**DRB1\*16:02 Associations for**

Yue, Zhenhua, Yonghu Sun, Chuan Wang, Wenjun Yu, Jing Cao, Fangfang Bao, Zhenzhen Wang, Hong Liu, and Furen Zhang. "Amino acid variants of HLA-DRB1 confer susceptibility to dapsone hypersensitivity syndrome in addition to HLA-B\* 13: 01." *Journal of Investigative Dermatology* 138, no. 5 (2018): 1101-1106.

Dapsone hypersensitivity syndrome is a rare yet severe adverse drug reaction caused by dapsone, a principal drug in multidrug therapy for leprosy. HLA-B\*13:01 has been identified as a strong risk factor of dapsone hypersensitivity syndrome; however, its low positive predictive value indicated that additional genetic variants may be involved in the disease development. To discover contributing genetic variants within HLA loci in addition to HLA-B\*13:01, we performed a high-coverage next-generation sequencing (NGS)-based HLA typing analysis in 103 dapsone-hypersensitive and 857 dapsone-tolerant HLA-B\*13:01-positive leprosy patients in a Chinese population. Five amino acid variants in high linkage disequilibrium of HLA-DRB1 were significantly associated with dapsone hypersensitivity syndrome (positions 133, 142, -17, 11, and 13). DRB1\*16:02 and DRB1\*15:01 tagged by these risk-conferring amino acid residues were associated at a nominal significance level. This study identifies five amino acid variants within HLA-DRB1 that are in high linkage disequilibrium and significantly associated with dapsone hypersensitivity syndrome in a Chinese population.

Chen, Yan, Shasha Li, Renliang Huang, Zhongjian Zhang, Frank Petersen, Junfeng Zheng, and Xinhua Yu. "Comprehensive meta-analysis reveals an association of the HLA-DRB1\* 1602 allele with autoimmune diseases mediated predominantly by autoantibodies." *Autoimmunity Reviews* 19, no. 6 (2020): 102532.

The human leukocytes antigen (HLA)-DRB1\*16:02 allele has been suggested to be associated with many autoimmune diseases. However, a validation of the results of the different studies by a comprehensive analysis of the corresponding meta data is lacking. In this study, we performed a meta-analysis of the association between HLA-DRB1\*16:02 allele with various autoimmune disorders. Our analysis shows that HLA-DRB1\*16:02 allele was associated with systemic lupus erythematosus, anti-N-Methyl-d-Aspartate receptor (NMDAR) encephalitis, Graves' disease, myasthenia gravis, neuromyelitis optica and antibody-associated systemic vasculitis with microscopic polyangiitis (AASV-MPA). However, no such association was found for multiple sclerosis, autoimmune hepatitis type 1, rheumatoid arthritis, type 1 diabetes and Vogt-Koyanagi-Harada syndrome. Re-analysis of the studies after their categorization into autoantibody-dependent and T cell-dependent autoimmune diseases revealed that the HLA-DRB1\*16:02 allele was strongly associated with disorder predominantly mediated by autoantibodies (OR = 1.93; 95% CI = 1.63-2.28, P = 1.95 × 10-14) but not with those predominantly mediated by T cells (OR = 1.08; 95% CI = 0.87-1.34, P = .474). In addition, amino acid sequence alignment of common HLA-DRB1 subtypes demonstrated that HLA-DRB1\*16:02 carries a unique motif of amino acid residues at position 67-74 which encodes the third hypervariable region. Taken together, the distinct pattern of disease association and the unique amino acid sequence of the third hypervariable region of the HLA-DRB1 provide some hints on how HLA-DRB1\*16:02 is involved in the pathogenesis of autoimmune diseases.

**DRB1\*04:05 Associations for**

Falfán-Valencia, Ramcés, Ángel Camarena, César Landa Pineda, Martha Montaño, Armida Juárez, Ivette Buendía-Roldán, Gloria Pérez-Rubio et al. "Genetic susceptibility to multicase hypersensitivity pneumonitis is associated with the TNF-238 GG genotype of the promoter region and HLA-DRB1\* 04 bearing HLA haplotypes." *Respiratory medicine* 108, no. 1 (2014): 211-217.

Hypersensitivity Pneumonitis (HP) is a lung inflammatory disorder caused by inhalation of organic particles by a susceptible host. Since only a small proportion of individuals exposed to HP-related antigens develop the disease, a genetic predisposition is largely suspected. However, studies regarding genetic susceptibility in this disease are scanty. We have previously found evidence supporting increased risk associated to the major histocompatibility complex (MHC) in sporadic HP. In the present study, we conducted a family-based research that includes nine multicase families with at least two related HP patients (RHP). We evaluated 19 RHP individuals, 25 additional healthy first-degree relatives (REA) and 246 healthy unrelated individuals (HUI). HLA class II typing (DRB1/3/4/5, DQA1, DQB1, DPA1, DPB1, DMA and DMB), and -863, -308 and -238 polymorphisms in the promoter region of TNF-α were performed by PCR based methods. We identified an increased frequency of HLA-DRB1\*04:07, DRB1\*04:05, DRB1\*11:01 and DRB1\*13:01 alleles in RHP individuals compared to healthy controls (p < 0.05). A significant higher frequency of DRB1\*04:07-DQB1\*03:02, DRB1\*04:05-DQB1\*03:02, and DRB1\*04:03-DQB1\*03:02 haplotypes was also detected in the group of patients. Likewise, TNF-238 GG genotype was more frequent in the RHP group as compared to REA (p = 0.01, OR = 7.2). Finally, the combination of HLA-DRB1\*04 alleles and TNF-238 GG was significantly increased in the RHP group (p = 0.01, OR = 6.93). These findings indicate that genes located within the MHC region confer susceptibility to familial HP in Mexicans.

Oka, Shomi, Hiroshi Furukawa, Aya Kawasaki, Kota Shimada, Shoji Sugii, Atsushi Hashimoto, Akiko Komiya et al. "Protective effect of the HLA-DRB1\* 13: 02 allele in Japanese rheumatoid arthritis patients." *PLoS One* 9, no. 6 (2014): e99453.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease. Certain HLA-DRB1 "shared-epitope" alleles are reported to be positively associated with increased RA susceptibility, whereas some of the other alleles may be negatively associated. However, studies on the latter are rare. Here, we focus on the protective effects of DRB1 alleles in Japanese RA patients in an association study. Relative predispositional effects (RPE) were analyzed by sequential elimination of carriers of each allele with the strongest association. The protective effects of DRB1 alleles were investigated in patients stratified according to whether they possessed anti-citrullinated peptide antibodies (ACPA). The DRB1\*13:02 allele was found to be negatively associated with RA (P = 4.59×10(-10), corrected P (Pc) = 1.42×10(-8), odds ratio [OR] 0.42, 95% CI 0.32-0.55, P [RPE] = 1.27×10(-6)); the genotypes DRB1\*04:05/\*13:02 and \*09:01/\*13:02 were also negatively associated with RA. The protective effect of \*13:02 was also present in ACPA-positive patients (P = 3.95×10(-8), Pc = 1.22×10(-6), OR 0.42, 95%CI 0.31-0.58) whereas \*15:02 was negatively associated only with ACPA-negative RA (P = 8.87×10(-5), Pc = 0.0026, OR 0.26, 95%CI 0.12-0.56). Thus, this study identified a negative association of DRB1\*13:02 with Japanese RA; our findings support the protective role of DRB1\*13:02 in the pathogenesis of ACPA-positive RA.

Dunstan, Sarah J., Nguyen Thi Hue, Buhm Han, Zheng Li, Trinh Thi Bich Tram, Kar Seng Sim, Christopher M. Parry et al. "Variation at HLA-DRB1 is associated with resistance to enteric fever." *Nature genetics* 46, no. 12 (2014): 1333-1336.

Enteric fever affects more than 25 million people annually and results from systemic infection with Salmonella enterica serovar Typhi or Paratyphi pathovars A, B or C(1). We conducted a genome-wide association study of 432 individuals with blood culture-confirmed enteric fever and 2,011 controls from Vietnam. We observed strong association at rs7765379 (odds ratio (OR) for the minor allele = 0.18, P = 4.5 × 10(-10)), a marker mapping to the HLA class II region, in proximity to HLA-DQB1 and HLA-DRB1. We replicated this association in 595 enteric fever cases and 386 controls from Nepal and also in a second independent collection of 151 cases and 668 controls from Vietnam. Imputation-based fine-mapping across the extended MHC region showed that the classical HLA-DRB1\*04:05 allele (OR = 0.14, P = 2.60 × 10(-11)) could entirely explain the association at rs7765379, thus implicating HLA-DRB1 as a major contributor to resistance against enteric fever, presumably through antigen presentation.

Khor, Seik-Soon, Ryoko Morino, Kazuyuki Nakazono, Shigeo Kamitsuji, Masanori Akita, Maiko Kawajiri, Tatsuya Yamasaki et al. "Genome-wide association study of self-reported food reactions in Japanese identifies shrimp and peach specific loci in the HLA-DR/DQ gene region." *Scientific reports* 8, no. 1 (2018): 1-17.

Food allergy is an increasingly important health problem in the world. Several genome-wide association studies (GWAS) focused on European ancestry samples have identified food allergy-specific loci in the HLA class II region. We conducted GWAS of self-reported reactivity with common foods using the data from 11011 Japanese women and identified shrimp and peach allergy-specific loci in the HLA-DR/DQ gene region tagged by rs74995702 (P = 6.30 × 10-17, OR = 1.91) and rs28359884 (P = 2.3 × 10-12, OR = 1.80), respectively. After HLA imputation using a Japanese population-specific reference, the most strongly associated haplotype was HLA-DRB1\*04:05-HLA-DQB1\*04:01 for shrimp allergy (P = 3.92 × 10-19, OR = 1.99) and HLA-DRB1\*09:01-HLA-DQB1\*03:03 for peach allergy (P = 1.15 × 10-7, OR = 1.68). Additionally, both allergies' associated variants were eQTLs for several HLA genes, with HLA-DQA2 the single eQTL gene shared between the two traits. Our study suggests that allergy to certain foods may be related to genetic differences that tag both HLA alleles having particular epitope binding specificities as well as variants modulating expression of particular HLA genes. Investigating this further could increase our understanding of food allergy aetiology and potentially lead to better therapeutic strategies for allergen immunotherapies.

Oka, Shomi, Takashi Higuchi, Hiroshi Furukawa, Minoru Nakamura, Atsumasa Komori, Seigo Abiru, Shinya Nagaoka et al. "Association of a single nucleotide polymorphism in TNIP1 with type-1 autoimmune hepatitis in the Japanese population." *Journal of Human Genetics* 63, no. 6 (2018): 739-744.

Several studies reported that autoimmune diseases share a number of susceptibility genes. Of these genes, a SNP rs7708392 in TNIP1 was reported to be associated with systemic lupus erythematosus (SLE). Autoimmune hepatitis (AIH), a rare chronic progressive liver disease, shares some clinical features with SLE. Therefore, we investigated whether the SNP is associated with Japanese AIH. An association study of rs7708392 was conducted in 343 Japanese AIH patients and 828 controls. We found that rs7708392 is associated with AIH (P = 0.0236, odds ratio (OR) 1.26, 95% confidence interval (CI): 1.03-1.54), under the allele model for C allele. Significant differences of clinical characteristics of the AIH patients with or without G allele of rs7708392 were not detected. Of interest, the association was stronger in AIH without HLA-DRB1\*04:05 allele (P = 0.0063, Q = 0.0127, OR 1.48, 95% CI: 1.12-1.96), though the association was not detected in AIH with DRB1\*04:05. The C allele of rs7708392 was associated with AIH, especially AIH without DRB1\*04:05, an already established risk factor.

**DQA1\*01:03 Associations for**

Sakai, Kazuya, Masataka Kuwana, Hidenori Tanaka, Kazuyoshi Hosomichi, Atsushi Hasegawa, Hiroki Uyama, Kenji Nishio et al. "HLA loci predisposing to immune TTP in Japanese: Potential role of the shared ADAMTS13 peptide bound to different HLA-DR." *Blood* 135, no. 26 (2020): 2413-2419.

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare autoimmune disorder caused by neutralizing anti-ADAMTS13 autoantibodies. In white individuals, HLA allele DRB1\*11 is a predisposing factor for iTTP, whereas DRB1\*04 is a protective factor. However, the role of HLA in Asians is unclear. In this study, we analyzed 10 HLA loci using next-generation sequencing in 52 Japanese patients with iTTP, and the allele frequency in the iTTP group was compared with that in a Japanese control group. We identified the following HLA alleles as predisposing factors for iTTP in the Japanese population: DRB1\*08:03 (odds ratio [OR], 3.06; corrected P [Pc] = .005), DRB3/4/5\*blank (OR, 2.3; Pc = .007), DQA1\*01:03 (OR, 2.25; Pc = .006), and DQB1\*06:01 (OR,: 2.41; Pc = .003). The estimated haplotype consisting of these 4 alleles was significantly more frequent in the iTTP group than in the control group (30.8% vs 6.0%; Pc < .001). DRB1\*15:01 and DRB5\*01:01 were weak protective factors for iTTP (OR, 0.23; Pc = .076; and OR, 0.23, Pc = .034, respectively). On the other hand, DRB1\*11 and DRB1\*04 were not associated with iTTP in the Japanese. These findings indicated that predisposing and protective factors for iTTP differ between Japanese and white individuals. HLA-DR molecules encoded by DRB1\*08:03 and DRB1\*11:01 have different peptide-binding motifs, but interestingly, bound to the shared ADAMTS13 peptide in an in silico prediction model.

DQB1\*06:02

Muro, Manuel, Pedro Mondejar‐López, María Rosa Moya‐Quiles, Gema Salgado, María Dolores Pastor‐Vivero, Ruth Lopez‐Hernandez, Francisco Boix et al. "HLA‐DRB1 and HLA–DQB1 genes on susceptibility to and protection from allergic bronchopulmonary aspergillosis in patients with cystic fibrosis." *Microbiology and immunology* 57, no. 3 (2013): 193-197.

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity pulmonary disease that affects both patients with cystic fibrosis (CF) and those with asthma. HLA-DRB1 alleles have previously been associated with ABPA-CF susceptibility; however, HLA-DQB1 allele associations have not been clearly established. The aim of the present study was to investigate HLA class II associations in patients with ABPA-CF and determine their roles in susceptibility or protection. Patients with ABPA-CF, patients with CF without ABPA, patients with asthma without ABPA (AST), and healthy controls were included in this study. DNA was extracted by automatic extractor. HLA-DRB1 and -DQB1 genotyping was performed by the Luminex PCR-SSOP method (One Lambda, Canoga Park, CA, USA). Allele specific PCR-SSP was also performed by high-resolution analysis (One Lambda). Statistical analysis was performed with SSPS and Arlequin software. Both HLA-DRB1\*5:01 and -DRB1\*11:04 alleles occurred with greater frequency in patients with ABPA-CF than in those with AST and CF and control subjects, corroborating previously published data. On the other hand, analysis of haplotypes revealed that almost all patients with ABPA-CF lacking DRB1\*15:01 or DRB1\*11:04 carry either DRB1\*04, DRB1\*11:01, or DRB1\*07:01 alleles. In the HLA-DQB1 region, the HLA-DQB1\*06:02 allele occurred more frequently in patients with ABPA-CF than in those with AST and CF and healthy controls, whereas HLA-DQB1\*02:01 occurred less frequently in patients with ABPA-CF. These data confirm that there is a correlation between HLA-DRB1\*15:01, -DRB1\*11:04, DRB1\*11:01, -DRB1\*04 and -DRB1\*07:01 alleles and ABPA-CF susceptibility and suggest that HLA-DQB1\*02:01 is an ABPA-CF resistance allele.