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Preliminary identification of N-Acetyltransferase 2 (NAT2) gene polymorphisms in the dayak population

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ABSTRACT

Polymorphism is a change or mutation in a gene that does not cause a change in the protein structure. The N-Acetyltransferase NAT enzyme is encoded by the N-Acetyltransferase 2 (NAT2) gene, the N-Acetyltransferase 2 (NAT2) gene, several variations of DNA known as single nucleotide polymorphisms (SNPs) that alter the genotype, haplotype, and phenotype. The NAcetyltransferase 2 (NAT2) genotype was classified into three phenotypes, namely fast acetylators, intermediate acetylators, and slow acetylators. The purpose of this study was to determine the type of polymorphism and the type of polymorphism of the NAT2 gene of the Dayak tribe. In this study, blood samples from the Dayak tribe were isolated from the Wizard Genomic DNA Purification kit and then identified Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). With stages 1. Denaturation 2. Anneling and 3. Extension using NAT2 N4 and N5 primers then RFLP with restriction enzymes KpnI, TaqI and BamHI then electrophoresed with 2% agarose gel. The results of the initial identification of the N-Acetyltransferase 2 (NAT2) gene polymorphism in the Dayak tribe obtained 5 types of genotypes NAT2*4/*5B (20%), NAT2*4/*6A (33.3%), NAT2*4/*7B (20%), NAT2*5B/5B (13.3%) and NAT2*7B/7B (13.3%). From the phenotype of the Dayak tribe, there are two medium acetylators (73.3%) and slow acetylators (26.3%).

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1. Introduction

Indonesia has more than 17,000 islands and 1,300 ethnic groups, making this ethnic diversity an opportunity to study genetic variations related to disease susceptibility and drug reactions [1]. N-acetyltransferase (NAT) is a phase II enzyme that catalyzes the acetylation of drugs with heterocyclic amine or hydrazine groups, playing a crucial role in the metabolism of isoniazid (INH) as well as various drugs and carcinogens in humans [2]–[4].

The N-acetyltransferase enzyme is encoded by the NAT2 gene, which has DNA variations in the form of single nucleotide polymorphisms (SNPs). These variations affect an individual's genotype, haplotype, and phenotype. Based on their ability to metabolize INH, the phenotypes of the NAT2 gene haplotypes are classified into three categories: rapid acetylator (RA, two rapid alleles), intermediate acetylator (IA, one rapid allele and one slow allele), and slow acetylator (SA, two slow alleles). At least one to four SNPs are required to determine the NAT2 genotype that influences the acetylation phenotype [5]–[7]. NAT2 polymorphism plays a crucial role in xenobiotic acetylation and therapeutic response, making it an important marker for detoxification processes in individuals [1], [6].

Previous studies on several ethnic groups in Indonesia have shown variations in the distribution of acetylator phenotypes. Among the Javanese and Sundanese ethnic groups, the fast acetylator phenotype was found in 13.6%, the intermediate in 50.8%, and the slow in 35.6%, while among the Malay ethnic group, the frequencies were 10%, 52%, and 38%, respectively [8]. The relatively high frequency of the slow acetylator phenotype in Indonesia is considered important in efforts to prevent hepatotoxicity and support the success of treatment. Meanwhile, a study on the Bugis ethnic group reported six genotypes consisting of six polymorphisms and 12 NAT2 variations, with the frequency distribution of NAT26A at 42% (the highest), followed by NAT24 (33%), NAT27B (15%), NAT25B (5%), NAT212A (3%), and NAT213 (2%). The phenotype in the Bugis ethnic group showed 18% fast acetylators, 40% intermediate acetylators, and 42% slow acetylators [1].

Given the diversity of ethnic groups in Indonesia and the significant influence of the slow acetylator phenotype of NAT2 on treatment, early identification of NAT2 gene polymorphisms is important. Studies on various ethnic groups are needed to understand genetic diversity and support appropriate therapy. This study establishes the initial identification of NAT2 gene polymorphisms in the Dayak ethnic group, which has not been studied previously, thereby providing the latest genetic profile related to NAT2 polymorphisms in that ethnic group.

2. Method

2.1. Materials

The materials used include Dayak tribe blood samples (10 samples) in EDTA tubes, NAT2 primers N5 (5′ TCAGCCTCAGGTGCCTTGCA-3′) and N4 (5′ AGCATGAATCACTCTGCTTC-3′), 2% agarose gel, 0.5x TBE buffer, sterile water, Wizard® Genomic DNA Purification Kit (lysis buffer, nuclear lysis buffer, protein precipitation buffer, rehydration buffer), master mix, isopropanol, 70% ethanol, loading buffer, 100 bp hyperlader, 1 mL Florosafe DNA dye, and restriction enzymes KpnI, TaqI, and BamHI.

2.2. Tools

The equipment used was electrophoresis, 1.5 mL microtubes, 1000 µL and 100 µL micropipettes (Eppendorf Research Plus), vortex mixer (Thermolyne), centrifuge, Maestronano (Maestrogen), EDTA Vacutainer tubes, Vacutainer holders, PCR (ESCO), PCR tubes (Axygen), gel electrophoresis, incubator, RFLP, analytical balance, thermocycler, a set of glassware such as beakers, 100 mL measuring cups, 250 mL Erlenmeyer flasks, stirrer, thermometer, microwave, and refrigerator.

2.3. Sample Collection

Blood samples were obtained from 10 Dayak subjects and collected in tubes containing ethylenediamine tetraacetic acid (EDTA) and stored in the UGM biochemistry laboratory in 3 ml EDTA vacutaine tubes placed in a 40°C freezer.

2.4. DNA isolation

DNA isolation was performed using the Wizard Genomic DNA Purification Kit. A total of 300 µL of blood was placed in a 1.5 mL microtube, 900 µL of lysis solution was added, incubated at room temperature for 10 minutes, then centrifuged at 12,500 rpm for 5 minutes. The precipitate was mixed with 300 µL of nuclei lysis solution, followed by 100 µL of protein precipitation solution, vortexed for 20 seconds, and centrifuged for 5 minutes. The supernatant is mixed with 300 µL isopropanol, centrifuged for 5 minutes, the supernatant is discarded, then 300 µL 70% ethanol is added and centrifuged again for 5 minutes. The pellet is dried for 10–15 minutes, then 100 µL of DNA rehydration solution is added and incubated for 1 hour at 60°C or overnight at 4°C. The isolated DNA is ready to use as a template.

2.5. RFLP technique

Detection of NAT2 gene polymorphism was performed by cutting PCR products using KpnI, TaqI, and BamHI enzymes. Polymorphism was indicated by the appearance of new restriction sites, then the restriction results were electrophoresed on a 2% agarose gel (100 volts) and analyzed to determine the type of polymorphism.

2.6. DNA Purity and Concentration Measurement

DNA concentration and purity measurements were performed using a Maestronano Pro spectrophotometer at a wavelength of 260/280 nm. A 2 µL blank was added for calibration, followed by alternating measurements of 2 µL samples. The concentration results and A260/A280 ratio are displayed on the screen, with DNA purity considered good if A260/280 $\geq$ 1.8.

2.7. Polymerase Chain Reaction (PCR)

This study used 15 µL master mix, 11 µL H_2O, 2 µL DNA, and 2 µL primer. PCR conditions included an initial denaturation at 95°C for 5 minutes, followed by 35 cycles: denaturation at 95°C for 40 seconds, annealing at 52°C for 40 seconds, extension at 72°C for 40 seconds, and a final extension at 72°C for 7 minutes.

2.8. Electrophoresis

2 g of agarose was dissolved in 100 mL of 0.5x TBE, heated for 2 minutes in a microwave, cooled, and then 1 µL of Florosafe was added. The gel was poured into a mold and left to stand for 20 minutes. DNA samples and markers were added, then electrophoresed at 100–150 V for 40 minutes.

2.9. RFLP of all enzymes

The restriction enzymes used were KpnI, TaqI, and BamHI with different compositions for each sample. For KpnI: 4 µL of PCR product, 4.5 µL of H_2O, 0.3 µL of enzyme, 1 µL of buffer (total 9.8 µL), incubated at 37°C for 1 hour. For TaqI: PCR product 3 µL, H_2O 2.7 µL, enzyme 0.3 µL, buffer 1 µL (total 7 µL), incubated at 37°C for 15 minutes. For BamHI: PCR product 3 µL, H_2O 2.7 µL, enzyme 0.3 µL, buffer 1 µL (total 7 µL), incubation at 37°C for 15 minutes. Restriction patterns were analyzed by 2% agarose gel electrophoresis at 100 V for 40 minutes.

2.10. RFLP technique

DNA analysis includes DNA isolation using the Wizard Genomic DNA Purification Kit, followed by 2 µL of DNA used for PCR using the NAT2 N5 and N4 primers. PCR conditions consist of an initial denaturation at 95°C for 5 minutes, 35 cycles (95°C for 40 seconds, 52°C for 40 seconds, 72°C for 40 seconds), and a final extension at 72°C for 7 minutes.

NAT2 polymorphisms were tested by RFLP using KpnI, TaqI, and BamHI enzymes. The KpnI enzyme mixture (9.8 µL) was incubated at 37°C for 1 hour, while TaqI and BamHI (7 µL) were incubated at 37°C for 15 minutes, and the results were electrophoresed. Identification was based on band patterns: NAT2*5B (KpnI: 655 bp & 710 bp), NAT2*6A (TaqI: wild 377, 170, 163 bp; mutant 377 & 333 bp), and NAT2*7B (BamHI: wild 431 & 279 bp; mutant 710 bp). The combination of restriction patterns determines the NAT2 genotype and phenotype.

3. Results and Discussion

3.1. DNA isolation

DNA isolation from blood in EDTA tubes was performed on 10 samples using the Wizard® Genomic DNA Purification Kit, which was proven to produce DNA with good quantity and quality. Common problems include contamination during initial washing, resulting in an A260/A280 ratio > 2, or damage due to improper storage. Purification aims to separate DNA from proteins and cellulose, with good purity if the A260/A280 ratio is between 1.8 and 2.0 [9], [10].

Table 1. Consentration and levels of Dayak Tribal DNA

Sample	Consentration (µg/ml)	A260/280
A	44.299	1.901
B	1.022	1.956
C	1.329	1.999
D	22.214	1.915
E	16.440	1.843
G	27.686	1.910

H	1.349	1.968
I	58.762	1.905
J	13.581	1.989
K	31.715	1.906

High DNA concentrations were obtained because isolation with the Wizard Genomic DNA Purification Kit involves purification and washing steps. The results of the Maestronano reading showed an A260/A280 ratio of 1.843–1.999, indicating pure DNA, with the highest concentration in sample I at 58.762 µg/mL. Since the DNA was already pure, the samples could proceed to the RFLP stage using the KpnI, TaqI, and BamHI enzymes.

3.2. RFLP Results Using the Kpn1 Restriction Enzyme

The KpnI enzyme is derived from Klebsiella pneumoniae OK8 with the recognition site GGTACC, functioning as both a cutting enzyme and a detector for NAT2*5B [11]. In this study, the NAT2 gene was analyzed using the PCR-RFLP method with the KpnI enzyme, and the cleavage products (655 bp and 710 bp) were observed via 2% agarose gel electrophoresis [12]. The KpnI test results are as follows.

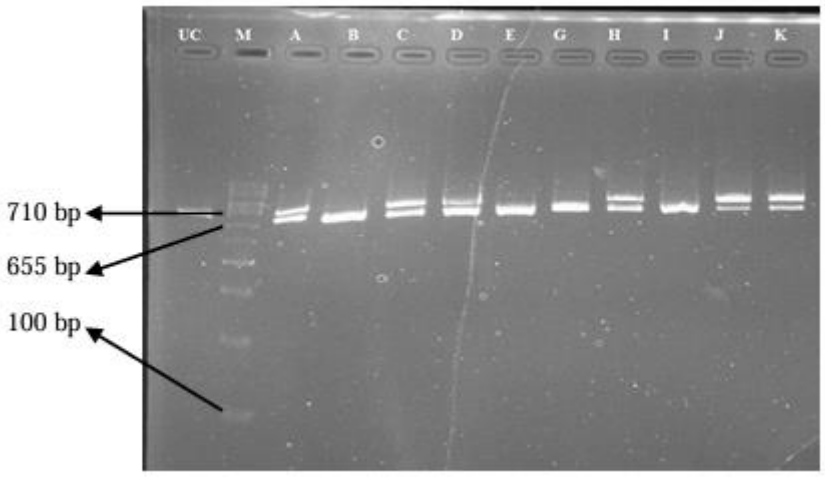

Figure 1. KpnI RFLP enzyme (M: 100bp marker, A, B, C, D, E, G, H, I, J, K: sample numbers, UC: uncut)

Table 2. KpnI enzyme RFLP reading result

Sequence number	Code Sample	Band size (Bp)	Type	Description
1	A	710, 655	NAT2*4/*5B	Mutant
2	B	710	NAT2*5B	Mutant
3	C	710, 655	NAT2*4/*5B	Mutant
4	D	710, 655	NAT2*4/*5B	Mutant
5	E	710	NAT2*5B	Mutant
6	G	710	NAT2*5B	Mutant
7	H	710, 655	NAT2*4/*5B	Mutant
8	I	710	NAT2*5B	Mutant
9	J	710, 655	NAT2*4/*5B	Mutant
10	K	710, 655	NAT2*4/*5B	Mutant

This study used a 100 bp marker, with KpnI restriction results showing bands of 710 bp and 655 bp. Samples A, C, D, H, J, and K had two bands (710 bp & 655 bp), while samples B, E, G, and I had only one band (710 bp). The wild-type NAT2*4 allele is marked by the 655 bp band, while the mutant NAT2*5B allele is marked by the 710 bp band. These results indicate the presence of mutations in the form of the NAT24/NAT25B allele combination or the homozygous NAT2*5B allele.

3.3. RFLP Results Using TaqI Restriction Enzyme

The TaqI enzyme is derived from Thermus aquaticus YTI with the TCGA recognition site, functioning as a cutting enzyme to detect NAT2*6A [13], [14]. In this study, the NAT2 gene was analyzed by PCR-RFLP using TaqI, and the target cleavage products (377 bp, 170 bp, 163 bp, and 333 bp) were observed by 2% agarose gel electrophoresis. The electrophoresis results are as follows.

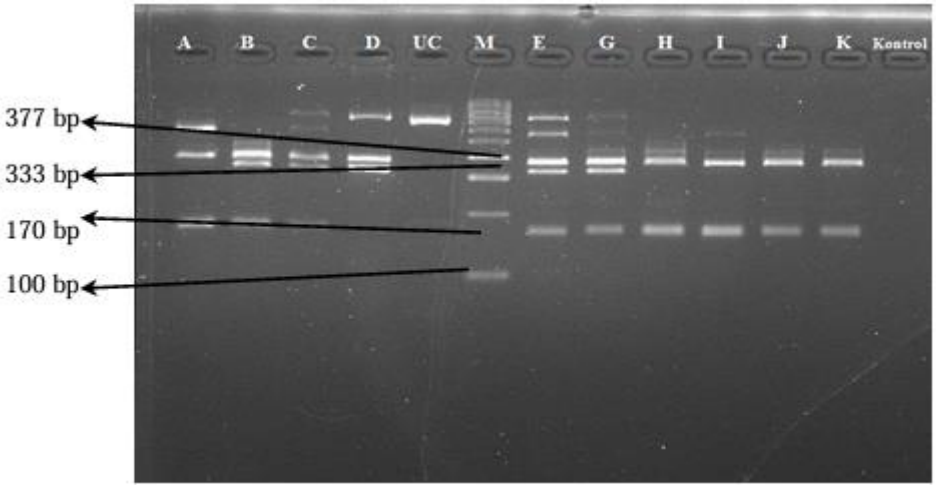

Figure 1. RFLP TaqI enzyme (M: Marker 100bp, A, B, C, D, E, G, H, I, J, K: sample number, UC: uncut)

Table 3. Results of TaqI enzyme RFLP reading

Sequence number	Code Sample	Band size (Bp)	Type	Description
1	A	377, 333, 170	NAT2*4/*6A	Mutant
2	B	377, 710	NAT2*4/*6A	Mutant
3	C	377, 710	NAT2*4/*6A	Mutant
4	D	377, 710	NAT2*4/*6A	Mutant
5	E	377, 710	NAT2*4/*6A	Mutant
6	G	377, 710	NAT2*4/*6A	Mutant
7	H	377, 710	NAT2*4/*6A	Mutant
8	I	377, 710	NAT2*4/*6A	Mutant
9	J	377, 710	NAT2*4/*6A	Mutant
10	K	377, 710	NAT2*4/*6A	Mutant

The electrophoresis results with a 100 bp marker showed that sample A had three bands (377 bp, 333 bp, 170 bp), while samples B–K (except A) had two bands (377 bp, 170 bp).

The wild-type NAT2*4 allele is marked by 3 bands (377, 170, 163 bp), while the mutant NAT2*6A allele is marked by 2 bands (377 and 333 bp). These results indicate that all samples exhibit the heterozygous NAT24/NAT26A mutation.

3.4. RFLP Results Using BamHI Restriction Enzyme

The BamHI enzyme from Bacillus amyloliquefaciens H with the GGATCC recognition sequence was used to detect NAT2*7B [14], [15]. Ten DNA samples were analyzed using the N-Acetyl Transferase 2 gene with the PCR-RFLP method, then electrophoresed on a 2% agarose gel with target bands of 431 bp, 279 bp, and 710 bp, and the following results were obtained.

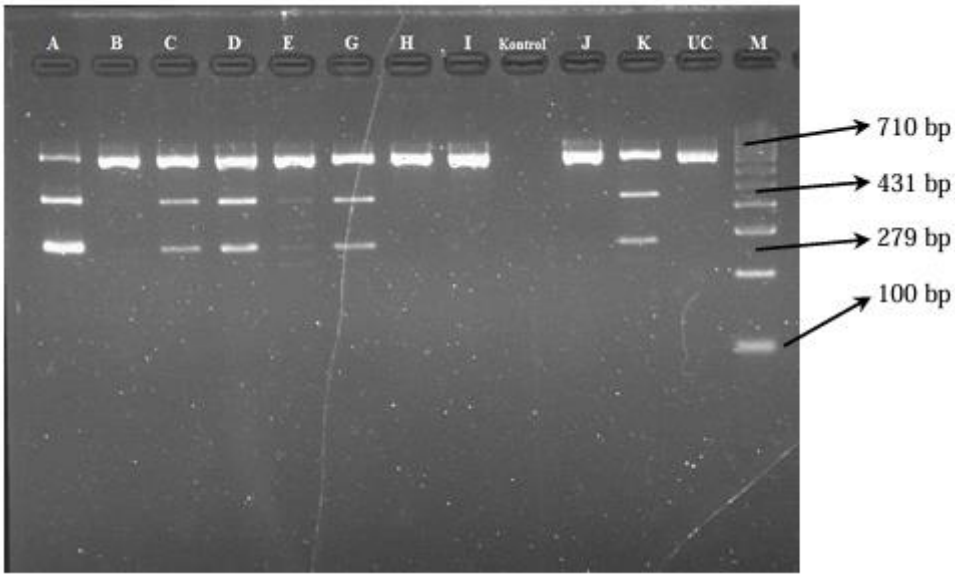

Figure 1. RFLP BamHI enzyme (M: 100bp marker, A, B, C, D, E, G, H, I, J, K: sample numbers, UC: uncut)

Table 4. Results of BamHI enzyme RFLP reading

Sequence number	Code Sample	Band size (Bp)	Type	Description
1	A	710, 431, 279	NAT2*4/*7B	Mutant
2	B	710	NAT2*7B	Mutant
3	C	710, 431, 279	NAT2*4/*7B	Mutant
4	D	710, 431, 279	NAT2*4/*7B	Mutant
5	E	710, 431, 279	NAT2*4/*7B	Mutant
6	G	710, 431, 279	NAT2*4/*7B	Mutant
7	H	710	NAT2*7B	Mutant
8	I	710	NAT2*7B	Mutant
9	J	710	NAT2*7B	Mutant
10	K	710, 431, 279	NAT2*4/*7B	Mutant

Of the 10 samples, electrophoresis showed clear bands with a 100 bp marker as a reference. Samples A, C, D, E, G, and K showed 3 bands (710 bp, 431 bp, 279 bp); samples B, H, I, and J showed 1 band (710 bp). Analysis revealed two allele types: wild (431 bp and

279 bp, NAT24) and mutant (710 bp, NAT27B). These results indicate mutations in NAT24/NAT27B and NAT2*7B. Previous studies in the Indonesian population reported the following genotype distribution: NAT24 (39.9%), NAT26A (36.8%), NAT27B (14.9%), NAT25B (9.0%), and minor alleles NAT212A and NAT213 (<2%) [16].

3.5. NAT2 Polymorphism Type

Based on the genotype data obtained above, the polymorphism types can be grouped according to their phenotypes, namely fast acetylators, moderate acetylators, and slow acetylators. From 10 Dayak tribe DNA samples that underwent PCR-RFLP, the following results were obtained:

Table 5. NAT2 Polymorphism Type

Type			Amount	Frequency (%)
Medium acetylator	NAT2*4/*5B	*Kpn*I	6	20
	NAT2*4/*6A	*Taq*I	10	33.3
	NAT2*4/*7B	*BamH*I	6	20
	Subtotal		22	73.3
slow acetylator	NAT2*5B/*5B	*Kpn*I	4	13.3
	NAT2*7B/*7B	*BamH*I	4	13.3
	Subtotal		8	26.3
	Total		30	100

The NAT2 genotype is divided into three phenotypes: fast acetylators (two fast alleles), intermediate acetylators (one fast, one slow allele), and slow acetylators (two slow alleles). Slow acetylators are more susceptible to drug side effects and certain diseases [17], [18]. In this study, two phenotypes were identified: intermediate acetylators (22 samples) with NAT2*4/5B alleles (20%), NAT24/6A (33.3%), NAT24/7B (20%), and slow acetylators (8 samples) with NAT25B/5B (13.3%) and NAT27B/* 7B (13.3%). The limited number of samples made it impossible to detect the fast acetylator phenotype, even though previous studies on Indonesian populations (Bugis, Javanese, Sundanese) showed the presence of fast acetylators, suggesting that they may also be present in the Dayak tribe [19].

In the Bugis population, the most common allele was **NAT26A/6A (18%), followed by NAT2*6A/* 7B (14%), with the following phenotype distribution: 18% fast acetylators, 40% intermediate, and 42% slow, which could serve as a biomarker for AT-DILI risk [1]. In the Thai population, the allele distribution is similar to East Asia and Southeast Asia, with high NAT2*4, very low NAT2*5, and relatively high NAT2*7, differing from Caucasians, Africans, and Arabs, who show the opposite pattern [20].

TB patients with slow acetylators have higher isoniazid concentrations than those with intermediate and fast acetylators, making them more susceptible to DILI. A study in India showed that isoniazid concentrations in all three groups were <3 g/ml, with slow acetylators having higher concentrations than intermediate acetylators. Hepatotoxicity also develops more rapidly in slow acetylators, while fast acetylators require a 1.5-fold higher dose for optimal effect. With a prevalence of slow acetylators at 35.6% in Indonesia,

the risk of liver injury from isoniazid must be considered. Conversely, in 13.6% of fast acetylators, the possibility of inadequate dosing should be considered [8], [21]–[23].

Research on NAT2 polymorphisms in the Bugis population influences TB therapy management. Fast acetylators are at risk of receiving suboptimal doses, while slow acetylators are prone to overdose and AT-DILI. This information is important for TB treatment policies to prevent hepatotoxicity and side effects, so further research is needed to determine the optimal dose for this population [1], [24], [25].

4. Conclusion

Based on the results of research on N-acetyltransferase 2 gene polymorphism using the Polymerase Chain Reaction method - Restriction Fragment Length Polymorphism in 10 blood samples from the Dayak ethnic group using three restriction enzymes (KpnI, TaqI, and BamHI), five polymorphism types were identified: NAT2*4/5B, NAT24/6A, NAT24/7B, NAT25B/5B, and NAT27B/7B. These polymorphism types were divided into two phenotypes: moderate acetylators, comprising 22 samples with three alleles, namely NAT24/5B at 20%, NAT24/6A at 33.3%, and NAT24/7B at 20%, and slow acetylators comprising 8 samples with two alleles, namely NAT25B/5B at 13.3% and NAT27B/*7B at 13.3%.

REFERENCES

[1] R. Yuliwulandari, R. W. Susilowati, I. Razari, K. Viyati, H. Umniyati, and K. Prayuni, "N-acetyltransferase 2 Polymorphism and Acetylation Profiles in Buginese Ethnics of Indonesia," *Ann. Hum. Genet.*, vol. 83, no. 6, pp. 465–471, Nov. 2019, doi: 10.1111/ahg.12341.

[2] N. J. Butcher, S. Boukouvala, E. Sim, and R. F. Minchin, "Pharmacogenetics of the arylamine N-acetyltransferases," *Pharmacogenomics J.*, vol. 2, no. 1, pp. 30–42, 2002, doi: 10.1038/sj.tpj.6500053.

[3] D. W. Hein and L. M. Millner, "Arylamine N-acetyltransferase Acetylation Polymorphisms: Paradigm for Pharmacogenomic-guided Therapy- a Focused Review," *Expert Opin. Drug Metab. Toxicol.*, vol. 17, no. 1, pp. 9–21, Jan. 2021, doi: 10.1080/17425255.2021.1840551.

[4] P. Wang *et al.*, "Deficiency of N-acetyltransferase Increases the Interactions of Isoniazid with Endobiotics in Mouse Liver," *Biochem. Pharmacol.*, vol. 145, pp. 218–225, Dec. 2017, doi: 10.1016/j.bcp.2017.09.001.

[5] A. D. Wahyudi and S. Soedarsono, "Farmakogenomik Hepatotoksisitas Obat Anti Tuberkulosis," *J. Respirasi*, vol. 1, no. 3, p. 103, 2019, doi: 10.20473/jr.v1-i.3.2015.103-108.

[6] K. Zhu *et al.*, "Association Between NAT2 Polymorphism and Lung Cancer Risk: A Systematic Review and Meta-Analysis," *Front. Oncol.*, vol. 11, no. March, pp. 1–9, 2021, doi: 10.3389/fonc.2021.567762.

[7] R. Yuliwulandari, K. Prayuni, H. Usman, Q. Sachrowardi, and K. Tokunaga, "Differentiation of n-acetyltransferase 2 (NAT2) Rapid and Intermediate Acetylator Based on Genotype and Urinary Assay," *Australas. Med. J.*, vol. 10, no. 10, pp. 879–883, 2017, doi: 10.21767/AMJ.2017.3105.

[8] R. W. Susilowati, K. Prayuni, I. Razari, S. Bahri, and R. Yuliwulandari, "High frequency of NAT2 slow acetylator alleles in the Malay population of Indonesia: An awareness to the anti-tuberculosis drug induced liver injury and cancer," *Med. J. Indones.*, vol. 26, no. 1, pp. 7–13, 2017, doi: 10.13181/mji.v26i1.1563.

[9] A. Dilhari *et al.*, "Evaluation of the Impact of Six Different DNA Extraction Methods for the Representation of the Microbial Community Associated with Human Chronic Wound Infections Using a Gel-based DNA Profiling Method," *AMB Express*, vol. 7, no. 1, p. 179, Sep. 2017, doi: 10.1186/s13568-017-0477-z.

[10] G. Lucena-Aguilar, A. M. Sánchez-López, C. Barberán-Aceituno, J. A. Carrillo-Ávila, J. A. López-Guerrero, and R. Aguilar-Quesada, "DNA Source Selection for Downstream Applications Based on DNA Quality Indicators Analysis," *Biopreserv. Biobank.*, vol. 14, no. 4, pp. 264–270, Aug. 2016, doi: 10.1089/bio.2015.0064.
[11] D. Yadav *et al.*, "Association of Nat2 Gene Polymorphism with Association of Nat2 Gene Polymorphism with Antitubercular Drug-induced Hepatotoxicity in the Eastern Uttar Pradesh Population," *Cureus*, vol. 11, no. 4, pp. 2–9, 2019, doi: 10.7759/cureus.4425.
[12] A. D. Malewa, "Diversity of the Palu Sheep Growth Hormone Gene using the PCR-RFLP Method," 2019, [Online]. Available: https://api.semanticscholar.org/CorpusID:226793995.
[13] P. M. Skowron *et al.*, "The Third Restriction-modification System from Thermus aquaticus YT-1: Solving the Riddle of Two TaqII Specificities," *Nucleic Acids Res.*, vol. 45, no. 15, pp. 9005–9018, Sep. 2017, doi: 10.1093/nar/gkx599.
[14] X. Lv *et al.*, "NAT2 Genetic Polymorphisms and Anti-tuberculosis Drug-Induced Hepatotoxicity in Chinese Community Population," *Ann. Hepatol.*, vol. 11, no. 5, pp. 700–707, 2012, doi: https://doi.org/10.1016/S1665-2681(19)31446-2.
[15] S. K. Sharma *et al.*, "Genetic Polymorphisms of N-acetyltransferase 2 & Susceptibility to Antituberculosis Drug-induced Hepatotoxicity," *Indian J. Med. Res.*, vol. 144, no. 6, pp. 924–928, Dec. 2016, doi: 10.4103/ijmr.IJMR_684_14.
[16] R. Yuliwulandari *et al.*, "Polymorphisms of promoter and coding regions of the arylamine N-acetyltransferase 2 (NAT2) gene in the Indonesian population: proposal for a new nomenclature.," *J. Hum. Genet.*, vol. 53, no. 3, pp. 201–209, 2008, doi: 10.1007/s10038-007-0237-z.
[17] R. A. Salazar-González, E. Turiján-Espinoza, D. W. Hein, R. C. Milán-Segovia, E. E. Uresti-Rivera, and D. P. Portales-Pérez, "Expression and Genotype-dependent Catalytic Activity of N-acetyltransferase 2 (NAT2) in Human Peripheral Blood Mononuclear Cells and Its Modulation by Sirtuin 1," *Biochem. Pharmacol.*, vol. 156, pp. 340–347, Oct. 2018, doi: 10.1016/j.bcp.2018.08.034.
[18] K. Fukino *et al.*, "Effects of N-acetyltransferase 2 (NAT2), CYP2E1 and Glutathione-S-transferase (GST) Genotypes on the Serum Concentrations of Isoniazid and Metabolites in Tuberculosis Patients.," *J. Toxicol. Sci.*, vol. 33, no. 2, pp. 187–195, May 2008, doi: 10.2131/jts.33.187.
[19] L. V. I. Dewi, "Hubungan Variasi Genetika NAT2 terhadap Risiko Adverse Drug Reaction (ADR) dan Outcome Klinis Pasien Tuberkulosis Suku Jawa," Universitas Gadjah Mada, 2020.
[20] V. Kukongviriyapan, A. Prawan, W. Tassaneyakul, J. Aiemsa-Ard, and B. Warasiha, "Arylamine N-acetyltransferase-2 Genotypes in the Thai Population.," *Br. J. Clin. Pharmacol.*, vol. 55, no. 3, pp. 278–281, Mar. 2003, doi: 10.1046/j.1365-2125.2003.01766.x.
[21] V. Yunivita *et al.*, "Isoniazid Exposures and Acetylator Status in Indonesian Tuberculous Meningitis Patients," *Tuberculosis (Edinb).*, vol. 144, p. 102465, Jan. 2024, doi: 10.1016/j.tube.2023.102465.
[22] A. Mukherjee, T. Velpandian, M. Singla, K. Kanhiya, S. K. Kabra, and R. Lodha, "Pharmacokinetics of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol in Indian Children," *BMC Infect. Dis.*, vol. 15, no. 1, p. 126, 2015, doi: 10.1186/s12879-015-0862-7.
[23] S. Soedarsono *et al.*, "Development of Population Pharmacokinetics Model of Isoniazid in Indonesian Patients with Tuberculosis," *Int. J. Infect. Dis.*, vol. 117, pp. 8–14, Apr. 2022, doi: 10.1016/j.ijid.2022.01.003.
[24] R. Mahajan and A. K. Tyagi, "Pharmacogenomic Insights Into Tuberculosis Treatment Shows the NAT2 Genetic Variants Linked to Hepatotoxicity Risk: a Systematic Review and Meta-Analysis," *BMC Genomic Data*, vol. 25, no. 1, p. 103, 2024, doi: 10.1186/s12863-024-01286-y.
[25] R. Yuliwulandari *et al.*, "NAT2 Variants are Associated with Drug-induced Liver Injury Caused by Anti-tuberculosis Drugs in Indonesian Patients with Tuberculosis.," *J. Hum. Genet.*, vol. 61, no. 6, pp. 533–537, Jun. 2016, doi: 10.1038/jhg.2016.10.