Increased Frequency of HLA A2/DR4 and A2/DR8 Haplotypes in Young Saskatchewan Aboriginal People with Diabetic End-Stage Renal Disease

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Key Words

HLA · Type 2 diabetes mellitus · Aboriginal · End-stage renal disease · Diabetic nephropathy · A2 · DR4 · DR8

Abstract

Aims: To determine the association of HLA with diabetic end-stage renal disease (ESRD) in Saskatchewan aboriginal people. **Methods:** This was a retrospective study of HLA profiles in four groups of Saskatchewan residents with ESRD diagnosed from 1980 to 1998: aboriginal people with and without ESRD, and non-aboriginal people with and without ESRD. The aboriginal ESRD group was also subdivided into those ≤ 50 and >50 years of age. Frequencies of individual and combinations of HLA antigens were compared between groups and subgroups. **Results:** HLA data were available for 634 subjects. Young aboriginal people with ESRD had a higher frequency of HLA-A2 than older AB ESRD subjects (69 vs. 36%; $p = 0.03$), and of HLA-DR4 and/or DR8 compared to older AB ESRD subjects (91 vs. 68%; $p = 0.07$) and AB non-ESRD subjects (91 vs. 67%; $p = 0.03$). Over 65% of young AB ESRD subjects had either an A2/DR4 or A2/DR8 haplotype (odds ratio 5.09 [confidence intervals 1.35, 20.15] versus older AB ESRD subjects; odds ratio 3.32 [confidence intervals 1.20, 9.3] versus AB non-ESRD subjects). Forty percent of young AB ESRD subjects were homozygous for at least one of A2, DR4 or

DR8. **Conclusions:** Our findings suggest that ESRD in young AB subjects with T2DM has a genetic basis related to HLA.

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Introduction

Canadian aboriginal people are experiencing an epidemic of diabetic end-stage renal disease (ESRD) [1] that cannot be wholly explained by increased rates of type 2 diabetes mellitus (T2DM) [2]. After adjusting for differences in rates of diabetes, for example, we found that Saskatchewan aboriginal people with diabetes were seven times more likely to develop ESRD than their non-aboriginal diabetic counterparts [3]. Reasons for the excessive burden of ESRD in this population likely relate to both environmental and genetic factors [4]. The former may include the intrauterine milieu, delayed diagnosis of T2DM, and poorer control of hypertension and hyperglycemia. A genetic contribution to T2DM nephropathy has long been suspected because of familial clustering of cases in populations with high rates of T2DM [5–8].

While the major histocompatibility complex has elicited great interest with respect to its possible role in the genetics of diabetes, a clear association between specific HLA antigens (particularly the class II antigens DR3 and DR4) has only been recognized in type 1 diabetes mellitus

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(T1DM) [9]. No similar association has been observed with consistency in populations with high rates of T2DM although an association between T2DM and HLA-A2 (a class I antigen) has been reported in Pima Indians [10]. In reviewing HLA data in the context of our renal transplant program over several years, it also appeared that certain HLA antigens might be increased among aboriginal people with DESRD caused by T2DM.

In view of the above, the purpose of this study was to determine if specific HLA antigens or combinations of antigens are associated with the presence of DESRD in Saskatchewan aboriginal people. A relationship between specific HLA antigens and DESRD in Canadian aboriginal people could contribute to an understanding of the pathogenesis of this devastating disorder, and provide possible opportunities for prevention, and early recognition and treatment of diabetic nephropathy. In addition, we considered it important to identify HLA profiles that might be associated with a higher risk of T2DM and diabetic nephropathy in potential kidney donors from aboriginal populations.

Methods

This was a retrospective study of Saskatchewan patients with end-stage renal disease (ESRD) diagnosed between January 1, 1980 and December 31, 1998. Serologically determined HLA data obtained from dialysis and transplant records maintained by the Saskatchewan Transplant Program, were linked with serial data submitted annually to the Canadian Organ Replacement Register (CORR). Parameters subsequently retrieved from CORR included a subject identifier, birth date, gender, ethnicity, cause of ESRD, and date and nature of first treatment of ESRD. For this study, ESRD was defined as the date when long-term treatment with dialysis was started, or a first transplant was carried out in an individual not yet on dialysis.

A person was considered to have DESRD if that was the diagnosis submitted to the register by the attending nephrologist. For the purpose of this study, we did not differentiate between T1DM and T2DM because T1DM is very unusual in aboriginal people, and because many diabetic non-aboriginal people had been incorrectly classified with respect to type. All patients with ESRD diagnoses other than DESRD were classified as having non-DESRD. Ethnic designation was that reported to CORR. The ethnic categories used in this study were 'aboriginal' (North American Indian, Inuit and Metis) and 'non-aboriginal' (ethnicity other than aboriginal). Over 90% of non-aboriginal subjects were Caucasian.

Analysis

Analyses were performed using SPSS (10.05) Microsoft (2000) and Epi-Info (6.02). Although our primary focus was on aboriginal people with ESRD, we were also interested in HLA profiles of non-aboriginal subjects with ESRD as a means of validating our data (non-aboriginal subjects with DESRD were expected to have higher frequencies of diabetes-related HLA antigens than non-aboriginal

subjects with non-DESRD because many of the former had T1DM). Subjects were therefore initially divided into 4 main groups: (1) aboriginal (AB) people with DESRD; (2) AB people with non-DESRD; (3) non-AB people with DESRD; (4) non-AB people with non-DESRD.

For our final analyses, the AB DESRD group was subdivided into those ≤ 50 years and those > 50 years at the time of ESRD diagnosis. We then compared the younger AB DESRD group (cases) with two control groups (older AB DESRD subjects and all AB non-DESRD subjects). Similar to the rationale used in studying the relationship between HLA and T2DM in the Pima [10], we speculated that an association between HLA and DESRD in the AB population should decrease with age among those with DESRD, and should be lowest in those with non-DESRD. Although somewhat arbitrary, we chose age 50 to subdivide the AB DESRD group because it seemed a biologically valid age to separate younger from older subjects with DESRD, and it provided us with subgroups of similar size for analysis. We did not subdivide the AB non-DESRD control group because only 6 subjects in that group were older than 50 years, and because the results of our analyses were the same regardless of whether we used the total AB non-DESRD group or just those ≤ 50 years as controls.

A basic descriptive analysis of the parameters listed above was carried out on all 4 groups. We looked for differences in these variables between subjects with and without HLA typing to detect possible selection bias in both ethnic groups. DESRD and non-DESRD subjects with HLA typing were then examined for comparability within each ethnic group.

Univariate analyses were used to determine the frequency of individual and combinations of HLA antigens. Bivariate variables were compared between groups with χ^2 tests (Yates corrected) or Fisher's exact test. Comparisons of continuous variables were carried out using independent samples mean *t* tests. The level of significance was set at $p \leq 0.05$ (two-tailed). The association of HLA antigens and HLA antigen combinations with the different ESRD groups was measured by the odds ratio (OR) with corresponding 95% confidence intervals (CI). χ^2 for linear trend was used to compare HLA antigen allele, phenotype and homozygous frequencies between AB DESRD subjects ≤ 50 years, AB DESRD subjects > 50 years and AB non-DESRD subjects. As above, an association between HLA and DESRD was considered to be most likely in the younger AB DESRD subjects and least likely in the AB non-DESRD group. For the purpose of calculating allele frequencies [10], it was assumed that HLA antigens were homozygous when only one HLA-A, B or DR antigen was detected in a subject.

Results

Over the 18-year study period, ESRD was diagnosed in 1,684 Saskatchewan residents. Of those, 1,011 had not been HLA typed and 39 had missing diagnostic and/or ethnic designation. This left a final study sample of 634 (38%) subjects of whom 110 were AB and 524 were non-AB. DESRD was diagnosed in 57 (52%) AB people and 136 (26%) non-AB people. These latter proportions were similar to those for the total ESRD population.

Table 1. Frequency of HLA antigens by group

HLA	AB				Non-AB			
	DESRD		non-DESRD		DESRD		non-DESRD	
	%	n	%	n	%	n	%	n
Subjects with A, B		57		53		136		388
A1	14	8	9	5	42	57	27	103 ^c
A2	54	31	59	31	51	69	50	192
A3	7	4	8	4	16	22	29	114 ^b
A9 (including A24)	46	26	47	25	25	34	17	66
A24(9)	42	24	34	18	15	21	13	52
A11	5	3	4	2	7	9	11	41
A30	7	4	9	5	11	15	6	25
A31	18	10	26	14	2	3	4	16
B5 (including B51)	30	17	43	23	15	20	12	48
B51(5)	28	16	32	17	7	10	10	39
B7	7	4	13	7	8	11	24	92 ^d
B8	11	6	8	4	44	60	20	77 ^d
B18	5	3	9	5	13	18	11	42
B27	18	10	9	5	18	24	9	35 ^a
B35	21	12	25	13	9	12	19	73
B39	12	7	13	7	4	5	3	13
B44	9	5	8	4	14	19	19	75
B60	11	6	4	2	9	12	8	29
B62(15)	25	14	21	11	16	22	15	58
Subjects with DR		54		52		124		365
DR1	9	5	14	7	17	21	14	52
DR2 (including DR15)	7	4	10	5	11	14	31	112 ^d
DR15(2)	2	1	4	2	2	3	13	47 ^b
DR3	7	4	14	7	50	61	21	75 ^d
DR4	56	30	60	31	54	67	31	112 ^d
DR6	22	12	19	10	11	14	11	40
DR7	7	4	4	2	13	16	23	82 ^a
DR8	30	16	15	8	2	2	5	19
DR9	7	4	17	9	2	3	3	9
Subjects with DQ		37		27		66		208
DQ1 (including DQ6)	22	8	26	7	30	20	54	112 ^c
DQ6(1)	5	2	4	1	3	2	11	22
DQ2	8	3	11	3	52	34	31	65 ^b
DQ3 (including DQ7, 8)	78	29	89	24	68	45	65	135
DQ7	43	16	41	11	15	10	39	80 ^c
DQ8	8	3	15	4	2	1	3	6
DQ4	19	7	7	2	2	1	1	3

χ^2 comparisons between AB DESRD and AB non-DESRD (there were no significant differences between the AB DESRD and AB non-DESRD groups); non-AB DESRD and non-AB non-DESRD.

^a $p < 0.05$; ^b $p \leq 0.01$; ^c $p \leq 0.001$; ^d $p \leq 0.0001$.

With respect to ethnicity, there were no significant differences in the proportion of AB and non-AB subjects who were tissue typed. There were also no differences in gender within and between groups. Among both AB and non-AB people, however, HLA-typed subjects were signif-

icantly younger when first treated for ESRD than those not tissue typed. (For AB subjects mean age 40.5 years versus 57.5 years respectively; $p < 0.001$. For non-AB subjects, mean age 42.5 years versus 65.7 years respectively; $p < 0.001$.) AB non-DESRD subjects were more likely to

Table 2. Frequency of selected HLA antigens by aboriginal group

HLA	AB DESRD						AB non-DESRD	
	all		≤ 50		> 50			
	%	n	%	n	%	n	%	n
Subjects with A, B		57		32		25		53
A1	14	8	6	2	24	6	9	5
A2	54	31	69	22	36	9 ^a	59	31
A9 (including A24)	46	26	44	14	48	12	47	25
A24(9)	42	24	38	12	48	12	34	18
A31	18	10	13	4	24	6	26	14
B27	18	10	16	5	20	5	9	5
B35	21	12	22	7	20	5	25	13
B39	12	7	19	6	4	1	13	7
B44	9	5	16	5	0	0	8	4
B5 (including B51)	30	17	28	9	32	8	43	23
B51(5)	28	16	28	9	28	7	32	17
B60	11	6	16	5	4	1	4	2
B62(15)	25	14	19	6	32	8	21	11
Subjects with DR		54		32		22		52
DR3	7	4	6	2	9	2	14	7
DR4	56	30	59	19	50	11	60	31
DR6	22	12	13	4	36	8	19	10
DR8	30	16	32	10	27	6	15	8
DR4 and/or DR8	81	44	91	29	68	15 ^b	67	35 ^a
Subjects with DQ		37		24		13		27
DQ1 (including DQ6)	22	8	21	5	23	3	26	7
DQ(6)	5	2	4	1	8	1	4	1
DQ3 (including DQ7, 8)	78	29	83	20	69	9	89	24
DQ7	43	16	44	10	46	6	41	11
DQ8	8	3	8	2	8	1	15	4
DQ4	19	7	21	5	15	2	7	2

χ^2 comparisons between AB-DESRD ≤ 50 and AB DESRD > 50; AB DESRD ≤ 50 and AB non-DESRD.

^a p = 0.03; ^b p = 0.07.

have been tissue typed than AB DESRD subjects ($p < 0.001$); however, AB non-DESRD subjects were much younger than those with DESRD.

Table 1 shows the frequency of HLA antigens that were present in at least 10% of subjects within any one of our four main study groups. The most common HLA antigens among AB subjects were A2, A9 (including A24) and A31; B5 (including B51), B27, B35, and B62; DR4, DR6 and DR8; and DQ1 (including DQ6), DQ3 (including DQ7 and 8) and DQ4. There was a somewhat higher frequency of the A24, B27, DR8 and DQ4 antigens in AB DESRD subjects; and of the A31 antigen in AB non-DESRD subjects. None of the differences, however, were statistically significant.

The most common HLA antigens in the non-AB groups were A1, A2, A3 and A9 (including A24); B7, B8, B27 and B35; DR2 (including DR15), DR3, DR4 and DR7; and DQ1 (including DQ6), DQ2, and DQ3 (including DQ7 and 8). Those with DESRD had significantly higher frequencies of the HLA antigens A1, B8, B27, DR3, DR4, and DQ2. The HLA antigens A3, B7, DR2 (including DR15), DR7, DQ1 and DQ7 (but not DQ3) were present in significantly higher frequencies in non-AB subjects with non-DESRD.

Table 2 shows the most common HLA antigens in AB subjects. AB DESRD subjects ≤ 50 years had a significantly higher frequency of the A2 antigen compared to AB DESRD subjects > 50 years of age (69 vs. 36%; $p = 0.03$), and also had higher frequencies of the DR4, DR8, DQ3

Table 3. Frequencies of selected HLA antigens in aboriginal people with renal failure

Antigen	Group	Homo-zygous	Hetero-zygous	No allele	Total subjects	Allele frequency	Phenotype frequency	Homozygous frequency
A2	DESRD $\leq$ 50	7	15	10	32	0.45	0.69	0.22
	DESRD $>$ 50	1	8	16	25	0.20	0.36	0.04
	Non-DESRD	6	25	22	53	0.35	0.59	0.11
	χ^2 linear trend					p = 0.005	p = 0.01	p = 0.04
DR4	DESRD $\leq$ 50	8	11	13	32	0.42	0.59	0.25
	DESRD $>$ 50	2	9	11	22	0.30	0.50	0.09
	Non-DESRD	9	22	21	52	0.39	0.60	0.17
	χ^2 linear trend					n.s.	n.s.	n.s.
DR8	DESRD $\leq$ 50	3	7	22	32	0.20	0.31	0.09
	DESRD $>$ 50	1	5	16	22	0.16	0.27	0.05
	Non-DESRD	1	7	44	52	0.09	0.15	0.02
	χ^2 linear trend					p = 0.03	n.s.	n.s.
DR4 and/or DR8	DESRD $\leq$ 50	11	18	3	32	0.63	0.91	0.34
	DESRD $>$ 50	3	12	7	22	0.41	0.68	0.14
	Non-DESRD	10	25	17	52	0.43	0.67	0.19
	χ^2 linear trend					p = 0.008	p = 0.01	p = 0.05

Linear trend (Mantel extension) analysis uses AB DESRD $\leq$ 50 as the comparison group.

and DQ4 antigens. While the frequency of the DR4 antigen was high in all AB groups, the frequency of the DR3 antigen was very low. When detected in diabetic subjects, the DQ4 antigen was always present with DR8. Ninety-one percent of younger AB DESRD subjects had either a DR4 or DR8 antigen (or both). This frequency was much higher than that observed in older AB DESRD subjects (68%; $p = 0.07$), and was significantly higher than that observed in AB non-DESRD subjects (67%; $p = 0.03$).

Table 3 shows the frequency of alleles, phenotypes and presumed homozygosity for HLA A2, DR4, DR8 and combined DR4/DR8 antigens in AB subjects. The frequencies of these parameters for each HLA antigen were highest in AB DESRD subjects $\leq$ 50 years. The χ^2 for linear trend was significant when comparing most A2, DR8, and DR4/DR8 frequencies between the three groups. As noted above, 91% of AB DESRD subjects $\leq$ 50 years had either a DR4 or DR8 antigen, and 1/3 appeared homozygous for one or the other.

Table 4 shows the frequencies of combinations of A2, DR4 and DR8 antigens within the AB groups. Over 65% of younger AB DESRD subjects had either an A2/DR4 or A2/DR8 haplotype (OR 5.09 [CI 1.35, 20.15] when compared to older AB DESRD subjects, and OR 3.32 [CI 1.20, 9.3] when compared to AB non-DESRD subjects). Over 40% of AB DESRD $\leq$ 50 subjects were homozygous

for at least one of the A2, DR4 or DR8 antigens. Using pairwise comparisons, the corresponding frequencies in older AB DESRD and AB non-DESRD subjects were significantly lower. The differences in all comparisons were also significant using χ^2 for linear trend. Fewer than 10% (three) of AB DESRD $\leq$ 50 subjects had no DR4 or DR8 antigen compared to 31.8% of older AB DESRD subjects and 32.7% of AB non-DESRD subjects. These differences were also highly significant.

Discussion

As far as we are aware, this is the first report of an association between specific HLA antigens and diabetic nephropathy in a Canadian aboriginal population. We have now shown that younger aboriginal people with DESRD have high frequencies of the HLA-A2, HLA-DR4 and DR8 antigens, compared to older AB DESRD subjects and AB subjects with non-DESRD. More significantly, AB DESRD $\leq$ 50 subjects were over three times as likely to have an HLA-A2/DR4 or HLA-A2/DR8 haplotype than the other two groups. Forty percent were homozygous (or had only one antigen identified) for at least one of A2, DR4 or DR8. We also observed high frequencies of other diabetes-associated HLA antigens

Table 4. Frequencies of HLA antigen combinations in aboriginal people with renal failure

HLA profile	AB DESRD ≤ 50		AB DESRD > 50		AB non-DESRD		χ^2 linear trend	AB DESRD ≤ 50 vs. AB DESRD > 50 OR (CI)	AB DESRD ≤ 50 vs. AB non-DESRD OR (CI)
	%	n	%	n	%	n			
A2/2 and DR4/4 or DR8/8	9.4	3	4.5	1	3.9	2			
A2/X and DR4/4 or DR8/8	18.8	6	4.5	1	5.8	3			
A2/2 and one DR4 or DR8	12.5	4	0	0	3.9	2			
A2/X and DR4/X or DR8/X	25.0	8	18.2	4	23.1	12			
Total of above	65.5	21	27.3	6	36.5	19	0.002	5.09 (1.35, 20.15) ^b	3.32 (1.20, 9.30) ^a
One or more homozygous	40.6	13	9.1	2	13.5	7	0.0009	6.84 (1.24, 68.18) ^a	4.40 (1.36, 14.67) ^b
AX/X and DR4/4 or DR8/8	6.3	2	4.5	1	9.6	5			
AX/X and DR4/X or DR8/X	18.8	6	36.4	8	21.2	11			
Total previous 2	25.0	8	40.9	9	30.8	16	n.s.	0.48 (0.13, 1.79)	0.75 (0.25, 2.24)
A2/2 and no DR4 or DR8	0	0	0	0	3.9	2			
A2/X and no DR4 or DR8	3.1	1	9.1	2	17.3	9			
No A2, DR4 or DR8	6.3	2	22.7	5	11.5	6			
Total previous 3	9.4	3	31.8	7	32.7	17	0.01	0.15 (0.02, 0.75) ^b	0.21 (0.04, 0.86) ^a
Total number of subjects	100	32	100	22	100	52			

^a $p < 0.05$; ^b $p \leq 0.01$.

Linear trend (Mantel extension) analysis uses AB DESRD ≤ 50 as the comparison group.

(A24, B62, DQ3, and DQ4) in the AB groups (see below), but differences between subgroups were not statistically significant.

We believe that our findings are compatible with the hypothesis that AB subjects with T2DM who are younger at the time of DESRD diagnosis, are more likely to have an HLA-associated genetic propensity for the disease. The fact that AB non-DESRD subjects had somewhat higher frequencies of HLA-A2 and DR4 (and the corresponding haplotype) than older AB DESRD subjects is likely explained by the younger age of the former. Consequently, they may still have been at risk of developing T2DM (and its complications) when they started ESRD treatment for causes of renal failure other than diabetes. Another possibility is that the HLA-A2/DR4 haplotype may predispose to AB renal failure regardless of etiology.

Our results are consistent with an earlier study in the Pima that showed an inverse relationship between HLA-A2 allele frequency and age of individuals with T2DM [10]. In contrast to findings in the Pima, however, Saskatchewan aboriginal subjects are from diverse origins including Cree, Dene, Saulteaux and Sioux First Nations, as well as a mixed Caucasian/aboriginal heritage (Metis). It is possible that there may be further HLA differences within these subpopulations, but we were unable to accurately determine the precise origins of our subjects, and

small numbers would likely have prevented us from carrying out subgroup analysis.

It is not clear from our study whether the associations that we have identified are between specific HLA antigens and DESRD, or between HLA antigens and T2DM. Either or both explanations are possible. The HLA antigens A2 [11], A24 [12–16], DR4 [9], DR8 [17–19], DQ4 [20–22], and DQ3-related alleles [23, 24] have all been linked to T1DM. Additionally, high frequencies of HLA A2 [10, 25], DR4 [25–27] and DQ7 [28] have been found in some populations with T2DM. HLA-A2 has also been associated with microalbuminuria in people with T1DM [29], and with mortality from cardiovascular disease in Pima Indians [30]. Finally, an increased occurrence of HLA-B62 has been reported in Blacks with T1DM and DESRD [31]. We expected and observed higher frequencies of some of these antigens (particularly HLA-DR4 and DR3) in non-AB DESRD subjects compared to non-AB with non-DESRD, because the former included large numbers of people with T1DM. Interestingly, both AB DESRD and AB non-DESRD groups in our study had higher frequencies of DR4 than the non-AB DESRD group, but had very low frequencies of DR3.

There are several limitations to this retrospective study. First, numbers were small and we particularly lacked HLA data for many older AB subjects with

DESRD. Second, our use of age at DESRD diagnosis to differentiate between younger and older AB DESRD subjects might not accurately parallel age of diagnosis of diabetic nephropathy. Third, we cannot be sure that identification of only a single HLA-A, -B or -DR antigen meant that an individual subject was homozygous for that allele; however, that does not affect the main findings of the study. Fourth, there may have been some misclassification of subjects by ethnicity and DESRD diagnosis, but that would tend to make our findings more conservative, rather than lead to a type 1 error. Finally, we were unable to compare HLA frequencies in our AB DESRD subjects with an optimal AB control population such as matched healthy subjects without a high risk for T2DM and renal disease; however, identifying such individuals might be very difficult. The fact that other North American Indian populations are also known to have high frequencies of A2, A24, DR4 and DR8 [32, 33] lends support to the sobering possibility that large proportions of these populations may have a genetic propensity to develop T2DM and its complications.

This preliminary report requires verification through larger studies that use more sophisticated genetic studies that were not available during the early part of our study period. Such investigations within native North American populations are beginning to emerge. For example, Mexican patients with T2DM have been shown to be eight times as likely to develop DESRD if they had the HLA class II gene DRB1*1502 (an HLA-DR2 allele) [34]. Segregation analysis carried out in the Pima also suggests a major gene effect contributing to diabetic nephropathy [35]; linkage analysis indicates that candidate genes may be on chromosome 7 [36, 37].

This report adds to the increasing evidence that T2DM and its complications have a defined genetic basis in aboriginal populations, and that the observed HLA associations have much in common with those reported in T1DM. Although a genetic susceptibility to diabetic nephropathy (and T2DM) in North American aboriginal peoples may partially explain the burgeoning rates of DESRD in these populations, it is important to put this in perspective. T2DM was distinctly uncommon if not absent in these populations prior to the middle of the last century [38]. It is therefore clear that environmental factors are responsible for the appearance of T2DM and T2DM complications that are ravaging indigenous peoples worldwide. Identifying and understanding the genetics of T2DM should therefore be seen as a reason for hope. In immediate terms, it can provide us with an opportunity to screen for high-risk individuals who may benefit from prevention strategies, or early diagnosis and treatment. If confirmed, our findings should also give reason for caution in recommending aboriginal persons with high risk HLA profiles for kidney donation. In the more distant future, there may be opportunities to prevent or cure T2DM and its complications by targeting the genetic basis for this disease.

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