HLA non-class II genes may confer type I diabetes susceptibility in a mapuche (Amerindian) affected family

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Abstract

A rare case of type I diabetes is studied in an Amerindian (Mapuche) family from Chile, analyzing glutamic acid decarboxylase, islet-cell autoantibodies and human leukocyte antigen (HLA) genes. The affected sib is the only one that has one specific HLA haplotype combination that differs from the other sibs only in the HLA class I genes. It is concluded that HLA diabetes susceptibility factors may be placed outside the class II region or even that susceptibility factors do not exist in the HLA region in this Amerindian family.

Keywords: Amerindian; HLA; Mapuche; Type I diabetes

1. Introduction

Insulin-dependent diabetes mellitus or type I diabetes (IDDM-1) is one of the most common diseases of childhood with an incidence rate that appears to be increasing in all studied countries [2]. Between 1986–1993, a low incidence of type I diabetes

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(2.5/100.000 inhabitants/year) was found in Santiago de Chile [8], but during the 1994–1998 period the incidence rose to 4.1/100.000 inhabitants/year [8]. Type I diabetes is thought to be in part an autoimmune process that destroys insulin-producing beta cells of the pancreas. In this disease several autoantibodies can be found, including, insulin antibodies (IAA), cytoplasmic islet cell antibodies (ICA) and glutamic acid decarboxylase antibodies (GAD) [4]. Human leukocyte antigen (HLA) genes bear most of the genetic susceptibility in Spanish or Mediterranean-descent Caucasoids [5,10] (http://www.ncbi.nlm.nih.gov/omim), and studies carried out revealed that the major histocompatibility complex (MHC), also designated IDDM-1, is the major, but not the exclusive, type 1 diabetes susceptibility locus. Genes outside the MHC have also been implicated in diabetes susceptibility, such as those of the insulin, the insulin receptor or cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) genes. On the other hand, not all carriers of the "susceptible genes" and autoantibodies develop the disease, which suggests that environmental factors also play a role in triggering the autoimmune process. Evidence of a protective influence of breast feeding was first derived from studies which reported a negative correlation between incidence rates of breast feeding and type I diabetes [5,6]. The Chilean population is formed by an admixture of Amerindian native groups and descendants of several European countries migrants [9]. Mapuche subjects are the largest native group in the country, and they might or might be not descendants of Asian migrations that settled in the southern part of Chile up to Patagonia [1]. The total Mapuche population is about 900,000 inhabitants distributed throughout the country, mainly living in rural areas. Data about the low incidence of diabetes (<0.001/100.000 inhabitants/year in type II and <0.4/100.000 inhabitants/year in type I diabetes) was published in the rural population of Mapuche Indians in 1985 [3].

In the present work, we have analyzed a rare case of type I diabetes that appeared for the first time in a rural Mapuche Amerindian family (Fig. 1) with at least four generations of Mapuche ancestors; both of the sib's parents showed a normal glucose tolerance test. It is shown that HLA factors other than HLA class II genes may be involved in the development of Amerindian type I diabetes [7] (http://www.ncbi.nlm.nih.gov/omim/) or even that not HLA factors may be involved.

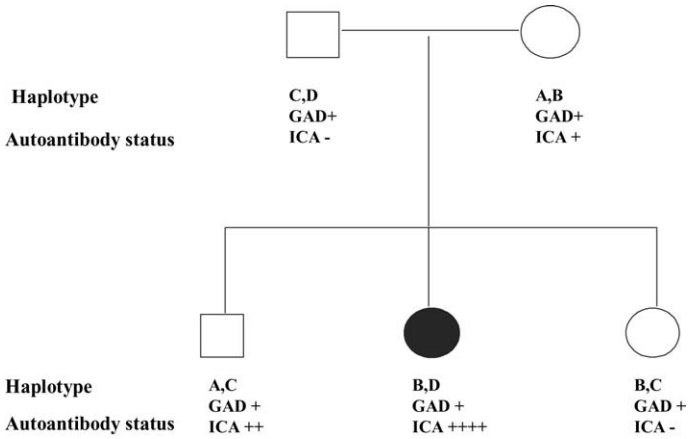

Fig. 1. Family tree indicating the haplotype composition of parents and children, along with the autoantibody status.

Table 1
Analytical parameters in an Amerindian (Mapuche) family with a type I diabetes sibling

	HLA			Typing		Haplotype	GAD [a]	ICA [b]
Mother	A*68012	B*51011	DRB1*0407	DRB4*0103/11	DQB1*0302	**A, B**	+	5 JDF
(37 y [c])	A*68012	B*4002	DRB1*0407	DRB4*0103/11	DQB1*0302			units
Father	A*02N [d]	B*3909	DRB1*0407	DRB4*0103/11	DQB1*0302	**C, D**	+	–
(39 y)	A*68012	B*3909	DRB1*0407	DRB4*0103/11	DQB1*0302			
Patient	A*68012	B*4002	DRB1*0407	DRB4*0103/11	DQB1*0302	**B, D**	+	80 JDF
(11 y)	A*68012	B*3909	DRB1*0407	DRB4*0103/11	DQB1*0302			units
Sister	A*68012	B*4002	DRB1*0407	DRB4*0103/11	DQB1*0302	**B, C**	+	–
(8 y)	A*02N	B*3909	DRB1*0407	DRB4*0103/11	DQB1*0302			
Brother	A*68012	B*51011	DRB1*0407	DRB4*0103/11	DQB1*0302	**A, C**	+	10 JDF
(12 y)	A*02N	B*3909	DRB1*0407	DRB4*0103/11	DQB1*0302			units

[a] GAD = glutamic acid decarboxylase antibodies.
[b] ICA = cytoplasmic islet cell antibodies.
[c] y = years old.
[d] A*02N = 0201, 0207, 0215N, 0218, 0220, 0224.

2. Materials and methods

The proband (a type I diabetic case) is 11 years old; his analytical profile and that of the rest of the family analytical data are detailed in Table 1; they live at Peleco community in Cañete city (at 800 km south Santiago). The proband family has typical Amerindian Mapuche anthropometry and this is the one type I diabetes case recorded in the region. Breast feeding was carried out in all three sibs during about 18 months; diagnosis was done at the age of seven and insulin dependence was absolute from disease onset. Viral infections like rubella, mumps or measles are not recorded in the family. The HLA–DNA typing was carried out as previously described by an indirect sequencing methodology [7]. The GAD antibodies, detected by an ELISA technique (specificity 98%, sensibility 71%), are found to be positive in all family members [4]; sera were reported as positive, when a result above 1500 arbitrary units (AU/ml) was achieved, standard curve was constructed by using a highly positive serum sample, obtained from GAD Workshops. Cut-off point represents mean three standard deviations of 75 healthy individuals. The ICA antibodies, as assessed by indirect immunofluorescence on cryocut sections of human pancreas, are strongly positive in the patient. The ICA and GAD autoantibodies in the healthy Mapuche population are “null” (individuals number = 83).

3. Results and discussion

The HLA genes are thought not to confer diabetes susceptibility to Amerindian populations, unless European admixture is present [7]. This does not seem to occur in the present case. Interestingly, HLA phenotyping of the family members revealed that the haplotypes and both the class I and II genes found (see Table 1) are characteristic of Amerindian populations, with no European admixture [1]. Haplotypes B and D are found simulta-

neously only in the propositus; this suggests that an HLA-linked pathogeny in this Amerindian type I diabetes case may exist. However, the HLA diabetogenic factors would be placed outside the HLA class II region since this is shared by all family members, who come from an endogamic Amerindian community. All individuals are HLA-DRB1*0407, HLA-DRB4*0103 and HLA-DQB1*0302. The combination of HLA-A and -B and other closely linked genes present in haplotypes B and D may be in part responsible for the diabetes development. It can be argued, based on the small family size, that HLA class I is not mediating this susceptibility, since haplo-identical sibs are GAD or ICA positive and may, in the long run, become diabetic. However, presence of autoantobodies does not necessarily mean that diabetes will develop and they may remain healthy, as exemplified by both parents. The only HLA difference between the patient and the other siblings is placed in the HLA class I region, and this supports our view. However, other interpretation may be that type I diabetes may not be linked to HLA in this Amerindian family. This is, to our knowledge, the first Amerindian type I diabetes reported case with apparently a recorded non-European (Caucasoid) HLA admixture. The very low incidence found in Mapuche children [8] does not completely discard an European admixture.

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References

[1] A. Arnaiz-Villena, G. Vargas-Alarcon, J. Granados, E. Gomez-Casado, J. Longas, M. Gonzalez-Hevilla, J. Zuniga, N. Salgado, G. Hernandez-Pacheco, J. Guillen, J. Martinez-Laso, HLA genes in Mexican Mazatecans, the peopling of the Americas and the uniqueness of Amerindians, Tissue Antigens 56 (2000) 405–416.

[2] J.S. Dorman, Molecular epidemiology of insulin-dependent diabetes mellitus, Epidemiol. Rev. 19 (1997) 91–98.

[3] G. Larenas, A. Montecinos, M. Manosalva, M. Barthou, T. Vidal, Incidence of insulin-dependent diabetes mellitus in the IX region of Chile: ethnic differences, Diabetes Res. Clin. Pr. 34 (1996) 147–151.

[4] R.D.G. Leslie, M.A. Atkinson, A.L. Notkins, Autoantigens IA-2 and GAD in Type 1 (insulin-dependent) diabetes, Diabetologia 42 (1999) 3–14.

[5] F. Perez-Bravo, M. Serrano-Rios, M.D. Gutierrez-Lopez, M. Calvillan, M. Garcia de los Rios, M. Kocova, J. Dorman, M. Trucco, Genetic analysis of HLA DRB1, DQA1 and DQB1 alleles and susceptibility to IDDM in Chilean subjects, Diabetologia 38 (1995) 378–379.

[6] F. Perez-Bravo, E. Carrasco, M.D. Gutierrez-Lopez, M.T. Martinez, G. Lopez, M. Garcia de los Rios, Genetic predisposition and environmental factors leading to the development of insulin-dependent diabetes mellitus in Chilean children, J. Mol. Med. 74 (1996) 105–109.

[7] E. Perez-Luque, J.M. Malacara, A. Olivo-Diaz, C. Alaez, H. Debaz, M. Vazquez-Garcia, M.E. Garay, L.E. Nava, A. Burguete, C. Gorodezky, Contribution of HLA class II genes to end stage renal disease in Mexican patients with type 2 diabetes mellitus, Hum. Immunol. 61 (2000) 1031–1038.

[8] J.L. Santos, D. Schaid, F. Perez-Bravo, F. Carrasco, M. Calvillan, C. Albala, Applicability of the case-parent design in the etiological research of Type I diabetes in Chile and other genetically mixed populations, Diabetes Res. Clin. Pr. 43 (1999) 143–146.

[9] C. Valenzuela, M. Acuña, Z. Harb, Socio-genetic gradient in Chilean population, Rev. Med. Chil. 115 (1987) 295–299.

[10] J.L. Vicario, J. Martinez-Laso, A. Corell, J.M. Martin-Villa, P. Morales, G. Lledo, et al., A. Arnaiz-Villena, Comparison between HLA-DRB and DQ DNA sequences and classic serological markers as type 1 (insulin-dependent) diabetes mellitus predictive risk markers in the Spanish population, Diabetologia 35 (1992) 475–481.