International Journal of Hematology
https://doi.org/10.1007/s12185-021-03130-w

CASE REPORT

A novel germline GATA2 frameshift mutation with a premature stop codon in a family with congenital sensory hearing loss and myelodysplastic syndrome

Hideyuki Nakazawa[1] · Tomomi Yamaguchi[2,3] · Hitoshi Sakai[1] · Masae Maruyama[4] · Toru Kawakami[1] · Fumihiro Kawakami[1] · Sayaka Nishina[1] · Masumi Ishikawa[2] · Tomoki Kosho[2,3] · Fumihiro Ishida[1,4]

Received: 10 September 2020 / Revised: 8 March 2021 / Accepted: 9 March 2021

Abstract

GATA2 is a zinc-finger transcription factor regulating early hematopoiesis and developmental processes. Heterozygous germline mutations in *GATA2* underlie a pleiotropic autosomal dominant disorder, GATA2 deficiency syndrome. The wide spectrum of its clinical features involves familial predisposition to myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and multiorgan dysfunction, including congenital sensorineural hearing loss (CSHL). We herein report a pedigree with a novel germline frameshift mutation presenting as CSHL and familial MDS. The proband was a 46-year-old man, and his daughter also presented with an identical set of clinical syndromes. Target DNA sequencing identified a novel eight-nucleotide duplicative insertion at exon 5 (NM_032638.4:c.1126_1133dup:p.Lys378Asnfs*12) of the *GATA2* gene. RT-PCR and subcloning analysis showed that the frameshift might result in a truncated mutation with an early stop codon without interfering with the predicted splice site. The predicted mutant protein had 388 amino acids and in silico analysis showed the variant was considered deleterious. This mutation was not detected in unaffected family members. Its deleterious effect is highly likely to have portended the familial MDS and CSHL in this pedigree. Genetic testing among suspected individuals may be warranted for adequate management, including timely transplantation.

Keywords GATA2 · Germline mutation · Familial MDS · Congenital sensory hearing loss

Background

GATA2 is a zinc-finger (ZF) transcription factor regulating early hematopoiesis, autoimmunity, and inflammatory and developmental processes by cooperating in a network of other transcription factors of thousands of genes in a dose-dependent manner [1, 2]. Inherited and de novo heterozygous germline mutations in *GATA2* underlie a pleiotropic autosomal dominant genetic disorder, GATA2 deficiency syndrome. Its wide spectrum of clinical features involves multiorgan systems and falls into four overlapping phenotypes: MonoMAC syndrome, DCML deficiency, Emberger syndrome and familial predisposition to MDS and AML [3, 4]. Congenital sensorineural hearing loss (CSHL) has also been described in 76% of mutated individuals [4].

While more than 100 different genetic mutations have been described to abate the expression of *GATA2* [5], most lesions occur in ZF2, which are categorized into three types of monoallelic mutations: (i) truncating or splice-site mutations leading to premature translation termination prior or within ZF2, (ii) missense mutations within ZF2, and (iii) non-coding variants in the + 9.5-kb enhancer region of intron 4 [6]. Genotype–phenotype associations are poorly understood [4, 5], and intrafamilial phenotypic variability has been described [7].

We herein report a pedigree with a novel germline frameshift mutation presenting as CSHL and familial MDS. This mutation seemed to cause a premature termination codon

✉ Hideyuki Nakazawa
hnaka@shinshu-u.ac.jp

[1] Division of Hematology, Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1, Matsumoto, Nagano 3908621, Japan

[2] Center for Medical Genetics, Shinshu University Hospital, Matsumoto, Japan

[3] Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan

[4] Department of Biomedical Laboratory Sciences, Shinshu University School of Medicine, Matsumoto, Japan

Published online: 23 March 2021