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## Increased Risk of Complex Regional Pain Syndrome in Siblings of Patients?

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**Abstract:** An increased risk among siblings of probands with complex regional pain syndrome (CRPS) may be indicative of a genetic contribution. We calculated the sibling recurrence risk ratio ( $\lambda_{\text{sibling}}$ ), a measure of familial aggregation. We surveyed 405 CRPS patients to collect information on the occurrence of CRPS in their siblings and compared this risk with the population risk to develop the syndrome. Information on disease status was collected from 1242 siblings, of which 24 were possibly affected according to their siblings. The diagnosis was confirmed in 16 patients, rejected in 2, and could not be verified in the remaining 6. Age-specific risk ratios were calculated for younger (<50 years) and older ( $\geq 50$  years) age groups. The strongest effects were seen in the younger age group, with a  $\lambda_{\text{sibling}}$  for possibly affected and confirmed cases of 5.6 (95% CI, 3.0 to 9.8) and 3.4 (95% CI, 1.5 to 6.8), respectively. We concluded that this study yielded no indications for an overall increased risk of developing CRPS for siblings of CRPS patients but that the risk was significantly increased in siblings younger than 50, which may indicate that genetic factors play a more pronounced role in this subgroup.

**Perspective:** We studied the risk of developing CRPS for siblings of patients with this syndrome. Although the overall risk for siblings was not increased compared with the population risk, the risk for younger siblings was elevated. To enhance chances of success, future genetic studies may consider restricting inclusion to younger-onset cases.

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**Key words:** Complex regional pain syndrome, sibling recurrence risk ratio, genetic predisposition, heritability.

Complex regional pain syndrome (CRPS) is characterized by pain in association with motor, sensory, vasomotor, sudomotor, and trophic disturbances.<sup>18</sup> CRPS predominantly affects women (~75%) and may occur at all ages, although the highest incidence is found between 50 and 70 years.<sup>4</sup> CRPS most often develops after a trauma, but spontaneous onsets have been described in about 10% of the cases.<sup>30</sup>

Several studies indicated that genetic factors may be involved in CRPS. Genetic associations were reported between CRPS and polymorphisms in, for instance, human

leukocyte antigens<sup>12,14,25,26,28</sup> and tumor necrosis factor- $\alpha$ .<sup>28</sup> An increased genetic susceptibility for CRPS is also apparent from the fact that patients with a more severe phenotype have a considerable younger age at onset compared with patients in whom the disease remits or stabilizes.<sup>27,29</sup>

Genetic factors, in addition to shared environmental factors, play an important role in causing familial aggregation of a disease.<sup>13</sup> Familial aggregation in CRPS was reported in several descriptive studies,<sup>1,3,6,8,9,11,30</sup> but these studies cannot be used to assess the familial risk to develop CRPS because the inherent oversampling of familial cases would result in severe selection bias.

A measure of familial risk is the sibling recurrence risk ratio, also referred to as  $\lambda_{\text{sibling}}$ . This is the ratio of risk of disease for a person given that a sibling is affected, compared with the risk to develop the disease in the general population.<sup>20,21</sup> Values higher than 1 are indicative of familial aggregation.

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The  $\lambda_{\text{sibling}}$  of a disease can be used to design studies aimed at identifying genes for complex diseases.<sup>17,21,22,23</sup> Information on the familial risk of CRPS is also important from a clinical point of view, because patients typically want to know whether their own diagnosis of CRPS translates to an increased risk of the syndrome in their closest relatives. The risk for relatives of CRPS patients to develop the syndrome has not been investigated.

In the present study, we calculated the  $\lambda_{\text{sibling}}$  of CRPS by comparing the risk among siblings of CRPS patients with the risk of the general population. Since previous studies in CRPS provided indications that the genetic contribution may be stronger in the younger onset cases,<sup>27,29</sup> the risk for younger and older age groups was also compared.

## Methods

### Patients

CRPS patients were recruited from 4 departments of anesthesiology and 1 department of neurology. All these patients participated in various studies that were carried out within TREND (Trauma RELATED Neuronal Dysfunction), a national consortium that integrates research on CRPS. Clinical data of all patients were collected using a questionnaire and a standard diagnostic form to evaluate the presence of signs and symptoms and were entered in a central internet-based database. CRPS was diagnosed according to the criteria of the International Association of the Study of Pain (IASP).<sup>18</sup>

Patients were contacted by telephone to ask (1) whether they had any siblings, (2) siblings' dates of birth, and (3) if applicable, dates of death of these siblings, and (4) if their siblings had been diagnosed with CRPS or had complaints that were suggestive of this condition. If they indicated that a sibling was possibly affected, patients were asked to provide contact information of that sibling. Subsequently, possibly affected siblings were visited at home and examined by a medical doctor with clinical experience in diagnosing CRPS (AdR) using the same diagnostic form and questionnaire as was used for probands. The diagnosis of CRPS was considered present if the IASP criteria were fulfilled. If a patient did not fulfill these criteria at examination, information on symptoms and signs of CRPS was retrieved from the general practitioner or consulted specialist to evaluate whether the criteria had previously been met, and, if this was the case, these siblings were considered to have been affected in the past.

One of the studies in TREND involves a family study in which we actively seek for families with 2 or more affected members. Patients who participated in that study as their first study within TREND (and thus had a known positive family history) were excluded from the present study, because the inherent oversampling of familial cases would have resulted in an overestimation of familial aggregation. If the first study in TREND involved another study than the aforementioned family study, patients were enrolled in the present study, even if

they had relatives with CRPS, since this situation could also occur in the control group (see below).

### Population Data

The population risk of CRPS has previously been established in a Dutch population-based study using the data of the Integrated Primary Care Information (IPCI) project.<sup>4</sup> This involved a retrospective cohort study that included the period between 1996 and 2005. The IPCI project is a large longitudinal observational database including electronic patients' records of more than 150 general practitioners throughout The Netherlands (at the time that the incidence study was performed). The patient population is representative of the Dutch population regarding age and sex.<sup>31</sup> Potential CRPS patients were identified using synonyms and abbreviations of CRPS listed in this database. Identified cases were validated using the patient's electronic records supplemented with specialist letters and by reconfirmation of the diagnosis by their general practitioners. Only the populations from the general practitioners that responded to a short questionnaire were included in the source population (in total, 190,902 individuals) for the calculation of the incidence rate. The estimated incidence rate for CRPS was 26.2 per 100,000 person-years.<sup>4</sup>

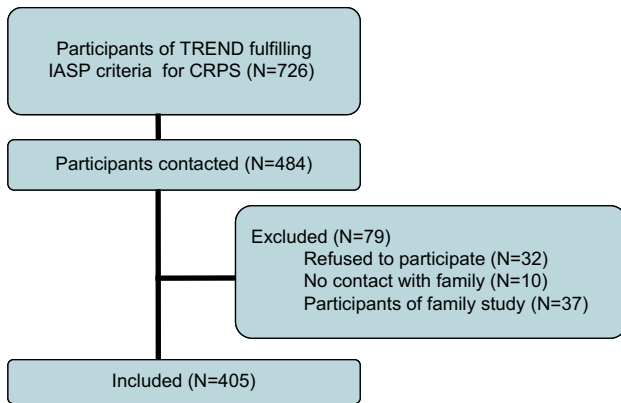
Subsequently, identified cases of the IPCI project were asked to participate in a case-control study.<sup>5</sup> If patients agreed, their diagnosis was additionally verified by a medical doctor with clinical experience in diagnosing CRPS (MdM) during a home visit, using the same standardized diagnostic form as used in the present study. Consequently, case definition was identical in both studies. Examination of the patients showed that a false-positive diagnosis of CRPS was likely in 19% of the cases and that the date of CRPS onset was misclassified in 6% (meaning that the CRPS had started before follow-up in the database). This suggested an overestimation of the incidence rate as calculated using the reported methods in the original study (namely validation by reconfirmation by the general practitioner). To ensure that the process of validation of diagnosis was identical in both groups, the incidence rate as reported by IPCI was decreased by 25%, which yielded a revised incidence of 19.5 incident cases per 100,000 person-years.<sup>5</sup>

The studies were approved by the involved institutional review boards, and all patients gave informed consent.

### Statistics

Person-years for each subject were computed as the length of time from date of birth to date of diagnosis of CRPS, date of death, or date of telephone contact, whichever came first.

The required number of sibling person-years was calculated on the premise that we wanted to detect a  $\lambda_{\text{sibling}}$  of at least 2.5, with an  $\alpha$  of 0.05 and a power of 80% ( $\beta = 0.2$ ). To find a risk ratio of 2.5 using the incidence rate of 19.5 per 100,000 person-years, 62,637 person years were required, as was evident from the following formula:



**Figure 1.** Flowchart recruitment index patients. IASP, International Association of the Study of Pain; N, number.

$$N = \frac{(Z_{\alpha} + Z_{2\beta})^2 * [p_0 * (1 - p_0) + p_1 * (1 - p_1)]}{(p_0 - p_1)^2} \quad (19)$$

where  $p_0$  was the population incidence and  $p_1$  was  $p_0$  times 2.5.

Data collection would stop if this number of person-years was achieved. Mid- $P$  exact values were calculated.<sup>16</sup> The 95% confidence intervals (95% CI) for the rate ratios were calculated using the conditional maximum likelihood estimate of rate ratio method.<sup>7,15</sup>

### Calculation of Sibling Recurrence Risk Ratio

Two sibling recurrence risk ratios of the total group were calculated, 1 including all possibly affected siblings in the numerator (some of whom could not be contacted), the other including only confirmed cases; the denominator was based on the total number of person-years. The obtained numbers were standardized to (ie, divided by) the adjusted incidence rate of 19.5 per 100,000 person-years.

To evaluate whether  $\lambda_{\text{sibling}}$  was different for both age groups, we calculated age-specific sibling recurrence risk ratios for 2 strata: <50 years and  $\geq 50$  years old. This threshold was chosen because the mean age at onset in the only 2 population-based studies was about 50 (ie, 46.9<sup>24</sup> and 52.7<sup>4</sup>).

For the 2 age groups, the recurrence risk ratio was calculated both for all possibly affected siblings and for the confirmed cases only, using the respective number of person-years and the adjusted general population incidence rates of those age groups.

## Results

### Study Population

In total, 405 probands with CRPS were included in the study (Fig 1). Patient characteristics are presented in Table 1. The 405 patients together had 1242 siblings. The number of siblings ranged from 0 to 13 with a median (interquartile range [IQR]) of 2 (1 to 4) siblings per

**Table 1. Characteristics of Index Patients**

No. of patients	405
Percentage (N) of females	85% (345)
Mean age at onset of CRPS, years (SD)	40.6 (15.3)
Median disease duration -years (IQR)	3.0 (0.5 to 8.7)
Percentage (N) patients with >1 affected extremity	30% (120)
Percentage (N) patients with observed dystonia	29% (115)
Preceding trauma, percentage (N)	
Trauma	87% (351)
Fracture	22% (88)
Surgery	27% (109)
Soft tissue	13% (54)
Other	25% (100)
Non-trauma	13% (53)
First affected extremity, percentage (N)	
Arm	52% (211)
Leg	48% (193)

N, number; SD, standard deviation; IQR, interquartile range.

case. The siblings contributed 63,090 person-years. Their mean (standard deviation [SD]) age was 50.8 (15.8), and 609 (49%) were female. A total of 109 siblings (9%) were deceased.

Of the 1242 siblings, 24 were possibly affected with CRPS according to their siblings. The diagnosis in 6 subjects could not be verified because (1) probands refused to provide contact information ( $n = 2$ ), (2) the sibling did not give consent ( $n = 3$ ), or (3) the sibling had died ( $n = 1$ ). Eighteen patients were visited at home, and the diagnosis was confirmed in 16 of them. The general practitioner or consulted specialists of the other 2 patients were contacted to verify whether diagnostic criteria had been fulfilled in the past, after which the diagnosis was rejected in both.

Of the 16 confirmed affected siblings, 81 % ( $n = 13$ ) were female. The mean (SD) age at onset was 46.8 (11.8), with a range of 21 to 63 years. Time between onset of CRPS and examination varied between 0.6 and 26 years (median, 5.6 years). The most common precipitating noxious events were fractures (38%) and operations (19%). Seven patients (44%) had 2 or more affected extremities. Two patients (13%) had dystonia on examination.

### Sibling Recurrence Risk Ratio

The  $\lambda_{\text{sibling}}$  for CRPS using all possibly affected siblings was 1.8 (95% CI, 1.1 to 2.7). Using only confirmed cases, a  $\lambda_{\text{sibling}}$  value of 1.3 (95% CI, 0.8 to 2.1) was obtained. Stratification by age group using all possibly affected siblings yielded a  $\lambda_{\text{sibling}}$  for the group <50 of 5.6 (95% CI, 3.0 to 9.8), whereas the  $\geq 50$  age group had a  $\lambda_{\text{sibling}}$  of 0.6 (95% CI, 0.3 to 1.1). Using only confirmed cases, we found a  $\lambda_{\text{sibling}}$  for the group <50 of 3.4 (95% CI: 1.5 to 6.8) and a  $\lambda_{\text{sibling}}$  of 0.5 (95% CI, 0.2 to 1.0) for the  $\geq 50$  age group (Table 2).

## Discussion

To the best of our knowledge, this is the first study that systematically evaluated the sibling recurrence risk ratio ( $\lambda_{\text{sibling}}$ ) of CRPS among siblings of patients with this

**Table 2. Total and Age-Stratified  $\lambda_{\text{sibling}}$  for Possibly Affected and Confirmed Cases**

	SIBLINGS			IPCI			$\lambda_{\text{SIBLING}}$	95% CI
	CASES	PY	IR PER 100,000 PY	CASES	PY	IR per 100,00 PY		
Possibly affected cases								
Total	22	63,090	34.8	177	909,444	19.5	1.8	1.1 to 2.7
<50 y	13	20,268	64.1	72	625,082	11.5	5.6	3.0 to 9.8
$\geq 50$ y	9	42,822	21.0	105	284,362	36.9	0.6	0.3 to 1.1
Confirmed cases								
Total	16	63,090	25.4	177	909,444	19.5	1.3	0.8 to 2.1
<50 y	8	20,268	39.5	72	625,082	11.5	3.4	1.5 to 6.8
$\geq 50$ y	8	42,822	18.7	105	284,362	36.9	0.5	0.2 to 1.0

PY, Person-years; IR, incidence rate. 95% CI, 95% confidence interval; IPCI, Integrated Primary Care Information.

condition. The  $\lambda_{\text{sibling}}$  is the risk of disease among siblings (ie, brothers and sisters) of patients compared with the risk of the general population. The parameter is a composite measure that reflects the combined influence of genetic factors and shared environment. Weak familial aggregation ( $\lambda_{\text{sibling}} < 2$ ) is generally considered not very convincing for a relevant contribution of genetic factors in the etiology of a disease.<sup>32</sup> Especially in diseases with a low incidence, a 2-fold increase in risk is not very meaningful. The present study was therefore designed to find a  $\lambda_{\text{sibling}}$  of 2.5 or higher.

The  $\lambda_{\text{sibling}}$  including all siblings reported affected was significantly increased to 1.8 (95% CI, 1.1 to 2.7). Using only confirmed affected siblings, the  $\lambda_{\text{sibling}}$  was 1.3 (95% CI, 0.8 to 2.1), but this increase did not reach significance. These rather low values, when all patients of all age groups were considered, suggest a complex etiology with a major involvement of nongenetic factors. However, in the youngest age group the  $\lambda_{\text{sibling}}$  was 5.6 (95% CI, 3.0 to 9.8). Using only confirmed cases, we found a significantly increased  $\lambda_{\text{sibling}}$  of 3.4 (95% CI, 1.5 to 6.8) for this age group. This indicates that the genetic component is more pronounced in younger CRPS patients. One may suggest that shared environmental factors could be a reason for the observed increased  $\lambda_{\text{sibling}}$  in the younger age group. However, this explanation is not very likely because it is difficult to envisage that the effect of exposure to shared environment would be different for both age groups of the 2 cohorts. Additionally, subjects in both age groups will have shared (on average) the same amount of years with their siblings. Of note is that our finding of an increased  $\lambda_{\text{sibling}}$  in the younger age group needs to be confirmed in future studies given the fact that this finding was the result of a subgroup analysis.

A limitation of this study is that we did not contact every sibling personally. This may have resulted in an underestimation of the number of affected siblings, because some patients may have been unaware of their sibling's disease. Conversely, the fact that we were unable to validate all diagnoses could have led to an overestimation in the analyses that included all possibly affected patients, although we think that this overestimation is small, given the experience that most of the

possibly affected cases (16 of 18) were indeed affected. Although it is not uncommon to use the information on disease status as provided by the index case,<sup>32</sup> we clearly would have preferred to validate all diagnoses. We therefore performed a sensitivity analysis and calculated 2 values of  $\lambda_{\text{sibling}}$ , based on reported or confirmed diagnosis. The  $\lambda_{\text{sibling}}$  using only confirmed cases may be interpreted as the lower boundary of the actual value. To prevent selection bias, patients who participated in the family study as their first study within TREND were excluded. This approach also probably led to an underestimation of the  $\lambda_{\text{sibling}}$ , because there were sibships with multiple affected sibs within the excluded families, whereas similar families may have been present in the population cohort (IPCI) from which they were not excluded. Although we thus aimed to prevent any selection bias, some remaining bias cannot be ruled out completely, because the index patients (who were all referred to specialists) were compared with patients identified in the general population (of whom 75% had been referred to specialist), which could have led to some overestimation of the  $\lambda_{\text{sibling}}$ . Weighing the possible consequences of all biases, however, the heritability estimates presented here probably reflect an underestimation, especially with respect to the analyses in which only confirmed cases were used.

One should take into account that the inclusion criteria of this study (the IASP criteria) are broad and that this may have resulted in a study population that is too heterogeneous to detect a genetic effect. The conclusions may have been more pronounced if we would have been able to select a more homogeneous phenotype of this condition,<sup>21</sup> for example, CRPS with dystonia, or if we had used more stringent diagnostic criteria, such as the criteria developed by Bruehl and Harden.<sup>2,10</sup> This stricter approach would, however, have led to a considerable increase in the number of people to be assessed, and it would have been an enormous endeavor to collect sufficient numbers of patient-years.<sup>30</sup>

The strength of our study is that we contacted a large group of index patients, which would have enabled us to find a  $\lambda_{\text{sibling}}$  of 2.5 or higher, if it were present. Because the  $\lambda_{\text{sibling}}$  in the total group of CRPS patients was low, it is unlikely that there are common CRPS genetic factors. It

is possible, however, that there are rare gene variants in CRPS families that have a larger effect. Logically, such gene variants have a very small contribution in the overall risk for CRPS in the general population.

In conclusion, the  $\lambda_{\text{sibling}}$  for CRPS is smaller than 2.5. In view of the relatively low a priori risk of this syndrome, the risk for relatives of CRPS patients to develop this condition is accordingly low. However, the risk for siblings who were younger than 50 years was increased, indicating that the potential effect of genetic factors is larger in this subgroup. Our results indicate that the best estimate for this age group lies between 3.4 and 5.6, although these numbers probably reflect an underestimation. It should be considered that results from studies like this should be interpreted with some caution when the conclusions rely on relatively small actual numbers, a situation that is very difficult to avoid in relative rare diseases such as CRPS. To enhance the chances of success, a focus on the younger age group is recommended for future genetic studies.

## References

- Albert J, Ott H: Three brothers with algodystrophy of the hip. *Ann Rheum Dis* 42:421-424, 1983
- Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M: External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria: International Association for the Study of Pain. *Pain* 81:147-154, 1999
- Bruscas IC, Beltran Audera CH, Jimenez ZF: [Polytopic and recurrent reflex sympathetic dystrophy in lower limbs in two siblings.]. *An Med Interna* 21:183-184, 2004
- de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC: The incidence of complex regional pain syndrome: A population-based study. *Pain* 129:12-20, 2007
- de Mos M, Huygen FJ, Dieleman JP, Koopman JS, Stricker BH, Sturkenboom MC: Medical history and the onset of complex regional pain syndrome (CRPS). *Pain* 139:458-466, 2008
- de Rooij AM, de Mos M, Sturkenboom MC, Marinus J, van den Maagdenberg AM, van Hilten JJ: Familial occurrence of complex regional pain syndrome. *Eur J Pain* 13:171-177, 2009
- OpenEpi: Open source Epidemiologic Statistics for Public Health. Available at: [www.OpenEpi.com](http://www.OpenEpi.com). Accessed January 23, 2009
- Erdmann MW, Wynn-Jones CH: 'Familial' reflex sympathetic dystrophy syndrome and amputation. *Injury* 23:136-138, 1992
- Galer BS, Henderson J, Perander J, Jensen MP: Course of symptoms and quality of life measurement in Complex Regional Pain Syndrome: A pilot survey. *J Pain Symptom Manage* 20:286-292, 2000
- Harden RN, Bruehl S, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M: Complex regional pain syndrome: Are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain* 83:211-219, 1999
- Huhne K, Leis S, Schmelz M, Rautenstrauss B, Birklein F: A polymorphic locus in the intron 16 of the human angiotensin-converting enzyme (ACE) gene is not correlated with complex regional pain syndrome I (CRPS I). *Eur J Pain* 8:221-225, 2004
- Kemler MA, van de Vusse AC, van den Berg-Loonen EM, Barendse GA, van Kleef M, Weber WE: HLA-DQ1 associated with reflex sympathetic dystrophy. *Neurology* 53:1350-1351, 1999
- Khouri MJ, Beaty TH, Liang KY: Can familial aggregation of disease be explained by familial aggregation of environmental risk factors? *Am J Epidemiol* 127:674-683, 1988
- Mailis A, Wade J: Profile of Caucasian women with possible genetic predisposition to reflex sympathetic dystrophy: A pilot study. *Clin J Pain* 10:210-217, 1994
- Martin D, Austin H: An efficient program for computing conditional maximum likelihood estimates and exact confidence limits for a common odds ratio. *Epidemiology* 2:359-362, 1991
- Martin DO, Austin H: Exact estimates for a rate ratio. *Epidemiology* 7:29-33, 1996
- McCarthy MI, Kruglyak L, Lander ES: Sib-pair collection strategies for complex diseases. *Genet Epidemiol* 15:317-340, 1998
- Merskey H, Bogduk N: Complex regional pain syndrome, type I, in Merskey H, Bogduk N (eds): *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle, IASP Press, 1994, pp 41-42
- Pocock SJ: *Clinical trials: A practical approach*. New York, Wiley & Sons, 1983
- Risch N: Linkage strategies for genetically complex traits, I: Multilocus models. *Am J Hum Genet* 46:222-228, 1990
- Risch N: Linkage strategies for genetically complex traits, II: The power of affected relative pairs. *Am J Hum Genet* 46:229-241, 1990
- Risch N, Teng J: The relative power of family-based and case-control designs for linkage disequilibrium studies of

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complex human diseases I. DNA pooling. *Genome Res* 8: 1273-1288, 1998

23. Risch NJ: Searching for genetic determinants in the new millennium. *Nature* 405:847-856, 2000

24. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA: Complex regional pain syndrome type I: Incidence and prevalence in Olmsted county, a population-based study. *Pain* 103:199-207, 2003

25. van de Beek WJ, Roep BO, van der Slik AR, Giphart MJ, van Hilten BJ: Susceptibility loci for complex regional pain syndrome. *Pain* 103:93-97, 2003

26. van Hilten JJ, van de Beek WJ, Roep BO: Multifocal or generalized tonic dystonia of complex regional pain syndrome: A distinct clinical entity associated with HLA-DR13. *Ann Neurol* 48:113-116, 2000

27. van Rijn MA, Marinus J, Putter H, van Hilten JJ: Onset and progression of dystonia in complex regional pain syndrome. *Pain* 130:287-293, 2007

28. Vaneker M, van der Laan L, Allebes WA, Goris RJ: Genetic factors associated with complex regional pain syndrome 1: HLA DRB and TNF alpha promotor gene polymorphism. *Disabil Med* 2:69-74, 2002

29. Veldman PH, Goris RJ: Multiple reflex sympathetic dystrophy: Which patients are at risk for developing a recurrence of reflex sympathetic dystrophy in the same or another limb. *Pain* 64:463-466, 1996

30. Veldman PH, Reynen HM, Arntz IE, Goris RJ: Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. *Lancet* 342:1012-1016, 1993

31. Vlug AE, van der LJ, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, van Bommel JH: Postmarketing surveillance based on electronic patient records: The IPCI project. *Methods Inf Med* 38:339-344, 1999

32. Weijnen CF, Rich SS, Meigs JB, Krolewski AS, Warram JH: Risk of diabetes in siblings of index cases with Type 2 diabetes: Implications for genetic studies. *Diabet Med* 19:41-50, 2002