

CASE REPORT

Iran J Allergy Asthma Immunol
August 2019; 18(4):441-446.

Identification of a Novel C16orf57 Mutation in Iranian Patient with Clericuzio-type Poikiloderma with Neutropenia (CPN): A Case Report

Farhad Abolnezhadian¹, and Sara Iranparast^{2,3}

¹Department of Pediatrics, Abuzar Children's Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

²Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

³Department of Immunology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Received: 2 January 2019; Received in revised form: 2 April 2019; Accepted: 20 April 2019

ABSTRACT

Poikiloderma is a hereditary pathologic situation in which the appearance of skin rash is associated with epidermal atrophy, telangiectasia, and reticular dyspigmentation skin symptoms of poikiloderma are usually caused by sun damage. The main reason for poikiloderma is unknown. We introduce a 14-month-old boy who referred to our center with a complaint of fever and cough. Furthermore, hepatosplenomegaly symptoms had been presented at the time of birth and were continuously observed at age one. He had transient thrombocytopenia when he was born due to his prematurity condition, which was resolved during Intravenous Immunoglobulin (IVIG) treatment. Therefore, the presence of various mutation can lead to distinct clinical symptoms. Immunohematologic abnormalities such as increased level of IgM and IgE antibodies, as well as increased C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR), have been reported. However, mutation of the C16orf57 gene was identified in this patient. We also introduced a new genetic mutation in a particular part of DNA sequence (NM_001195302: exon6: c.T703C) that leads to new clinical finding in PN.

Keywords: Hepatosplenomegaly; Poikiloderma; Thrombocytopenia

INTRODUCTION

Poikiloderma is a hereditary pathologic situation in which the appearance of skin rash is associated with epidermal atrophy, telangiectasia, and reticular dyspigmentation skin symptoms of poikiloderma.¹⁻³

Corresponding Author: Sara Iranparast, PhD;
Department of Immunology, Ahvaz Jundishapur University of
Medical Sciences, Ahvaz, Iran. Tel: (+98 916) 8031 786, Fax:
(+98 61) 3444 711, E-mail: Sara.Iranparast@yahoo.com

Poikiloderma is known as a congenital disease including Rubinstein-taybi syndrome (RTS), Degos-touraine syndrome, Macular Atrophic dermatosis, Kindler syndrome, and xeroderma pigmentosum. Also, this clinical situation may be formed by peripheral elements such as cold, heat, ionizing radiation, and some sensitizing chemicals. By mid-2017 about 50 patients with clericuzio-type poikiloderma with neutropenia (CPN) have been reported.⁴ This complication was first noticed in 14 Indians living in

Navajo and was named CPN (or PN) (OMIM# 604173).⁵ These patients have a specific panel of clinical symptoms, most notably poikiloderma, non-cyclic neutropenia, functional impairment of neutrophils,^{6,7} nail abnormalities, recurrent infections, especially respiratory tract infections, and etc.^{3,8-11} This disease is autosomal recessive, the main cause of which is the mutation in the C16ORF57 gene that has been reported in most patients with CPN.^{11,12}

This study describes the pathological characteristics of a CPN boy whose mutation has occurred in a novel locus position.

CASE PRESENTATION

Our patient was a 14-month-old boy who referred to the Center for Allergy and Immune Deficiency in Abuzar children's Hospital in Ahvaz, with a complaint of fever and cough. This baby was born in the thirty-fifth week by Caesarean section and at birth, he had a height of 46 cm, a weight of 2380 gr and a head circumference of 32.5 cm. Furthermore, hepatosplenomegaly symptoms were present at the time of birth and were continuously observed at age one. He had transient thrombocytopenia when he was born due to his prematurity condition, which was resolved during intravenous immunoglobulin (IVIG) treatment. There was a history of consanguineous

marriage in the baby's parents (the cousin- the daughter of aunt type). His birth weight, length, and head circumference were all normal and the growth rate of the baby was normal. His first skin rash was observed in the wrist of hands at approximately 6 months of age. It spread centripetally along with the hands, forearms, on the fingers, legs, and also palms of hands and feet, but hyperkeratosis of the soles of the feet and hands was not observed. Gradually, hypopigmentation and hyperpigmentation skin patches appeared on the skin of the patient. Simultaneously, some neurological symptoms, such as telangiectasia, were observed. On the hands and feet also showed poikilodermatous changes (Figure 1a, b), but no vesicular or bullous rashes were observed. Nails, hair, teeth, palms, and soles were all normal. Hepatosplenomegaly was detected during the physical examination. Bones were inspected carefully and were normal. The brain development of this baby has been normal until one year of age, and no neurological disorder was observed in him. This patient had a history of multiple infections, including Urinary tract infections (UTI) at 2 months of the age, lung infection at approximately 8 months of age, and also after each vaccination, the lung infection recurred in a form similar to the disease of a cough. In addition, there has been a history of leukemia in this family. As kid's grandmother recently died of acute myeloid leukemia.



(a)

(b)

Figure 1. The symptoms of poikiloderma in form of patches that has been appeared on the baby's hand. (b) A demonstration of poikiloderma rash on the soles of the foot and leg.

Table 1. The results of the initial laboratory examination patient who had Clericuzio-type poikiloderma with neutropenia (CPN) associated with a novel C16orf57 mutation

Laboratory test	Result	Normal Value
Leukocyte number	3400/mm ³ *	4,000–10,000/mm ³
Neutrophil number	16-23 %	40-80%
Platelet (PLT)	412-420/mm ³	150-410/mm ³
Hemoglobin (HGB)	9.9–11.6 g/dL	12-16 g/dL
Ferritin	278 ng/mL	7-140 ng/mL
C-reactive protein (CRP)	+1	Negative
Erythrocyte sedimentation rate (ESR)	36-40 mm per hour	0-10 mm per hour in children
Antibody titration		
IgG	103 mg/dL	453-916mg/dL
IgM	1891mg/dL	19-146mg/dL
IgA	125 mg/dL; NV	20-100mg/dL
IgE	Up to 50	1.03-161.3mg/dL

*This data shows a leukopenia situation in the patient.

Complete blood count demonstrated low neutrophil count since the age of 12 months. However, platelet counts were normal or slightly increased. The bone marrow smear was also normal; despite the lack of malignant cells, the reduced level of megakaryocytes in bone marrow has been reported that can indicate an infection in this patient. Neutrophil function test was done. The result of NBT and DHR tests have been reported 80 and 104, respectively that show normal phagocyte function of neutrophils. The result of Sweat chloride test was also normal. The result of his blood culture was negative, however, The CRP test was and Erythrocyte sedimentation rate (ESR) result was increased (Table 1). Additionally, his TSH, T4, Alkaline phosphatase, Sodium, Calcium, Potassium serum levels, and BUN were normal. His stool was examined for stability and fat drop and this result of this test was also normal.

He was initially diagnosed with hyper IgE syndrome because of the sharply increased level of serum IgE and IgM. But the presence of clinical symptoms unrelated to hyper IgE syndrome forced us to perform more precise molecular tests on gene sequencing. Whole exome sequencing (WES) is a

genetic test used to identify a heritable cause of a disorder. WES searches through all coding regions of all genes currently identified, yielding a high chance of finding the cause of heritable disease. Whole exome testing can be used if a patient has symptoms which cannot be linked to diagnosis and corrective treatment is desired to improve a patient's prognosis. Once a pathogenic variant has been identified, this information can then be linked back to the phenotype of the patient to clarify the pathway to a correct diagnosis and the development of a suitable treatment plan. The sample was taken from the patient after obtaining informed consent and WES is done for him. The result of whole genome examination revealed a new mutation in USB1 gene (Figure 2) and following a change in a particular part of DNA sequence (NM_001195302: exon6: c.T703C), it leads to the formation of a modified form of C235R protein, in which the symptoms of PN follow these changes. Then this gene change was introduced as a novel gene mutation for poikiloderma with neutropenia patients (Table 2) (OMIM# 613276). In addition, the serum level of IgA has also increased, but the amount of serum IgG decreases (Table 1).

Table 2. This table shows the result of leukocyte rate of the patient with clericuzio-type poikiloderma with neutropenia (CPN). Examinations were done in three steps (at a time interval of one month) and all of them showed neutropenia.

Laboratory test	Step 1	Step 2	Step 3	Normal Value
White blood cell (W.B.C)	3.4/ml	2.9/ml	4.1	4-10/ml
Lymphocyte	49%	70%	76%	20-30%
Neutrophils	51%	25%	24%	60-70%

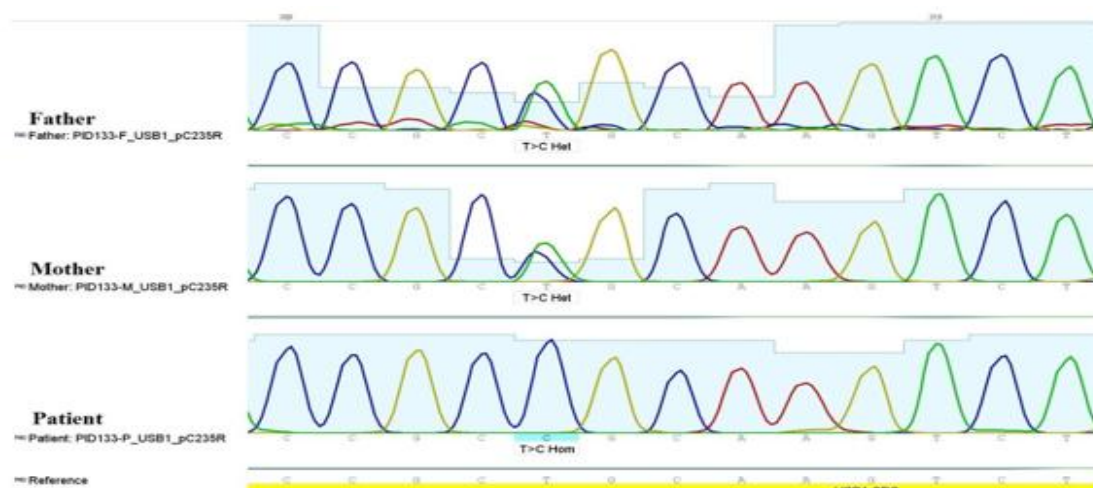


Figure 2. A current novel mutation in USB1 (NM_001195302: exon6: c.T703C) leads to amino acid change p.C235R which is deleterious based on most predictors. Sanger sequencing confirmed that a novel homozygous mutation of USB1 (NM_001195302: exon6: c.T703C) in the 14-month-old patient studied, while his parents (father and mother) were both heterozygous carriers for this mutation..

DISCUSSION

CPN (OMIM #604173) is an autosomal recessive genodermatosis characterized by poikiloderma and neutropenia. The onset of CNP is associated with a papular erythematous rash on the limbs during the first year of life. It gradually extends and this rash is resolved, and eventually, poikiloderma rash is created. This inherited disorder is characterized by poikiloderma, thickened nails, facial dysmorphism, hyperkeratosis, recurrent sinopulmonary infections, chronic lung disease, and hepatosplenomegaly, severe and persists neutropenia, the low killing power of neutrophils, development of telangiectasia, and skeletal defect.^{3,8-11} The skin rashes in these patients, appear in the peripheral extremities and gradually develop to the upper organs, face, etc. One of the most important features of CPN is the high susceptibility of these individuals for various infections. Due to neutrophilic deficiencies, chronic neutropenia, and stopping at the stage of myeloid-line maturity, the respiratory system of CPN patients is mostly vulnerable.

In 2010, USB1 (U6 snRNA biogenesis phosphodiesterase-1), that is located on 16q21 position of the chromosome, is identified as the causative gene of C16orf57/USB1 CPN. The USB-1 encodes a protein containing 265 amino acids, which is responsible for the U6 snRNA 3' end processing. This enzyme acts as an exoribonuclease responsible for trimming the

poly(U) tract of the last nucleotides in the pre-U6 snRNA molecule, leading to the formation of mature U6 snRNA 3' end-terminated with a 2',3'-cyclic phosphate.¹³ Additionally, USB-1 mutated can interfere in myeloid hemostasis and maturation of neutrophils and ultimately leads to neutropenia.^{14,15}

CPN symptoms have overlap with Rothmund tomson syndrome (RTS) and Dyskeratosis congenital (DC).¹⁶⁻¹⁹ (OMIM#224230) is identified with three attributes, including dystrophy, hyper and hypopigmentation, and oral leukoplakia.²⁰ Presence of oral leukoplakia and the absence of persist neutropenia are not seen in CPN patients and help to distinguish these two disorders. RTS is another autosomal recessive hereditary disease characterized by poikiloderma, congenital skeletal disorders, being short, premature aging and increased risk of malignancy. RTS disease is often caused by a mutation in the RECQ14 gene on chromosome 8q23,^{6,21} which connects to USB-1 via SMAD4, which can explain the cause of overlapping between the PN and RTS symptoms.¹² Despite the same characteristics, there are unique features of each of the two disorders that help to diagnose them. In addition, in patients with RTS, poikiloderma appears in the sun-exposed parts of the skin such as facial skin.²² Additionally, in PN subjects, unlike RTS, persist neutropenia occurs. Unlike with RTS, some symptoms are rare in patients with CPN including alopecia, leukoplakia, bony disorders, and

accompanied by malignancies. Of course, cases of AML, MDS, and SCC have been reported in patients with CPN.^{6,7,9,11,17,23-25} In addition, neutropenia and susceptibility to infections, especially respiratory infections, have been reported in all patients with CPN, but not RTS. Generally, all of these symptoms help us to differentiate these disorders with more confidence.

Therefore, the presence of various mutations can lead to distinct clinical symptoms. Immunohematologic abnormalities such as increased level of IgM and IgE antibodies, as well as increased CRP and ESR, have been reported. RECQL4 gene mutation analysis was negative. Mutations of the C16orf57 gene were identified in this patient. We also introduced a new genetic mutation in a particular part of DNA sequence (NM_001195302: exon6: c.T703C) that leads to new clinical finding in PN.

ACKNOWLEDGEMENTS

The authors particularly would like to thank the patient family and the clinic staff of the Immune Deficiency and Allergy unit of Abuzar Hospital for their valuable help.

REFERENCES

- Graham R. What is poikiloderma of Civatte? *Practitioner* 1989; 233(1475):1210.
- Geronemus R. Poikiloderma of civatte. *Arch Dermatol* 1990; 126(4):547-8.
- Arnold A, Itin P, Pigors M, Kohlhase J, Bruckner Tuderman L, Has C. Poikiloderma with neutropenia: a novel C16orf57 mutation and clinical diagnostic criteria. *Br J Dermatol* 2010; 163(4):866-9.
- Walne AJ, Collopy L, Cardoso S, Ellison A, Plagnol V, Albayrak C, et al. Marked overlap of four genetic syndromes with dyskeratosis congenita confounds clinical diagnosis. *Haematologica* 2016; 101(10):1180-9.
- Clericuzio C, Hoyme H, Aase J, editors. *Immune Deficient Poikiloderma-a new Genodermatosis*. American Journal of Human Genetics; 1991: Univ Chicago Press 5720 s Woodlawn Ave, Chicago, IL 60637.
- Van Hove JL, Jaeken J, Proesmans M, Boeck KD, Minner K, Matthijs G, et al. Clericuzio type poikiloderma with neutropenia is distinct from Rothmund–Thomson syndrome. *Am J Med Genet A* 2005; 132(2):152-8.
- Mostefai R, Morice- Picard F, Boralevi F, Sautarel M, Lacombe D, Stasia MJ, et al. Poikiloderma with neutropenia, Clericuzio type, in a family from Morocco. *Am J Med Genet A* 2008; 146(21):2762-9.
- Miller S, Dykes D, Polesky H. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res* 1988; 16(3):1215.
- Pianigiani E, De Aloe G, Andreassi A, Rubegni P, Fimiani M. Rothmund Thomson Syndrome (Thomson Type) and Myelodysplasia. *Pediatr Dermatol* 2001; 18(5):422-5.
- Wang LL, Gannavarapu A, Kozinetz CA, Levy ML, Lewis RA, Chintagumpala MM, et al. Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund–Thomson syndrome. *J Natl Cancer Inst* 2003; 95(9):669-74.
- Concolino D, Roversi G, Muzzi G, Sestito S, Colombo E, Volpi L, et al. Clericuzio- type poikiloderma with neutropenia syndrome in three sibs with mutations in the C16orf57 gene: delineation of the phenotype. *Am J Med Genet A* 2010; 152(10):2588-94.
- Volpi L, Roversi G, Colombo EA, Leijsten N, Concolino D, Calabria A, et al. Targeted next-generation sequencing appoints c16orf57 as clericuzio-type poikiloderma with neutropenia gene. *The Am J Hum Genet* 2010; 86(1):72-6.
- Wahl MC, Will CL, Lührmann R. The spliceosome: design principles of a dynamic RNP machine. *Cell* 2009; 136(4):701-18.
- Hilcenko C, Simpson PJ, Finch AJ, Bowler FR, Churcher MJ, Jin L, et al. Aberrant 3' oligoadenylation of spliceosomal U6 small nuclear RNA in poikiloderma with neutropenia. *Blood* 2013; 121(6):1028-38.
- Mason PJ, Bessler M. Poikiloderma with neutropenia: beginning at the end. *Blood* 2013; 121(6):872-4.
- Patiroglu T, Akar HHJJJoA, Asthma, Immunology. Clericuzio-type Poikiloderma with Neutropenia Syndrome in a Turkish Family: a Three Report of Siblings with Mutation in the C16orf57 gene. 2015; 14(3):331-7.
- Walne AJ, Vulliamy T, Beswick R, Kirwan M, Dokal I. Mutations in C16orf57 and normal-length telomeres unify a subset of patients with dyskeratosis congenita, poikiloderma with neutropenia and Rothmund–Thomson syndrome. *Hum Mol Genet* 2010; 19(22):4453-61.
- Clericuzio C, Harutyunyan K, Jin W, Erickson RP, Irvine AD, McLean W, et al. Identification of a novel C16orf57 mutation in Athabaskan patients with Poikiloderma with Neutropenia. *Am J Med Genet A* 2011; 155(2):337-42.
- Piard J, Holder-Espinasse M, Aral B, Gigot N, Rio M, Tardieu M, et al. Systematic search for neutropenia

- should be part of the first screening in patients with poikiloderma. *Eur J Med Genet* 2012; 55(1):8-11.
20. Dokal I. Dyskeratosis congenita in all its forms. *Br J Haematol* 2000; 110(4):768-79.
 21. Chantorn R, Shwayder T. Poikiloderma with neutropenia: report of three cases including one with calcinosis cutis. *Pediatr Dermatol* 2012; 29(4):463-72.
 22. Larizza L, Roversi G, Volpi L. Rothmund-thomson syndrome. *Orphanet J Rare Dis* 2010; 5(1):2.
 23. Porter W, Hardman C, Abdalla S, Powles A. Haematological disease in siblings with Rothmund Thomson syndrome. *Clin Exp Dermatol* 1999; 24(6):452-4.
 24. Colombo EA, Bazan JF, Negri G, Gervasini C, Elcioglu NH, Yucelten D, et al. Novel C16orf57 mutations in patients with Poikiloderma with Neutropenia: bioinformatic analysis of the protein and predicted effects of all reported mutations. *Orphanet J Rare Dis* 2012; 7(1):7.
 25. Rodgers W, Ancliff P, Ponting C, Sanchez- Pulido L, Burns S, Hayman M, et al. Squamous cell carcinoma in a child with Clericuziotype poikiloderma with neutropenia. *Br J Haematol* 2013; 168(3):665-7.