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IDENTIFICATION OF AN INHERITED FORM OF PEYRONIE'S DISEASE WITH AUTOSOMAL DOMINANT INHERITANCE AND ASSOCIATION WITH DUPUYTREN'S CONTRACTURE AND HISTOCOMPATIBILITY B7 CROSS-REACTING ANTIGENS

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ABSTRACT

Peyronie's disease is an inflammatory disorder with no confirmed etiology. We have documented the familial transmission of the disease as an autosomal dominant trait in 3 pedigrees. The occurrence of Dupuytren's contracture in 7 of 9 (78 per cent) affected individuals, which is a significant increase over the average 10 per cent reported in sporadic cases, suggests that both of these fibrosing disorders are pleiotropic effects of the same gene in these families. Similarly, the histocompatibility B7 cross-reacting antigens were present in 90 per cent of the patients with Peyronie's disease. Additional studies, including careful family histories and histocompatibility antigen typing, are necessary to elucidate the role of histocompatibility antigens as a relative risk factor.

Peyronie's disease is characterized by the development of localized fibrous plaques on the dorsum of the penis. These plaques cause the erect penis to be angulated and frequently painful, making sexual intercourse difficult or impossible. The incidence of Peyronie's disease is not known. A review of the literature until 1966 revealed 3,600 cases[1] and a survey of the English literature since 1966 has revealed >850 additional cases. Since the intimate nature of the disease inhibits discussion of its symptomatology and, thus, limits accurate documentation of its presence, it must be assumed that the occurrence of the disease is much higher than the reported cases.

The disease was first mentioned in 1687 and was discussed clinically by de la Peyronie in 1743.[2] No etiology for the disease has been documented for >200 years since that time. Sexual intemperance, venereal disease, gout, diabetes, arteriosclerosis and changes in hormonal balance have all been proposed and subsequently discredited as etiologies.[3] However, in a small percentage of patients repeated minor trauma cannot be discounted as an inciting factor in the disease.[1] Even this etiology has been amended with the suggestion that some underlying connective tissue abnormality is of greater etiological importance than the trauma.[4]

The only documented cases of a definite inciting agent for the changes of Peyronie's disease implicate the β-blocking medications propranolol and metoprolol.[5-7] Bivens and associates reported 1 other case of induced Peyronie's disease.[8] The symptoms of Peyronie's disease occurred concurrently with the carcinoid syndrome in association with other fibrotic changes of the retroperitoneum and endocardium.

The presence of other fibrotic changes with Peyronie's disease is relatively common. Fibrosis of the male breast[9] and auricular cartilage,[10] and the formation of knuckle pads of dense fibrous tissue over the interphalangeal joints[11] all have been associated with Peyronie's disease.

Dupuytren's contracture is a localized fibrosing connective tissue disorder with pathological changes similar to those of Peyronie's disease.[12] The simultaneous occurrence of Dupuytren's contracture with Peyronie's disease was first reported in 1849 by Kirby[13] and presently is reported to occur in about 10 per cent of the patients with Peyronie's disease.[1] The familial occurrence of Dupuytren's contracture has been demonstrated in 10 to 40 per cent of the families of affected patients, the inheritance pattern being autosomal dominant.[14]

Because of the documented familial inheritance pattern of Dupuytren's contracture and because of its significant association with Peyronie's disease, Byström and Rubio sought but did not find familial aggregation of Peyronie's disease in 106 patients.[15] These investigators concluded that "the intimate nature of the disease, with its symptoms not calling for an open discussion" might have been the reason for the failure to find an affected relative.

Other diseases with localized fibrotic lesions similar to Peyronie's disease have been shown to be associated with specific histocompatibility antigens (HLAs). The most studied of these diseases is ankylosing spondylitis, which is significantly associated with HLA-B27, an antigen of the HLA-B7 cross-reacting group.[16,17] The B7 cross-reacting group includes B7, B27, Bw22, B40 and Bw42. Willscher and associates cited this association between localized fibrotic lesions and specific HLA antigens, and tissue typed all patients seen with Peyronie's disease.[18] Of the 8 patients with no history of trauma 7 had an HLA-B7 cross-reacting group antigen. This significant association of HLA specificity with Peyronie's disease suggests an immunogenetic influence on the pathogenesis of the disease.

We investigated the pedigrees of 3 individuals who had a positive family history for Peyronie's disease. We herein give evidence that Peyronie's disease is inherited as an autosomal dominant trait in these patients. The simultaneous occurrence of Dupuytren's contracture with Peyronie's disease in these families is significantly greater than the reported average. Antigens of the HLA-B7 cross-reacting group occurred in all 3 kindreds. Concordant inheritance was demonstrable in 1 family that possessed 3 HLA-A3, B7 haplotypes. However, the same HLA-A3, B7 haplotypes did not co-segregate with disease.

MATERIALS AND METHODS

Patient selection. Families chosen for analysis were those in which the proband had a positive family history for Peyronie's disease. Patients who did not have knowledge of a family history for Peyronie's disease were not included in the study nor were they serotyped. The diagnosis of Peyronie's disease and Dupuytren's contracture was determined by examination by a qualified physician. To document the presence of

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Dupuytren's contracture there must have been nodular fibrosis of the palmar fascia.

HLA typing. HLA-A, B and C serologic determinations were done by the standard microtoxicity methods.[19] In family S mixed lymphocyte culture testing was done to genotype the family more accurately.

RESULTS

Family R. This family first suggested the possible inheritance of Peyronie's disease (fig. 1). The proband (III-37) was a 49-year-old white man with Peyronie's disease who was referred by his 48-year-old brother (III-36). The brother had Peyronie's disease, Dupuytren's contracture and Reiter's syndrome. The proband's sister (III-38) had Dupuytren's contracture. His mother denied that the deceased father (II-21) had been affected with either Dupuytren's contracture or Peyronie's disease. The occurrence of Dupuytren's contracture on the maternal side of the family in II-7, II-10, II-14 and III-24 was associated with the identical HLA type (A2, B15, Cw2/A24, B15, Cw3) in 3 of these 4 family members. The proband's mother (II-20), who did not have Dupuytren's contracture, did not share either of these HLA haplotypes with her affected siblings. Her 3 children inherited the maternal haplotype A2, Bw51. The son affected with Peyronie's disease (III-37) and the son affected with both diseases (III-36) share the same paternal haplotype A2, B27, Cw3. Their sister (III-38) inherited the alternate haplotype A3, B44, also carried by her paternal cousins III-39 and III-40, 1 of whom had Peyronie's disease. These segregation patterns suggest that the gene for Peyronie's disease was transmitted by II-21 to his offspring as was the A2, B27, Cw3 haplotype. The pattern also suggests transmission of the gene by II-22 to his son (III-40). However, since III-40 did not inherit the A2, B27, Cw3 haplotype, the hypothetical gene for Peyronie's disease cannot be linked closely to HLA. Inasmuch as Dupuytren's contracture is more prevalent than Peyronie's disease it is likely that the multiple cases of Dupuytren's contracture on the maternal side are coincidental, especially since Peyronie's disease did not occur in that kindred. Because of this coincidence it is not possible to determine whether the Dupuytren's contracture of III-38 is of maternal or paternal origin.

Family S. This kindred has a 3-generation history of father-to-son transmission of Peyronie's disease and a 4-generation history of Dupuytren's contracture (fig. 2). The proband (IV-1) was a 28-year-old white man with both diseases. His siblings IV-2 and IV-3 (25 and 20 years old, respectively) were unaffected. The proband's father (III-5) and paternal uncle (III-2) also were doubly affected, while the other 3 paternal siblings (III-1, III-3 and III-4), including 1 female subject, had Dupuytren's contracture. The deceased paternal grandfather (II-1) was said to have been doubly affected and the great grandfather (I-1) was reported to have had Dupuytren's contracture. Blood samples were obtained on all living members of this kindred except III-4. This kindred provides the most convincing evidence for the autosomal dominant inheritance of Peyronie's disease. Furthermore, the presence of Dupuytren's contracture in all affected male subjects indicates pleiotropism. The relationship of HLA to the disease is obscured in this kindred because everyone in the family, including the mother (III-6), carries an A3, B7 haplotype. The father (III-5) was homozygous for HLA-A3, B7, as was his brother (III-2). The unaffected brother of the proband (IV-2) also was an A3, B7 homozygote. However, absence of the disease in IV-2 cannot yet be ruled out because at his present age of 20 years one would not expect the disease to be manifest. The HLA-A3, B7 haplotypes of the father's siblings were assigned by inferring the genotypes of their parents. Clearly, each grandparent was an obligatory carrier of A3, B7. The alternate haplotypes of each grandparent were inherited by III-1 and III-3. While the paternal side of this family has 2 successively transmitted A3, B7 haplotypes, there is, coincidentally, a third A3, B7 haplotype transmitted by the mother.

Family A. The proband (II-2) was a 60-year-old white man doubly affected with Peyronie's disease and Dupuytren's contractures (fig. 3). He had 1 similarly affected 54-year-old brother (II-4) and 1 unaffected 56-year-old brother (II-3). His 79-year-old maternal aunt (I-3) had Dupuytren's contracture. His 82-year-old mother (I-2) and a 78-year-old uncle (I-4) were unaffected, as were his 2 children (III-1 and III-2, ages 36 and 31 years, respectively). The HLA haplotypes show that the proband (II-2) inherited HLA-B7. However, the A3, B7 haplotype, which also is associated with the affected kindred of family S, is inherited from the mother. This pedigree also is consistent with the inheritance of Peyronie's disease as a Mendelian dominant trait. The occurrence of both diseases in the affected siblings (II-2 and II-4) again supports a pleiotropic gene expression of Dupuytren's contracture in this inherited form of Peyronie's disease.

DISCUSSION

The 3 families studied herein show that Peyronie's disease can be transmitted as an autosomal dominant trait. This is the first time that an inheritance pattern has been documented for this disease of unknown etiology. The concomitant occurrence of Dupuytren's contracture in 7 of the 9 patients with Peyronie's disease (78 per cent) is a significant increase over the average 10 per cent reported by other investigators.[1, 10, 20] This finding suggests that by selecting for study only those patients with familial occurrence of Peyronie's disease, we have selected a population in which both of these fibrotic conditions may

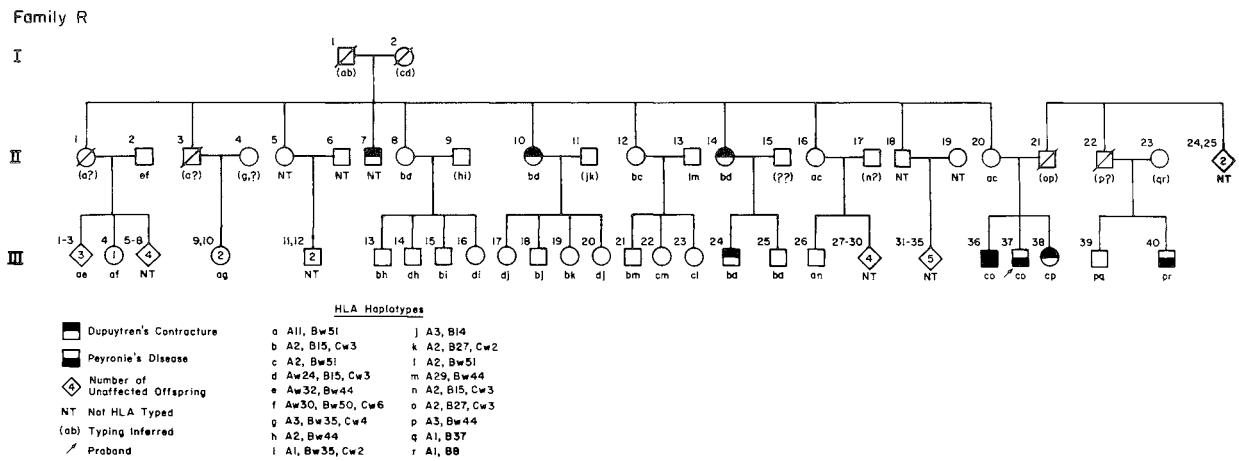

FIG. 1. Pedigree of family R with HLA haplotypes, Peyronie's disease and Dupuytren's contracture phenotypes

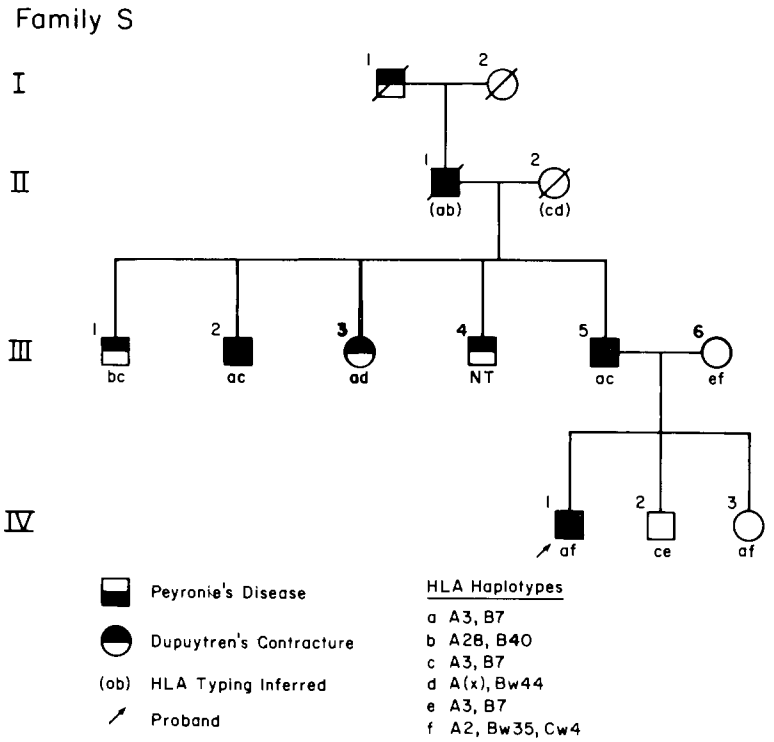

FIG. 2. Pedigree of family S with HLA haplotypes, Peyronie's disease and Dupuytren's contracture phenotypes

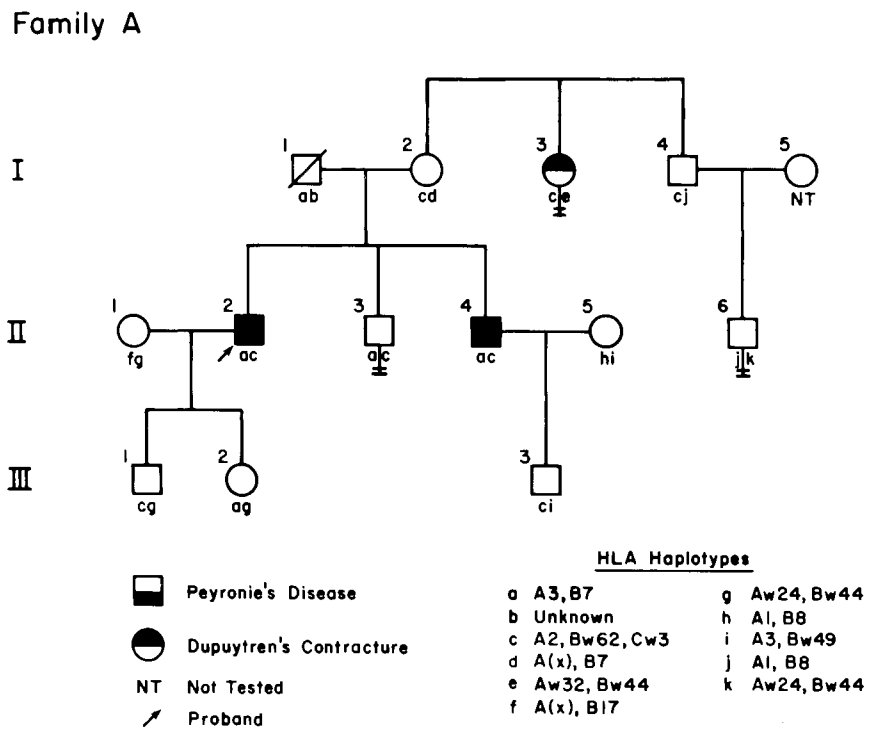

FIG. 3. Pedigree of family A with HLA haplotypes, Peyronie's disease and Dupuytren's contracture phenotypes

represent pleiotropic effects of the same gene.

The gene for Peyronie's disease exhibits incomplete penetrance in relation to Dupuytren's contracture. Not all male patients manifest both conditions and presumed female carriers, such as I-2 of family A, may be unaffected. The trait also may be incompletely penetrant for the expression of penile fibrosis, as evidenced by III-1 and III-4 of family S with Dupuytren's contracture and not Peyronie's disease. The presence of the HLA-B7 cross-reacting group antigen does not appear to affect penetrance in these kindreds since all 3 of the subjects were B7 positive.

Dupuytren's contracture is a disease that varies in incidence according to the country of origin. It has been estimated that 1 to 3 per cent of the general population has Dupuytren's contracture.[20] Ling showed the incidence of Dupuytren's contracture among elderly men to vary from 18 per cent in Lancashire, England to 29 per cent in Edinburgh, Scotland and Victoria, Australia.[14] The incidence in Norway was reported to be 9.4 per cent for male subjects.[21] This high incidence, coupled with a variable family inheritance, suggests that Dupuytren's contrac-

ture is etiologically heterogeneous and that it can be attributed to a gene for Peyronie's disease in only a percentage of the patients affected with Peyronie's disease. Similarly, we assume that Peyronie's disease is etiologically heterogeneous and that we have studied only 1 subgroup, isolated as an inherited disease. Diseases that are manifest by idiopathic fibrous proliferation have been grouped into 2 general categories:[22] 1) those with a localized, noninvasive, self-limiting presentation, including keloid, Dupuytren's contracture and Peyronie's disease, and 2) the inflammatory fibroses, including retroperitoneal fibrosis, pseudotumor of the orbit, mediastinal fibrosis, Reidel's fibrous thyroiditis and sclerosing cholangitis. Histological and biochemical studies have shown identical changes in the lesions of the first group.[12, 23] This finding suggests that a heterogeneous etiology can produce identical pathological changes.

The identification of familial transmission and association of the HLA-B7 antigens with Peyronie's disease support the concept of a common etiology for Peyronie's disease in these patients. In contrast to the small study of Willscher and associates that suggested a B7 cross-reacting group association with idiopathic Peyronie's disease,[18] in a series of 22 white patients Leffell and associates found only 6 (27 per cent) with B7 and 1 (5 per cent) with B27. This frequency approximates that of the general population. It is significant that only 3 of their patients also were affected with Dupuytren's contracture, 2 of whom (67 per cent) had the HLA-B7 cross-reacting antigens. This suggests that their study did not select a specific subgroup from the heterogeneous population of Peyronie's disease.

The 3 families discussed present a complex interaction between an autosomal dominant trait with pleiotropic expression and antigens of the HLA-B7 cross-reacting group. Reviews of Peyronie's disease have failed to document either a true incidence or etiology for the disease. Inflammation, infection and trauma frequently are mentioned as speculative considerations for the cause of the disease but no direct relationship has been documented. This study, which demonstrates a form of Peyronie's disease with a genetic inheritance pattern, significant association with Dupuytren's contracture and the presence of the HLA-B7 cross-reacting antigens in all kindred, will provide an opportunity to gain insight into the etiology of Peyronie's disease in susceptible individuals. Additional studies, including careful family histories and HLA typing, will be necessary to elucidate the role of HLA as a relative risk factor.

REFERENCES

1. Billig, R., Baker, R., Immergut, M. and Maxted, W.: Peyronie's disease. Urology, **6:** 409, 1975.
2. de la Peyronie, F.: Sur quelques obstacles qui s'opposent a'l'ejaculation naturelle de la semence. Mem. de l'Acad. Roy. de Chir., p. 425, 1743.
3. Callomon, F. T.: Induratio penis plastica. The problem of its etiology and pathogenesis: a critical review. Urol. Cutan. Rev., **49:** 742, 1945.
4. Ashworth, A.: Peyronie's disease. Proc. Roy. Soc. Med., **53:** 692, 1960.
5. Osborne, D. R.: Propranolol and Peyronie's disease. Letter to the Editor. Lancet, **1:** 1111, 1977.
6. Wallis, A. A., Bell, R. and Sutherland, P. W.: Propranolol and Peyronie's disease. Letter to the Editor. Lancet, **2:** 980, 1977.
7. Yudkin, J. S.: Peyronie's disease in association with metoprolol. Letter to the Editor. Lancet, **2:** 1355, 1977.
8. Bivens, C. H., Maracek, R. L. and Feldman, J. M.: Peyronie's disease—a presenting complaint of the carcinoid syndrome. New Engl. J. Med., **289:** 844, 1973.
9. Heite, H. J. and Siebrecht, H. H.: Beitrag zur pathogenese der induratio penis plastica. Derm. Wchnschr., **121:** 1, 1950.
10. Gallizia, M. F.: Triade collagene: maladie de la Peyronie, maladie de Dupuytren et fibrose du cartilage auriculaire. J. d'Urol. Nephrol., **70:** 424, 1964.
11. Gossrau, G. and Selle, W.: Zur Koinzidenz der Induratio penis plastica der Dupuytrenschen Kontraktur und der Knuckle pads. Derm. Wchnschr., **151:** 1039, 1965.
12. Ariyan, S., Enriquez, R. and Krizek, T. J.: Wound contraction and fibrocontractive disorders. Arch. Surg., **113:** 1034, 1978.
13. Kirby, J.: On an unusual affection of the penis. Dublin Med. Press, **22:** 209, 1849.
14. Ling, R. S.: The genetic factor in Dupuytren's disease. J. Bone Joint Surg., **45:** 709, 1963.
15. Byström, J. and Rubio, C.: Induratio penis plastica (Peyronie's disease). Clinical features and etiology. Scand. J. Urol. Nephrol., **10:** 12, 1976.
16. Schlosstein, L., Terasaki, P. I., Bluestone, R. and Pearson, C. M.: High association of an HL-A antigen, W-27, with ankylosing spondylitis. New Engl. J. Med., **288:** 704, 1973.
17. Brewerton, D. A., Caffrey, M., Hart, F. D., James, D. C. O., Nichols, A. and Sturrock, R. D.: Ankylosing spondylitis and HLA-A27. Lancet, **1:** 904, 1973.
18. Willscher, M. K., Cwazka, W. F. and Novicki, D. E.: The association of histocompatibility antigens of the B7 cross-reacting group with Peyronie's disease. J. Urol., **122:** 34, 1979.
19. Amos, D. B., Bashir, H., Boyle, W., MacQueen, M. and Tiilikainen, A.: A simple micro cytotoxicity test. Transplantation, **7:** 220, 1969.
20. Desanctis, P. N. and Furey, C. A., Jr.: Steroid injection therapy for Peyronie's disease: a 10-year summary and review of 38 cases. J. Urol., **97:** 114, 1967.
21. Mikkelsen, O. A.: The prevalence of Dupuytren's disease in Norway. A study in a representative population sample of the municipality of Haugesund. Acta Chir. Scand., **138:** 695, 1972.
22. Lepor, H. and Walsh, P. C.: Idiopathic retroperitoneal fibrosis. J. Urol., **122:** 1, 1979.
23. Tavormina, V., Gambolo, P. and Gaggioti, G.: Collagénoses (triade de Galligia) et hydroxyprolline tissulaire. J. Urol. Nephrol., **83:** 630, 1977.
24. Leffell, M. S., Devine, C. J., Jr., Horton, C. E., Somers, K. D., Rowe, M. J., Vande Berg, J. S., Bluemink, G. G., Dawson, D. and Wright, G. L., Jr.: An analysis of histocompatibility antigens in association with Peyronie's disease. Read at annual meeting of American Urological Association, Boston, Massachusetts, May 10–14, 1981.