Genetic Aspect of Complex Regional Pain Syndrome Type I (Syndroma Algodystrophicum) Based on Quantitative Analysis of Digitopalmar Dermatoglyphics in Forty Women

Miljenko Cvjetičanin¹, Zrinka Jajić², Nijaz Burgić³ & Timon Cvjetičanin⁴

¹ Zagreb Rehabilitation Center, N. Andrića 3, Novi Zagreb, Croatia
² University Clinical Center, Sestre milosrdnice, Department of Rheumatology, Physical Medicine and Rehabilitation, Vinogradska 29, Zagreb, Croatia
³ Office for Physical Medicine and Rehabilitation, E. Pascalia 3A, Umag, Croatia
⁴ University Clinical Center, Sestre milosrdnice, Neurology Clinic, Vinogradska 29, Croatia

To Jehovah

Abstract: We have made research by the analysis of digitopalmar dermatoglyphics in quantitative traits in forty women with regional complex pain syndrome type I (CRPS1), as a measure of disease prevention: by the early recognition, making the risk groups and promptly cure of patients. The study included 25 dermatoglyphic variables: number of epidermal ridges on all ten fingers; their sum for five and ten fingers; four variables on both palm, i.e. between a-b, b-c and c-d triradii, and angles, then their bilateral sum. The data obtained were compared with those recorded in a control group of 200 pairs imprints phenotypically healthy female adults from the Zagreb area of Anthropological Institute in Zagreb. Statistically significant differences from control values were found in five variables: an increased sum of ridges between triradii b-c and total palmar ridge count on the right palm then, increased sum of ridges between triradii c-d and total palmar ridge count on left palm and their sum on both palm. Accordingly, a few major genes, with an impact of many modification genes, are identical in some loci to the predisposing to algodystrophy syndrome susceptibility, and might be found responsible to dermatoglyphic pattern development changes. Moreover, these findings suggested, because of craniocaudal development of dermatoglyphics, on some different genetic impact, at least in terms of time, a few weeks earlier than in our previous research in sixty men. It means, that some external, hormonal and sex factors play a role together by genetic in development this mytserious syndrome too.

Key words: dermatoglyphics, regional complex pain syndrome type I, female sex, quantitative dermatoglyphics analysis, prevention

1. Introduction

The most characteristic sign of the syndrome is a persistent pain, according Mc Gill Index Pain Chart is ranked as the most painful form of chronic pain that exist today – a whopping 48, fracture of the bone 17, phantom limb pain and cancer-non terminal 26, chronic back pain nearly 30, prepared childbirth 31, and unprepared childbirth 37, amputation of digit 39, for example - which cause deep psychical effects and usually develops as a consequence of injury of the bone or of some other irritating stimulus, picture 1(1)

Picture 1
Modified McGill Pain Chart Index
Complex regional pain syndrome is characterized by heterogeneous dysfunctions of muscle and osseous system, skin and vascular structures, then, by rapid bone demineralization, burning pain, hyperesthesia, swelling, hyperhidrosis, and trophic lesions of the skin and nails (2,3). The clinical symptoms are persistent to treatment. It is very important early recognition of the syndrome and start by healing as soon as possible. The first notification of what is currently named complex regional pain syndrome stems from 1634, when surgeon Ambroise Pare described that King Charles IX form persistent pain and contractures of his arm following a blood letting procedure (4). The next description of the disorder has been attributed to Hunter, who drew attention to the more distal effects of articular trauma as early as 1776 (5). Then, it was reported by Mitchell and his colleagues Morehouse and Keen in their book 1864, and his papers in 1867 and 1872, as a complication of gunshot wounds of peripheral nerves during American Civil War (6,7). The first scientific publication on disorder was issued in 1900 from a German surgeon named Paul Sudeck. His name became tied to the syndrome for long – Sudeck’s dystrophy (8). The epidemiological data suggest that the CRPS incidence is 26.2 in 100,000 per year. The highest incidence occurred in females in the age category 61-70 years, and women are at least three times more frequently affected. The upper extremity is affected more frequently than lower extremity and a fracture is the most common precipitating event (9).

Experts CRPS proposed in review article 2007, the new diagnostic criteria, The Budapest criteria, of two group of disorders: complex regional pain syndrome type I – posttraumatic and complex regional pain syndrome type II neuropathic pain (10) and their validation (11). A third category, CRPS-NOS, was added to address patients who appear to have CRPS but do not meet the diagnostic criteria (12).

There are three stages according to Lankford and Evans by the variations (13,14,15) (or four to some authors) of CRPS: I Acute stage, 0-3 months: warmth, coolness, burning pain, increased sensitivity of touch, increased pain, accelerated hair/nail growth, tenderness or stiffness in the joint, spasms, limited mobility and spotty bone changes. II Dystrophic stage, 3-6 months: pain is constant, throbbing, burning, aching, churning in nature and is exacerbated by any stimuli. The affected limb still be swollen (edematous), cool, cyanotic, and nails are brittle and ridged. III Atrophic stage, can last an unlimited amount of time. Pain is usual, constant but can increase or decrease. Irreversible tissue damage may occur. Skin becomes cool, thin. Contraction of the extremity may occur (decreased joint movement and further changes in bone density. For those who recognise stage four, it is the most advanced stage of CRPS. It is suggested that many patients receive CRPS treatment will never advance to CRPS stage four. In stage four of CRPS the condition becomes resistant to the most types of treatment, for example damage of limb may be so critical that a medical professional may recommend amputation.
Additionally, the patients internal organs may become affected by condition (16). Further, there is very interesting CRPS severity score, as a measure of evaluation, and might be useful for documenting the course of disorder: It consist of the two group: I. Reported symptoms, 1. allodynia (hyperpathia), 2. temperature asymmetry, 3 skin color asymmetry, 4. sweating asymmetry, 5. asymmetric edema, 6. trophic changes, 7. motor changes, 8. decreased active range of motion, and group II. Signs observed: 1. hyperpathia to pinprick, 2. allodynia, 3. temperature asymmetry by palpation, 4. skin color asymmetry, 5. sweating asymmetry, 6. asymmetric oedema, 7. trophic changes, 8. motor changes, 9. decreased active range of motion. The maximum score is 17, which means the most severe condition (17). Clinical course of syndrome may considerably be improved by the early recognition of symptoms and therapeutic measures, which include medication by oral steroids, calcitonin, peripheral and central analgesics and non-steroidal antiinflammatory drugs, bisphosphonates, C-vitamine (18), K-vitamine (19), local anaesthesia infiltrations, and by modalities of physical therapy, transcutaneous electrical nerve stimulation, magnetotherapy, dosing kineziotherapy and exercises on healthy extremity and mirror box therapy. However, the treatment for this long term and still obscure syndrome is not always successful (20). Clinical picture of the heavy trauma of the right hand female patient by flag stone hitting manhole and fracture of capitatumbone, with X-ray, is shown on the pictures 2-5, and 7-10. As all our 40 female patients developed algodystrophy syndrome following extremity injury, they fell into the type I group. This is a second paper dealing with, our in 60 male patients was the first (21) in the quantitative analysis of dermatoglyphics, which is the one of genetic method. Genetic impact has been noted in the syndrome development. In 1983, Albert and Ott reported on hip algodystrophy in three brothers (22). Based on the analysis performed in three families with two or more members affected with algodystrophy, Greipp and Thomas conclude in their selected abstracts from 1991, that there must be a genetic susceptibility to disorder (23). In 1994, Mailis and Wade found a higher frequency of HLA A3, B7 and DR2 antigens in 15 female Caucasians (24). In 1999, Kemler et al, reported on association of HLA DQ1 antigen and reflex sympathetic dystrophy (25, 26), as we mentioned in previous paper (21).

2. Material and methods

Dermograms of 40 female patients with post-traumatic algodystrophy were examined by quantitative dermatoglyphic analysis according to Budapest diagnostic criteria, from 2007 (10), and methodically as suggested by Miličić et al. (27). Results were compared with those obtained in 200 pairs of dermatoglyphic palm and finger imprints of phenotypically healthy women from Zagreb area, kept at Institute of Anthropology from Zagreb (28). Student’s t-test was used to test statistically significant differences in the ridge count between the patient and control group. Patient imprints were taken onto a transparent adhesive tape by use fine-granulated silver-gray powder used in crime investigation (29).

The following 25 traits were examined by the quantitative dermatoglyphic analysis: 1. FRD1 number of ridges on the right hand first finger; 2. FRD2 number of ridges on the right hand second finger; 3. FRD3 number of ridges on the right hand third finger; 4. FRD4 number of ridges on the right hand fourth finger; 5. FRD5 number of ridges on the right hand fifth finger; 6. FRD 1-5 pooled number of ridges on the right all five hand fingers; 7. PRD1 number of ridges between a-b triradii on the right palm, 8. PRD2 number of ridges between b-c triradii on the right palm; 9. PRD3 number of ridges between c-d triradii on the right hand; 10. pooled number of ridges between a-b, b-c and c-d triradii on the right palmall together; 11. ATDD atd angle on the right hand in degrees; 12 FRL1 number of ridges on the left hand first finger, 13. FRL2 number of ridges on the left hand second finger; 14. FRL3 number of ridges on the left hand third finger; 15. FRL4 number of ridges on the left hand fourth finger; 16. FRL5 number of ridges on the left hand fifth finger; 17. FRL 1-5 pooled number of ridges on the all five left hand fingers, 18. PRL1 number of

Picture 5
Final stage of patient's conservative treatment, a few plastic surgeon didn't want to operate injury.
ridges between a-b triradii on the left palm; 19. PRL2 number of ridges between b-c triradii on the left palm; 20. PRL3 number of ridges between c-d triradii on the left palm; 21. PRL1-3 pooled number of ridges between a-b, b-c and c-d triradii on the left palm; 22. ATDL atd angle on the left palm in degrees; 23. TFRC FRD1-5+FRL1-5 pooled number of ridges on all ten fingers, 24. TPRC a sum of epidermal ridges between triradii a-b, b-c and c-d on both palms; 25. ATDDL bilateral sum of atd angle in degrees on both palms. Picture 2.

The areas of the quantitative digitopalmar dermatoglyphic analysis

The following five of 25 study variables showed a statistically significant difference between patients and control imprints in terms of increase: 1. PRD2, number of ridges between b-c triradii on right hand, 2. TPRCD, pooled number of epidermal ridges between triradii a-b, b-c and c-d on the right palm, 3. PRL3, number of epidermal ridges between c-d triradii on the left hand, 4. TPRL, pooled epidermal ridges between triradii a-b, b-c and c-d on the left palm. 5. TPRC the number of epidermal ridges between triradii a-b, b-c and c-d on the both palm.

3. Results

Results are tabularly presented in Tables 1-3.

Table 1. Quantitative properties of right hand digitopalmar dermatoglyphics in patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient group</th>
<th>Control group</th>
<th>Risk level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n x      SD</td>
<td>n x      SD</td>
<td></td>
</tr>
<tr>
<td>FRD1</td>
<td>40 18,23 5,53</td>
<td>200 17,23 5,56</td>
<td>0,302</td>
</tr>
<tr>
<td>FRD2</td>
<td>40 12,33 7,16</td>
<td>200 11,62 6,56</td>
<td>0,539</td>
</tr>
<tr>
<td>FRD3</td>
<td>40 12,45 5,92</td>
<td>200 11,44 5,31</td>
<td>0,283</td>
</tr>
<tr>
<td>FRD4</td>
<td>40 16,58 5,90</td>
<td>200 15,78 5,72</td>
<td>0,425</td>
</tr>
<tr>
<td>FRD5</td>
<td>40 13,75 5,41</td>
<td>200 12,70 4,83</td>
<td>0,220</td>
</tr>
<tr>
<td>TFRCD</td>
<td>40 73,33 24,0</td>
<td>200 68,77 21,65</td>
<td>0,234</td>
</tr>
<tr>
<td>a-b rcD</td>
<td>40 42,23 4,24</td>
<td>200 41,03 6,02</td>
<td>0,164</td>
</tr>
<tr>
<td>b-c rcD</td>
<td>40 29,60 4,96</td>
<td>194 27,31 6,00</td>
<td>0,025</td>
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<tr>
<td>c-d rcD</td>
<td>40 38,48 6,82</td>
<td>194 36,70 6,43</td>
<td>0,116</td>
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<tr>
<td>TPR rcD</td>
<td>40 110,50 10,9</td>
<td>194 105,05 12,68</td>
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<tr>
<td>ATD D</td>
<td>40 46,85 8,82</td>
<td>200 46,87 8,67</td>
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Table 2. Quantitative properties of left hand digitopalmar dermatoglyphics in patients and controls

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<td></td>
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<td>n x      SD</td>
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</tr>
<tr>
<td>FRL1</td>
<td>40 16,38 5,54</td>
<td>200 14,80 5,76</td>
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<tr>
<td>FRL2</td>
<td>40 11,90 7,18</td>
<td>200 10,87 6,88</td>
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<tr>
<td>FRL3</td>
<td>40 11,58 6,65</td>
<td>200 11,58 5,72</td>
<td>1,000</td>
</tr>
<tr>
<td>FRL4</td>
<td>40 15,13 6,45</td>
<td>200 15,13 5,25</td>
<td>1,000</td>
</tr>
<tr>
<td>FRL5</td>
<td>40 13,25 4,84</td>
<td>200 12,26 4,80</td>
<td>0,234</td>
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<td>TFRCL</td>
<td>40 68,22 25,46</td>
<td>200 64,62 22,08</td>
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<tr>
<td>a-b rcL</td>
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<td>200 41,82 5,90</td>
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<tr>
<td>b-c rcL</td>
<td>40 27,83 4,68</td>
<td>200 26,90 5,67</td>
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<tr>
<td>c-d rcL</td>
<td>40 39,35 6,18</td>
<td>200 35,34 6,86</td>
<td>0,110</td>
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<tr>
<td>TPR rcL</td>
<td>40 110,93 10,72</td>
<td>200 105,20 13,28</td>
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<tr>
<td>ATD L</td>
<td>40 47,50 9,56</td>
<td>200 47,70 8,39</td>
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Table 3. Quantitative properties of digitopalmar complex on both hands in patients and controls

<table>
<thead>
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<th>Control group</th>
<th>Risk level</th>
</tr>
</thead>
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<td></td>
<td>n x      SD</td>
<td>n x      SD</td>
<td></td>
</tr>
<tr>
<td>TFRC</td>
<td>40 141,55 48,57</td>
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<tr>
<td>TPRC</td>
<td>40 110,93 10,72</td>
<td>200 105,20 13,20</td>
<td>0,130</td>
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<tr>
<td>ATDDL</td>
<td>40 94,35 2,43</td>
<td>200 94,56 15,88</td>
<td>0,939</td>
</tr>
</tbody>
</table>

4. Discussion

This is a second paper to the best of our knowledge dealing with. First was our in sixty men, (21). We have mentioned in the introduction some papers in genetics of complex regional pain syndrome. The next in line of papers which include genetic basis of syndrome are that of van Hilten et al, 2000, who
have found significant elevation HLA DR13 antigen in fixed dystonia and HLA DR15 and HLA DQ1 increases of CRPS without motor symptoms (30). Vaneker et al, 2002. in their paper concluded: this study has demonstrated a statistically significant association of HLA DR6 and DQ1 in a subgroup CRPS I patients. For the first time it is shown that the presence of TNF 2 allele are associated with certain presentations of CRPS I. The finding of a significantly increased TNF2 allele, may open the new pathways in the treatment of these presentations of CRPS (31). Van de Beek et al, 2003, reported of the connection of HLA DR13 and CRPS, and a new locus, D6S1014, in (24 female and 2 male patient) (32). De Rooij et al, 2009, identified 31 CRPS families with two or more affected relatives, including two families with five, four with four, eight with three and 17 with two affected relatives. In comparison with eCRPS patients, fCRPS patients had a younger age of onset and more often had multiple affected extremities and dystonia. They concluded that CRPS may occur in familial form, but they did not find clear inheritance pattern. Patients with fCRPS develop the disease at a younger age and have a more severe phenotype than sporadic cases, suggesting a genetic predisposition to develop CRPS. (33). De Rooij et al, 2009, concluded that their 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 (34). De Rooij et al, 2009, on the basis of 150 patients were found that HLA antigens B62 i DQ8 are significantly associated with CRPS and dystonia. The association remained significant after correction (HLA-B62 P(corrected) /P(c)=0.02 and HLA DQ8/P(c)=0.04. The involvement of HLA62 and DQ8 in CRPS with dystonia may indicate that these loci are implicated in the susceptibility or expression of the disease (35). Van Rooijen et al, 2012, tested the possible association with HLAB62 and HLADQ8 in a clinically homogeneous group of 131 CRPS patients without dystonia. They showed an increased prevalence of HLA DQ8 (molecularly typed as HLA-DQB1*03:02; OR=1.65 (95% CI 1.12-2.42), P=0.14) in CRPS without dystonia, whereas no association was observed for HLA B62 (molecularly typed as HLA-B*15:01; OR=1.22 (95% CI. 78-1.92/ P=.458). Their data suggest that CRPS with and CRPS without dystonia may be genetically different, but overlapping disease entities because only HLA-DQ8 is associated with both. The findings also indicate, that distinct biological pathways may play a role in both CRPS subtypes (36). Eun Heiu Jin et al, 2013, in 24 patients (13 CRPS I and 11 CRPS II) have found, that the expression level of HLA-A29,1, MMP9, ANPEP, HDC, G-CSFR3, STAT3 genes
is nearer to 14th week - earlier genetic impact (38). Some explanation could be given by different gender perception of pain and hormonal influences. From the very beginning it seems that females are more sensitive to pain than males. In one research study scientist looked at normal pain responses of newborn babies. When nurses pricked their heels to get blood for a lab test, girl babies showed more pain on their faces than boy babies. It suggests that females may be more sensitive to pain than males right from the birth. Pain disorders seem to be related to sex hormone levels in many women. For instance, after puberty, when sex hormone levels rise, girls start to have more migraines than boys, but other painful conditions, such a joint pain, don't became more common in women until after menopause, when sex hormone levels drop. In research studies with adults that look at normal pain responses, women usually report more pain than men. Women also have more sensitive pain reflexes. For instance, women pull their leg up sooner than men when increasingly greater electric shocks are applied to a nerve in the foot. Research has shown that women become more sensitive to pain after repeated exposure to painful stimuli than men. Some think that lifetime of painful experiences, such as painful periods (menstrual cycles, childbirth), may make a woman's nervous system more sensitive to pain (39). Lastly, very interesting remarks we cite from Box 4 of pain genes Foulkes and Wood: gender difference in pain perception have reported by many studies, in both animals and humans. For example, women are more likely to suffer from variety of chronic pain disorders, including fibromyalgia, complex regional pain syndrome (40,41), and trigeminal neuralgia. Experimentally, pain thresholds for pressure pain and electrical stimulation have been shown to lower for females than for males, while less variation has been observed for thermal pain stimuli (42). For a detailed treatment of gender difference in pain perception, see the recent and comprehensive review from Greenspan at al, (43). A proportion of these variations may result from genetic differences at loci on the sex chromosomes. Gonadal factors testosterone and estradiol modulate sensitivity to pain and...
analgesia (44), resulting in gender difference in pain perception. Mogil et al (45) reported that certain sex differences in pain analgesia appear genetically mediated. The investigation of genetically linked factors affecting pain sensitivity, however, is confused by contributions of gender disease processes, and by social influences. Nevertheless, several interesting findings have been reported, including greater opioid-induced analgesia in man than females (46,47). A broad spectrum of complexity of pain and its course and perception has described Inna Belfer (48) and others (49,50). Afterwards, there is a basic difference between DNA „fingerprint“ and dermatoglyphic fingerprints. DNA „fingerprint“ is identical in monzygotic twins, but dermatoglyphic fingerprints are distinctive in all human beings, including identical twins (51). That is why, in dermatoglyphic research, there is sufficiently room – and that is fascinating challenge – for the explanations which mentioned above of pain CRPS females patients and genetics.

On the end, it is very important to emphasise, it seems that be some connections on the fourth chromosome loci for complex regional pain syndrome type I on 4p12 (52), dermatoglyphics SMARCAD1 on 4q22-23 (53), psoriatic arthritis on 4q27(54), and psoriasis on 4q28-32 (55), picture 11, because it is noticed an association in many cases, CRPS with psoriatic arthritis (56). Very often trauma/algodystrophy is a trigger for appearance of psoriasis and psoriatic arthritis (57,58), our female patient has HLA positive loci for psoriatic arthritis A2, AND, B39, BND, Cw3, Cw12, DR4, DR12, DQ1. After all, positive ANA prevalence of 30% in 82 patients include some elements of immunity too (59), our patient is borderline ANA positive. And on the very end, worth of mention is the paper entitled: Complex Regional Pain Syndrome type I does not exist (can it be a contradiction in many cases, CRPS with psoriatic arthritis (56). Very often trauma/algodystrophy is a trigger for appearance of psoriasis and psoriatic arthritis (57,58), our female patient has HLA positive loci for psoriatic arthritis A2, AND, B39, BND, Cw3, Cw12, DR4, DR12, DQ1. After all, positive ANA prevalence of 30% in 82 patients include some elements of immunity too (59), our patient is borderline ANA positive. And on the very end, worth of mention is the paper entitled: Complex Regional Pain Syndrome type I does not exist (can it be a normal reaction after immobilization?) (60). It sounds very strange, and shows a lack of clinical experience, but we have already made a comment about, in our previous paper: „While traumatologist would argue that cases of algodystrophy are less frequently encountered since fractures have been even more commonly managed by osteosynthesis rather than plaster immobilization it still occur to an to be highly refractory to treatment“ (21).

5. Conclusion

By the one of very cheap method of genetic research, quantitative digitopalmar dermatoglyphic analysis (one Euro to 1000 Euro for eight loci HLA typisation in the sixth chromosome), in increasing of sum of epidermal ridges between triradii b-c and total ridge count on the right palm, and between triradii c-d and and triradii c-d and total ridge count on the left palm, then total palmar ridge count on both palm, it is possible to make female risk group of patients very early after trauma and start by curing as sun as possible, (see the new est paper in 86 female cerebral patients too, 61), what is the basing meaning of this research.

6. Ethics

There is not any danger for the patients from this kind of research. Dermatoglyphic analysis, which is one of generic method, is without any harmful consequence for sick persons. The procedure are in accordance with ethical standards in scientific research at Croatian Medical Association’s Codex of Medical Ethic and Deontology, and Helsinki Declaration of World Medical Association Edinburg, 2000.

7. Conflict of interest

There is no conflicts of interest among the authors.

8. Acknowledgements

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The Fourth Chromosome
Genetic loci SMARCAD1, deletes dermatoglyphic drawings, algodystrophy syndrome, psoriatic arthritis, psoriasis and primary hypertrophic osteoarthropathy in the fourth chromosome.

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