# HLA-DRB1*0102 is associated with TINU Syndrome and bilateral, sudden onset anterior uveitis but not with interstitial nephritis alone

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Abstract

Background: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare, form of uveitis. In the past, we demonstrated a strong association of HLA DRB1*0102 with TINU. Here, we performed HLA analysis on subjects with isolated bilateral sudden onset uveitis (as in the TINU subtype) or with isolated tubulointerstitial nephritis (TIN).

**Methods:**Patients with sudden onset, anterior, bilateral uveitis not fulfilling a diagnosis of TINU, were identified . Pathology reports were reviewed to identify subjects with biopsy proven TIN. Molecular typing of HLA-DRB1 gene was performed by Luminex technology-based sequence-specific oligonucleotide (SSO) hybridization method (One Lambda, Canoga Park, CA). HLA-DRB1 allele frequencies were compared to normal published controls (http://www.ncbi.nlm.nih.gov/projects/gv/mhc/ihwg.cgi dbMHC Europe cohort) and the published TINU cohort (n=18).

**Results**: We included 28 subjects with uveitis and 14 with TIN. There was a significantly higher frequency of DRB1*0102 in the isolated uveitis cohort versus in normal controls (10.7 % vs. 0.6%, respectively, p <0.0001; RR 14.3 (6.9-29.8)). None of the nephritis patients showed this HLA subtype. Another association with HLA-DRB1*08 was seen in the isolated uveitis cohort with an allele frequency of 10.7% versus 2.7% in normal controls (p=0.0019; RR 4.0 (1.8-9.0)). In contrast, the HLA-DRB1*08 was not different from controls in the TINU cohort (allele frequency 2.8%, p=not significant).

**Conclusion**: The incidence of HLA-DRB1*0102 is increased in sudden onset bilateral anterior uveitis, as is seen in patients with TINU. The same allele does not appear to occur in increased frequency in patients with isolated TIN. HLA DRB1*0102 might predispose to this subset of uveitis..

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## Introduction

Tubulointerstitial nephritis and uveitis (TINU) was first described in 1975 by Dobrin[1]. The syndrome is rare even in specialized uveitis clinics, but it was shown to be more frequent in patients with sudden onset, anterior, bilateral uveitis, especially when the patients are less than 20 years of age[2]. Even this study might have underestimated the syndrome´s incidence [2] because laboratory evaluations needed for the clinical diagnosis of TINU are often not obtained or not obtained in a timely manner. The uveitis of the TINU Syndrome can have a prolonged course of several months to years[3] but generally has a favorable prognosis and usually can be treated with local therapy alone[2]. Still, the possibility of missing renal disease and the consequence of not treating it is of some concern. Even though earlier publications reported the benign outcome of nephritis in TINU and suggested that possibly no treatment would be necessary[4], more recent publications of serial renal biopsies in patients with biopsy proven TINU showed histological changes of acute inflammation despite systemic prednisone treatment even 6-9 months after the first diagnosis[5-6]. Later biopsies in one case showed scarring[6]. Moreover, there have been recent reports of the development of end-stage renal failure in patients with idiopathic tubulointerstitial nephritis not treated with systemic steroid therapy[7]. Even if the tissue changes might be minimal, any residual tissue damage might lead to chronic kidney disease, hypertension and similar problems.

As uveitis patients often are referred to specialized centers several months after onset of disease, a time-independent marker would be helpful to suggest the diagnosis and give prognostic information to the patient.

Previously, we demonstrated a very strong association of HLA DRB1*0102 with definite TINU[8]. Now, we tested the hypothesis that DRB1*0102 may be associated

with isolated bilateral, sudden onset, anterior uveitis (U), isolated tubulointerstitial nephritis (TIN) or both.

**Material and Methods**

IRB approval was obtained for all institutions. Patients with sudden onset, anterior, bilateral uveitis (U) and inadequate criteria to meet a diagnosis of TINU (allowing maximum one unspecific criterion, e.g.minor urinary abnormalities) [3] (see Table 1)

| **Table 1: Diagnostic criteria for TINU (modified from Mandeville et al) [3]** |
|---|
| **Uveitis +** |
| Biopsy proven TIN or ≥1 of the following: |
| 1) abnormal renal function |
| 2) abnormal Urinalysis |
| 3) systemic disease > 2 weeks, non-specific lab abnormalities |

were identified by database search in 2 centers (OHSU, Heidelberg) and asked for informed consent.. At the same time pathology reports from 1998 on were reviewed to identify subjects with biopsy proven TIN (see Fig. 1) in these centers. The principal pathologic abnormalities in the kidney biopsy were interstitial edema and infiltration by lymphocytes, plasma cells, macrophages and, variable numbers of eosinophils. Small noncaseating granulomas were present in some cases. Focal proximal tubular cell injury and regeneration were sometimes apparent. To qualify, the glomeruli had to appear normal histologically. Excluded were patients with other systemic diseases that might have caused the nephritis as e.g. sarcoidosis, lupus, Sjogren's, and systemic infections. Equally excluded were patients with a likely or suspected hypersensitivity reaction/disease or renal toxicity, and anyone with known anatomic and/or functional lower urinary tract disease or patients with both TIN and uveitis. We

identified 33 eligible TIN patients from a total of 43 biopsy proven TIN patients in that period. Patients were excluded for: Hantan virus infection (n=5), uveitis, sarcoidosis, multiple myeloma, missing chart and salofalk induced nephritis in a patient with crohn´s (each n=1). 20 patients could be contacted and finally 14 agreed to take part in the study. TIN patients were given a questionnaire to rule out uveitis at the time of nephritis diagnosis and if possible an ophthalmologic exam was performed at the time patients came in for the blood draw. Blood specimens were shipped to a single center (OHSU) where DNA was isolated from peripheral blood leukocytes using standard salt extraction techniques. HLA typing was performed on genomic DNA at another center (UCLA) by a Luminex-based PCR-SSO typing method (One Lambda Inc Canoga Park, CA Product information LABType® SSO Typing Tests). HLA frequencies were compared to normal published controls (dbMHC Europe cohort: http://www.ncbi.nlm.nih.gov/projects/gv/mhc/ihwg.cgi) and to the previously published TINU cohort[8].

Chi-square (2-sided with Yates) and Mann-Whitney U (MWU) tests were applied and uncorrected $p < 0.005$ was used as cut-off for significance in multiple comparisons for HLA testing evaluation and $p < 0.05$ in single comparisons.

**Results**

We included 28 subjects with U and 14 with TIN. Demographic and clinical data are given in Table 2.

Table 2. Demographic and Clinical Data

| | **U (n = 28)** | **TIN (n =14)** | **TINU (n = 18)** [8] |
|---|---|---|---|
| age at onset(median, years) (range) | 30.0 (3-77) | 59.5 (11-76) | 42 (10 - 56) |
| Caucasian race (%) | 26 (93) | 14 (100) | 17 (94) |

| | | | |
|---|---|---|---|
| African American race (%) | 2 (7) | 0 | 1 (6) |
| Female (%) | 18 (64) | 11 (79) | 15 (83) |
| Disease onset age ≤ 20 years (%) | 12 (43) | 2 (14) | Not given |
| Female (%) with onset ≤ 20 years | 5 (42) | 2 (100) | Not given |
| Urine irregularities | 5 | Not known | |
| Urinalysis not done | 15 | Not known | |
| Creatinine elevation | 0 | 11 | |
| Creatinine not obtained | 6 | 0 | |
| Other lab. Abnormalities | 8 | 3 | |
| Elevated ESR/CRP | 8 | 2 | |
| Anemia | 2 | 1 | |
| Abnormal liver function | 3 | 1 | |
| Liver function not done | 4 | 0 | |

The median age of onset in the U group was lower than in the TIN group (MWU p= 0.0055). Gender and race distributions were similar across the groups. However, a gender difference was seen in the group with age of onset ≤ 20 years where there were 58% males in the U group and only females in the TIN group.

Minor urinary findings such as a few cells or mild proteinuria as evidenced solely by beta-2 microglobulin elevations were found in 5 subjects with U. Other, non-specific laboratory abnormalities were found in 8. None out of the U group showed a creatinine rise or other signs of renal dysfunction.

Thirteen of the 14 TIN patients filled out the questionnaire. None had symptoms typical for uveitis. Nine reported seeing an ophthalmologist around the time of nephritis diagnosis without uveitis having been found.

The frequencies of HLA-DRB1 allelic variants are shown in Table 3 for the U and TIN cohorts recruited for this study as well as the TINU cohort previously published [8] and a published control group (European dbMHC). As in the published TINU cohort,

there was an increased allele frequency of HLA DRB1*0102 in the isolated U cohort compared to normal controls (10.7% vs. 0.6%; p <0.0001; RR 14.3 (6.9-29.8)). All DRB1*0102 positive individuals in the U group were heterozygous for this allele. All positive patients were Caucasian.

Table 3: HLA-DRB1 Typing Results

| **DRB1** | **TINU, 2n=36** [8] | **U, 2n=56** | **TIN, 2n=28** | **control, 2n=2587**♦♦ |
|---|---|---|---|---|
| *0101/05/07/08/11/13 | 3 (8.3)♦ | 5 (8.9) | 3 (10.7) | 218 (8.4) |
| *0102 | **12 (33.3)** | **6 (10.7)** | 0 | 16 (0.6) |
| *0103 | 1 (2.8) | 1 (1.8) | 0 | 67 (2.6) |
| *03 | 6 (16.7) | 4 (7.1) | 5 (17.9) | 376 (14.5) |
| *04 | 3 (8.3) | 7 (12.5) | 3 (10.7) | 458 (17.7) |
| *07 | 4 (11.1) | 6 (10.7) | 5 (17.9) | 383 (14.8) |
| *08 | 1 (2.8) | **6 (10.7)** | 2 (7.1) | 71 (2.7) |
| *11 | 1 (2.8) | 4 (7.1) | 0 | 143 (5.5) |
| *12 | 0 | 0 | 1 (3.6) | 38 (1.5) |
| *13 | 2 (5.5) | 4 (7.1) | 3 (10.7) | 254 (9.8) |
| *14 | 2 (5.5) | 2 (3.6) | 1 (3.6) | 47 (1.8) |
| *15 | 1 (2.8) | 10 (17.9) | 5 (17.9) | 445 (17.2) |
| *16 | 0 | 1 (1.8) | 0 | 35 (1.4) |

♦ number of alleles (%)

♦♦http://www.ncbi.nlm.nih.gov/projects/gv/mhc/ihwg.cgi (dbMHC Europe cohort, accessed Nov. 20, 2007)

Interestingly, when the subset of the U cohort with early disease onset (≤20 years old, n=12) was considered, the allele frequency of DRB1*0102 was higher than that of the entire U group (16.7%, see Table 4). None of the TIN patients showed this HLA subtype (see Table 3 and 4). More than half (58.3%) of the U subjects ≤ 20 years old were male (Table 2), and there were some differences in DRB1*0102 allele frequencies between genders overall (8.3% in female versus 15% in male subjects) and even more pronounced in the age group ≤ 20 years old (4.2% in female versus 12.5% in male subjects). But the numbers in the subgroups were small.

Table 4: Allele frequencies and gender distribution of DRB1*0102 and *08 in different age groups

| | **U all 2n = 56** | **U ≤20 y 2n = 24** | **U >20 y 2n = 32** | **TIN all 2n = 28** | **TIN ≤ 20 y 2n = 4** | **TIN >20 y 2n = 24** | **TINU all 2n = 36** [8] |
|---|---|---|---|---|---|---|---|
| **DRB1*0102** | 6 (10.7)♦ | 4 (16.7) | 2 (6.3) | 0 | 0 | 0 | 12 (33.3) |
| **Male** | 3♦♦ | 3 | 0 | | | | |
| **Female** | 3 | 1 | 2 | | | | |
| **DRB1*08** | 6 (10.7) | 3 (12.5) | 3(9.4) | 2 (7.1) | 1 (25.0) | 1 (4.2) | 1 (2.8) |
| **Male** | 4 | 2 | 2 | 1 | 0 | 1 | |
| **Female** | 2 | 1 | 1 | 1 | 1 | 0 | |

♦number of alleles (%)
♦♦number of individuals

There was no statistically significant difference in the frequency of minor laboratory or urinary changes between the U subgroup with the DRB1*0102 compared to those with other DRB1 types (MWU p = 0.1769). The number with urinalyses not obtained

was lower in the subgroup with the DRB1*0102 (43%) as compared to those with other HLA DRB1 types (62%).

An association with the HLA-DRB1*08 allele was also seen in the U cohort with an allele frequency of 10.7% versus 2.7% in normal controls (p=0.0019; RR 4.0 (1.8-9.0)). In contrast, the HLA-DRB1*08 was not different from controls in the TINU cohort (allele frequency 2.8%, p=0.9903). No age differences were seen here, but we noticed a slightly higher frequency in males (see Table 4).Five of the patients positive for this allele were Caucasian and only one African American.

In the U vs. control comparisons, only HLA-DRB1*0102 and *08 showed statistically different frequencies. When comparing TIN vs. control, no differences were significant for any of the DRB1 alleles (see Table 5).

Table 5: Statistical analysis of HLA-DRB1 alleles for each patient group compared to controls.

| **DRB1** | **TINU vs control*** | **U vs control** | **TIN vs control** |
|---|---|---|---|
| *0101/05/07/08/11/13 | 0.9840 ♦ | 0.8937 | 0.9273 |
| *0102 | **<0.0001; 46.3 (25.8-83.1)** ♦♦ | **<0.0001; 14.3 (6.9-29.8)** | 0.6764 |
| *0103 | 0.9438 | 0.7069 | 0.7938 |
| *03 | 0.9026 | 0.1716 | 0.8209 |
| *04 | 0.2126 | 0.4040 | 0.4740 |
| *07 | 0.7010 | 0.5066 | 0.8535 |
| *08 | 0.9903 | **0.0019; 4.0 (1.8-9.0)** | 0.4074 |
| *11 | 0.7256 | 0.8203 | 0.3888 |
| *12 | 0.9759 | 0.7292 | 0.8972 |
| *13 | 0.5665 | 0.6600 | 0.8741 |
| *14 | 0.3050 | 0.6438 | 0.4915 |
| *15 | 0.0390 | 0.8977 | 0.9271 |
| *16 | 0.4823 | 0.7822 | 0.5355 |

Chi-square (2-sided with Yates); ♦ P value. ♦♦ P value; RR (95% CI); in bold, only shown for those with P < 0.005.

## Discussion

Our results indicate that HLA-DRB1*0102 is an independent risk factor for the uveitis characteristic of the TINU phenotype, i.e., bilateral, anterior and of sudden onset. Interestingly, this allele was found even more frequently in the group of patients 20 years old and younger.

Since DRB1*0102 was not found in the interstitial nephritis group, this allele is not a risk factor for the renal disease that occurs in the absence of uveitis. DRB1*0102 is an isolated risk factor for uveitis independent of clinically detectable renal disease.

A possible interpretation of our data is that many patients with bilateral, sudden onset, anterior uveitis might have a subclinical form of TINU. This latter conclusion is supported by observations from Japan demonstrating biopsy confirmed TINU in patients with normal renal function[9]. Our patients were seen at referral centers. Due to referral patterns, urinalysis and other studies of renal function were not always obtained at the onset of uveitis and in a subset of our patients especially, urinalysis was never performed (n=15) or not available for our interpretation. A diagnosis of TINU might have been established in some of our patients if these studies had been done in a timely manner. Still, in the subgroup with the DRB1*0102, laboratory tests (urinalysis) had been performed more often than in the other subgroups and there was no statistically significant difference in the frequency of minor laboratory or urinary changes between the uveitis subgroup with the DRB1*0102 compared to those with other DRB1 types. An alternative explanation of our data is that DRB1*0102 is a risk factor for bilateral, anterior, sudden onset uveitis regardless of whether this is associated with interstitial nephritis. Levinson and coworkers published a case series of mestizo patients with Vogt-Koyanaghi-Harada syndrome,

a uveitis subtype that often presents first with a bilateral anterior uveitis, where they also found a high frequency of DRB1*0102[10]

We used strict exclusion criteria for the TIN cohort, to obtain a clearcut phenotype. So it may be that in other subgroups of TIN, eg. those where the treating physicians had thought an infection or a medication to be the cause of the nephritis, DRB1*0102 might have been found. Admittedly the proof of a systemic infection or a triggering medication is not always easy and thus the physician's interpretation may be debatable. In the planning of the study we had still decided to exclude these patients as we would exclude uveitis patients where an infection was thought to cause the uveitis as this in our opinion would be a different disease subtype. As only 10 out of 43 patients with TIN were excluded, and only five due to an assumed infectious origin, we do not think we introduced too high a bias.Prior to the 18 TINU cases published by Levinson, et al.[8], several other small series (3-8 cases) or sibling reports examined HLA data for disease association. These studies provide evidence for possible TINU associations with HLA-A*02 [9, 11-12], -A*24 [12-14], and the Cw3 serotype [12, 14]. Regarding HLA-DRB1, studies have implicated DRB1*14 (or the DR6 serotype) [13, 15-16], DRB1*01 [17], DRB1*0101 [11, 18], and DRB1*0102 [8] with TINU. The later study result was further defined by the DRB1*01-/DQA1*01-/DQB1*05 haplotype [8].

Single case reports of monozygotic twins[11, 19] or siblings[16, 20] and even in a mother and her son[21] diagnosed with TINU syndrome several years apart have been reported, underlining the genetic component. As the family members did not fall ill at the same time a common environmental influence seems unlikely. The report of monozygotic twins in which one sibling had acute interstitial nephritis without uveitis and the other sibling had TINU syndrome implies that the same genotype in two

individuals may result in different disease presentations, perhaps depending on the nature of the environmental triggers[19] and other non-MHC genetic factors.

The HLA shared epitope is known to be a rheumatoid arthritis (RA) susceptibility factor and consists of several HLA-DRB1 alleles, including –DRB1*0101 and *0102. While much of the genetic effect of the shared epitope is attributed to –DRB1*04 alleles, evidence exists for –DRB1*01 to play a specific role in the predisposition to late-onset RA[22]. In addition to RA, other immune-mediated diseases in which –DRB1*01 has been implicated include Crohn's disease[23], atopic asthma[24], autoimmune idiopathic hypoparathyroidism[25], and allergic pollinosis in response to the mugwort allergen[26]. With regard to uveitis conditions other than TINU, VKH has been found to be associated with –DRB1*0101[27] and –DRB1*0102[10], both in Mestizo patients. Behcet's disease has been linked to –DRB1*01 in the Mestizo population[28] as well. HLA-DRB1 associations in a Hungarian juvenile idiopathic arthritis cohort included –DRB1*01 which was more prevalent in rheumatoid factor-positive polyarthritic patients[29]. In addition to inflammatory or allergic diseases, -DRB1*01 is an important contributor to infectious disease responses. For example, -DRB1*01 is associated with spontaneous clearance of hepatitis C virus[30], acute human parvovirus B19 infection[31], rheumatic heart disease[32], and idiopathic bronchiectasis[33]. Collectively, these data serve to highlight the fundamental role of HLA-DRB1*01 in important and varied aspects of immune-mediated responses.

The most known HLA (class-I) association with uveitis certainly is HLA-B27 for acute, unilateral, anterior uveitis (AAU) in approximately 50% of patients[34]. This correlation is even higher at 90% in patients of European descent with ankylosing spondylitis [35]. However, the relative genetic contribution from the major histocompatibility complex (MHC) has been estimated at 31–45% [36-38].

It is likely that in addition to HLA-B27 there will be a small number of genes with moderate effect, and a large number of genes with small effect. A case in point is the finding of an association with AAU at a genetic on chromosome 9p[39]. There have also been candidate gene studies implicating several small effect genes in AAU [40]. But also HLA class II associations have been found. In 1995 Monowarul and colleagues described an association of AAU in spondylarthritis patients with HLA-DR8[40]. We found an allele frequency of 12.7% for HLA-DR8 in a cohort of AAU, an association not seen for ankylosing spondylitis [41] (Tammy Martin, unpublished data). DRB1*0102 was not frequent in this cohort of AAU. Thus, a similar allele frequency of DRB1*08 in our patients with isolated U was a surprising finding.
How HLA associations exactly promote immune mediated disease is not clear yet, but it is important to consider that the major histocompatibility complex on chromosome 6 contains an abundance of genes that encode products critical to the immune response. It is possible, that the HLA-DRB1*0102 positive haplotype is in linkage disequilibrium with genes on chromosome 6 that may be related to disease pathogenesis such as the TNF superfamily. TNF-857T, for example has been shown to be a genetic risk marker for AAU in HLA B27+ patients[42]. HLA-class II is expressed on antigen presenting cells, the first line defense in innate as well as the crucial informant in cellular immunity. From the existing data we hypothesize that a specific class II subtype makes a subject more susceptible to a pathogenic immune response to a pathogen or to a normally harmless antigen. This would equally explain the sudden onset nature of the “TINU-type” uveitis as the “HLA-B27-type” AAU. So far this pathogen or antigen has not been discovered.

**Conclusion**

A significant number of patients with isolated, sudden onset, anterior, bilateral uveitis have the same HLA class II genotype as patients with TINU. HLA-DRB1*0102 might predispose to this subset of uveitis and provide a time-independent marker. It remains to be shown if the patients with the isolated uveitis really are subclinical TINU patients as renal biopsy generally is not performed or if there are other genes apart from DRB1*0102 leading to the U plus or minus renal disease. As a consequence, treating patients with this genotype with oral corticosteroids for subclinical renal disease might be considered, even when anterior uveitis is controlled with topical treatment alone. Further study should be done to determine if patients with this genotype have a distinct course of uveitis as indicated by prognosis or response to therapy.

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**Figurelegend:**

**Figure 1:** Histological kidney section of a patient with tubulointerstitial nephritis. A dense mixed inflammatory infiltrate expands the interstitium. Infiltrating cells are

predominantly lymphocytes and plasma cells, but include eosinophils. Individual lymphocytes have infiltrated several tubules. (hematoxylin and eosin; x550; bar = 50 microns)