQ8. An association of HLA-B62 and HLA-DQ8 with CRPS with fixed dystonia was suggested.

As some association between HLA-B62 and HLA-DQ8 and CRPS with fixed dystonia has been proven in previous studies, another study was conducted to investigate the association between HLA-B62 and HLA-DQ8 in CRPS without dystonia and CRPS with fixed dystonia [15]. This primary analysis demonstrated a significant association between HLA-DQ8 and CRPS without dystonia but no association between CRPS and HLA-B62. In a secondary study, 93 HLA alleles were analyzed for their association with CRPS without dystonia. The uncorrected analysis value confirmed the disease association with 6 HLA alleles; however, after statistical correction, HLA alleles were not found to be associated with CRPS.

Genome-wide expression and protein expression

In a recent study on CRPS, the association between CRPS and specific genes was investigated using gene expression profiling followed by quantitative real-time-polymerase chain reaction (qRT-PCR) [6]. The study confirmed that 11 selected genes (*HLA-DRB1*, *HLA-A29.1*, *HLA-DRB6*, matrix metalloproteinase *(MMP)9*, *PTGS2*, *IL-8*, *MMP26*, *ANPEP*, *HDC*, *G-CS-*

F3R, and *STAT3*) were up-regulated and one selected gene (*ARHGEF10*) was down-regulated using gene expression profiling. Subsequently, qRT-PCR was performed to validate the data from gene expression profiling; the secondary analysis of *HLA-A29.1*, *MMP9*, *PTGS2*, *IL-8*, *MMP25*, *ANPEP*, *HDC*, *G-CSF3R*, and *STAT3* genes indicated a concordant result with the gene expression profiling data. Further, the case group was separated, and the gene expression level was analyzed. In the CRPS I patient group, *HLA-A29.1*, *MMP9*, *IL8*, *HDC*, and *ARHGEF10* indicated a significant difference. In addition, the expression of *HLA-A29.1*, *MMP9*, *ANPEP*, *HDC*, *G-CSF3R*, and *STAT3* were statistically different in the CRPS II group. As a result, *HLA-A29.1*, *MMP9*, and *HDC* genes perform the function of pain regulation in both CRPS I and CRPS II, and the up-regulation of *IL8* and down-regulation of *ARHGEF10* were associated with pain progression in CRPS I. Further, the up-regulation of *ANPEP*, *G-CSF3R*, and *STAT3* was suggested to be associated with CRPS II pathogenesis. This study emphasized the role of *MMP9*. Notably, *MMP9* expression was characteristically up-regulated in CRPS I and CRPS II patients; MMP9, which plays an important role in neuropathic pain, is closely associated with CRPS I.

In another study, the researchers explained the associated genes and proteins of CRPS using functional enrichment analysis and protein–protein interaction (PPI) [7]. They used the same dataset as that in a previous study [6]. They found that HLA family genes, *HLA-DQB1* and *HLA-DRB1*, which are biomarkers of CRPS, are significantly associated with CRPS. Further, they revealed some critical genes of CRPS development, such as those of early region 1A binding protein (EP300), CREB-binding protein (CREBBP), signal transducer and activator of transcription (STAT)3, STAT5A, and integrin α M, using PPI.

Unlike previous researchers who studied the genome-wide expression profiling of MMP genes using microarray, MMP protein expression was studied using enzyme-linked immunosorbent assay in subsequent studies [16].

DISCUSSION

Many researchers studied the role of genes in CRPS; a few studies published significant findings. Other studies indicated findings that were poorly supported or unclear due to limitations, such as statistical errors [8, 10].

Further, researchers studied genetic association in patients with certain types of CRPS. The first study proved that the specific clinical phenotype of CRPS with progressive multifocal or generalized tonic dystonia was associated with HLA-DR13. A follow-up study confirmed the previous finding using microsatellite marker analysis. Further, the researchers suggested specific alleles that were associated with genetic protection and susceptibility to CRPS. Additionally, their study results supported the previous findings that the tonic dystonia of CRPS markedly responded to the intrathecal infusion with baclofen, a $GABA_B$ agonist. These findings suggest that *HLA-DR13* is a potential marker for predicting genetic susceptibility to CRPS with dystonia.

Recent studies reported an association between HLA-B62 and HLA-DQ8. In a study on

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patients with fixed dystonia, a significant association between the specific phenotype of CRPS with HLA-B62 and HLA-DQ8 was found. However, in another survey on patients without fixed dystonia, an association with HLA-DQ8 was found, but no association with HLA-B62 was observed.

Notably, HLA-Class II antigens (HLA-DR, DQ, and DP) play a pivotal role in the immune response by presenting extracellular antigen peptides to CD4+ T cells [17]. In particular, recognizing the HLA-DR antigen is essential for inducing an immune response. Therefore, this antigen is significantly associated with inflammatory responses.

In previous studies on the association between HLA-DR and autoimmune diseases, the aberrant expression of this antigen suggested severe autoimmune diseases such as Grave's disease and type 1 diabetes (T1D) [18,19]. However, a recent study indicated that DRB1*13, a specific HLA-DR serotype, was underrepresented in six autoimmune diseases, systemic lupus erythematosus, psoriasis or psoriatic arthritis, systemic sclerosis, multiple sclerosis, and proved that this specific serotype could provide adequate protection against systemic and rheumatoid diseases [20]. In contrast, the association studies between HLA-DR13 and CRPS with dystonia identified the overrepresentation of the HLA-DR13 serotype. Therefore, further studies are needed to determine whether this aberrant expression of *HLA-DR13* only has the role of a biomarker of CRPS or function as a factor that represents susceptibility or worsening of the disease.

Further, HLA-DQ is a cell-surface receptor protein that plays a central role in presenting antigens to CD4+ T cells [21]; HLA-DQ8 was found to have significant association with T1D [22]. Particularly, HLA-DQ8 worsens T1D because it promotes the autoimmune response of CD4 T cells to human B cells. In addition, CD4+ T-cell clones with specific pro-insulin receptors were analyzed, and some overlap with epitopes was found in the C-peptide of proinsulin [23]. Further, the association of HLA-DQ8 and the autoimmune response with human T1D was suggested. Multiple studies reported increased CD4+ T-cell population in CRPS patients, and CRPS is closely associated with T-cell mediated immune response [24–26]. Determining whether CD4 T-cell clones with specific receptors penetrate and destroy certain nerve cells using a mechanism similar to that of T1D is necessary.

Further, MMP-9 plays an essential role in various diseases, involving many physiologic and pathologic processes such as reproduction, inflammation, and vascular and proliferative diseases [27]. In addition, MMP-2 and MMP-9 selectively cleave chemokines and extracellular matrix receptors in neuro-inflammation, expression, and secretion of MMP-2 and MMP-9, promoting the neuro-inflammatory process [28]. The increased levels of neuro-inflammation and cytokines, which can cause the excitation of primary afferent nociceptors, is suggested to have a significant role in CRPS [29]. Further studies are required to study the association between neuro-inflammation and *MMP-9* gene expression.

A limitation in several studies is the small number of case groups. Although in some recent studies, the number of case-control tools was > 200, in many studies, the number of case groups is < 50, sometimes < 10. This limitation can cause statistical errors in studies. As CRPS is a sporadic disease, increasing the number of case groups is essential.

In addition, no clear criteria for CRPS, such as serological or radiological diagnostic criteria, is established; only the clinical criteria for IASP is used to diagnose CRPS. Therefore, researchers conduct studies using different criteria to classify CRPS subtypes or perform studies without classifying subtypes. Since the pathophysiology of each CRPS subtype varies [30], studies that perform investigations by organizing CRPS on a unified basis are recommended.

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