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DELETION OF EXONS 4-10 IN THE *IKBKG* GENE CAUSES INCONTINENTIA PIGMENTI IN A VIETNAMESE CHILD

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ABSTRACT

Incontinentia pigmenti (IP) is an X-linked dominant genetic disorder caused by mutations in the inhibitor of kappa B kinase gamma (*IKBKG*) gene. Common symptoms of this disease include skin manifestations such as blisters, warty lesions, and hyperpigmentation, as well as skin atrophy and abnormalities in nails, hair, teeth, and the central nervous system. This study aims to identify the pathogenic mutation of a Vietnamese female infant suspected of having IP conditions. Using multiple genotyping methods, including whole-exome sequencing (WES), multiplex ligation-dependent probe amplification (MLPA), and polymerase chain reaction (PCR), we identified that the patient carried a heterozygous deletion encompassing exons 4-10 of the *IKBKG* gene. This mutation was reported as the most prevalent genetic cause in IP patients worldwide. The patient's mutation was *de novo*, as her parents were negative for it. This is the first case of IP reported with the identified genetic etiology in Vietnam and provides valuable information to the Vietnamese population's genetic database of ectodermal dysplastic disorders. Given the high prevalence of the exons 4-10 deletion in the *IKBKG* gene among IP patients worldwide, we recommend using a low-cost PCR to detect this deletion as the initial screening test for pathogenic mutations in Vietnamese IP patients, followed by sequencing methods if the PCR test is negative.

Keywords: Ectodermal dysplastic disorder, gene deletion mutation, *IKBKG* gene, incontinentia pigmenti, MLPA.

INTRODUCTION

Incontinentia pigmenti (IP; #OMIM: 308300), also known as Bloch-Sulzberger syndrome, is a rare, X-linked dominant dermatological disorder caused by mutations in the inhibitor of kappa B kinase gamma (*IKBKG*) gene. Most patients with incontinentia pigmenti are female, presenting with a variety of clinical

manifestations, while the condition can be fatal in males during fetal development (Cammarata-Scalisi *et al*., 2019). Skin lesions are the most common clinical manifestations and the primary criterion for diagnosis. Typically, the disease progresses through four stages: (1) blisters and vesicles appear on the skin (within the first 4 months after birth); (2) the extremities exhibit hyperkeratosis and verrucous lesions (a few months old); (3) widespread pigmentary changes leading to increased pigmentation, typically gray or brown in color (from 6 months of age onwards); (4) the skin returns to normal, but other manifestations may appear during childhood development (Kawai *et al*., 2020). Central nervous system and retinal dysfunction are less common but may result in lifelong sequelae for IP patients (Bodemer *et al*., 2020). These pigmentary disorders arise due to a deficiency of the NEMO/IKK$_\gamma$ protein and are the result of pathogenic mutations in the *IKBKG* gene (Berlin *et al*., 2002).

IKBKG (formerly known as *NEMO*) is a 23 kb gene located at locus Xq28 on the X chromosome, comprising two promoter regions A and B, four non-coding first exons, and nine coding exons (Kawai *et al*., 2020; Minić *et al*., 2023). Mutations in the *IKBKG* gene can cause various syndromes or diseases and have been catalogued in the ClinVar database. Among these, only approximately 10 distinct mutations cause IP, including substitutions, deletions, and nucleotide duplications. Notably, deletion of exons 4–10 of the *IKBKG* gene (*IKBKG*$^{\Delta 4\text{-}10}$) has been reported in about 80% of IP cases (Guevara *et al*., 2016).

The *IKBKG* gene encodes the NEMO/IKK$_\gamma$ protein, which is essential for activating the nuclear factor kappa B (NF-kB). NF-kB plays a crucial role in regulating the activity of numerous genes that control the body's inflammatory and immune responses (Courtois & Gilmore, 2006). NF-kB also plays an essential role in the signaling pathway for the formation of skin tissues, protecting cells from certain signals that may trigger apoptosis (Berlin *et al*., 2002). Abnormal cell death can lead to the signs and symptoms of pigmentary disorders. Dermatological manifestations in IP patients may be confused with epidermolysis bullosa, punctate chondrodysplasia, or Naegeli syndrome (Chen *et al*., 2023). Therefore, based on characteristic dermatological manifestations and other organ involvement, combined with histological findings and family history, physicians may suggest IP and order genetic testing to confirm the diagnosis. For single-nucleotide variants (SNVs) or small indels, whole-genome or partial gene sequencing of *IKBKG* is used for detection (How *et al*., 2022). Meanwhile, large deletions or duplications are detected using standard techniques such as multiplex ligation-dependent probe amplification (MLPA) or PCR.

Due to the rarity of IP in Vietnam, no reports of its clinical expression or genetic cause have been published to date. We report the first genetic etiology results for a pediatric patient with skin lesions diagnosed with IP and discuss the genetic analysis approach for this disease in the Vietnamese population.

MATERIALS AND METHODS

Sample collection and DNA extraction

A three-year-old girl was evaluated at Hanoi National Children's Hospital and Vietnam National Eye Hospital for features suggestive of IP. Both parents were healthy, non-consanguineous, and reported no family history of this disorder. The family was informed and counseled by the doctor and

geneticist about the IP condition and the benefits of genetic examination. The approval of this study was provided by the Institutional Review Board of the Institute of Genome Research, Vietnam Academy of Science and Technology (No. 4-2024/NCHG-HĐĐĐ). The parents signed informed consent to participate in this study to explore the genetic factors underlying the patient's condition and the risk of disease for family members.

Two milliliters of peripheral blood from the patient and her parents were collected in EDTA.K3 tubes and then stored at –20°C until analysis. Genomic DNA was isolated by the Exgene™ Blood SV Mini Kit (GeneAll, Korea) according to the manufacturer's instructions. The integrity of the DNA was confirmed by electrophoresis in 1% agarose gel, and its yield and purity were assessed using a NanoDrop Lite Spectrophotometer (Thermo Scientific, USA).

Whole-exome sequencing

The proband's DNA was subjected to whole-exome sequencing (WES, Macrogen, Korea). WES data were used to screen variants in the *IKBKG* gene and archived for extended gene panel analysis as needed. Variants were classified for clinical significance according to the American College of Medical Genetics and Genomics (ACMG) recommendations. Variants that were classified as benign/likely benign in ClinVar, the minor-allele frequency (MAF) was more than 0.1% in the 1000 Genomes Project (www.1000geneomes.org/), and/or located in non-coding regions were removed. Novel and rare variants that fit any of the genetic models were considered as potential pathogenic variants and selected for further evaluation.

Multiplex ligation-dependent probe amplification analysis

For identifying deletion/duplication variants in the *IKBKG* gene, MLPA was performed using the SALSA MLPA Probemix P073 *IKBKG* kit (Netherlands) according to the manufacturer's instructions. The MLPA reaction was performed on total DNA samples from patients and healthy individuals as controls. The SALSA MLPA Probemix P073 *IKBKG* kit includes 13 probes for the *IKBKG* gene detecting large deletion/duplication mutations and 9 standard probes to check the quality of the reaction.

To prepare for the MLPA reaction, total DNA was diluted to 10 ng/µL in Tris-EDTA (TE 0.1X) buffer (1 mM Tris-HCl and 0.1 mM EDTA, pH 8.0). Five (5) µL of DNA was denatured and hybridized with MLPA probemix, then incubated at 60°C from 16 to 20 h. Subsequently, the annealed probes were ligated using Ligase 65 at 54°C for 5 min. All ligated products were then used as templates for DNA amplification. Each ligated product was added with 3.75 µL of deionized water, 1 µL of SALSA PCR primer mix, and 0.25 µL of SALSA polymerase, and then PCR was performed in 35 cycles (95°C for 30 s, 60°C for 30 s, 72°C for 1 min), extension at 72°C for 20 min, and stored at 15°C. The amplified products were subjected to capillary electrophoresis on a Genetic Analyzer 3500 (Applied Biosystems, USA). The collected data were analyzed using Coffalyzer software. Samples with normal copy number are expected to produce a dosage quotient (DQ) of approximately 0.8–1.2, with 0.65 and 1.3 used as cut-off values for heterozygous deletions or duplications, respectively.

Amplification of the *IKBKG* gene by long-range PCR

Long-range PCR was performed to detect the *IKBKG*$^{\Delta 4\text{-}10}$ mutation. Genomic DNA of the control sample (healthy individual), patient (IP003), father (IP003B), and mother (IP003M) were used for long-range PCR. Two primer pairs for PCRs are posited outside of the deletion region (Figure 1), with the sequences referenced from the previous study (Table 1) (Kawai *et al*., 2020; Lee *et al*., 2009; Steffann *et al*., 2004). The first PCR reaction was performed in a total volume of 20 µL containing the following components: 6.5 µL deionized water, 10 µL Go Taq Mastermix 2X, 0.75 µL each primer (10 pmol/µL), and 2.0 µL total DNA. The thermal cycling was carried out as follows: 94°C for 2 min, 35 cycles (94°C for 30 s, 60°C for 30 s, 72°C for 3 min), an extension at 72°C for 5 min, and storage at 4°C. The second PCR was performed continuously to detect low-level mosaic mutations. The PCR products obtained in the first amplification were diluted 1:100 with TE (0.1X) buffer. For the second amplification, each PCR reaction included 7.5 µL deionized water, 10 µL Go Taq Mastermix 2X, 0.75 µL each primer (10 pmol/µL), and 1.0 µL diluted DNA. The amplification cycle was run as follows: 94°C for 2 min, 20 cycles (94°C for 30 s, 60°C for 30 s, 72°C for 1 min 10 s), an extension at 72°C for 10 min, and storage at 4°C. All PCR products from two amplifications were checked by electrophoresis on a 1% agarose gel, and their sizes were compared with the DNA ladder. Successful amplification of the target gene region will yield a clearly visible electrophoretic band, suggesting the presence of an *IKBKG* deletion. In contrast, if the visible band is absent, the sample does not carry a mutation.

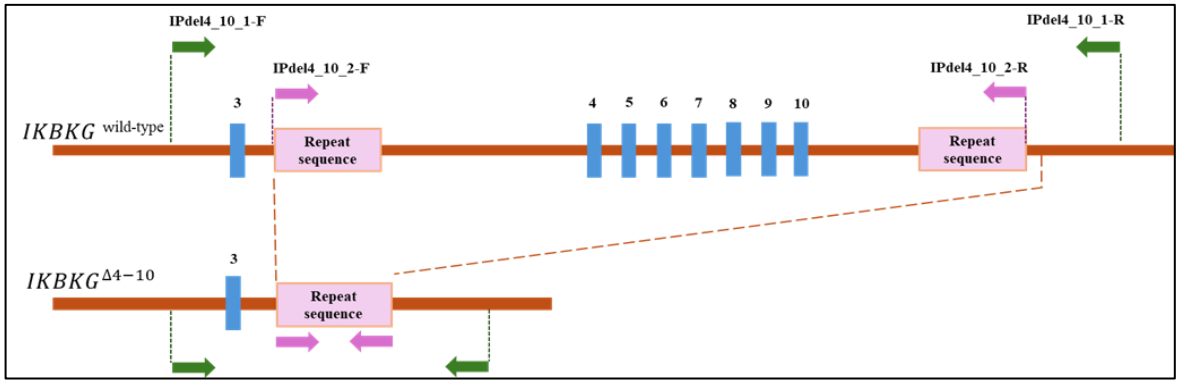

Figure 1. Illustration of primer design for two PCR reactions in the *IKBKG* gene. The numbers 3-10 indicate the coding exons of the *IKBKG* gene.

Table 1. Sequences of primer pairs used for long-range and nested PCR.

No	Primer name	Forward primer*	Reverse primer*	Amplicon size (bp)
1	IPdel4_10_1	GAGGACCAATACCGAGCATC	GAATTCGGGAGTCAGCTCGGAGAC	2800
2	IPdel4_10_2	TCCTGTGTGGGAAGTGGATG	CACAGGAACCAGCAAGGAGC	1000

** Primer sequences were referenced from the study of Kawai et al. (2020).*

RESULTS AND DISCUSSION

Genomic DNA extraction

The peripheral blood samples from the patient and her parents were used to extract genomic DNA. The extracted DNA was tested for quality and quantity. Electrophoresis on a 1% agarose gel revealed that all three DNA samples had high integrity, low breakage level, and no RNA contamination. Spectrophotometric analysis showed that the DNA concentration of IP003, IP003B, and IP003M samples was 44.00, 57.01, and 65.08 ng/µL, with high purity indicated by the OD (A260/280) ratio, which was 1.86, 1.81, and 1.82, respectively. These results showed that the genomic DNA extracted from all three samples met the quality requirements for downstream genetic analysis.

Whole exome sequencing and mutation screening

WES was an effective tool for detecting causative mutations and has been widely applied globally for the analysis of genetic diseases. The advantage of this technology is its ability to provide data on all variants of more than 22,000 known functional genes. This enables researchers to screen variants according to target gene panels associated with specific diseases. For the patient in this study, WES was selected as the first-line analysis due to its effectiveness in our previous studies of dermatological disease (Ma *et al*., 2021). Unfortunately, WES analysis of the patient's genomic DNA showed that she did not carry any coding-region variants in the *IKBKG* gene. Only an intronic variant with a MAF of 0.3283 in the Exome Aggregation Consortium (ExAC) database was found to be homozygous. Therefore, it is not considered a potential pathogenic variant (Table 2).

Table 2. The *IKBKG* intronic variant detected by WES analysis for the patient sample.

Chromosome	Mutation	Gene	Location	State	Allele frequency	
					1000 Genomes	ExAC
X	g.153792168T>C	*IKBKG*	Intron	Hom	-	0.3283

Hom: homozygous; -: absence; 1000 Genomes: The 1000 Genomes Project database; ExAC: The Exome Aggregation Consortium (ExAC) dataset.

Pathogenic variant screening by MLPA

Since no pathogenic SNVs or small indel mutations were detected by WES in the patient sample, the large structural variations of the *IKBKG* gene were focused on. The common MLPA method for detecting copy number variations in specific target genes was used. This method has been proven to be effective, accurate, and capable of analyzing multiple target genes on the same sample, thereby increasing efficiency and saving time. The MLPA results showed that the DQ at exons 4-10 of the control sample was all within the normal range (0.8-1.2), indicating the reaction efficiency and the correct data normalization while the DQ values at exons 4-10 of the *IKBKG* gene of patient sample (IP003) ranged from 0.71 to 0.84 (>0.65) (Table 3 and Figure 2). All other probes in the probemix, including the internal control probes such as FAM3A, G6PD, CTAG1A,

and FAM223B, showed stable signals around the normalization threshold of 1.0. The simultaneous reduction in signal across multiple consecutive exons 4-10 of the *IKBKG* gene, without affecting the neighboring regions, indicates a single-allele deletion at this locus in the patient. This represents a typical molecular genetic feature observed in female carriers of *IKBKG* gene mutations associated with IP.

Table 3. The dosage quotient corresponds to each position of exons 4-10 of the *IKBKG* gene.

Sample	MLPA probe positions and DQ ratio								
	Exon 4 – 208 nt	Exon 5 – 426 nt	Exon 6 – 391 nt	Exon 7 – 355 nt	Exon 8 – 171 nt	Exon 9 – 238 nt	Exon 10 – 373 nt	Exon 10 – 319 nt	Exon 10 – 265 nt
Control	0.96	0.96	1.0	0.99	1.0	0.96	0.98	0.96	0.95
IP003	0.71	0.83	0.83	0.81	0.84	0.79	0.82	0.77	0.76

nt: nucleotide

IKBKG gene deletion validation by PCR

Long-range PCR is another valuable method for identifying deletion mutations, alongside MLPA. The DNA region containing exons 4-10 of the *IKBKG* gene is flanked by two highly homologous repeat sequences that are structurally prone to this specific deletion error. This is why the deletion of approximately 11.7 kilobases, encompassing exons 4 through 10, accounts for roughly 65-80% of all identified *IKBKG* mutations in IP patients.

In this study, the primer pair (IPdel4_10_1) binds specifically to the flanking region of $IKBKG^{\Delta 4\text{-}10}$, allowing amplification of a ~2800 bp DNA fragment of the *IKBKG* allele containing the deletion mutation but not the wild-type allele. The second primer pair binds to homologous repeat sequences, allowing amplification of ~1000 bp of the deletion mutant *IKBKG* allele, thereby increasing the ability to detect low-level mosaic deletions.

According to the PCR results, the $IKBKG^{\Delta 4\text{-}10}$ allele of the *IKBKG* gene was amplified in the patient sample (Figure 3, lane 2). Specifically, long-range PCR using the primer pair IPdel4_10_1 amplified a bright and clear electrophoretic band with a size of ~2800 bp, which is consistent with the theoretical design (Figure 3a). The second PCR using the primer pair IPdel4_10_2 amplified a band with a size of 1000 bp, which is also the same as the theory (Figure 3b). No PCR products were detected in the control and the parents' samples (lanes 1, 3, and 4), indicating that none of those DNA genome samples contains the $IKBKG^{\Delta 4\text{-}10}$ allele. The IP was first described by Garrod with the symptom of hyperpigmentation in newborns and following a dominant inheritance pattern. In Europe, IP has an incidence of about 0.7/100,000 births, while there has been currently no report about the incidence of this disease in Vietnam. The manifestations of IP patients are the consequence of protein function loss associated with mutations in the *IKBKG* gene (Eksambe *et al*., 2015). This gene activates the NF-kB signaling pathway, which plays a vital role in skin keratinocytes.

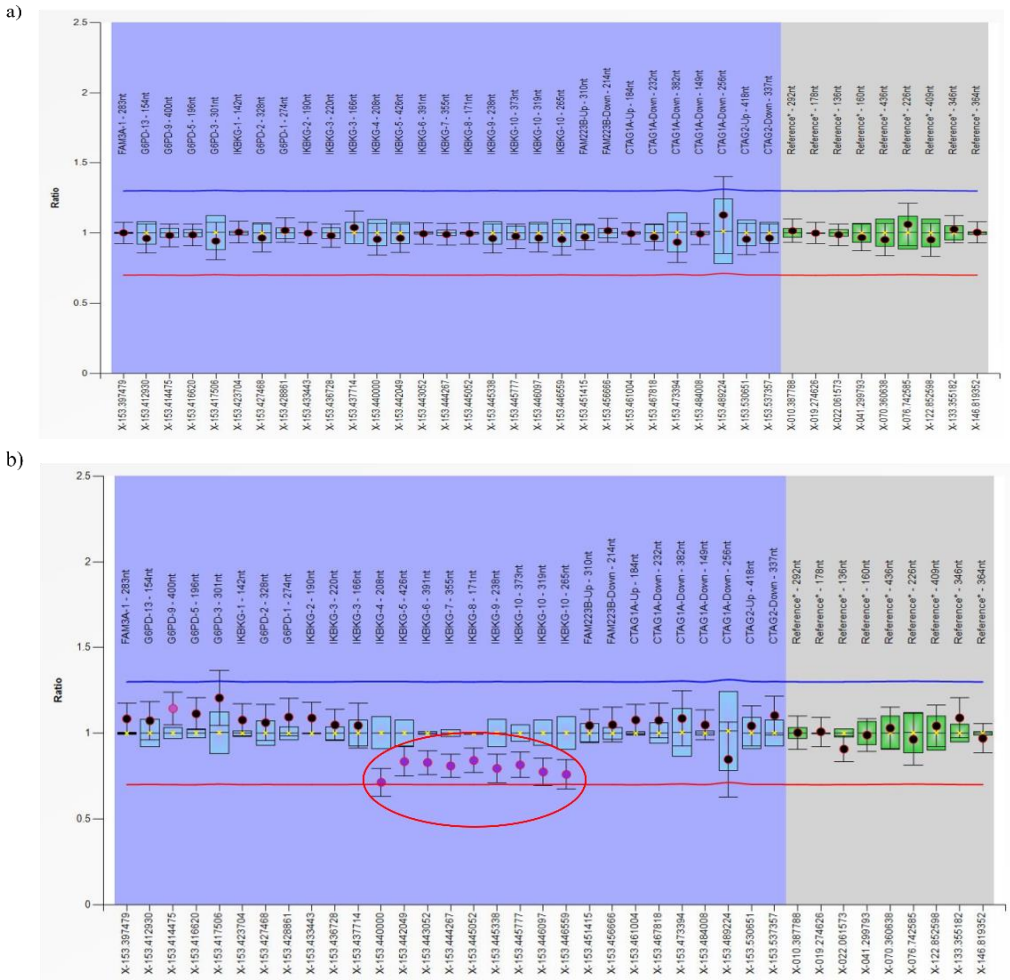

Figure 2. MLPA results of the control and patient samples. (a) MLPA results of the control sample with normal *IKBKG* gene copy number. (b) MLPA results of the patient (IP003) with a single-allele deletion mutation of exons 4-10 in the *IKBKG* gene. The red-circled area shows reduced copy number/deletion of the *IKBKG* gene. Horizontal axis: chromosomal position of each probe; vertical axis: the DQ ratio.

In the case of *IKBKG*$^{\Delta 4\text{-}10}$ mutation, the mRNA lacks a long segment, leading to an open reading frame error or the appearance of a premature termination codon, resulting in the production of an incomplete NEMO protein or its premature degradation. NF-kB is not activated, rendering cells unable to respond to stimulating signals (such as TNF-α), and the ectoderm cells are susceptible to apoptosis or massive necrosis during embryonic development (Okita *et al*., 2013; Puel *et al*., 2006; Song *et al*., 2010).

Activating signals generated from apoptotic or necrotic cells include released DAMPS signals that lead to immune cell activation and the production of chemokines and cytokines. Cytokines mobilize eosinophils, leading to degeneration and the release of proteases that reduce keratinocyte adhesion, causing spongiosis and blister formation on the skin.

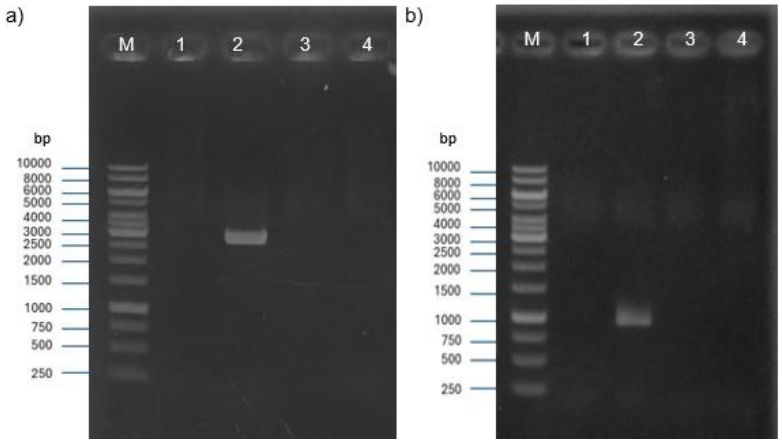

Figure 3. Electrophoresis results of PCR products on a 1% agarose gel. (a) First long-range PCR. (b) Second long-range PCR. M. DNA ladder of 1 kb, 1. Control sample, 2. IP003 sample, 3. IP003B sample, 4. IP003M sample.

In addition, released chemokines cause widespread endothelial inflammation and eye abnormalities involving the retina or central nervous system, such as vascular occlusion and ischemia (How *et al*., 2022).This also suggests the cause of the clinical manifestations in the 3-year-old patient whose sample we collected for research. In the world, the phenotypes of IP patients who had exon 4-10 deletions are diverse. For instance, both females who showed blistering, hyperkeratotic lesions, hypodontia, and her brother, who revealed IP rash, were normally developed without ocular anomalies. They were all having an 11.7 kb deletion of the *IKBKG* gene and skewed X-inactivation (Wojcik *et al*., 2025). Another research demonstrated that 72% of 54 patients in the Danish IP cohort had the $IKBKG^{\Delta 4\text{-}10}$ mutation. Of that, 20 patients were diagnosed with ophthalmologic manifestations, including retinal vasculopathy and visual loss, along with other ectodermal involvements (Herlin *et al*., 2024). As reported by Fusco *et al*., IP patients with $IKBKG^{\Delta 4\text{-}10}$ mutation showed greater phenotypic variability and larger phenotypic effects, especially in cases of ocular defects (Fusco *et al*., 2004). Same as the above studies, our identification of the pathogenic variant in the patient's *IKBKG* gene has contributed to the understanding of the IP's genetic cause, providing a convenient process of treatment and disease management. In addition, the patient's mother, who does not carry the pathogenic gene variant, brings positive information to the patient's family, especially when the parents have plans for the next pregnancy.

Recently, next-generation sequencing technology, especially WES, has been widely applied to identify genetic factors underlying inherited diseases in Vietnamese people. The effectiveness of this technology has been demonstrated through a series of publications related to skin and eye diseases in children, making it the first approach to analysis for the majority of cases (Ma *et al*., 2021; Nguyen *et al*., 2021). However, using WES analysis as the primary analysis for the IP group may not be effective due to its limitations in detecting structural variants, which exist in 80% of IP cases (Guevara *et al*., 2016). Therefore, we recommend using MLPA or PCR as the first genetic analysis

for IP patients in Vietnam, and WES can be performed after the patient has been determined to have no structural variation. This approach may increase analysis efficiency, reduce costs, and save time in the genetic testing process.

CONCLUSION

In this study, we successfully used MLPA and PCR for the molecular diagnosis of IP in a Vietnamese patient. The patient carried a single-allele deletion mutation in the *IKBKG* gene, resulting in her IP manifestations. This is the first *IKBKG* mutation reported in a Vietnamese, extending knowledge of the genetic etiology of ectodermal dysplasia syndromes in the Vietnamese population and effectively contributing to the accurate diagnosis and treatment of patients. In addition, this result provides a basis for future genetic counseling for patients, as she can pass the *IKBKG*$^{\Delta 4\text{-}10}$ mutation to her children.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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