Small ubiquitin-like modifier 4 (SUMO4) polymorphisms and Vogt-Koyanagi-Harada (VKH) syndrome in the Chinese Han population

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Purpose: To examine whether small ubiquitin-like modifier 4 (SUMO4) polymorphisms were associated with Vogt-Koyanagi-Harada (VKH) syndrome in the Chinese Han population.

Methods: Genotyping for SUMO4 polymorphisms at G-847A, A-504G, A+163G, and C+438T loci was performed on 231 VKH patients and 302 controls using polymerase chain reaction restriction fragment length polymorphism.

Results: A decreased frequency of SUMO4 +438 TT genotype was found in VKH patients compared with healthy controls (p=0.009). However, the significance was lost after Bonferroni correction. Human leukocyte antigens (HLA)-DR4 and HLA-DRw53 were significantly associated with susceptibility to VKH syndrome (p=3.21×10^-16 and 7.08×10^-5, respectively). Stratification analysis based on HLA-DR4 and HLA-DRw53 did not show any associations between SUMO4 polymorphisms and VKH syndrome, although there was a big difference in the percentage of certain allele and genotype frequencies between HLA-DRw53 negative patients and controls. There was no significance in clinical findings and gender stratification analysis.

Conclusions: HLA-DR4 and HLA-DRw53 are strongly associated with the susceptibility to VKH syndrome in the Chinese Han population. However, none of the currently known single nucleotide polymorphisms (SNPs) of SUMO4 are associated with this syndrome.

Vogt-Koyanagi-Harada (VKH) syndrome is one of the most common uveitis entities in China [1]. It is characterized by a granulomatous panuveitis frequently in association with extraocular findings such as pleocytosis in the cerebrospinal fluid (CSF), dysacusis, alopecia, poliosis, and vitiligo [2-4]. Although the exact pathogenesis of VKH syndrome remains unclear, numerous studies have shown that immunogenetic factors are involved in the development of this syndrome. T cells autoreactive against tyrosinase family proteins are possibly involved in VKH syndrome. Meanwhile, genetic factors also play an important role in VKH syndrome as evidenced by the increased rates of this syndrome in pigmented groups [2], familial aggregation [5-7], and strong association with human leukocyte antigens (HLA)-DR4 and HLA-DRw53 in various ethnic groups including the Chinese and Japanese [8-10]. However, little is known about the genes that present susceptibility to the VKH syndrome except HLA [11-13].

Recently, studies have demonstrated that multiple autoimmune diseases may share common susceptibility genes by whole genome association and family based association studies [14-17]. Therefore, susceptibility genes associated with other autoimmune diseases may be candidates in the study of gene susceptibility to VKH syndrome, an autoimmune uveitis commonly seen in China. Small ubiquitin-like modifier 4 (SUMO4) is located on chromosome 6p25. Recently, certain SUMO4 polymorphisms have been shown to be clearly associated with type 1 diabetes in multiple Asian populations [18,19] as well as with other autoimmune diseases [19-22], despite controversial observations in Caucasians [18,23-25]. SUMO4 polymorphisms could also be involved in the pathogenesis of VKH syndrome, and this hypothesis was therefore the subject of the study presented here.

METHODS

Subjects: Blood samples were collected from 231 Chinese Han VKH patients (128 males and 103 females) and 302 age- and sex-matched, unrelated Chinese Han healthy controls (164 males and 138 females), which were recruited from the Uveitis Study Center of the Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, P.R. China and The First Affiliated Hospital, Chongqing Medical University, Chongqing, P.R. China. The institutional ethics committee of Zhongshan Ophthalmic Center, Sun Yat-sen University,
Hardy–Weinberg equilibrium (HWE). The distribution of genotype for each SNP (A-504G, G-847A, A+163G, and C+438T) was observed in VKH patients 

Statistical analysis: The $\chi^2$ test was applied to analyze the Hardy–Weinberg equilibrium (HWE). The $\chi^2$ test or Fisher’s exact test was performed to compare the allelic, genotypic, and haplotypic distribution between VKH patients and healthy controls using version 12.0 of SPSS for Windows (SPSS Inc., Chicago, IL). Analysis of linkage disequilibrium (LD) of each SNP and haplotype was performed using the Haplovew v3.32 program [28,29]. The p values were corrected using the Bonferroni correction to account for multiple testing. Sample sizes were estimated by Quanto 1.2 software (Department of Preventive Medicine, University of Southern California, Los Angles, CA).

RESULTS

Detailed clinical findings of the enrolled VKH patients are shown in Table 1. The average age of the VKH patients was 33.6±12.4 years and that of healthy controls was 35.4±12.0 years. No statistical difference was observed between VKH patients and controls in the distribution of age and gender (p>0.05).

Single nucleotide polymorphism and haplotypes analyses between polymorphisms of SUMO4 and Vogt-Koyanagi-Harada syndrome: The distribution of genotype for each SNP including G-847A, A-504G, A+163G, and C+438T did not deviate from the HWE in VKH patients and healthy controls (p>0.05). A decreased frequency of SUMO4 +438 TT genotype was observed in VKH patients compared with healthy controls (p=0.009, $\chi^2$=9.36). However, it did not remain significant after Bonferroni correction (Table 2).

Haplotypes analysis using the Haplovew 3.32 software showed that the four SNPs were in strong linkage (D’=84–91). A decreased frequency of SUMO4 haplotype (−847A, −504G, A+163G, and +438T) was observed in VKH patients compared with healthy controls (p=0.008, $\chi^2$=7.07). However, the significance was lost after Bonferroni correction (Table 3).

Stratification analysis of SUMO4 polymorphisms with the status of HLA-DR4, HLA-DRw53, the clinical findings, and gender: Our study showed that the frequency of HLA-DR4

### Table 1. HLA-DR4 and HLA-DRw53 distribution and clinical findings of patients with VKH syndrome.

| Characteristics          | HLA-DR4 + | HLA-DR4 - | HLA-DRw53 + | HLA-DRw53 - |
|--------------------------|-----------|-----------|-------------|-------------|
| Number of patients (%)   | 179 (77.5%) | 52 (22.5%) | 203 (87.9%) | 28 (12.1%)  |
| Male                     | 103 (80.5%) | 25 (19.5%) | 116 (90.6%) | 12 (9.4%)   |
| Female                   | 76 (73.8%)  | 27 (26.2%) | 87 (84.5%)  | 16 (15.5%)  |
| Neck stiffness           | 74 (72.5%)  | 28 (27.5%) | 89 (87.3%)  | 13 (12.7%)  |
| Alopecia                 | 26 (72.2%)  | 10 (27.8%) | 30 (83.3%)  | 6 (16.7%)   |
| Poliosis                 | 65 (73.9%)  | 23 (26.1%) | 78 (88.6%)  | 10 (11.4%)  |
| Vitiligo                 | 41 (74.5%)  | 14 (25.5%) | 48 (87.3%)  | 7 (12.7%)   |
| Dysacusia                | 57 (69.5%)  | 25 (30.5%) | 70 (85.4%)  | 12 (14.6%)  |
| Tinnitus                 | 61 (84.7%)  | 11 (15.3%) | 67 (93.1%)  | 5 (6.9%)    |
| Scalp hypersensitivity   | 32 (74.4%)  | 11 (25.6%) | 38 (88.4%)  | 5 (11.6%)   |

The age at onset (years±SD) for all VKH patients was 33.6±12.4 years. The age at onset (years±SD) for all VKH patients was 33.6±12.4 years.

Guangzhou, P.R. China approved this study, and informed consent was obtained from all tested subjects.

**DNA extraction:** Genomic DNA samples were extracted and isolated from ethylene diamine tetraacetic acid (EDTA) anti-coagulated peripheral blood mononuclear cells (PBMCs) of VKH patients and healthy controls by a conventional salting out method. These DNA samples were diluted in PCR grade water and stored at −70 °C until used.

**Genotyping:** Polymerase chain reaction (PCR) was performed using primers at G-847A locate (Forward, 5′-TCC CAA CCA ATA ATA GCA AGT CT-3′; Reverse, 5′-ATG CCT GGA TCA AAA CAC ACA-3′), A-504G locate (Forward, 5′-TGT GTG TTT TGA TCC AGG CAT TA-3′; Reverse, 5′-TGT TTT GCT CCT CTT TTC TT-3′), A+163G locate (Forward, 5′-ATT GTG AAC CAC GGG GAT TGT TA-3′; Reverse, 5′-CAGCGTTCTGGAGTAAAGAAG-3′), and C +438T locate (Forward, 5′-ATA CTA CCT GGG GAT TGT TA-3′; Reverse, 5′-ATG CCA AAC CAC ACA-3′). PCR products at G-847A (rs237026), A-504G (rs600739), A+163G (rs237025), and C+438T (rs237024) loci were incubated with Sspl at 37 °C, Alw21I at 37 °C, MseI at 65 °C, and MnlI at 37 °C (MBI Fermentas, Vilnius, Lithuania) for at least 4 h, respectively. PCR fragments were separated on 3% agarose gels. Twenty percent of the PCR samples were directly sequenced to confirm the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) results (Invitrogen Biotechnology Co., Guangzhou, China). *HLA-DR4* genotyping was performed using the PCR sequence specific primers (SSP) method as previously described [26]. *HLA-DRw53* genotyping was performed as previously described [27].
was significantly increased in 231 VKH patients as compared with that in 302 healthy controls (77.5% versus 19.5%, \( p = 3.21 \times 10^{-16}, \chi^2 = 66.67, \text{OR} = 13.74, 95\% \text{ CI} = 6.99–26.98\)). HLA-DRw53 was also shown to be significantly associated with susceptibility to VKH syndrome in the Chinese Han population (87.9% versus 63.9%, \( p = 7.08 \times 10^{-5}, \chi^2 = 15.79, \text{OR} = 4.13, 95\% \text{ CI} = 1.99–8.55\)).

To test whether there was an influence of HLA-DR4 and DRw53 on the SUMO4 association, stratification analysis was performed according to these parameters. The allele and genotype frequencies of the four SNPs of SUMO4 were not different between HLA-DR4 positive patients and HLA-DR4 positive controls and between HLA-DR4 negative patients and HLA-DR4 negative controls (Table 4). Similar results were also observed in HLA-DRw53 stratification analysis (Table 5). However, a big difference was observed in HLA-DRw53 negative patients compared with HLA-DRw53 negative controls (G-847A: AA genotype, HLA-DRw53- patients versus HLA-DRw53- controls: 40.8% versus 21.5%, A allele, HLA-DRw53- patients versus HLA-DRw53- controls: 59.3% versus 43.9%, A+163G: AG genotype, HLA-DRw53- patients versus HLA-DRw53- controls: 50.0% versus 33.0%; Table 5).

Stratification analysis was also performed according to clinical findings including neck stiffness, tinnitus, alopecia, poliosis, dysacusis, scalp hypersensitivity, and vitiligo. No association was found between the four SNPs and any extraocular findings. The analysis of gender stratification also showed no association of SUMO4 polymorphisms with VKH syndrome.

**DISCUSSION**

In this study, we examined the association of SUMO4 polymorphisms with VKH syndrome in the Chinese Han population. Our results failed to find an association between SUMO4 polymorphisms and VKH syndrome even after stratification for HLA-DR4, HLA-DRw53, clinical features, and gender.
SUMO4 has been shown to be involved in the regulation of NF-κB, an important transcription factor in autoimmune diseases. It has been reported that the SUMO4 A+163G (M55V) polymorphism is an essential polymorphism involved in regulating its own sumoylation, and it has been shown to be associated with certain autoimmune diseases such as type 1 diabetes, autoimmune thyroid disease, and rheumatoid arthritis without amyloidosis [19]. These results suggest that this polymorphism could be a susceptibility gene shared by certain autoimmune diseases, although conflicting data have been reported in Sjögren’s syndrome [19]. The identification of a general susceptibility gene for several autoimmune diseases could make an important contribution to the understanding of the pathogenesis and modulation of these diseases. The question was therefore raised whether the SUMO4 A+163G polymorphism may not be involved in the development of susceptibility to VKH syndrome. Unexpectedly, we failed to find an association of the SUMO4 A+163G polymorphism with VKH syndrome. This suggests that this polymorphism may not be involved in the development of susceptibility to VKH syndrome.

Others SNPs including G-847A, A-504G, and C+438T polymorphisms have been identified by direct sequencing of the whole SUMO4 gene in the Japanese population [20,32]. Our previous results showed an association of SUMO4 C+438T polymorphism with Behcet’s disease [22], another common uveitis entity observed in China. The present study also failed to show any association of the SUMO4 G-847A, A-504G, and C+438T polymorphisms with VKH syndrome. This difference may result from the different features of these two uveitis entities. One of the striking features of Behcet’s disease is its characteristic non-granulomatous inflammation while VKH syndrome is in fact a granulomatous inflammation [33].

Like HLA-DR4, HLA-DRw53 have been demonstrated to be strongly associated with VKH syndrome. Therefore, genotyping of HLA-DR4 and HLA-DRw53 was performed. The association of HLA-DR4 and HLA-DRw53 with VKH syndrome was extremely strong in this study. The results were generally consistent with those previously reported in Chinese [4,8,34] and Spanish patients [35]. Furthermore, stratification analysis according to HLA-DR4 and HLA-DRw53 did not show any association of SUMO4 with VKH syndrome in our study. This result is consistent with the previous studies that sample size was large enough to detect a possible association.

| SNPs | Genotype allele | HLA-DR4+ Patients n=179 (%) | HLA-DR4+ Controls n=59 (%) | p value | p<0.01 value | HLA-DR4+ Patients n=52 (%) | HLA-DR4+ Controls n=243 (%) | p value | p<0.01 value |
|------|----------------|--------------------------|---------------------------|--------|-------------|--------------------------|-----------------------------|--------|-------------|
| −847 G→A | GG | 12 (6.8) | 10 (17.2) | 0.041 | NS | 4 (8.0) | 20 (8.4) | 0.757 | NS |
| | AG | 81 (46.0) | 20 (34.5) | | | 23 (46.0) | 96 (40.3) | | |
| | AA | 83 (47.2) | 28 (48.3) | | | 23 (46.0) | 122 (51.3) | | |
| | G | 105 (59.2) | 40 (34.5) | 0.347 | NS | 31 (31.0) | 136 (28.6) | 0.627 | NS |
| | A | 247 (70.2) | 76 (65.5) | | | 69 (69.0) | 340 (71.4) | | |
| −504 A→G | AA | 40 (22.9) | 11 (19.0) | 0.656 | NS | 14 (28.0) | 55 (23.0) | 0.696 | NS |
| | AG | 85 (48.6) | 27 (46.6) | | | 22 (44.0) | 119 (49.8) | | |
| | GG | 50 (28.6) | 20 (34.5) | | | 14 (28.0) | 65 (27.2) | | |
| | A | 165 (47.1) | 49 (42.2) | 0.359 | NS | 50 (50.0) | 249 (49.8) | 0.703 | NS |
| | G | 185 (52.9) | 67 (57.8) | | | 50 (50.0) | 229 (47.9) | | |
| +163 A→G | AA | 84 (46.9) | 29 (49.2) | 0.820 | NS | 23 (45.1) | 116 (47.7) | 0.872 | NS |
| | AG | 83 (46.4) | 25 (42.4) | | | 24 (47.1) | 105 (43.2) | | |
| | GG | 5 (8.5) | 5 (8.5) | | | 4 (7.8) | 22 (9.1) | | |
| | A | 251 (70.1) | 83 (70.3) | 0.963 | NS | 70 (68.6) | 337 (69.3) | 0.887 | NS |
| | G | 107 (29.9) | 35 (29.7) | | | 32 (31.4) | 149 (30.7) | | |
| +438 C→T | CC | 82 (46.3) | 29 (49.2) | 0.089 | NS | 25 (48.1) | 106 (43.6) | 0.562 | NS |
| | CT | 85 (48.0) | 22 (37.3) | | | 22 (42.3) | 100 (41.2) | | |
| | TT | 10 (5.6) | 8 (13.6) | | | 5 (9.6) | 37 (15.2) | | |
| | C | 249 (70.3) | 80 (67.8) | 0.603 | NS | 72 (69.2) | 312 (64.2) | 0.328 | NS |
| | T | 105 (29.7) | 38 (32.2) | | | 32 (30.8) | 174 (35.8) | | |

a Bonferroni corrected p value; b Not significant.
SUMO4 M55V polymorphism was independent of the HLA class II haplotype [19,32], which is located on the same chromosome 6 as SUMO4. It is worthy to point out that there was a big difference in the percentages of certain alleles and genotypes between HLA-DRw53 negative patients and controls, although the difference did not reach statistical significance. As the sample size of HLA-DRw53 negative is small (28 patients), it is necessary to further test the association of SUMO4 polymorphisms with HLA-DRw53 negative patients using larger samples.

In conclusion, we failed to detect an association of SUMO4 polymorphisms with VKH syndrome in Chinese Han population. In agreement with earlier studies, we found a strong association of HLA-DR4 and HLA-DRw53 with susceptibility to VKH syndrome. A big but insignificant difference of allele and genotype frequency was noted in HLA-DRw53 negative patients when compared with HLA-DRw53 negative controls. Further studies are necessary to elucidate the association of SUMO4 polymorphisms with VKH syndrome in an HLA-DRw53 negative population using larger samples.

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REFERENCES

1. Yang P, Zhang Z, Zhou H, Li B, Huang X, Gao Y, Zhu L, Ren Y, Klooster J, Kijlstra A. Clinical patterns and characteristics of uveitis in a tertiary center for uveitis in China. Curr Eye Res 2005; 30:943-8. [PMID: 16282128]

| SNPs  | Genotype allele | HLA-DRw53+ Patients n=203 (%) | HLA-DRw53+ Controls n=193 (%) | p value | pc value | HLA-DRw53+ Patients n=28 (%) | HLA-DRw53+ Controls n=109 (%) | p value | pc value |
|-------|-----------------|--------------------------------|--------------------------------|---------|---------|-----------------------------|-------------------------------|---------|---------|
| −847  | G→A             | GG 13 (6.5)                    | 20 (10.5)                       | 0.368   | NS b    | 3 (11.1)                   | 10 (9.4)                      | 0.200   | NS      |
|       |                 | AG 91 (45.7)                   | 83 (43.7)                       |         |         | 13 (48.1)                  | 33 (31.1)                     |         |         |
|       |                 | AA 95 (47.7)                   | 87 (45.8)                       |         |         | 11 (40.7)                  | 63 (59.4)                     |         |         |
|       |                 | G 117 (58.6)                   | 123 (62.4)                      | 0.370   | NS      | 19 (68.5)                  | 53 (25.0)                     | 0.133   | NS      |
|       |                 | A 281 (70.6)                   | 257 (67.6)                      |         |         | 35 (64.8)                  | 159 (75.0)                    |         |         |
| −504  | A→G             | AA 43 (21.7)                   | 43 (22.6)                       | 0.742   | NS      | 11 (40.8)                  | 23 (21.5)                     | 0.114   | NS      |
|       |                 | AG 97 (49.0)                   | 98 (51.6)                       |         |         | 10 (37.0)                  | 48 (44.9)                     |         |         |
|       |                 | GG 58 (29.3)                   | 49 (25.8)                       |         |         | 6 (22.2)                   | 36 (33.6)                     |         |         |
|       |                 | A 183 (46.2)                   | 184 (48.4)                      | 0.538   | NS      | 32 (59.3)                  | 94 (43.9)                     | 0.044   | NS      |
|       |                 | G 213 (53.8)                   | 196 (51.6)                      |         |         | 22 (40.7)                  | 120 (56.1)                    |         |         |
| +163  | A→G             | AA 96 (47.5)                   | 83 (43.0)                       | 0.590   | NS      | 11 (39.3)                  | 62 (56.9)                     | 0.216   | NS      |
|       |                 | AG 93 (46.0)                   | 94 (48.7)                       |         |         | 14 (50.0)                  | 36 (33.0)                     |         |         |
|       |                 | GG 13 (6.4)                    | 16 (8.3)                        |         |         | 3 (10.7)                   | 11 (10.1)                     |         |         |
|       |                 | A 285 (70.5)                   | 260 (67.4)                      | 0.333   | NS      | 36 (64.3)                  | 160 (73.4)                    | 0.178   | NS      |
|       |                 | G 119 (29.5)                   | 126 (32.6)                      |         |         | 20 (35.7)                  | 58 (26.6)                     |         |         |
| +438  | C→T             | CC 95 (47.3)                   | 82 (42.5)                       | 0.035   | NS      | 12 (42.9)                  | 53 (48.6)                     | 0.613   | NS      |
|       |                 | CT 95 (47.3)                   | 86 (44.6)                       |         |         | 12 (42.9)                  | 36 (33.0)                     |         |         |
|       |                 | TT 11 (5.5)                    | 25 (13.0)                       |         |         | 4 (14.3)                   | 20 (18.3)                     |         |         |
|       |                 | C 285 (70.9)                   | 250 (64.8)                      | 0.065   | NS      | 36 (64.3)                  | 142 (65.1)                    | 0.905   | NS      |
|       |                 | T 117 (29.1)                   | 136 (35.2)                      |         |         | 20 (35.7)                  | 76 (34.9)                     |         |         |

a Bonferroni corrected p value; b Not significant.
2. Moorhey RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol 1995; 39:265-92. [PMID: 7725227]

3. Forster DJ, Cano MR, Green RL, Rao NA. Echographic features of the Vogt-Koyanagi-Harada syndrome. Arch Ophthalmol 1990; 108:1421-6. [PMID: 2222275]

4. Yang P, Ren Y, Li B, Fang W, Meng Q, Kijlstra A. Clinical characteristics of Vogt-Koyanagi-Harada syndrome in Chinese patients. Ophthalmology 2007; 114:606-14. [PMID: 17123618]

5. Ishikawa A, Shiono T, Uchida S. Vogt-Koyanagi-Harada disease in identical twins. Retina 1994; 14:435-7. [PMID: 8799719]

6. Rutzen AR, Ortega-Larrocea G, Schwab IR, Rao NA. Simultaneous onset of Vogt-Koyanagi-Harada syndrome in monozygotic twins. Am J Ophthalmol 1995; 119:239-40. [PMID: 7832237]

7. Itho S, Kurimoto S, Kouno T. Vogt-Koyanagi-Harada disease in monozygotic twins. Arch Ophthalmol 1992; 164:94. [PMID: 1537650]

8. Zhao M, Jiang Y, Abrahams IW. Association of HLA antigens with Vogt-Koyanagi-Harada syndrome in a Han Chinese population. Arch Ophthalmol 1991; 109:368-70. [PMID: 2003797]

9. Zhang XY, Wang XM, Hu TS. Profiling human leukocyte antigens in Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 1992; 113:567-72. [PMID: 1575232]

10. Islam SM, Numaga J, Fujino Y, Hirata R, Matsuki K, Maeda H, Masuda K. HLA class II genes in Vogt-Koyanagi-Harada disease. Invest Ophthalmol Vis Sci 1994; 35:3890-6. [PMID: 7928186]

11. Du L, Yang P, Hou S, Lin X, Zhou H, Huang X, Wang L, Kijlstra A. Association of the CTLA-4 gene with Vogt-Koyanagi-Harada syndrome. Clin Immunol 2008; 127:43-8. [PMID: 18282809]

12. Horie Y, Takemoto Y, Miyazaki A, Namba K, Kase S, Yoshida K, Ota M, Hasumi Y, Inoko H, Mizuki N, Ohno S. Tyrosinase gene family and Vogt-Koyanagi-Harada disease in Japanese patients. Mol Vis 2006; 12:1601-5. [PMID: 17200659]

13. Horie Y, Kitaitchi N, Takemoto Y, Namba K, Yoshida K, Hirose S, Hasumi Y, Ota M, Inoko H, Mizuki N, Ohno S. Polymorphism of IFN-gamma gene and Vogt-Koyanagi-Harada disease. Mol Vis 2007; 13:2334-8. [PMID: 18199975]

14. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447:661-78. [PMID: 17123612]

15. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouweland WH, Samani NJ, Todd JA, Donnelly P, Barrett JC, Davison D, Easton D, Evans DM, Leung HT, Marchini JL, Morris AP, Spencer CC, Tobin MD, Attwood AP, Boorman JP, Cant B, Everson U, Hussey JM, Jolley JD, Knight AS, Koch K, Meech E, Nuttall S, Prowse CV, Stevens HE, Taylor NC, Walters GR, Walker NM, Watkins NA, Winzer T, Jones RW, McArdele WL, Ring SM, Strachan DP, Pembrey M, Breen G, St Clair D, Caesar S, Gordon-Smith K, Jones L, Fraser C, Green EK, Grozeva D, Hamshere ML, Holmans PA, Jones IR, Kirov G, Moskivina V, Nikolov I, O’Donovan MC, Owen MJ, Collar DA, Elkin A, Farmer A, Williamson R, McGuffin P, Young AH, Ferrier IN, Ball SG, Balmforth AJ, Barrett JH, Bishop TD, Iles MM, Maqbool O, Yudassena N, Hall AS, Braund PS, Dixon RJ, Mangino M, Stevens S, Thompson JR, Bredin F, Tremelling M, Parkes M, Drummond H, Lees CW, Nimmo ER, Satsangi J, Fisher SA, Forbes A, Lewis CM, Onnie CM, Prescott NJ, Sanderson J, Matthew CG, Barbour J, Mohiuddin MK, Todhunter CE, Mansfield JC, Ahmad T, Cummings FR, Jewell DP, Webster J, Brown MJ, Lathrop MG, Connell J, Dominiczak A, Marcano CA, Burke B, Dobson R, Gungadoo J, Lee KL, Munroe PB, Newhouse SJ, Onipinla A, Wallace C, Xue M, Caullfield M, Farrall M, Barton A, Bruce IN, Donovan H, Eyre S, Gilbert PD, Hilder SL, Hinks AM, John SL, Potter C, Silman AJ, Symmons DP, Thomson W, Worthington J, Dunger DB, Widmer B, Frayling TM, Freathy RM, Lango H, Perry JR, Shields BM, Weedon MN, Hattersley AT, Howie BN, Walker M, Elliott KS, Groves CJ, Lindgren CM, Rayner NW, Timpson NJ, Zeggini E, Newport M, Sirugo G, Lyons E, Vannberg F, Hill AV, Bradbury LA, Farrar C, Pointon JJ, Wordsworth P, Brown MA, Franklyn JA, Heward JM, Simmonds MJ, Gough SC, Seal S, Stratton MR, Rahman N, Ban M, Goris A, Sawcer SJ, Compston A, Conway D, Jallow M, Newport M, Sirugo G, Rockett KA, Bumpstead SJ, Chaney A, Downes K, Ghorji MJ, Gwilliam R, Hunt SE, Inouye M, Keniry A, King E, McGinnis R, Potter S, Ravindrarajah R, Whittaker P, Widdell C, Withers D, Cardin NJ, Davison D, Ferreira T, O’Reilly-Gale J, Hallgrimsdottir IB, Howie BN, Su Z, Teo YY, Vukcevic D, Bentley D, Brown MA, Compston A, Farrall M, Hall AS, Hattersley AT, Hill AV, Parkes M, Pembring M, Stratton MR, Mitchell SL, Newby PR, Brand OJ, Carr-Smith J, Pearce SH, McGinnis R, Keniry A, Deloukas P, Reveille JD, Zhou X, Sims AM, Dowling A, Taylor J, Doan T, Davis JC, Savage L, Ward MM, Leach TL, Weisman MH, Brown M. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet 2007; 39:1329-37. [PMID: 17952073]

16. Guo D, Li M, Zhang Y, Pang P, Eckenrode S, Hopkins D, Zheng W, Purohit S, Poddolsky RH, Mui A, Wang J, Dong Z, Brusko T, Atkinson M, Pozzilli P, Ziedler A, Raffel LJ, Jacob CO, Park Y, Serrano-Rios M, Larrad MT, Zhang Z, Garchon HJ, Bach JF, Rotter JI, She JX, Wang CY. A functional variant of SUMO4, a new I kappa B alpha modifier, is associated with type 1 diabetes. Nat Genet 2004; 36:837-41. [PMID: 15247916]
19. Tsurumaru M, Kawasaki E, Ida H, Migita K, Moriuchi A, Fukushima K, Fukushima T, Abiru N, Yamazaki H, Nosō S, Ikegami H, Awata T, Sasaki H, Eguchi K. Evidence for the role of small ubiquitin-like modifier 4 as a general autoimmunity locus in the Japanese population. J Clin Endocrinol Metab 2006; 91:3138-43. [PMID: 16735488]

20. Nosō S, Fujisawa T, Kawabata Y, Asano K, Hiromine Y, Fukai A, Ogihara T, Ikegami H. Association of small ubiquitin-like modifier 4 (SUMO4) variant, located in IDDM5 locus, with type 2 diabetes in the Japanese population. J Clin Endocrinol Metab 2007; 92:2358-62. [PMID: 17374705]

21. Lin HY, Wang CL, Hsiao PJ, Lu YC, Chen SY, Lin KD, Hsin SC, Hsieh MC, Shin SJ. SUMO4 M55V variant is associated with diabetic nephropathy in type 2 diabetes. Diabetes 2007; 56:1177-80. [PMID: 17229939]

22. Hou S, Yang P, Du L, Zhou H, Lin X, Kijlstra A. SUMO4 gene polymorphisms in Chinese Han patients with Behcet's disease. Clin Immunol 2008; 129:170-5. [PMID: 18657476]

23. Owerbach D, Pina L, Gabbay KH. A 212-kb region on chromosome 6q25 containing the TAB2 gene is associated with susceptibility to type 1 diabetes. Diabetes 2004; 53:1890-3. [PMID: 15220215]

24. Qu H, Bharaj B, Liu XQ, Curtis JA, Newhook LA, Paterson AD, Hudson TJ, Polychronakos C. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. Nat Genet 2005; 37:111-2. [PMID: 15678135] author reply 2–3

25. Smyth DJ, Howson JM, Lowe CE, Walker NM, Lam AC, Nutland S, Hutchings J, Tuomilehto-Wolf E, Tuomilehto J, Guja C, Ionescu-Tirgoviste C, Undlien DE, Ronningen KS, Savage D, Dunger DB, Twells RC, McArdrle WL, Strachan DP, Todd JA. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. Nat Genet 2005; 37:110-1. [PMID: 15678134] author reply 2–3

26. Zetterquist H, Olerup O. Identification of the HLA-DRB1*04, -DRB1*07, and -DRB1*09 alleles by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours. Hum Immunol 1992; 34:64-74. [PMID: 1356957]