

This Week's Citation Classic®

Cudworth A G & Woodrow J C. Evidence for HL-A-linked genes in "juvenile" diabetes mellitus. *Brit. Med. J.* 3:133-5, 1975.
[University Department of Medicine, University of Liverpool, England]

HLA typing of 150 patients with early onset diabetes mellitus showed a significant association with B8 and Bw15. Determination of the HLA haplotypes inherited by siblings affected with this type of diabetes showed an increase in identity of haplotypes above random expectation, strongly supporting the existence of HLA-linked disease susceptibility genes. [The *SC1*® indicates that this paper has been cited in over 205 publications.]

New Paths in Diabetes Genetics

J.C. Woodrow
Department of Medicine
University of Liverpool
Liverpool L69 3BX
England

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For several years Cyril Clarke and his associates in the Department of Medicine at the University of Liverpool had been interested in the possible role of genetic polymorphisms in the pathogenesis of disease, and studies were carried out involving the ABO and other blood group systems.

When the HLA polymorphism was revealed, it seemed to many people likely that association studies of various clinical disorders might well reveal the existence of disease susceptibility genes. The striking association of B27 with ankylosing spondylitis had just been reported. With the help of good friends at the Blood Transfusion Centre in Bristol who supplied typing sera, we were soon able to tissue type. I was at the time developing a rheumatology service, and my first research reports concerned HLA in Reiter's syndrome and anterior uveitis and one of the early studies of HLA in psoriasis.

Andrew G. Cudworth was working on diabetes mellitus in the department, and discussions with him regarding the genetics of diabetes led us to think that an HLA association study of the two main clinical types of diabetes might be fruitful. The finding of an

apparent association of "juvenile" diabetes with B8 and Bw15 in the first 50 patients led to a more extended study.

Linkage and association had been a frequent topic for discussion in the department, and I thought that we should also be doing some type of segregation analysis in families having more than one individual with insulin-dependent diabetes (Type I). Lionel S. Penrose had proposed a study of siblings as a method of testing for linkage.¹ (It is of interest that the first demonstration of autosomal linkage in humans, between the Lutheran and Lewis blood group loci, used this approach.) The finding that siblings affected with Type I diabetes tended to inherit the same HLA haplotypes gave strong support to the concept of HLA-linked susceptibility genes. A suggestion for a method of analysis, put forward with the help of Jack Green, gave further publicity to this approach to HLA and disease studies.²

Cudworth subsequently moved to St. Bartholomew's Hospital, where he immediately coordinated an extensive study of the HLA association and of islet-cell antibodies in families with Type I diabetes. His untimely death represented a great loss to this area of clinical research.

Following these early reports, the affected sibling method has been applied to numerous clinical disorders. It was soon appreciated that the pattern of inheritance of HLA haplotypes by affected siblings would throw considerable light on the genetic behaviour (dominant, recessive, etc.) of the HLA susceptibility genes.³ However, because of the considerable number of unknown variables, for example, gene frequency, recombination fraction, and genetic heterogeneity, a formidable amount of genetic analysis has been necessary, and Glenys Thomson and several other geneticists (largely in the US) made important contributions.⁴

The other major area of progress has been in the application of increasing knowledge of the major histocompatibility complex genetic region, applying cellular typing methods and restriction fragment length polymorphism using cDNA probes. This has allowed for increasingly detailed definition of those haplotypes that increase or decrease susceptibility to Type I diabetes. It is often said that things have to become very complex before they become clear, and John A. Todd's recent review⁵ of the present situation suggests that a good deal of further work will be necessary before the fog disperses and the genetic structure of Type I diabetes is revealed.

1. Penrose L S. The detection of autosomal linkage in data which consist of pairs of brothers and sisters of uncertain parentage. *Ann. Eugen.* 6:133-8, 1935. (Cited 75 times since 1945.)
2. Green J R & Woodrow J C. Sibling method for detecting HLA-linked genes in disease. *Tissue Antigen.* 9:31-5, 1977. (Cited 70 times.)
3. Thomson G & Bodmer W F. The genetic analysis of HLA and disease associations. *HLA and disease.* (Dausset J & Svejgaard A, eds.) Copenhagen, Denmark: Munksgaard, 1977. p. 84-93. (Cited 140 times.)
4. Motro U & Thomson G. The affected sib method. I. Statistical features of the affected sib-pair method. *Genetics* 110:525-38, 1985. (Cited 15 times.)
5. Todd J A. Genetic control of autoimmunity in type 1 diabetes. *Immunol. Today* 11:122-9, 1990.