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A Novel Mutation in *IKBKG* Gene in A Female Child with Incontinentia Pigmenti

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Abstract Incontinentia pigmenti (IP; OMIM# 308300) is a rare inherited disease caused by a mutation of IKBKG, which is also known as NEMO, located on Xq28. IP patients usually present with abnormalities of skin, eyes, nails and central nervous system. The neurological damege, which occur usually from neonatal through the early infantile period, leads to neulogical complication such as development retardation, motor paralysis and epilepsy. However, there has been little study done concerning the effect of therapy for the neural abnormalities. We have investigated the clinical findings in a female IP case with a novel mutation of IKBKG for six years due to disclosing the neurological prognosis and the immunological features. It is hoped that the present study will contribute to a better management of IP patients.

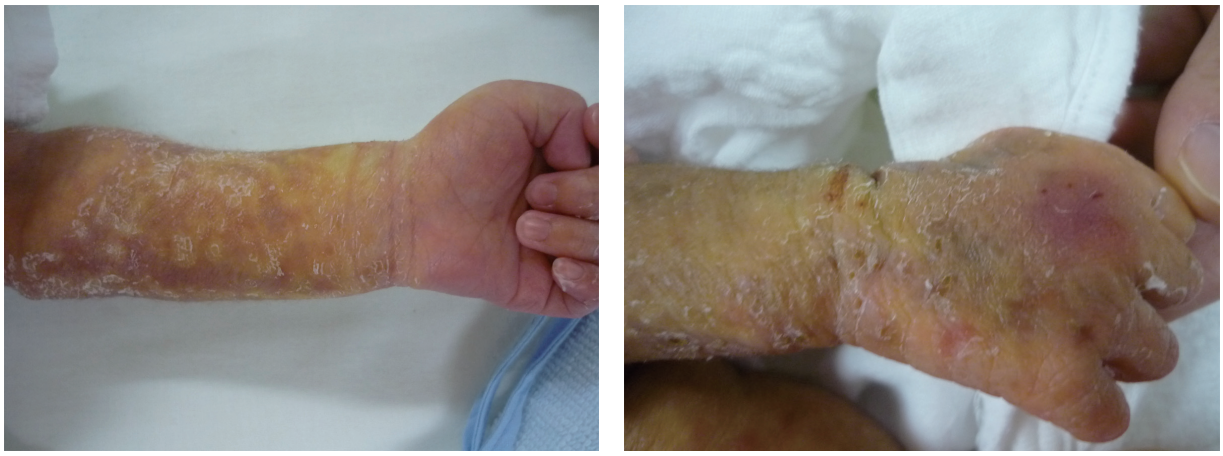
Key words: incontinentia pigmenti, *IKBKG* gene, CNS, X-linked, frameshift

Introduction

Incontinentia pigmenti (IP; OMIM# 308300) is an X-linked dominant disorder, affecting ectodermal tissues involving skin, hair, nails, eyes, and central nervous system (CNS).[1] The skin lesions progress in four stages: inflammatory, verrucous, hyperpigmented, and hypopigmented/atrophic.[2] CNS abnormalities are present in approximately 30% of patients.[1] The disease gene of IP is *Inhibitor of Kappa light polypeptide gene enhancer in B cells, Kinase Gamma/Nuclear factor kappa B, Essential Modulator (IKBKG/NEMO)* (GenBank NM_003639.3).[1] The common deletion spanning exons 4 through 10 of the *IKBKG* occurs in approximately 60~80% of IP.[3] In addition, cytosine stretches in the exon 9-10 region are well-known mutation hotspots.[3] Here, we report a case of a female IP patient with a novel frame-shift mutation in the cytosine stretches in exon 9 of the IKBKG.

Case description

A 5-day female infant was hospitalized presenting partial and clonic seizures in the right upper and lower limb. The patient presented with linear erythematous on her extremities at birth with subsiding vesicles on the back of the hands (Fig. 1a, b). Laboratory tests on admission revealed a white blood cell of 1.42×10^9/L (eosinophils 25%). Magnetic resonance imaging showed diffused high intensity in subcortical white matter on diffusion-weighted imaging, suggesting multiple lesions of brain infarction, that were the cause for the seizure (Fig. 2). A skin biopsy from a bulla on the thigh at 1 month



(a) (b)

Fig. 1
Skin changes when she was 5-day-old were recognized. (a) Erythematous skin with a linear pattern in extremities. (b) Small pustular regions in the right hand.

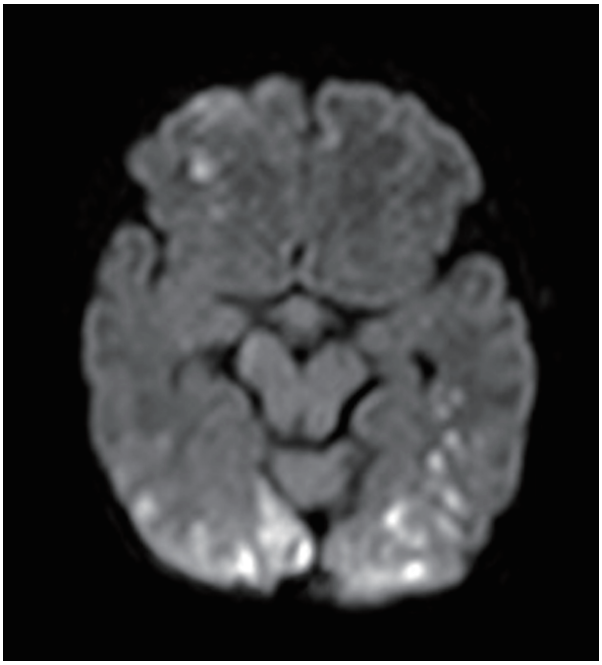


Fig. 2
Hign intensity regions were observed in the occipital lobe on diffusion-weighted image when she was 7days of age.

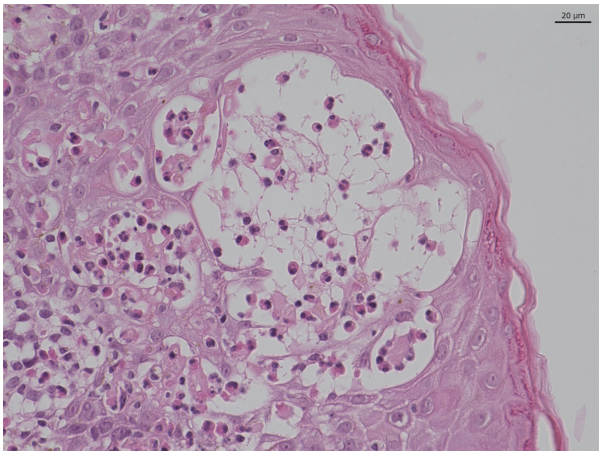


Fig. 3
Spongiosis with intraepidermal blisters and the infiltration of eosinophils in the epidermis and the upper layer of the dermis (hematoxylin-eosin, original magnification x100) in her age 1 year.

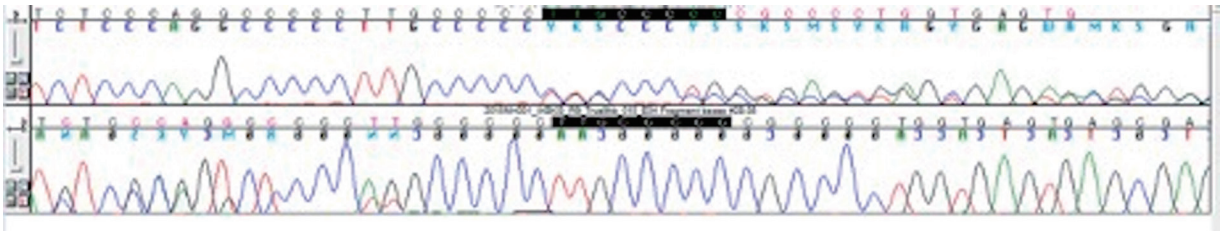


Fig. 4
A novel heterozygous mutation consisting of a 8-bp insertion (c.1109_1100insTTGCCCCC) in exon 9 of IKBKG (p.Ala371Cysfs*83) in the patient.

of age showed epidermal spongiosis with the formation of intraepidermal blisters and infiltration of numerous eosinophils, compatible with IP (Fig. 3). After obtaining written informed consent, we performed long polymerase chain reaction (PCR) amplification of the *IKBKG* followed by direct sequencing analysis.[4] The results revealed a novel heterozygous mutation consisting of an 8-bp insertion (c.1109_1110insTTGCCCCC) in exon 9 of *IKBKG* (p.Ala371Cysfs*83) in the patient but not in her mother (Fig. 4), suggesting a *de novo* mutation. Linear erythematous has subsided by 4 months with brown whorled and linear pigmentation developing on the extremities. No dental abnormality, nail dystrophy, ocular or hair abnormalities were found. Currently, the patient aged 6 years and 9 months had received routine immunization and has no vaccine-related adverse event, especially a reactivation of skin lesions. The status of her skin has been normal except for the pigmentation in the inguinal region (Fig. 5). When her 3-month-old and 4-year-old, immunocompetence was evaluated. The levels of immunoglobulin (IgG, IgA, IgM) were normal and the T-cell activation was ascertained by lymphocyte proliferation test. Moreover, the TNF-α production induced by stimulation of lipopolysaccharide was confirmed. At her 4 years and 10 months, antibody titers against hepatitis B virus, varicella-zoster virus, rubella virus and measles virus were evaluated for the assessment of vaccine response. The titers of Hepatitis B surface antigen were 0.3 mIU/mL in chemiluminescent enzyme immunoassay test (effective value > 9.9 mIU/mL) and the titers of varicella-zoster virus were less than 4-fold in complement fixation test (effective value > 4-fold). Fortunately, there have been no episodes of severe infection including hepatitis B and chickenpox. She has mild developmental retardation and left side dominant spastic paralysis. Rehabilitation therapy and an administration of botulinum toxin have been performed. No epileptic events have occurred beyond neonatal periods.

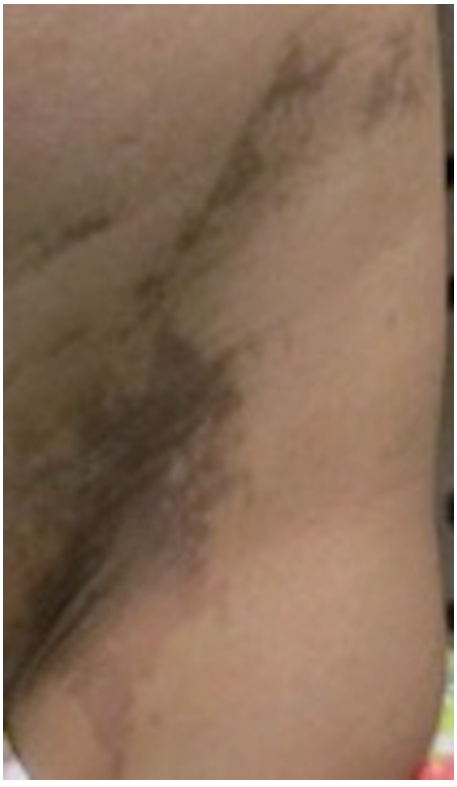


Fig. 5
Hyperpigmentation on the left inguinal region when she was 4 years of age.

Discussion

Generally, frameshift mutations occur in stretches of repetitive DNA nucleotide runs that probably cause slippage errors of the DNA polymerase at the replication fork.[5] Fusco et al.[3] reported that the cytosine stretches in the exon 9-10 are mutational hotspots and it harbors only frameshift mutations in cytosine residues in the exon 9-cytosine stretches, which were consistent with our case. Five cases of IP with a mutation in exon 9 were reported.[3] There are no notable differences between our patient and the reported cases about the clinical course. The variability in the IP phenotype unrelated to genotype is ascribed to the variability in X-inactivation affecting the function of NF-κB.[3]

In IP patients, CNS anomalies are one of the major manifestations, which are committed to neurological dysfunction and life-threatening event. The most frequent type of CNS involvement is seizures, comprising approximately 40% of all CNS disorders.[6] The initial neurological manifestations occurred in the first week in 58.3% of IP patients.[6] As our patient, some IP patients can suffer from neurological lesions in the early neonatal period. Brain imaging revealed serious abnormal changes including infarction, atrophies and corpus callosum lesions.[6] It is required to differentiate possible diseases such as encephalitis.[7] In the acute phase, some reports have mentioned the efficacy of corticosteroid therapy.[8,9] However, there is no well-established treatment for cerebral disorders. As we know, few studies have attempted to investigate long-term prognosis. Our patient has had a developmental disability and motor paralysis for six years or more. To establish the treatment for CNS impairment, an accumulation and consecutive observation is needed.

The nuclear factor kappa-B essential modulator (NEMO) is the main regulator in the NF-κB signaling pathway involved in apoptosis, inflammation and immune system. The NEMO dysfunction is associated with IP and ectodermal dysplasia, anhidrotic, with immunodeficiency (EDA-ID) resulting from hypomorphic mutations in the IKBKG/NEMO gene.[10] Immunodeficiency is usually presented in EDA-ID patients. However, there is a report of IP female cases presenting immune disorder.[11] Therefore, immune responsiveness should be assessed as possible, especially before immunization of live vaccines such as BCG.[12] As far as vaccination is concerned, vaccine potency and adverse reactions are also controversial. Some cases of reactivation of skin lesions after immunization are described. The present case has no reactivation episodes related to vaccination. Moreover, it should be evaluated for the elevation of antibody titer against each pathogen, which could demonstrate the ability of antibody production associated with NEMO deficiency. We validated no increased virus titer against hepatitis B and chickenpox. To our knowledge, there has been little study done concerning vaccine efficacy. The correlation between the unresponsiveness of immunization and NEMO abnormality remains unclear. The question has remained unanswered whether the responsiveness of immunization is negatively impacted by NEMO abnormality. A further investigation of the immune system in IP should be conducted.

Conclusion

We reported a female case of incontinetia pigmenti with a novel mutation of the IKBKG gene. A comprehensive assessment of disease complications in IP is necessary. It is hoped that this study will contribute to better management of the incontinentia pigmenti.

Conflict of Interest

The authors declare no conflict of interest.

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