# Poster The Distribution of IL-10 Gene Promoter Region -1082 G/A Polymorphism in Indonesian Rheumatic Heart Disease Patients

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# THE DISTRIBUTION OF *IL-10* GENE PROMOTER REGION -1082G/A POLYMORPHISM IN INDONESIAN RHEUMATIC HEART DISEASE PATIENTS

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**Background:** Rheumatic heart disease (RHD) still becomes a burden in developing countries. It is a chronic complication of recurrent acute rheumatic fever which is caused by*Streptococcus* group A. Cross reactivation of *Streptococcus*group Aprotein M triggers immunological response due to molecular mimicry. Interleukin-10 (*IL-10*) gene polymorphism in the promoter region at -1082 A/G was hypothesized to reduce the production of IL-10 and affected particular individual's susceptibility tothe development of RHD.
**Aim:** To describe the distribution of *IL-10* gene polymorphism -1082 A/G in Indonesian RHD patients and their clinical characteristics.

**METHODS:** The study was conducted from June 2016 to Oktober 2016. The inclusion criteria were: patients with mitral valve stenosis/regurgitation with/without other valve involvement who subjected to valve replacement surgery. The exclusion criteria: showing signs of infections, or received immunosuppressive steroid therapy or high-dose aspirin. The study was approved by hospital's research ethics committee.

During the study period, there were 65 patients who underwent the valve replacement surgery in Dr. Kariadi General Hospital, Semarang (DKGHS) from November 2014 to March 2016. Out of 65 patientsts, 9 passed away, 2 were found to have prolapse mitral valve, 10 patients were not referred from local hospital to DKGHS, and 18 could not be contacted. So, the total study subjects were 26 patients .

Patients' data were summarized in a Case Report Form consist of: Anamnesis data, physical examination, ECG, Echocardiogram. Genomic DNA was isolated from whole blood-EDTA according to the salting-out method. Identification of *IL-10* gene polymorphism in promoter region -1082 was done using High Resolution Melting (HRM) Analysis.

The PCR amplification reactions were performed in a final volume of 10 ul, using HRM PCR Master Mix 2X (Qiagen), 10 uM of each primer. Forward primer F: 5'-GACAACACTACTAAGGCTTCTTTGG-3' and reverse primer 5'-AGATGGGGTGG AAGAAGTTG-3' and ±40 ng of genomic DNA as a template. After amplification, all the samples were analyzed by heating to 95 C for 1 min, cooling to 40 C for 1 min and then melting at 0.1 C/s with continuous acquisition of fluorescence from 60 to 95 ◦C. All samples were examined by direct sequencing to confirm the data obtained by the HRM method. Chi square test was used to compare variables between genotypes whenever appropriate, otherwise Fisher test was used.

| Variabel | Wildtype | | Polymorphic | | |
|---|---|---|---|---|---|
| | *n* | (%) | *n* | (%) | |
| | mean±SD | | mean±SD | | |
| **Age** | 44.4±12.59 | | 39,8±10,08 | | 0.49 |
| **Sex** | | | | | |
| • Male | 6 | (27.3) | 1 | (25) | 1.00 |
| • Female | 16 | (72.7) | 3 | (75) | |
| **Chief Complaint** | | | | | |
| • Dyspneu | 20 | (90.9) | 4 | (100) | 1.00 |
| • Fatique | 2 | (9.1) | 0 | (0) | |
| **ECG** | | | | | |
| • Sinus | 6 | (27,3) | 3 | (75) | 0.10 |
| • Atrial Fibrillation | 16 | (72,7) | 1 | (25) | |
| **Echocardiography** | | | | | |
| • Primary valve damage | | | | | |
| ✓ Mitral only | 14 | (63,6) | 1 | (25) | |
| ✓ Mitral and Aortic | 8 | (36,4) | 3 | (75) | |
| • Rheumatic valve damage | | | | | 0.43 |
| ✓ MS | 2 | (18.2) | 0 | (0) | |
| ✓ MR | 9 | (9.1) | 3 | (75.0) | |
| ✓ MS and MR | 11 | (50.0) | 1 | (25.0) | |
| • MS severity | | | | | 0.41 |
| ✓ No MS | 9 | (40.9) | 3 | (75.0) | |
| ✓ Moderate | 4 | (18.2) | 0 | (0) | |
| ✓ Severe | 9 | (40.9) | 1 | (25.0) | |
| • MR severity | | | | | 0.91 |
| ✓ No MR | 2 | (9.1) | 0 | (0) | |
| ✓ Mild | 4 | (18.2) | 1 | (25.0) | |
| ✓ Moderate | 4 | (18.2) | 1 | (25.0) | |
| ✓ Severe | 12 | (54.5) | 2 | (50.0) | |
| • AR severity | | | | | |
| ✓ No AR | 14 | (63.6) | 1 | (25.0) | 0.17 |
| ✓ Mild | 4 | (18.2) | 1 | (25.0) | |
| ✓ Moderate | 2 | (9.1) | 0 | (0) | |
| ✓ Severe | 2 | (9.1) | 2 | (50.0) | |
| • AS severity | | | | | |
| ✓ No AS | 22 | (100) | 3 | (75.0) | 0.15 |
| ✓ Mild | 0 | (0) | 1 | (25.0) | |
| • PH | 16 | (72,7) | 3 | (75) | |
| • PH severity | | | | | 0.88 |
| ✓ No PH | 6 | (27.3) | 1 | (25.0) | |
| ✓ Mild | 2 | (9.1) | 0 | (0) | |
| ✓ Moderate | 11 | (50.0) | 2 | (50.0) | |
| ✓ Severe | 3 | (13.6) | 1 | (25.0) | |

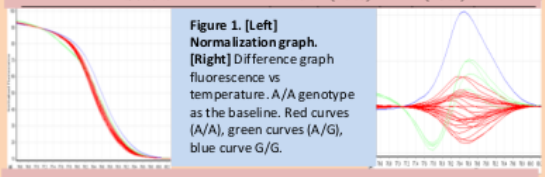

**Figure 1. [Left] Normalization graph. [Right]** Difference graph fluorescence vs temperature. A/A genotype as the baseline. Red curves (A/A), green curves (A/G), blue curve G/G.

**DISCUSSION :** Settin *et al* who studied RHD patients in Egypt reported that A/A was found in 21.7% population, A/G in 56.5%, while G/G in 21.7%. The A/G genotype was the majority.[6] Abdallah *et al* studied RHD patients in Saudi Arabia and reported similar result, A/G as the majority. The proportion of A/A was 25%, A/G was 58% and G/G was 16%.[24] Other study done by Rehman *et al* in Pakistani RHD showed that A/A was found 30.7% population, A/G in 36.6% while G/G in 32.7%. The three genotypes shared the same proportion.[22] Egypt (south-west Asia) and Saudi Arabia (west Asia) had similar patern, A/G as the major genotype, while Pakistan (south Asia) had equal proportion for each possible genotype. This study showed high proportion of A/A genotype in Indonesia (south-east Asia).

Isolated mitral damage was more common in the wildtype group. Severe mitral stenosis (MS) were more observed in the wildtype group. This was different with lower proportion of mitral valve disease in A/A genotype (40% vs 60%) reported by Sherif M. Yousry. Double mitral damanges (both stenosis and regurgitation) were higher in the wildtype group, while isolated mitral regurgitation (MR) were higher in the polymorphic group. The higher proportion was different with Yousry's study which showed similar proportion between A/A genotype and G allele in combined valve disease patients.

**CONCLUSION :** The wildtype A/A genotype was the majority of Indonesian patients (84.6%), heterozygous (AG) allele was found in 11.53%, while homozygous type (G/G) of *IL-10* gene polymorphism -1082 was found in 3.85%. Atrial fibrillation was more common in the wildtype group as well as the mitral valve disease.

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