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HLA AND LEUKEMIA: Is it a Simple Allelic Association?*

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The first association between a disease and MHC antigens was established for viral leukemogenesis in mice. Since then, numerous studies in humans have been carried out and the data obtained suggest that Cw3 and Cw4 may be markers for leukemia susceptibility genes. Given the relatively weak relevance of HLA-C locus antigens in immune response, unrecognized properties of Cw3 and Cw4 should be considered to explain this association. Family studies have consistently revealed limited heterogeneity of HLA antigens in those families, increased parental HLA antigen sharing resulting in increased homozygosity among offspring and high frequency of recombinations within the MHC. Furthermore, the HLA genotype of leukemic patients was found more frequently among their siblings than the anticipated 25 percent. Another significant deviation from the Mendelian expectation was increased HLA-DR identity of offspring to that of their mother in those families. These and other observations imply that in leukemia families unknown MHC-linked recessive factors linked to Cw3 and Cw4 alleles may be susceptibility genes which also cause segregation distortion of HLA genes and probably developmental errors. *Key words: HLA antigens, acute lymphoblastic leukemia, segregation, family, chromosome 6.*

The existence of a major histocompatibility complex (MHC) linked susceptibility factor has long been postulated from the well-known role of H-2 haplotypes and virus-induced leukemogenesis in mice[1]. The resistance loci for the Friend, Gross and Moloney murine leukemia viruses have all been mapped in the H-2 region[2-4]. To date, the strongest associations have been established in humans between HLA-Cw3, Cw4, A30, B17, DPw2 and DPw5 and acute leukemias whereas HLA-Aw19, B14, DR7 and DPw1 have been found to be decreased in leukemia patients[5-12]. Most other antigens reported to be increased in leukemia patients are indeed in strong linkage disequilibrium with Cw3 and Cw4[13]. The HLA-Cw3, Cw4 and HLA-DP association is most significant in acute lymphoblastic leukemia (ALL) patients[5-9]. In a family study, two of four sibs with ALL had the HLA haplotype "Aw31, Cw3, Bw61, DR5"[14]. In a subgroup of adult ALL patients of whom 45.5 percent had at least one close relative with familial leukemia, HLA-Cw3 was consistently positive along with high transcortin levels[7]. A strong association of the acute type of adult T-cell leukemia with "HLA-A26, Bw62,

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Cw3" haplotype has recently been reported[15]. Survival following bone marrow transplantation is good for individuals bearing a DRw52 haplotype and poor for those bearing a DRw53 haplotype[13]. The strong positive association of Cw3 and Cw4 with leukemia supports the possibility that the genes encoding them are, or are closely linked with, putative leukemia susceptibility gene(s)[6].

In a survey of 194 families of patients with acute leukemia, Chan et al[16] found that a genotypically HLA-identical sibling was available for 35 percent of leukemic patients although 25 percent had been anticipated. In a different series of ALL patients, more than 25 percent HLA identity was reported in sibs of patients[17]. A striking excess of identical antigens (especially HLA-DR) among the parents of leukemic patients has been reported by a number of authors[6,16,18,19]. Limited heterogeneity of HLA antigens has also been reported in parents of children with Down's syndrome which is associated with an increased risk of acute leukemia[20].

In the study of Carpentier et al[18], the HLA genotype was determined in 73 unrelated patients with acute myeloblastic leukemia (AML) and also in their first degree relatives. A significant finding was the presence of a clear genetic distortion favoring HLA homozygosity in the affected offspring. In offspring with leukemia of such families, there is a significant deviation from the Mendelian expectation of the number of patients homozygous for DR alleles shared by parents but not in healthy sibships. Von Vliedner et al[19] reported a two-fold increase in the number of homozygotes among patients compared to the expected value in families where parents shared a B or DR antigen, and significantly more heterozygotes for the shared antigens among the healthy siblings. In the same patient population of Carpentier et al[18]. The distribution of DR antigens shared by parents markedly favored phenotypic HLA identity of patients with their mothers as compared with their fathers. Obviously, this is possible only if the parental shared haplotype has a high transmission ratio as compared to the homologous haplotype (Fig. 1).

On the other hand, in a very large data set of non-diseased families, parental sharing of one or two HLA class-I antigens did not result in altered allele segregation among the 2569 healthy offspring tested[21]. In the same study, homozygous children of HLA-sharing couples and children histocompatible with their mothers were observed with frequencies close to that envisaged. In another comprehensive survey, no evidence was obtained for segregation distortion of MHC in non-diseased families[22].

The possible implications of these studies are: the segment of chromosome 6 carrying the HLA genes also carry the recessive gene(s) influencing leukemogenesis and thus the HLA alleles per se are not the critical genes; haplotypes including shared antigens should also bear a gene or genes which confer(s) the ability of preferential (male-specific) gametic transmission to those haplotypes, and if there

is a leukemia susceptibility locus on chromosome 6, it is likely linked to the MHC, as in the case of mice[1].

As mentioned above, in general, more unaffected sibs than anticipated are found to have the same HLA genotypes as their sibs with ALL, which conforms with segregation distortion. However, the subgroup of ALL patients with both HLA-Cw3 and high transcortin levels and familial tendency reacts in the opposite way. Instead of more HLA-identical sibs, fewer are found, suggesting fetal wastage of the latter combination[23].

If one can explain the association of certain HLA antigens with leukemia along with segregation distortion and relevance of homozygosity to expression of leukemic phenotype, this may well be a major step towards understanding the mysteries of leukemogenesis. The same explanation should clarify the typical maternal reproductive history of childhood leukemia seen with recurrent abortions or fetal wastage[24], and how paternal but not maternal preconceptional accumulated doses of radiation may confer a risk for leukemia in offspring[25]. Another observation which is yet unexplained is the high recombination frequency within MHC in leukemic families[26,27].

It is a well-known phenomenon that couples experiencing recurrent abortions share HLA antigens more frequently than control couples[28]. Not only recurrent abortions and leukemia but also aplastic anemia[29], gestational trophoblastic tumors[30] and anencephaly[31] seem to be associated with parental sharing of HLA antigens. The properties of the HLA system are not sufficient to rationalize these associations, but some HLA-linked factors influencing embryogenesis, as well as carcinogenesis may be responsible. Previously, these associations have been interpreted from the point of view that increased maternal-fetal HLA compatibility may somehow cause defects in embryogenesis and recurrent abortions. However, in cases of HLA antigen sharing between parents, repetitive maternal-fetal HLA compatibility is possible only if male transmission distortion exists.

The oncogene pim-1 (located at 6p21 adjacent to the MHC)[32] and the myb oncogene (located at "6q22-q24)[33] have been reported to be over-expressed in acute leukemias. There are even more oncogenes at or beyond 6q21, such as mas-1, fyn, syn, and ros-1[34]. A Friend murine leukemia virus integration site (fim-1) was recently mapped onto the human chromosome 6p23[35]. This retroviral integration region is known to be involved in mouse myeloblastic leukemias. Furthermore, there are six fragile sites on chromosome 6, three of which are located within 6p22.2-p25.1[36]. Various translocations involving 6p23 or 6q27, and more frequently (particularly in ALL) deletions at 6q15, 6q21 and 6q23 have been reported at considerable frequencies in acute leukemias[34]. Accumulation of oncogenes and fragile sites at two regions on the same chromosome with MHC may have some implications regarding the relevance of chromosome 6 in leukemogenesis in humans.

Considering the current hypothesis[37] regarding the development of childhood ALL, the first developmental error initiating a preleukemic clone in utero might be homozygosity of putative lethal factors linked to the MHC, and rearrangements on chromosome 6, such as deletions in the long arm may fit this hypothesis as a subsequent genetic error. In conclusion, investigators attempting to establish an association between HLA and leukemia should consider the entire chromosome 6 along with the genetic evolution of this particular region of the human genome.

REFERENCES

1. Lilly F, Boyse EA, Old LJ. Genetic basis of susceptibility to viral leukaemogenesis. *Lancet* 2:1207, 1964.
2. Chesebro B, Wehrly K, Stimpfling J. Host genetic control of recovery from Friend leukemia virus-induced splenomegaly: mapping of a gene within the major histocompatibility complex. *J Exp Med* 140:1457, 1974.
3. Lilly F, Pincus T. Genetic control of murine viral leukemogenesis. *Adv Cancer Res* 17:231, 1973.
4. Debre P, Boyer B, Gisselbrecht S, et al. Genetic control of sensitivity to Moloney leukemia virus in mice. III. The three H-2 linked Rmv genes are immune response genes controlling the antiviral antibody response. *Eur J Immunol* 10:914, 1980.
5. D'Amaro J, Bach FH, Van Rood JJ, et al. HLA C associations with acute leukemia. *Lancet* 2:1176, 1984.
6. Bortin MM, D'Amaro J, Bach FH, et al. HLA associations with leukemia. *Blood* 70:227, 1987.
7. De Moor P, Boogaerts M, Louwagie A. More familial leukaemia in ALL patients with both unexplained high transcortin levels and an HLA antigen Cw3. *Br J Haematol* 69:225, 1988.
8. Pawelec G, Rehbein A, Schaudt K, Busch FW. Frequencies of HLA-DP alleles in the four major types of leukemia. *Tissue Antigens* 34:138, 1989.
9. Baldauf C, Kubel M. HLA and Leukämie. *Folia Haematol* (Leipz) 116:123, 1989.
10. Caruso C, Cammarata G, Sireci G, Modica MA. HLA-Cw4 association with acute lymphoblastic leukaemia in Sicilian patients. *Vox Sang* 54:57, 1988.
11. Orgad S, Cohen IJ, Neumann Y, et al. Poor prognosis in childhood acute lymphoblastic leukemia (ALL) is associated with HLA-A11. In Dupont B (ed). *Immunobiology of HLA*. Vol. 2. New York: Springer-Verlag, 1989, pp 474-475.
12. Timonova LA, Rumiantsev AG. HLA-antigeny I; II klassov pri ostrom limfoblastnom leikoze u detěi. *Gematol Transfuziol* 34:19, 1989.
13. Honeyman M, Doran T, Rouse S. The relevance of HLA in survival following bone marrow transplantation. *Transplant Proc* 21:3062, 1989.
14. Kato S, Tsuji K, Tsunematsu Y, et al. Familial leukemia: HLA system and leukemia predisposition in a family. *Am J Dis Child* 137:641, 1983.
15. Uno H, Kawano K, Matsuoka H, Tsuda K. HLA and adult T cell leukaemia: HLA-linked genes controlling susceptibility to human T cell leukaemia virus type I. *Clin Exp Immunol* 71:211, 1988.
16. Chan KW, Pollack MS, Braun D Jr, et al. Distribution of HLA genotypes in families of patients with acute leukemia. Implications for transplantation. *Transplantation* 33:613, 1982.
17. de Moor P, Louwagie A. Distribution of HLA genotypes in sibs of patients with acute leukaemia. *Scand J Haematol* 34:68, 1985.

18. Carpentier NA, Jeannet M. Increased HLA-DR compatibility between patients with acute myeloid leukemia and their parents: implication for bone marrow transplantation. *Transplant Proc* 19:2644, 1987.

19. Von Fliedner VE, Merica H, Jeannet M, et al. Evidence for HLA-linked susceptibility factors in childhood leukemia. *Hum Immunol* 8:183, 1983.

20. Mottironi VD, Hook EB, Willey AM, et al. Decreased HLA heterogeneity in parents of children with Down syndrome. *Am J Hum Genet* 35:1289, 1983.

21. Wenk RE, Boughman JA. Inheritance of HLA class I alleles by children of parents who share antigens: A reassessment of genetic and interactive hypotheses (abstract no. 988). *Am J Hum Genet* 45:(4 Suppl), A251, 1989.

22. Klitz W, Lo SK, Neugebauer M, et al. A comprehensive search for segregation distortion in HLA. *Hum Immunol* 18:163, 1987.

23. de Moor P. Distribution of HLA genotypes in sibs of patients with acute lymphoblastic leukemia [letter]. *Eur J Haematol* 42:317, 1989.

24. van Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, van Zanen GE. Are maternal fertility problems related to childhood leukaemia? *Int J Epidemiol* 14:555, 1985.

25. Gardner MJ, Snee MP, Hall AJ, et al. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *B M J* 300:423, 1990.

26. Betuel H, Freidel AC, Gebuhrer L, ARTMO Cooperative Group. HLA antigens and haplotypes in families of leukaemic patients, eventual recipients of a bone marrow graft. In Touraine JL, et al (eds). *Bone Marrow Transplantation in Europe*. Vol. 2. Amsterdam: Excerpta Medica, 1981, pp 255-263.

27. Bashir H, Honeyman M, Doran T, Lane J. Increased frequency of recombination in HLA region in leukaemic families [letter] *Lancet* 2:44, 1982.

28. Scott JR, Rote NS, Branch DW. Immunologic aspects of recurrent abortion and fetal death. *Obstet Gynecol* 70:645, 1987.

29. Chapuis B, Von Fliedner VE, Jeannet M, et al. Increased frequency of DR2 in patients with aplastic anaemia and increased DR sharing in their parents. *Br J Haematol* 63:51, 1986.

30. Ho HN, Gill TJ 3d, Klionsky B, et al. Differences between white and Chinese populations in human leukocyte antigen sharing and gestational trophoblastic tumors. *Am J Obstet Gynecol* 161:942, 1989.

31. Fujisawa S, Aoki K, Yagami Y. Anencephalus immunogenetic factor. *Nippon Sanka Fujinka Gakkai Zasshi* 38:470, 1986.

32. Amson R, Sigaux F, Przedborski S, et al. The human protooncogene product p33pim is expressed during fetal hematopoiesis and in diverse leukemias. *Proc Natl Acad Sci USA* 86:8857, 1989.

33. Slamon DJ, Boone TC, Murdock DC, et al. Studies of the human c-myb gene and its product in human acute leukemias. *Science* 233:347, 1986.

34. Mitelman F, Heim S. Consistent involvement of only 71 of the 329 chromosomal bands of the human genome in primary neoplasia-associated rearrangements. *Cancer Res* 48:7115, 1988.

35. Van Cong N, Fichelson S, Gross MS, et al. The human homologues of Fim1, Fim 2/c-Fms, and Fim 3, three retroviral integration regions involved in mouse myeloblastic leukemias, are respectively located on chromosomes 6p23, 5q33, and 3q27. *Hum Genet* 81:257, 1989.

36. Hecht F, Ramesh KH, Lockwood DH. A guide to fragile sites on human chromosomes. *Cancer Genet Cytogenet* 44:37, 1990.

37. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia* 2:120, 1988.