

Clustering Haplotypes in Native Papuans Based on Polymorphisms in the Sequence of the LDLR Gene

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Abstract. Single-nucleotide polymorphisms (SNPs) within the LDLR can serve as genetic markers for diagnosing susceptibility to coronary heart disease. The presence of SNPs in this gene can serve as a basis for the formation of haplotype clusters within a population. Papua exhibits significant ethnic diversity, potentially influencing genetic variation within the LDLR gene. This study aimed to cluster the haplotypes of native Papuans based on SNPs in the LDLR gene sequence. In this study, the rear end of the LDLR gene was sequenced in 20 native Papuans from tribes inhabiting different ecological zones. Sequence analysis revealed four SNPs that formed six haplotypes. Two SNPs were located at intron 17, namely IVS17–80 G>A and VS17–42 A>G, and two SNPs were located at the 3'UTR, namely *52G>A and *504G>A, with a nucleotide diversity of 0.00185. The identified haplotypes were GAGG, GGGG, GGGA, AGGG, GAAA, and AAAA, with a diversity of 0.726 ± 0.075 . Four haplotypes (GAGG, GGGG, GGGA and AGGG) were clustered into one group (Cluster A), whereas the remaining two haplotypes (GAAA and AAAA) formed another distinct cluster (Cluster B). These findings highlight the potential of haplotype clustering in characterizing the population structure of Papuan tribes across diverse ecological regions.

1 Introduction

Low-density lipoprotein receptor (LDL-R) is a glycoprotein present on the cell surface that plays a pivotal role in maintaining normal plasma cholesterol levels and facilitating the endocytosis of LDL and other cholesterol-carrying particles. LDL-R is encoded by the LDLR gene, which spans approximately 45 kb, comprises 18 exons and 17 introns, and is located on chromosome 19p13.2. This gene generates mRNA with a size of 5.3 kb, of which nearly half (2.5 kb) constitutes the 3'UTR region. Mutations in LDLR lead to familial hypercholesterolemia (FH), a hereditary condition characterized by elevated plasma cholesterol levels in affected individuals. To date, more than 18,000 variants, including 3,000 rare variants, have been identified in LDLR [1].

Single-nucleotide polymorphisms (SNPs) are among the most common forms of polymorphisms within the LDLR gene. SNPs of this gene are commonly associated with variations in plasma cholesterol levels and susceptibility or resistance to coronary heart disease (CHD), as evidenced by genome-wide association studies (GWASs). Specific SNPs within LDLR have been identified as genetic markers associated with CHD.

Beyond their role as markers for assessing susceptibility to CHD, SNPs within the LDLR gene have been used in population genetic studies to explore patterns of genetic diversity among different ethnic groups [2]. These SNPs may form haplotype clusters within populations, which may be informative for preliminary assessments of population structure. Genetic variation within the 3'-untranslated region (3'UTR) of the LDLR gene has been reported to be

sufficiently informative to support exploratory analyses of population genetic diversity. In particular, haplotype-based approaches using polymorphisms in this region may provide initial insights into patterns of genetic differentiation among ethnic groups or sub-populations, although such analyses are inherently preliminary rather than definitive [3][4].

Papua is a region in Indonesia that boasts a homogeneous identity among its people while simultaneously exhibiting a diverse range of social and cultural characteristics. In Papua, over 254 tribes and subtribes are spread across various ecological zones. They speak approximately 251 different languages and dialects. This reflects the diverse characteristics and cultural traits of Papua [5]. Despite extensive research on phenotypic features such as skin color, hair shape, height, weight, face shape, head shape (cephalic index), and skull index of Papua tribes, studies related to genotype remain relatively scarce. Indigenous Papuans are a group of people consisting of native tribes in Papua, encompassing (1) individuals or ethnic groups originating from or residing in a region within Papua whose lineage is pure, and (2) individuals or ethnic groups of mixed or hybrid lineage.

Genetic variation within the 3'UTR of the LDLR gene provides an opportunity to explore the genetic diversity among native Papuan populations distributed across diverse ecological zones. In this context, the present study was designed as a preliminary investigation to analyze single nucleotide polymorphisms (SNPs) within a partial segment of the LDLR 3'UTR and examine haplotype clustering among native Papuan sub-populations. By characterizing haplotype patterns, this study aims to provide initial

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insights into genetic diversity that may be informative for understanding population structure among Papuan tribes.

2 Materials and Methods

2.1 Study design and Scope

This study was designed as an exploratory (pilot) investigation to obtain preliminary insights into haplotype clustering among native Papuan populations based on polymorphisms in LDLR. The analysis was restricted to a partial segment of the 3'UTR of the LDLR gene and did not encompass the complete 3'UTR or the entire gene. A total of 20 individuals were analyzed, with each Papuan sub-tribe represented by approximately one to six individuals. Although this design enables an initial comparison of haplotype patterns across sub-populations, the limited sample size and partial genomic coverage reduce statistical power and population-level representativeness. Accordingly, the results are intended to be interpreted as preliminary and hypothesis-generating.

2.2 Sample and blood collection

The sample used in this study was comprised of indigenous Papuan students currently studying at the University of Papua in Manokwari. The total sample size was 20 individuals, all of which were male and originated from various tribes inhabiting different ecological zones in Papua. The origins and tribes of the sampled students are as follows: Serui (six individuals), Biak (three individuals), Nabire (one individual), Maybrat (two individuals), Jayapura (one individual), Nduga (two individuals), Yahukimo (one individual), Pegunungan Bintang (one individual), Wamena (one individual), and Asmat (two individuals). Before becoming a sample, the students explained the research objectives and asked for voluntary consent to participate. Those who agreed to participate signed a consent form and underwent a health examination before their blood was drawn.

Blood samples were taken from the veins of the hand, totaling 1 mL using a syringe, and then placed into vacuum tubes prefilled with EDTA anticoagulant. The entire process of health examination and blood collection was conducted by the medical personnel at the Amban Manokwari Community Health Center. All treatment procedures applied to humans were approved by the Human Research Ethics Committee of Bogor Agricultural University (protocol number 1976/IT3.KEPMSM-IPB/SK/2025).

2.3 Genomic DNA extraction and amplification

Genomic DNA was extracted using the Genomic DNA Mini Kit (Tissue), following the manufacturer's instructions. Primer pairs used for amplification were as described in a previous study [6], namely F: 5'-GAGGGATCAGGATGTGGAG-3' and R: 5'-ACCACGGATTCAGCCAGATC-3', resulting in a 753

bp product amplification. Reactions were conducted in a 25 μ L volume that contained 5 μ L genomic DNA, 1 μ L of each primer at 10 pmol, 12.5 μ L of GoTaq Green, and 5.5 μ L of nuclease-free water. Amplification was performed using a SimpliAmp Thermal Cycler (Applied Biosystems) with the following cycling parameters: denaturation at 94 $^{\circ}$ C for 5 min, followed by 40 cycles. Each cycle was performed as follows: denaturation at 94 $^{\circ}$ C for 30 seconds, annealing at 56 $^{\circ}$ C for 30 seconds, and extension at 72 $^{\circ}$ C for 30 seconds. After that, post-extension was performed at 72 $^{\circ}$ C for 5 min, and then it ended at 25 $^{\circ}$ C for 2 min [6].

2.4 Electrophoresis and sequencing

The PCR products were detected using 1.8% agarose gel electrophoresis. The electrophoresis results were observed using a UV-Vis transilluminator. The presence of PCR products was indicated by a specific band on agarose gel. Subsequently, the PCR product was sent to the 1st BASE Sequencing Service Sdn. Bhd (Malaysia), for sequencing.

2.5 Data analysis

The forward and reverse sequences were edited using MEGA XI software to generate consensus sequences. This consensus sequence was subsequently aligned with the reference sequence in GenBank (accession number FJ525879.1) using the Basic Local Alignment Search Tool (BLAST) method at the online National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov). Alignment of all consensus sequences of amplicons and analysis of nucleotide diversity (π), genetic distance and phylogenetic trees were conducted using the MEGA XI software. Alignment was performed using Clustal W, and phylogenetic tree reconstruction was based on the neighbor-joining method Kimura 2-Parameter. Polymorphism sites and haplotypes were analyzed using DnaSP 6.12 software.

3 Result and Discussion

3.1 Ecological zone of indigenous Papuan students

The origin region of the indigenous Papuan students included in this study can be grouped into several ecological zones [5]. Serui and Biak were in the coastal ecological zone, whereas Nabire was in the lowland ecological zone. Both ecological zones fell into zone 4. Maybrat is situated in the ecological zone at the foothills of mountains and along river flows, whereas Jayapura is located in the ecological zone of mountain foothills and valleys. Both ecological zones are categorized as zone 3. Nduga, Yahokimo, Pegunungan Bintang, and Wamena are ecological zones characterized by highlands (high mountains) that fall into zone 2. Asmat is an ecological zone consisting of swamps, beaches, and areas along river flows, and is categorized as zone 1. Therefore, the samples used in this study represent all

the zone in Papua. The conditions of the ecological zones influence the interaction between the social and cultural aspects of the tribes inhabiting these zones. The grouping of the ecological zones and the number of samples in each ecological zone are shown in Table 1.

Table 1. Grouping of ecological zones and number of samples in this study.

Place of Origin/Tribes	Ecological zone	The zone category	Number of samples
Serui	Coastal	4	10
Biak			
Nabire	Lowland		
Maybrat	Foothills of mountains and along river flows	3	3
Jayapura			
Nduga	High mountains	2	5
Yahukimo			
Pegunungan Bintang			
Wamena			
Asmat	Swamps, beaches, and areas along river flows	1	2

3.2 Amplification and sequencing

A total of 20 DNA samples from indigenous papuans were successfully amplified and sequenced. The amplified product was 753 bp. Alignment of the amplicon consensus sequences with reference sequences in GenBank revealed a level of 98-100% similarity to the human LDLR gene (accession number FJ525879.1), which is part of intron 17, comprising 114 bp; exon 18, comprising 36 bp; and 3'UTR, comprising 603 bp.

3.3 Polymorphism of single nucleotides and haplotypes

Alignment of all 20 amplicon sequences to the reference sequence in GenBank (accession number FJ525879.1) revealed four polymorphic sites: IVS17-80 G>A and IVS17-42 A>G, located within intron 17, and *52 G>A and *504 G>A located in the 3'UTR section, with a nucleotide diversity of 0.00185. All four polymorphic sites yielded six haplotypes with a diversity of 0.726 ± 0.075 . The resulting haplotypes are as follows: (1) GAGG, (2) GGGG, (3) GGGA, (4) AGGG, (5) GAAA, and (6) AAAA. Haplotype 1 was shared by six individuals: one from the lowland ecological zone, one from the small mountain foothills and valleys ecological zone, two from the swamp, beach, and river ecological zones, and two from the highland zone. Haplotype 1 is similar to the reference haplotype in GenBank. Haplotype 2 was shared by six individuals from the coastal zone and three individuals from the highland zone. Haplotype 3 was present in one individual from the coastal zone, haplotype 4 in one individual from the

mountain foothills along the river, haplotype 5 in one individual from the coastal zone, and haplotype 6 in one individual each from the coastal zone and mountain foothills along the river. The haplotypes, positions of the polymorphic sites, and frequencies are detailed in Table 2, and the electropherogram is presented in Fig. 1.

Table 2. Haplotypes, positions of polymorphic sites, and frequencies.

Haplotype	Position of nucleotides in the sequence				Amount of individual	Frequency	Sample IDs
	IVS 17-80	IVS 17-42	*52	*504			
Ref	G	A	G	G			FJ525879.1
1	G	A	G	G	6	0, 30	Nabire, Jayapura, Peg. Bintang, Wamena, Asmat-1, Asmat-2
2	G	G	G	G	9	0.45	Biak-1, Biak-3, Biak-4, Biak-5, Serui-2, Nduga-1, Nduga-2, Yahukimo, Serui 6
3	G	G	G	A	1	0,05	Serui-1,
4	A	G	G	G	1	0,05	Maybrat-1
5	G	A	A	A	1	0,05	Serui-3
6	A	A	A	A	2	0,1	Biak-2, Maybrat-2

Note: Positions IVS17-80 and IVS17-42 are located within intron 17, whereas positions *52 and *504 are located in the 3'UTR

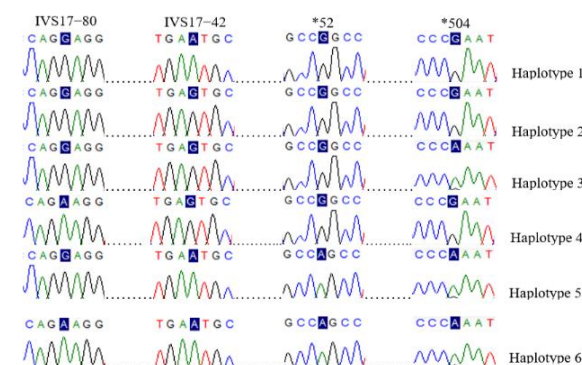


Fig. 1. Electropherogram of six haplotypes

The analysis of the genetic distance between sequence pairs showed a range of genetic distances from 0.0013 (0.13%) to 0.0053 (0.53%). Individuals Biak_2 and Maybrat_2 (haplotype 6) exhibited the greatest genetic distance at 0.0053 (0.53%), followed by Serui_3 (haplotype 5) with a genetic distance of 0.0040 (0.4%), and Maybrat_1 (haplotype 4) and Serui_1 (haplotype 3) with a genetic distance of 0.0027 (0.27%). Genetic distances between 0.0013 and 0.0027 indicated high genetic similarity among these samples, with minimal genetic variation detected among them. Conversely,

Table 3. Genetic distances between sequence pairs.

Sample IDs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Jayapura																				
2. Biak_1	0,0013																			
3. Yahukimo	0,0013	0,0000																		
4. Serui_1	0,0027	0,0013	0,0013																	
5. Nabire	0,0000	0,0013	0,0013	0,0027																
6. Peg_Bintang	0,0000	0,0013	0,0013	0,0027	0,0000															
7. Wamena	0,0000	0,0013	0,0013	0,0027	0,0000	0,0000														
8. Serui_2	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013													
9. Biak_2	0,0040	0,0053	0,0053	0,0040	0,0040	0,0040	0,0040	0,0053												
10. Nduga_1	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013	0,0000	0,0053											
11. Nduga_2	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013	0,0000	0,0053	0,0000										
12. Onate	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013	0,0000	0,0053	0,0000	0,0000									
13. Biak_3	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013	0,0000	0,0053	0,0000	0,0000	0,0000								
14. Serui_3	0,0027	0,0040	0,0040	0,0027	0,0027	0,0027	0,0027	0,0040	0,0013	0,0040	0,0040	0,0040	0,0040							
15. Biak_4	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013	0,0000	0,0053	0,0000	0,0000	0,0000	0,0000	0,0040						
16. Biak_5	0,0013	0,0000	0,0000	0,0013	0,0013	0,0013	0,0013	0,0000	0,0053	0,0000	0,0000	0,0000	0,0000	0,0040	0,0000					
17. Asmat_1	0,0000	0,0013	0,0013	0,0027	0,0000	0,0000	0,0000	0,0013	0,0040	0,0013	0,0013	0,0013	0,0013	0,0027	0,0013	0,0013				
18. Maybrat_1	0,0027	0,0013	0,0013	0,0027	0,0027	0,0027	0,0027	0,0013	0,0040	0,0013	0,0013	0,0013	0,0013	0,0053	0,0013	0,0013	0,0027			
19. Maybrat_2	0,0040	0,0053	0,0053	0,0040	0,0040	0,0040	0,0040	0,0053	0,0000	0,0053	0,0053	0,0053	0,0053	0,0013	0,0053	0,0053	0,0040	0,0040		
20. Asmat_2	0,0000	0,0013	0,0013	0,0027	0,0000	0,0000	0,0000	0,0013	0,0040	0,0013	0,0013	0,0013	0,0013	0,0027	0,0013	0,0013	0,0000	0,0027	0,0040	

genetic distances between 0.0040 and 0.0053 suggest more significant genetic variation between the compared samples. The genetic distances between the sequence pairs are presented in Table 3.

The results of the reconstruction of the phylogenetic tree indicated that individuals with haplotypes 1, 2, 3, and 4 form their own group, cluster A, whereas individuals with haplotypes 5 and 6 form a separate group, cluster B (Fig. 2). Haplotypes within cluster A are common among indigenous people of Papua, as they encompass individuals from every ecological zone, whereas haplotypes within cluster B are specific and being possess only a few individuals from the coastal and riverine zones. Reconstruction of the phylogenetic tree indicated that individuals possessing haplotypes 5 and 6 formed a separate cluster with a high confidence level of 72% (Fig. 2). High bootstrap values served as benchmarks for determining the confidence level of the grouping. This means that individuals from Serui 3, Biak 2, and Maybrat 2 were in separate groups based on their haplotypes. The clustering of haplotypes into two distinct clusters highlights an interesting fact: individuals occupying the coastal and riverine zones exhibit a greater diversity of haplotypes.

3.4 Discussion

The terminology of indigenous Papuans historically emerged from the experiences of expressing and showing Papuanese identity and, therefore, has been accepted and became a consensus with all stakeholders in Papua. Moreover, native Papuans have been identified as indigenous Papuans and legally accommodated in the Law of the Republic of Indonesia No. 21/2001 on special autonomy for Papua. The identification of indigenous Papuans, especially based on lineage, whether pure or mixed, is very important because it has an impact on the legal recognition and

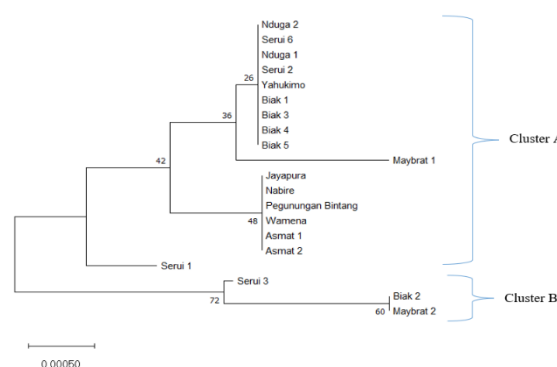


Fig. 2. A phylogenetic tree based on sequences of the *LDLR* gene using the Neighbor-Joining method with a 1,000-fold bootstrap

protection of human rights and consumer rights of indigenous Papuans. One method of identification is genetic analysis of polymorphisms in the *LDLR* gene.

This study demonstrated the existence of common genetic polymorphisms within the rear end of the *LDLR* gene in native papuans. Two single nucleotide polymorphisms (SNPs) found in the 3'UTR, namely *52 G>A and *504 G>A, were also detected in populations from South Africa [7], Brazil [8], Spain [9], Mexico [10], America [11], and China [12]. Two SNPs were identified in intron 17, of which only one SNP, IVS17-42 A>G, was also reported by [7]. Conversely, the SNP IVS17-80 G>A has not been reported previously. Conversely, polymorphic sites in the 3' UTR that were not found in the indigenous people of Papuan are located at positions *141, *315, and *415. This indicates a low genetic diversity of the samples studied, particularly in the 3' UTR. Nevertheless, the presence of SNPs in intron 7 adds to the genetic diversity of native Papuans, as seen from the diversity of haplotypes they possess.

The observed haplotype clustering based on polymorphisms within the 3'UTR of the *LDLR* gene suggests potential genetic structuring among the

sampled Papuan sub-populations. However, given the exploratory nature of the study, the small number of individuals per sub-tribe, and the restriction of the analysis to a partial 3'UTR region, these patterns should be interpreted with caution. The clustering identified in this study may reflect localized variation within the analyzed region rather than comprehensive genetic differentiation across the LDLR locus or broader genome. Nevertheless, these preliminary findings provide a basis for generating hypotheses regarding population-specific haplotype patterns in Papuan populations.

An interesting fact revealed by the analysis of the phylogenetic tree reconstruction is that individuals living in coastal areas, such as Serui and Biak, as well as mountain foothill regions along river streams in Maybrat, show a greater diversity of haplotypes. This diversity leads to the formation of distinct clusters, known as cluster B. The diversity of haplotypes primarily results from the frequent interaction between communities in these areas and individuals from diverse ethnic groups, including coastal tribes within and outside Papua. The accessibility and openness of the topography in these areas facilitate such interactions, unlike the steep and difficult-to-reach mountainous and valley regions. Consequently, tribes in mountainous and valley areas tend to be more isolated.

For the Biak ethnic group, renowned as explorers, interactions with inhabitants from various ethnic groups have occurred. This occurred through expansion toward the western regions of Papua Island, settling along the coastal areas of Bird's Head Peninsula. Consequently, they acquired names such as Mar, Warsai, Karoon, and Warfandu people in the Sorong region. Additionally, they merged with the Moi ethnic group in the southwestern part of Bird's Head Peninsula, extending up to Yefman, Arar, and even the Raja Ampat Islands. The "Tanah Besar (land of Papua)" expedition in the 16th century led by Sultan Al-Mansur or also known as the Sultan of Tidore together with Sangaji Patani Sahmardan with the aim of expanding Tidore's territory was one of the events that showed interaction between tribes outside Papua and tribes on the islands and coastal areas of Papua. Expedition like this were not only about the development of territory and resources, but also about political and social dynamics, which could take the form of marriage, trade, diplomacy, or conflict. This expedition also illustrates the relationship between the regions in eastern Indonesia during that period. The Maybrat region, situated on the western coast of Papua, had access to maritime trade routes that linked them to the regional and international trade networks overseen by Sultan Tidore. These interactions typically involve the exchange of commodities such as spices, ivory, and other goods. Additionally, there may have been exchanges of cultural influences and political affiliation [13].

Furthermore, the presence of Hongi Armadas dispatched from the Sultanate of Tidore in the 17th century, tasked with collecting taxes in the form of forest products on the Bird's Head Peninsula and the western coast of Papua, facilitated interactions between outsiders and indigenous Papuans [13]. The existence of

Chinese ethnic trade routes, which traversed kingdoms in eastern Indonesia such as Gowa/Tallo, Ternate, and Tidore, and eventually settled in Serui in the 17th century, also indicates intensive interaction between coastal indigenous Papuans and outsiders [14]. All these factors enabled the occurrence of marital bonds that impacted the genetic diversity of indigenous Papuan people.

The marriage between Kurabesi, a legendary figure from Biak, and Boki Taiba, the sister of Sultan Tidore, in the late 15th century, gave birth to four sons who later became the founders of four life domains in Raja Ampat: Raja Misol, Raja Waigeo, Raja Salawati, and Raja Batanta. This demonstrates kinship ties between coastal tribes in Papua through marriages with tribes outside Papua [13]. The marriage between a man from the Hokkien and Cantonese ethnic groups, originating from southern mainland China, who traveled for trade in the kingdoms of eastern Indonesia, and a native woman from Serui eventually resulted in the descendants known as "Chinese Peranakans" These descendants indicate genetic mixing between the Serui tribe and non-Papuan inhabitants [14].

4. Conclusion

Analysis of polymorphisms within a partial segment of the 3'UTR of the LDLR gene revealed an initial pattern of haplotype-based clustering among the analyzed native Papuan sub-populations. Although the genetic variation assessed represents only a limited region of the LDLR locus and the sample size per sub-tribe was small, the observed haplotype grouping suggests the presence of underlying genetic differentiation within the studied populations.

These findings should be interpreted as preliminary or exploratory in nature. Rather than providing definitive evidence of population structure, the results highlight the potential utility of LDLR haplotypes as informative markers for investigating the genetic diversity in Papuan populations. Future studies incorporating larger and more representative sample sizes, along with broader genomic coverage are necessary to confirm and refine the haplotype patterns identified in this study.

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