

CASE REPORT

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Two Cases of Syndromic Neutropenia with a Report of Novel Mutation in *G6PC3*

Zahra Alizadeh¹, Mohammad Reza Fazlollahi¹, Payman Eshghi², Amir Ali Hamidieh³, Mohsen Ghadami¹,
and Zahra Pourpak¹

¹ Immunology, Asthma & Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

² Department of Pediatrics Department, Mofid Children Hospital, Shaheed Beheshti Medical University, Tehran, Iran

³ Hematology-Oncology & SCT Research Centre, Shariati Hospital,
Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Severe congenital neutropenia (SCN) is a rare primary immunodeficiency. Different genes are found to be associated with SCN, including *ELA2*, *HAX1*, *WAS*, *GFI1*, *G-CSFR*. Also, recently *G6PC3* as a rare gene in SCN has been reported.

Patients with *G6PC3* often have cardiac and/or urogenital malformations. Two patients with persistent severe neutropenia, recurrent infections and maturation arrest at promyelocyte-myelocyte stage in their bone marrow were assessed in this study.

Both patients showed structural heart disease and one of them also showed urogenital anomaly. Sequence analyses of *G6PC3* in 2 patients revealed two different homozygous mutations, one in exon 6 (Asn 313 fs), and the other in exon 3 (Ser 139 Met), the latter is a new mutation which has not been reported in previous studies.

It can be concluded that *G6PC3* is one of the responsible gene for SCN in Iranian patients. Based on the results, a new mutation in *G6PC3* observed in one patient.

Key words: Cardiorascular & urogenital malformations; *G6PC3*; Severe Congenital Neutropenia

INTRODUCTION

Severe congenital neutropenia (SCN) includes heterogeneous disorders characterized by severe neutropenia from early infancy with low absolute neutrophil counts (mostly less than 500/ μ l), increased life threatening infections, and maturation arrest at bone marrow in promyelocyte/myelocyte stage.¹ Different

genes including *ELA2*, *HAX1*, *WAS*, *GFI1*, are found to be associated with SCN,^{2,3} and recently *G6PC3* (catalytic subunit 3 of glucose-6-phosphate) was shown as a rare gene involved in SCN.⁴⁻⁶ Patients with *G6PC3* gene homozygous mutation often have cardiovascular abnormalities and or/urogenital malformations.⁴

CASE REPORT

Here we report two Iranian patients who referred to Immunology, Asthma and Allergy Research Institute, with a syndromic form of SCN, resembling to patients described by Boztug et al.⁴

Corresponding Author: Mohammad Reza Fazlollahi, MD;
Immunology, Asthma & Allergy Research Institute, Tehran University
of Medical Sciences, Tehran, Iran. Tel: (+98 21) 6693 5855, Fax: (+98
21)6642 8995, E-mail: fazlollahi@tums.ac.ir

Table 1. Clinical and molecular findings in two SCN patients with G6PC3 deficiency

Topics	Patient 1	Patient2
Parent consanguinity	Yes	Yes
Sex	Male	Male
Age at symptom onset	1 mth	4 mths
Age at study time	48 mths	Dead at 9 mths
Infection history	Pneumonia, Neonatal sepsis	Pneumonia, sepsis
ANC*	28-450	40-170
Bone marrow aspiration	Maturation arrest in Myelocyte stage	Maturation arrest in myelocyte stage
Average G-CSF** dose	3-5 µg/kg (2 times per week)	5-10 µg/kg/day
Response to G-CSF	Excellent	good
Other findings	Arterial septal defect (type2), unilateral hydronephrosis, prominent superficial venous pattern	Arterial septal defect (type 2), failure to thrive
ELA2	No mutation	No mutation
WAS	Not determined	No mutation
HAX1	Not determined	No mutation
G6PC3	Asn313fs	S139M

*Indicates absolute neutrophil counts before G-CSF treatment

**Granulocyte colony stimulating factor

These cases were registered in Iranian Primary Immunodeficiency Registry (IPIDR). Genomic DNA of the patients were extracted from whole blood of the patients and 6 exons of G6PC3 gene were amplified using primers as described before⁴ by PCR and sequenced.

The first patient was a four-year-old boy of consanguineous parents, diagnosed at early infancy with low neutrophil count, lung infection and fever and also maturation arrest at myelocyte stage. His physical examination showed heart and urogenital abnormalities. He has referred to our center for G-CSF treatment and has been followed for 3 years monthly. His infections well controlled during these years and he was in a good condition (Table 1). Sequence analyses of G6PC3 gene revealed a known mutation in the exon 6 (Asn 313 fs). It should be noted that we got the same result for this patient which have been previously reported^{4, 7}

The second patient was a nine-month-old boy of consanguineous parents with heart abnormalities and severe recurrent infections and fever. His severe neutropenia was diagnosed at 4 months of age and he

referred to our center at 7 months of age for more evaluation and making decision about SCT (stem cell transplantation). Finally, he died at 9 months because of serious lung infection (Table 1). DNA sequencing of his G6PC3 gene revealed a novel homozygous mutation in the exon 3 (Ser 139 Met), (Figure 1). Also, sequence analyses of *ELA2*, *HAX1* and *WAS* were performed and no mutations identified in these associated SCN genes.

In order to determine that this G6PC3 variant is a novel mutation which caused neutropenia in the patient and it was not a polymorphism, 100 healthy controls were entered in the study. The exclusion of polymorphism at codon 139 was confirmed among the healthy population in this study. Both parents and two aunts (sisters of his mother) of the patient found to be carriers of the G>T without noticeable clinical phenotype (Figure 1). Also, the CVS examination of the current pregnancy of the mother indicates the fetus does not harbor the respective mutation. To the best of our knowledge this is the first report of the amino acid substitution mutation in exon 3. This Novel mutation in *G6PC3* can be added to 10 mutations reported previously^{4,8,9,10}.

CONCLUSION

Finding further mutations in G6PC3 will assist to define the molecular and clinical aspects of this disease.

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CONFLICT OF INTEREST

None of the authors have any potential conflicts of interest.

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