








BMJ Open Implementation of genetic screening test to reduce the incidence of dapsone hypersensitivity syndrome among patients with leprosy in Papua, Indonesia: a study protocol

Hana Krismawati ¹, Astri Ferdiana ^{2,3,4}, Astrid Irwanto ⁵,
Teky Budiawan ², Clara Imaniar ¹, Tri Wahyuni,¹ Pushpendra Singh ⁶,
Liesbeth Mieras ⁷, Arry Pongtiku⁸

To cite: Krismawati H, Ferdiana A, Irwanto A, *et al*. Implementation of genetic screening test to reduce the incidence of dapsone hypersensitivity syndrome among patients with leprosy in Papua, Indonesia: a study protocol. *BMJ Open* 2022;**12**:e057173. doi:10.1136/bmjopen-2021-057173

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-057173>).

Received 10 September 2021
Accepted 28 February 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Astri Ferdiana;
astri@nlrindonesia.or.id

ABSTRACT

Introduction The mainstay of leprosy treatment is multidrug treatment (MDT), which contains rifampicin, dapsone and clofazimine. The occurrence of dapsone hypersensitivity syndrome (DHS), a sudden, potentially fatal and traumatic adverse reaction due to dapsone, may affect treatment adherence and may result in fatality if untreated. Before MDT administration, screening for *HLA-B*13:01* in patients with leprosy can potentially reduce DHS risk. The study aims to assess the effectiveness of using a screening test for *HLA-B*13:01* in reducing the incidence of DHS and to evaluate the feasibility of using the quantitative PCR-based screening tool as DHS predictors before dapsone administration using individual patient testing in a referral centralised-lab model.

Methods and analysis A total of 310 newly diagnosed patients with leprosy will be recruited from health centres in two highly endemic districts in Indonesia. Dried blood will be taken on filter paper as the specimen receptacle to collect DNA from the patients and transported at room temperature to the leprosy referral laboratory before MDT administration. Checking for *HLA-B*13:01* from human DNA is performed using the Nala PGx 1301 V.1 kit. The results will be shared with the leprosy health workers on the site via phone call and courier. Patients with a positive test result will be treated with MDT without dapsone, and patients with a negative result will be treated with complete MDT. Physical examination (weight, height, skin, muscle and nerve function examination), complete blood tests (including renal function test) will be carried out at baseline. Follow-up will be performed at the fourth and eighth weeks to observe any development of adverse drug reactions.

Ethics and dissemination The ethical approval for the study was issued by the Ethical Committee of the National Institute of Health Research and Development, Ministry of Health, Indonesia. Written informed consent will be sought from all participants.

Strengths and limitations of this study

- ⇒ The study aims to reduce the incidence of dapsone hypersensitivity syndrome (DHS), a severe idiosyncratic drug reaction to dapsone, one of the components of multidrug therapy (MDT) in leprosy, as well as to assess the feasibility and acceptability of a genetic screening test.
- ⇒ This is the first study to reduce the incidence of DHS using a genetic biomarker, the *HLA-B*13:01* allele.
- ⇒ This study will screen the presence of *HLA-B*13:01* using quantitative PCR in patients with leprosy in high endemic areas in Indonesia before the administration of MDT and patients with positive *HLA-B*13:01* results will be treated with MDT without dapsone.
- ⇒ There is no control group, therefore the study cannot accurately capture the effectiveness of screening tests in reducing DHS.

INTRODUCTION

Leprosy remains a significant public health problem in Indonesia. According to WHO, Indonesia contributed 8.6% of the global leprosy cases in 2019. It ranked third after India and Brazil in terms of an absolute number of cases.¹ In the same year, the prevalence of leprosy in Indonesia was 0.73 per 10 000 population and the new cases detection rate (NCDR) was at 6.04 per 100 000 population with >17 000 new cases found annually. More than 300 districts in 17 provinces in Indonesia are endemic for leprosy.² Papua and West Papua provinces are among the highly endemic provinces in Indonesia with an NCDR of 45.4 per 100 000 and 132.3 per 100 000 populations, respectively, higher than the national NCDR.³

The current standard treatment for leprosy is a combination of rifampicin, dapsone and clofazimine, referred to as multidrug therapy (MDT).⁴ Dapsone works by inhibiting the bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid for the active site of dihydropteroate synthase, thus resembling the action of sulfonamides. Dapsone is characterised by dual function: besides being antimicrobial, dapsone is also anti-inflammatory.⁵

One of the significant barriers to achieving optimum drug efficacy and treatment adherence is dapsone hypersensitivity syndrome (DHS), a sudden, potentially fatal and traumatic adverse reaction due to dapsone.⁶ DHS is a severe idiosyncratic drug reaction characterised by the clinical triad of fever, rash and systemic involvement (most commonly of the liver and the haematological system), which can cause severe organ dysfunction.⁷ The global estimates of DHS incidence vary from 0.5% to 3.6% among the patients treated by dapsone.⁸ The occurrence of DHS requires months to a year of hospital treatment, with a fatality rate of at least 10% of those who report to a hospital or health centre.⁹ Due to the potential severe and even fatal effects, this syndrome is a burden for the patients and their families, and for the health services and the leprosy elimination programme. The definitive mechanism for DHS is not fully understood, but it is hypothesised that it is mediated by immune activation and elaboration of inflammatory cytokines.⁷

Genetic studies in China have shown that the *HLA-B*13:01* allele is highly associated with occurrence of DHS (OR: 20.53, P: 6.84×10^{-25}).¹⁰ Our validation study also confirmed this genetic association in the Papuan population. We also showed the *HLA-B*13:01* association with DHS, but with a much larger effect size (OR: 233.64, P: 7.11×10^{-9}).¹¹ The Dapsone Hypersensitivity Syndrome Prevention Working Group concluded that at least 85% of DHS cases could have been prevented if the *HLA-B*13:01* carrier status would be available prior to dapsone administration.²

While a database of HLA for Indonesia does not exist, studies have shown that the Papua New Guinea population, which shares similar anthropological characteristics with the Papuan population, have a higher allele frequency of *HLA-B*13:01*.¹² Our previous study in Papua also found that 20% of all patients with leprosy were carrier of the *HLA-B*13:01* allele,¹¹ while the surveillance report in 2019 showed an incidence of DHS of 11%.¹³ The high frequency of the allele might explain the high incidence of DHS among patients with leprosy in this area.

Testing of *HLA-B*13:01* as a highly predictive biomarker for DHS could potentially ensure safe administration of MDT while keeping its efficacy in leprosy treatment and elimination. Until now, dapsone remains part of the standard MDT, thus this screening allows the health workers to plan personalised medication for patients with leprosy without having to remove dapsone from the overall treatment regimen for all patients with leprosy. Early identification of *HLA-B*13:01* carriers and treatment regimen

modification can possibly eliminate the risks of DHS, as reported by Liu *et al* in China.² In this study, patients testing positive for *HLA-B*13:01* were excluded from receiving dapsone. After 3 months of follow-up among 1497 patients, the authors found that the number of DHS decreased from 1% to zero cases.²

It is estimated that testing for the presence of *HLA-B*13:01* could reduce the risk of DHS by sevenfold if implemented in clinical screening.¹¹ With >200 000 new leprosy cases worldwide, theoretically one case of DHS could be prevented for at least every 84 patients with leprosy tested prior to the administration of dapsone within MDT,¹⁴ although this estimation depends on the allele frequency in the population. For example in Papua, theoretically we only need to screen 10 patients with leprosy to prevent one case of DHS.¹¹

The primary aim of this study is to assess the effectiveness of using a screening test for *HLA-B*13:01* in reducing the incidence of DHS. According to the surveillance data of Papua Provincial Health Department in 2019, the incidence of DHS among patients with leprosy is 11% and we aim to reduce the incidence to <1%. The secondary aim is to evaluate the feasibility and acceptability of quantitative PCR (qPCR)-based screening tool for DHS before dapsone administration to assess the risk and reduce its incidence by testing in a centralised-lab model in Papua and West Papua, Indonesia.

METHODS

Study design

This study will use a quasi-experimental design.

Study setting

The study will be conducted in two endemic districts in Indonesia namely Jayapura District in Papua Province and Manokwari District in West Papua Province. The study will involve 13 primary health centres (PHCs) in Jayapura and 6 in Manokwari.

In Indonesia, the leprosy health workers in the PHCs are the frontline workers carrying out leprosy control activities. They are responsible for screening for leprosy signs and symptoms, for diagnosing leprosy and for the administration of MDT.

Study population

Patients with leprosy diagnosed between April 2021 and December 2022 at the participating PHCs who meet the following criteria will be recruited for the study: (1) newly diagnosed patients with leprosy, (2) age above 5 years, (3) a permanent residence in the study areas, indicated by residential ID and (4) willing to give written consent to participate in the study. Since patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are not eligible for treatment by sulfonamide drug including dapsone, we will screen for G6PD deficiency among patients in this study.¹⁵ Patients with a G6PD deficiency will be excluded from the study and administered the

standard MDT treatment without dapsone. Patients with other severe diseases or complications will be disqualified from the study.

Patients and public involvement

No patients have been involved.

Sample size rationale

The frequency of the *HLA-B*13:01* allele among patients with leprosy found in our earlier study was 20%.¹⁶ In order to obtain a statistical power of 90% during the targeted reduction in the DHS incidence from the current 11% to 1% at a statistical significance level of 5%, we need to screen at least 58 patients with leprosy in the population. Furthermore, we calculate the sample size using Epi Calc with the parameters proportion 3%, precision 2% and confidence level 95%. The sample size calculation as per the above criteria is 279. In addition, to account for 10% loss to follow-up, we will recruit a total of 310 subjects.

Outcome measurement

The primary outcome of the study is the occurrence of DHS in patients with leprosy that have been screened for *HLA-B*13:01* before MDT treatment. The diagnosis of DHS will be made by a leprosy doctor as per the national guidelines.¹⁷ The criteria of DHS are as follows: skin lesion, maculopapular lesions or skin rash with systemic symptoms such as fever, jaundice, malaise, and haematological abnormalities (leukocytosis, atypical lymphocytosis, eosinophilia).¹⁶

Study procedure

Recruitment

All patients diagnosed with leprosy at the PHCs during the study period will be screened for eligibility. Eligible patients will be provided with information on the study and asked to give written informed consent. Screened patients who are not enrolled will be recorded in the screening log with reasons for exclusion, and will receive the standard-of-care: MDT including dapsone. All eligible and consenting patients will be consecutively enrolled. At baseline, a physical examination (including weight, height, nerve function and sensory testing), basic laboratory investigation and an interview, using the questionnaire in online supplemental appendix 1 (including sociodemographic data, socioeconomic characteristics and household environment) will be carried out.

Specimen collection

Slit skin smear collection will be carried out according to The National Guidelines for Leprosy, Ministry of Health Republic of Indonesia, to confirm the classification of leprosy.¹⁷ The material collected by a slit in the skin from the earlobe will be divided into two parts, the first will be applied on a slide and the second will be placed into an Eppendorf tube containing 2% phosphate-buffered saline buffer. Five mL of venous blood is collected in an EDTA tube for complete blood examination and liver

function assay. The rest of the blood, about 10–50 µL will be dried on 1×1 cm Whatman filter paper for qPCR assay of *HLA-B*13:01*. This will be done using qPCR test developed by the Genome Institute of Singapore and Nalagenetics, a company on pharmacogenomics assays that can adequately test for the allele in an inexpensive, quick and robust manner.¹⁴ This kit targets two genes: *HLA-B*13:01* (as the target loci) and GAPDH gene (as an internal control).¹⁸

All specimens will be taken by leprosy health workers at the PHCs from a newly diagnosed patient before the drug administration. Once the specimen is collected, the Eppendorf tube will be placed in a cool box with a temperature of 4°C–8°C. Together with the filter paper that is kept at room temperature,¹⁹ these specimen will be sent to the Papua Health Research and Development Center at the end of working hours.

Genotyping of *HLA-B*13:01*

In this study, genotyping of *HLA-B*13:01* is performed using the qPCR procedure using commercial kit from Nalagenetics.²⁰ Human DNA will be extracted from the dried blood spot on the filter paper in the referral laboratory. The paper with dried blood will be cut in 1×1 cm pieces, then scribed using a sterile scalpel and placed into a 1.5 mL microtube using forceps for DNA extraction. Extraction of DNA will be carried out using Monarch Genomic DNA Purification Kit (150 Preps) as per the manufacturer's instructions for tissue specimens with slight increase in the incubation time from 15 to 30 min.²¹ The DNA sample will be eluted in 50 µL elution buffer provided in the kit. This assay will be done using Nala PGx 1301 V.1 (100 reactions) from Nalagenetics, Singapore. Five µL of DNA on concentration 1 ng/µL will be loaded to 20 µL master mix that contains primers and probes.²⁰ PCR amplification will be performed in the CFX 96 qPCR machine BioRad as follows: initial heat 95°C for 10 min, 45 cycles of denaturation (94°C for 10s and combined annealing and extension at 61°C for 30s). We will also run positive and negative controls supplied by Nala PGx 1301 V.1. The positive result will be identified by amplification graph of *HLA-B*13:01* gene while the graph of GAPDH gene will be used as the internal control.

Administration of qPCR DHS predictors and treatment intervention

At the first visit, all participants will undergo baseline physical examination, blood and slit skin smear tests. The patient will be asked to visit the clinic again when the qPCR testing results of *HLA-B*13:01* are ready. In this first visit, all participants will receive MDT without dapsone until the PHC worker obtains the result from the laboratory. The result of the laboratory assay and *HLA-B*13:01* qPCR will be sent to the PHC health workers via phone and airmail courier in 3–5 days.

At the second visit, the patients will be informed about the laboratory result. Complete MDT regimen (for Multibacillary (MB) leprosy: dapsone, rifampicin and

clofazimine; for Paucibacillary (PB) leprosy: dapsone and rifampicin) will be administered to patients with a negative result for *HLA-B*13:01*, while MDT without dapsone (for MB leprosy: rifampicin and clofazimine; for PB leprosy: clofazimine and rifampicin) will be prescribed to patients with a positive result for *HLA-B:13*01*.

Follow-up

After the baseline assessment and treatment meeting, a total of two follow-up visits will be conducted on the fourth and eighth weeks. During the first follow-up, a blood sample will be taken for aspartate transaminase, alanine transaminase and white blood cell count. A physical examination will be done. The health worker will check whether the patient has a reaction or allergy because of the therapy using a questionnaire (online supplemental appendix 1). The second follow-up is at the eighth week with the same procedures as the first follow-up. As DHS occurs within a maximum of 8 weeks after the initiation of dapsone treatment, no follow-up is planned beyond the eighth week. The diagnosis of DHS will be done by a well-trained leprosy physician or leprosy doctor and referral dermatologist if necessary.

Acceptability and feasibility

Acceptability and feasibility of screening for genetic predisposition of DHS will be assessed through in-depth interviews with the programme implementers. Participants will be purposively selected from patients with leprosy, leprosy health workers, head of PHCs and programme managers at provincial and district level. This interview will assess the perception of the participants towards genetic screening. The feasibility of the proposed qPCR-based *HLA-B*13:01* genetic screening in terms of logistics, facilities and manpower as well as the acceptability of the genetic screening test as part of the regular service in the leprosy programme will also be explored.

Data collection and management

The source document of this study is a standardised data collection sheet including baseline and follow-up questionnaire as the record information for each patient enrolled in the study. Information from the laboratory sheet as well as the national standard leprosy examination form will also be recorded. All data entered on the data collection sheet will be hand written. Completed data collection sheets will be signed and dated. These forms will be secured in the investigator file in a locked office at the study site. Information recorded on the data collection sheet will be inputted in Epidata and located on a secure server.

Analysis plan

A two-sided, one sample binomial test will be used to compare the rate of DHS in the prospective screening population with the historical incidence (11%). We will also compare the incidence of DHS in patients treated in the participating health centres compared with those that have not been included in this study. A p-value of <0.05 will

be considered as statistically significant. Statistical analysis will be performed using SPSS version 25.0.

Ethics and dissemination

The ethical approval for the study was issued by the Ethical Committee of National Institute of Health Research and Development, Ministry of Health Indonesia LB.02.01/2/KE.543/2020. The proposal of this study has been reviewed by international peer reviewers of the Leprosy Research Initiative.

All recruitment and data collection is being managed by appropriately trained and experienced PHC leprosy health workers, who are also familiar with the local Papua community. They are trained in Good Clinical Practice by the team from WHO Regional Training Center at Universitas Gadjah Mada in Indonesia. Written informed consent will be requested from all participants prior to enrolment in the study. For illiterate participants, finger stamps will be asked and informed consent will be explained in the presence of a literate witness. Parental consent will be asked in children participants.

The principal investigator will ensure the confidentiality of participants by assigning coded ID numbers to anonymise the patient data. Documents for which anonymity cannot be maintained such as signed informed consent forms and laboratory sheets will be kept in a strictly confidential file by the principal investigator.

Serious adverse event occurring to a participant will be reported within 15 days, or designee becoming aware where in the opinion of the principal investigator the event was related and unexpected. We will inform the patients to report all adverse reactions during their participation in this study to the leprosy health worker.

This study result will be published as scientific paper in an international and national peer-reviewed journal. To disseminate the output of study, we will develop a policy brief and recommendation for the health authority at the national, province and district level. All publications and presentations relating to the study will be authorised by the research team. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Our sponsor will review all documents prior to publication.

DISCUSSION

Until now, although Indonesia is highly endemic for leprosy, limited knowledge exists on the occurrence of DHS. Cases are often reported in the eastern part of Indonesia such as Papua, West Papua and the Mollucas, however, the actual incidence of DHS is not known. Studies have suggested that DHS is associated with *HLA-B*13:01*, which is quite prevalent among leprosy-affected persons in Papua. This study will have positive implications for the leprosy control programme because dapsone allergy can be prevented by individualising the choice of leprosy treatment before it is initiated.

The strong association between *HLA-B*13:01* and DHS suggests that *HLA-B*13:01* could be a useful biomarker to predict the risk of developing DHS in a patient with leprosy initiating MDT.¹¹ In this study, we have proposed to use an easy and cost-effective qPCR-based assay instead of high-cost sequencing-based genotyping technology to detect *HLA-B*13:01* gene. We will also develop a simple referral system for DHS identification. In Indonesia, the leprosy programme is implemented at PHC level with modest laboratory facilities to support diagnostics. To overcome this constraint, reference laboratory with qPCR facilities is a necessity.

To our knowledge, this is the first study aiming at preventing the occurrence of DHS in highly endemic areas in Indonesia using a genetic marker. Until now, there has been no detection and prevention of dapsone allergy in leprosy treatment. We will use a low cost, sensitive test kit that can be easily used by frontline health workers.

The weakness of this study is the limited availability of actual data of DHS in Indonesia, especially in Papua, so it cannot accurately capture the effectiveness of screening tests in reducing the incidence of DHS. We will overcome this by collecting annual surveillance data from all PHCs in Papua to obtain estimate of the incidence. In addition, the study does not employ control group to compare the difference in the DHS incidence after the intervention. To address this limitation, we will compare the DHS incidence in the same PHCs before and after the intervention.

Author affiliations

¹Papua Agency, National Institute of Health Research and Development, Ministry of Health, Indonesia, Jayapura, Indonesia

²NLR Indonesia, Jakarta, Indonesia

³Department of Public Health, Faculty of Medicine, University of Mataram, Mataram, Indonesia

⁴Center for Tropical Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

⁵Nalagenetics, Singapore

⁶ICMR-National Institute of Research in Tribal Health, Jabalpur, India

⁷NLR, Amsterdam, The Netherlands

⁸Papua Provincial Health Office, Jayapura, Indonesia

Twitter Hana Krismawati @hana_krisma and Astri Ferdiana @astriferdiana

Contributors The study concept and design were conceived by HK, AI and AP. HK, CI and TW will oversee the data collection. Analysis and interpretation of data will be performed by HK, AF, AI, TB, PS and LM. HK and AF prepared the first draft of the manuscript. All authors have provided edits and critiqued the manuscript for intellectual content, as well as have given final approval for manuscript.

Funding This work was supported by Leprosy Research Initiative grant number FP 196.

Competing interests AI works for Nalagenetics which develops the qPCR test for the allele.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and

responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Hana Krismawati <http://orcid.org/0000-0003-1952-1802>

Astri Ferdiana <http://orcid.org/0000-0003-0666-4302>

Astrid Irwanto <http://orcid.org/0000-0003-1371-3862>

Teky Budiawan <http://orcid.org/0000-0001-5379-3399>

Clara Imaniar <http://orcid.org/0000-0002-4060-9502>

Pushendra Singh <http://orcid.org/0000-0001-9453-8669>

Liesbeth Mieras <http://orcid.org/0000-0001-6943-1712>

REFERENCES

- 1 Pusat Data dan Informasi Kementerian Kesehatan RI. *InfoDatin-kusta-2018.pdf* [Internet]. Jakarta: Kementerian Kesehatan RI, 2018. www.depkes.go.id/download.php?file=download/pusdatin/kusta
- 2 Liu H, Wang Z, Bao F, et al. Evaluation of prospective HLA-B*13:01 screening to prevent dapsone hypersensitivity syndrome in patients with leprosy. *JAMA Dermatol* 2019;155:666–72.
- 3 World Health Organization. Leprosy - New cases detection rate per 100 000 population Data by country [Internet]. World Health Organization, 2020. Available: <https://apps.who.int/gho/data/node.main.NTDLEPR2?lang=en>
- 4 Wibawa T, Satoto TBT. Magnitude of neglected tropical diseases in Indonesia at Postmillennium development goals era. *J Trop Med* 2016;2016:1–9.
- 5 Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res* 2014;306:103–24.
- 6 Vinod KV, Arun K, Dutta TK. Dapsone hypersensitivity syndrome: a rare life threatening complication of dapsone therapy. *J Pharmacol Pharmacother* 2013;4:158–60.
- 7 Kosseifi SG, Guha B, Nassour DN, et al. The dapsone hypersensitivity syndrome revisited: a potentially fatal multisystem disorder with prominent hepatopulmonary manifestations. *J Occup Med Toxicol* 2006;1:1–9.
- 8 Wang N, Parimi L, Liu H, et al. A review on dapsone hypersensitivity syndrome among Chinese patients with an emphasis on preventing adverse drug reactions with genetic testing. *Am J Trop Med Hyg* 2017;96:16–0628.
- 9 Sudarsono S. Treatment of multibacillary leprosy following the development of dapsone hypersensitivity syndrome. *J Gen Proced Dermatol Venereol Indones* 2019;4:48–52.
- 10 Zhang F-R, Liu H, Irwanto A, et al. HLA-B*13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med* 2013;369:1620–8.
- 11 Krismawati H, Irwanto A, Pongtiku A, et al. Validation study of HLA-B*13:01 as a biomarker of dapsone hypersensitivity syndrome in leprosy patients in Indonesia. *PLoS Negl Trop Dis* 2020;14:e0008746.
- 12 Robinson J, Halliwell JA, Hayhurst JD, et al. The IPD and IMGT/HLA database: allele variant databases. *Nucleic Acids Res* 2015;43:D423–31.
- 13 Papua Provincial Health Office. *Papua Province annual report of leprosy*. Jayapura, 2020.
- 14 Krismawati H, Maladan Y, Rohman MF. Detection of HLA-B 13:01 gene among dapsone hypersensitivity patients of leprosy in Papua ethnics group using sequence based typing and qPCR rapid detection. *AIP Conf Proc [Internet]*. 2020;2260.
- 15 Poirot E, Vittinghoff E, Ishengoma D, et al. Risks of hemolysis in glucose-6-phosphate dehydrogenase deficient infants exposed to chlorproguanil-dapsone, mefloquine and sulfadoxine-pyrimethamine as part of intermittent presumptive treatment of malaria in infants. *PLoS One* 2015;10:e0142414.
- 16 General Directorate of Disease Preventive and control Ministry of Health I. *National guideline of leprosy preventive and control*. Indonesia: General Directorate of Disease Preventive and control Ministry of Health, 2012: 192.



- 17 Kemenkes RI. Permenkes RI Nomor 11 Tahun 2019. Vol. Nomor 65, Menteri Kesehatan Republik Indonesia Peraturan Menteri Kesehatan Republik Indonesia 2019.
- 18 Barber RD, Harmer DW, Coleman RA, *et al.* GAPDH as a housekeeping gene: analysis of GAPDH mRNA expression in a panel of 72 human tissues. *Physiol Genomics* 2005;21:389–95.
- 19 Fischer A, Lejczak C, Lambert C, *et al.* Simple DNA extraction method for dried blood spots and comparison of two PCR assays for diagnosis of vertical human immunodeficiency virus type 1 transmission in Rwanda. *J Clin Microbiol* 2004;42:16–20.
- 20 NalaGenetics. *Nala TM PGx core kit*. Singapore, 2021.
- 21 BioLabs NE. *Monarch ® genomic DNA purification kit table of contents*, 2020: 1–24. www.neb.com