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## Introduction

The Toll-like receptors (TLRs) are germline-encoded receptors that play an essential role in initiating the immune response against pathogens.

## Objective

We assess the association of TLR polymorphism with autoimmune thyroid disease (AITD) in Korean children.

## Methods

We defined the polymorphism of TLR10 gene (rs4129009, rs11096956 and rs10004195) in 85 Korean AITD (Graves disease [GD]=50, Hashimoto disease [HD]=35; thyroid-associated ophthalmopathy [TAO]=23, non-TAO=62; M=16, F=69; mean age=12.9± 3.1 years) and 279 healthy control subjects.

## Results

- In patients with AITD, frequencies of the *TLR10* rs4129009 A allele (OR=3.9, *cP*=0.04) and rs10004195 T allele (OR=2.8, *cP*=0.02) were higher than in the healthy controls, whereas the *TLR10* rs4129009 GG genotype (OR=0.3, *cP*=0.04) and rs10004195 AA genotype (OR=0.4, *cP*=0.02) showed lower frequencies.
- The *TLR10* rs11096956 did not show any significant association.
- These significant associations were also found in non-thyroid associated ophthalmopathy (TAO) group, whereas not in TAO group.
- The haplotype (AGT) frequency of *TLR10* rs4129009, rs11096956 and rs10004195 was higher in the AITD group than in healthy controls (OR=2.1, *cP*=0.03).

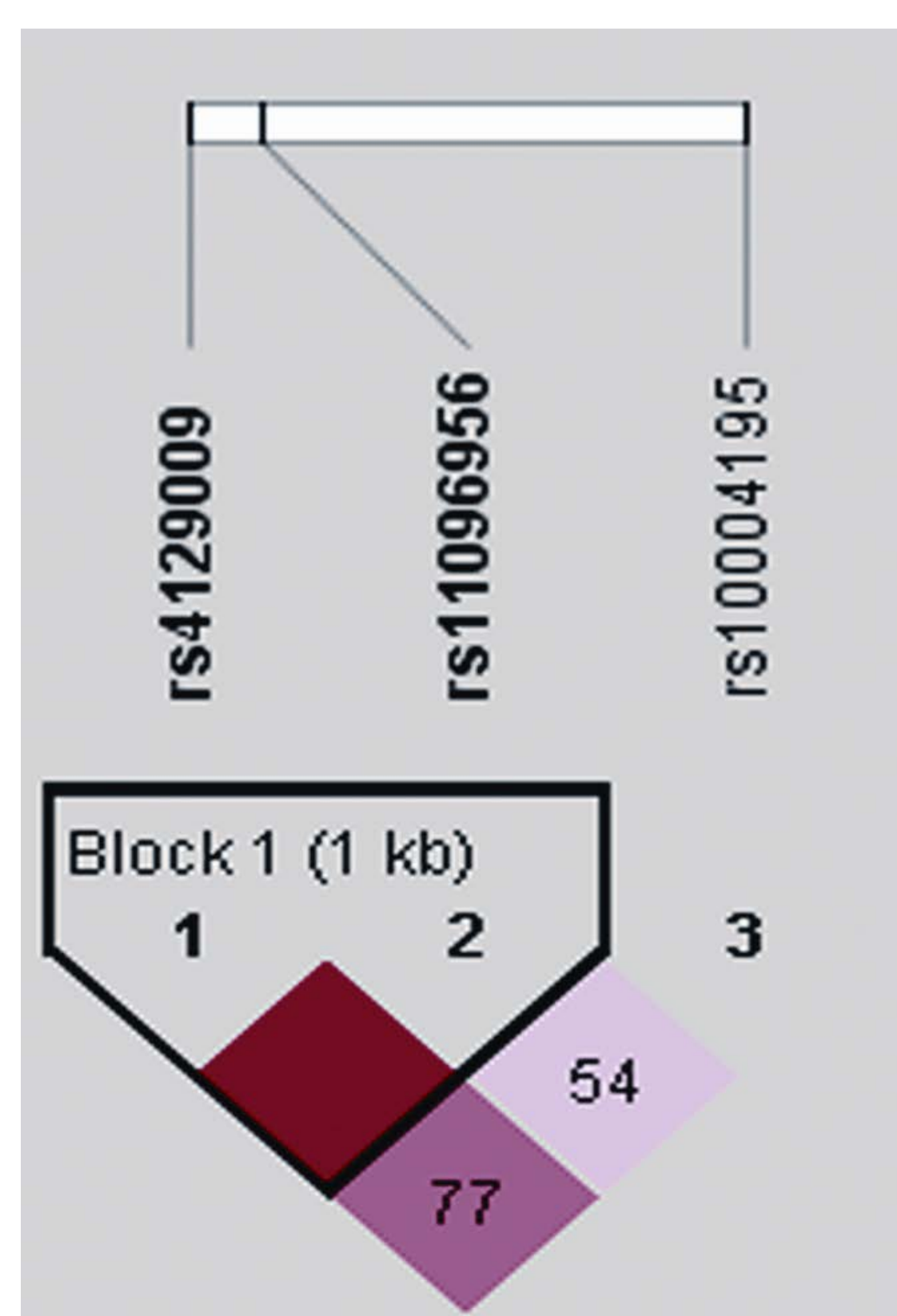


Figure 1. Linkage disequilibrium (LD) blocks of single nucleotide polymorphisms in Toll-like receptor 10 (TLR10) genes.

Boxes are colored deep red if the *D'* values are high, which means LD is strong.

Table 1. Primer sequences for each SNP

| Gene  | SNP        |   | Primer Sequence                                       |
|-------|------------|---|-------------------------------------------------------|
| TLR10 | rs4129009  | F | CTTACTGGAACCCATTCCATTCTATTGC                          |
|       |            | R | TCAATGTACATCCCAACAGTGTATGTGG                          |
|       | rs11096956 | F | AGTTGATTT ACTCTGGGAC GACC                             |
|       |            | R | CTGTTAAGATATTATTGGCAAATTTAA                           |
|       | rs10004195 | F | AAAGCTAAGGTTCTTACCCACG                                |
|       |            | R | AAGATGGTGAGCATGATAACTCCTATGT<br>TATGTGTATTGACCACAAGTT |

Table 2. Frequencies of genotype and allele of TLR10 genes in controls and patients with thyroid disease

| Gene       | SNP      | geno type | Controls   | AITD                    | GD       | HD                      | TAO        | Non-TAO                 |
|------------|----------|-----------|------------|-------------------------|----------|-------------------------|------------|-------------------------|
|            |          |           | N=279 (%)  | N=85 (%)                | N=50 (%) | N=35 (%)                | N= 23(%)   | N=62 (%)                |
| rs4129009  | (+2322)  | AA        | 96(34.4%)  | 34 (40%)                | 20 (40%) | 14 (40%)                | 8 (34.8%)  | 26 (41.9%)              |
|            |          | AG        | 138(49.5%) | 47 (55.3%)              | 27 (54%) | 20 (57.1%)              | 13 (56.5%) | 34 (54.8%)              |
|            |          | GG        | 45(16.1%)  | 4 (4.7%) <sup>a</sup>   | 3 (6%)   | 1 (2.9%) <sup>g</sup>   | 2 (8.7%)   | 2 (3.2%) <sup>m</sup>   |
|            |          | A         | 234(83.9%) | 81 (95.3%) <sup>b</sup> | 47 (94%) | 34 (97.1%) <sup>h</sup> | 21 (91.3%) | 60 (96.8%) <sup>n</sup> |
|            |          | G         | 183(65.6%) | 51 (60%)                | 30 (60%) | 21 (60%)                | 15 (65.2%) | 36 (58.1%)              |
| rs11096956 | (C.1032) | GG        | 51(18.3%)  | 22 (25.9%)              | 12 (24%) | 10 (28.6%)              | 3 (13%)    | 19 (30.6%) <sup>o</sup> |
|            |          | GT        | 132(47.3%) | 42 (49.4%)              | 25 (50%) | 17 (48.6%)              | 14 (60.9%) | 28 (45.2%)              |
|            |          | TT        | 96(34.4%)  | 21 (24.7%)              | 13 (26%) | 8 (22.9%)               | 6 (26.1%)  | 15 (24.2%)              |
|            |          | G         | 183(65.6%) | 64 (75.3%)              | 37 (74%) | 27 (77.1%)              | 17 (73.9%) | 47 (75.8%)              |
|            |          | T         | 228(81.7%) | 63 (74.1%)              | 38 (76%) | 25 (71.4%)              | 20 (87%)   | 43 (69.3%) <sup>p</sup> |
| rs10004195 | (-113)   | AA        | 75(26.9%)  | 10 (11.8%) <sup>c</sup> | 7 (14%)  | 3 (8.6%) <sup>i</sup>   | 4 (17.4%)  | 6 (9.7%) <sup>q</sup>   |
|            |          | AT        | 150(53.8%) | 48 (56.5%)              | 28 (56%) | 20 (57.1%)              | 14 (60.9%) | 34 (54.8%)              |
|            |          | TT        | 54(19.4%)  | 27 (31.8%) <sup>d</sup> | 15 (30%) | 12 (34.3%) <sup>j</sup> | 5 (21.7%)  | 22 (35.5%) <sup>r</sup> |
|            |          | A         | 225(80.6%) | 58 (68.2%) <sup>e</sup> | 35 (70%) | 23 (65.7%) <sup>k</sup> | 18 (78.3%) | 40 (64.5%) <sup>s</sup> |
|            |          | T         | 204(73.1%) | 75 (88.2%) <sup>f</sup> | 43 (86%) | 32 (91.4%) <sup>l</sup> | 19 (82.6%) | 56 (90.3%) <sup>t</sup> |

AITD, Autoimmune thyroid diseases; HD, Hashimoto disease; GD, Graves disease; TAO, Thyroid associated ophthalmopathy;

Normal vs AITD: a; OR=0.3 (0.1-0.7), *P*=0.007, *cP*=0.04, b; OR=3.9 (1.4-11.2), *P*=0.007, *cP*=0.04, c; OR=0.4 (0.2-0.7), *P*=0.004, *cP*=0.02, d; OR=1.9 (1.1-3.3), *P*=0.02, e; OR=0.5 (0.3-0.9), *P*=0.01, f; OR=2.8 (1.4-5.6), *P*=0.004, *cP*=0.02;

Normal vs. HD: g; OR=0.2 (0.02-1.1), *P*=0.04, h; OR=6.5 (0.9-49.0), *P*=0.04, i; OR=0.3 (0.08-0.9), *P*=0.02, j; OR=2.2 (1.1-4.6), *P*=0.04, k; OR=0.5 (0.2-1.0), *P*=0.04, l; OR=3.9 (1.2-13.2), *P*=0.02,

Normal vs. Non-TAO: m; OR=0.2 (0.04-0.7), *P*=0.008, *cP*=0.048, n; OR= 5.8(1.4-24.5), *P*= 0.008, *cP*=0.048, o; OR= 2.0(1.1-3.7), *P*= 0.03, p; OR= 0.5(0.3-0.9), *P*=0.03, q; OR= 0.3(0.1-0.7), *P*=0.004, *cP*=0.02, r; OR= 2.3(1.3-4.2), *P*=0.006, *cP*=0.04, s; OR= 0.4(0.2-0.8), *P*= 0.006, *cP*=0.04, t; OR= 3.4(1.4-8.3), *P*=0.004, *cP*=0.02.

Table 3. TLR10 haplotype frequencies identified in controls and AITD patients.

| Haplotype           | Controls   | AITD                    |
|---------------------|------------|-------------------------|
| (+2322/C.1032/-113) | N=279 (%)  | N=85 (%)                |
| GTA                 | 97 (34.8%) | 27 (31.8%)              |
| AGT                 | 84 (30.0%) | 40 (47.1%) <sup>a</sup> |
| ATT                 | 29 (10.3%) | 11 (12.9%)              |
| AGA                 | 33 (11.9%) | 3 (3.5%)                |
| ATA                 | 20 (7.0%)  | 4 (4.7%)                |
| GTT                 | 16 (6.0%)  | 0 (0%)                  |
| GGA                 | 0 (0%)     | 0 (0%)                  |

AITD, Autoimmune thyroid diseases; Normal vs AITD: a; OR=2.1 (1.3-3.4), *P*=0.004, *cP*=0.03

## Conclusion

Our results suggest that TLR10 polymorphisms may contribute to the pathogenesis of AITD.