

Immunodeficiency, Centromeric Instability and Facial Dysmorphism Syndrome: A Case Report

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Abstract

Immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome is a rare autosomal recessive disorder, characterized by a variable reduction in serum immunoglobulins, sometimes combined with defective cellular immunity. Here, we report an 18-month-old boy, who presented with colonic perforation. The molecular diagnosis was confirmed by whole-exome sequencing that revealed a homozygous c.2506G>A, (p.Val836Met) mutation in *DNMT3B* gene. This report expands the clinical and immunological features of ICF syndrome.

Keywords: ICF syndrome; Clinical presentation; Intestinal perforation

Introduction

ICF syndrome (OMIM 242860) is an autosomal recessive disorder first described in the late 70's [1,2]. This syndrome characterized by the variable extent of immunodeficiency, mild facial dysmorphism and chromosomal instability involving the pericentromeric regions of chromosome 1, 9 and 16. The facial anomalies may include flat nasal bridge, hypertelorism, micrognathia, epicanthus, upturned nose, and low-set ears. Although their intelligence status is variable, the majority of ICF patients have developmental delay in both gross and fine motor domains [3].

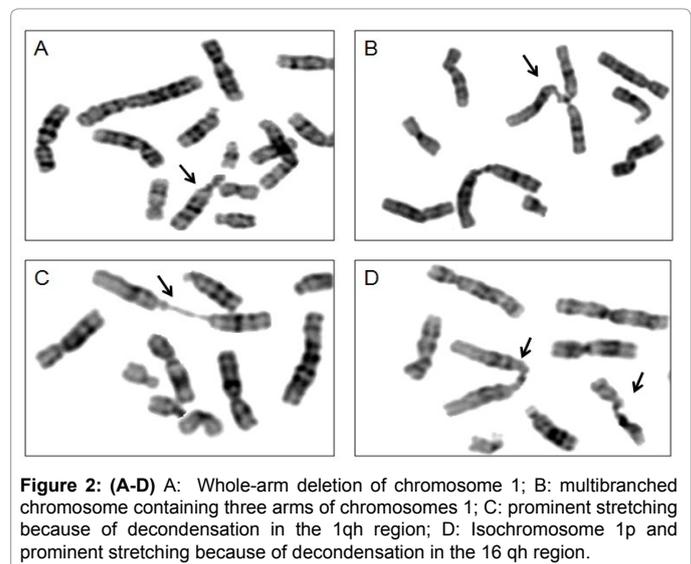
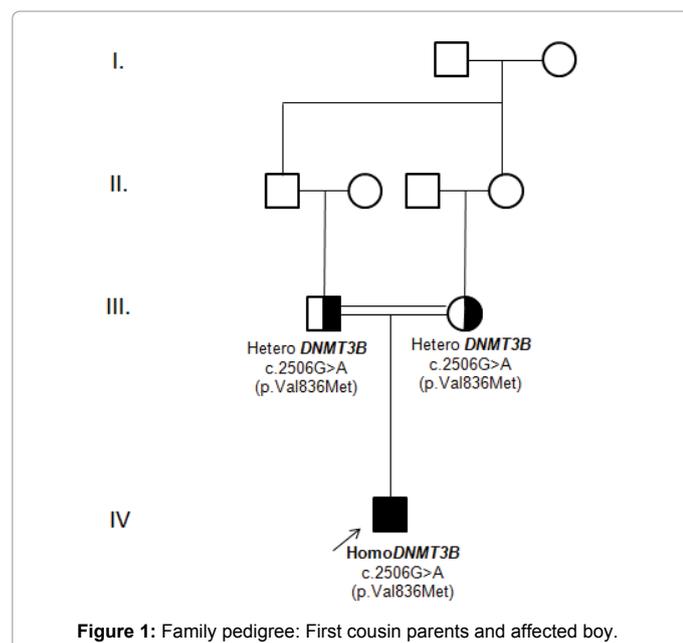
Around 50% of the ICF patients have mutations in the DNA methyltransferase 3B (*DNMT3B*) gene (OMIM 602900; ICF1) [3]. Other autosomal recessive mutations in the zinc-finger and BTB domain-containing 24 (*ZBTB24*) gene were observed in 30% of patients (OMIM 614064; ICF2) [3,4]. The etiology of the remaining small groups of patients with ICF is unknown [4]. Most of the patients with ICF present early in life with recurrent sinopulmonary infection, characteristic facial anomaly and hypogammaglobulinemia or agammaglobulinemia which is the hallmark of ICF; however, some cases have normal serum immunoglobulins. In addition, T- cells become deficient over time [5].

An association between ICF and malignancies such Angiosarcoma and adrenocortical adenoma has been reported in some patients [3,6]. Early diagnosis and regular immunoglobulin supplementation can improve the course of the disease [7]. Allergenic stem cell transplantation is considered as a therapeutic option in ICF patients with severe recurrent infections and for those with failure to thrive [8,9]. Here, we report a young child with ICF syndrome with an unusual presentation.

Case Report

The proband is a 2-year-old Saudi boy, a product of an emergency Cesarean section due to fetal distress. He was born at term with good APGAR score and low birth weight (2.1 kg). his parents are first cousins with no history of a genetic disease (Figure 1).

At ten months of age, our patient presents with pneumonia which



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Received January 02, 2019; Accepted January 08, 2019; Published January 14, 2019

Citation: Alonazi NA, Mohamed S, Alonazi A, Elshazaly H, Jori B, et al. (2019) Immunodeficiency, Centromeric Instability and Facial Dysmorphism Syndrome: A Case Report. J Clin Case Rep 9: 1201. doi: 10.4172/2165-7920.10001201

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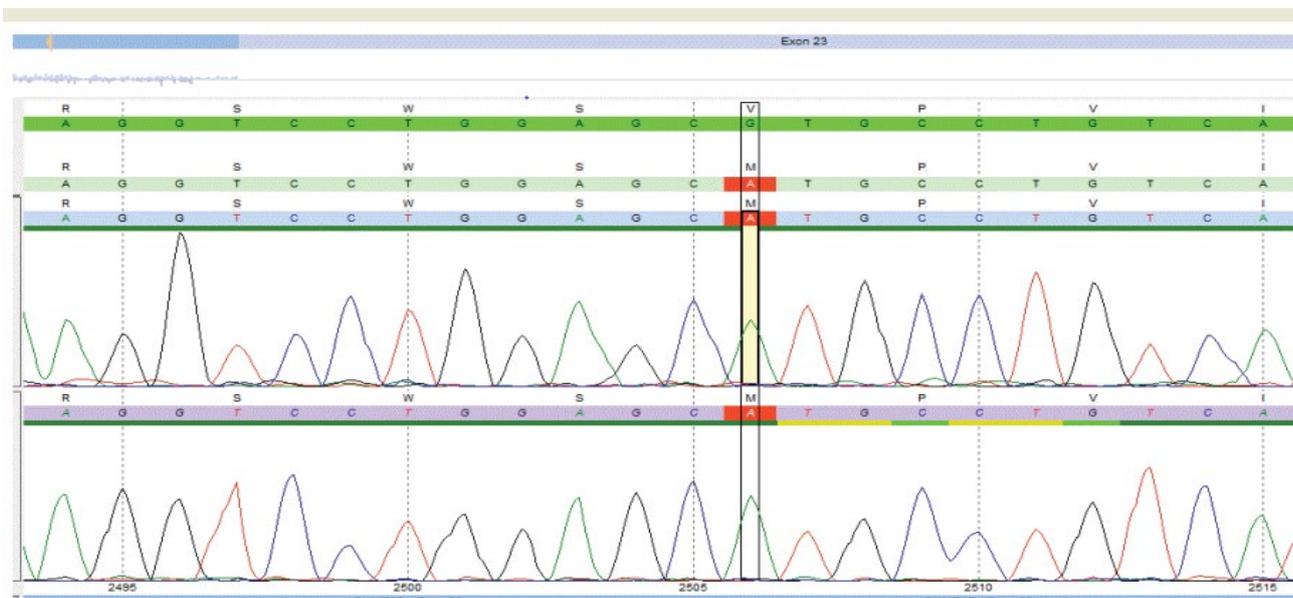


Figure 3: DNMT3B gene and sequence chromatographs of wild-type and patient DNA amplicons showing sequence variations.

responded to intravenous antibiotic. He had failure to thrive with both weight and length below the third centile. There was no history of oral thrush, skin rash or chronic diarrhea. At the age of one year, he presented to the emergency room with high fever, vomiting, and abdominal distention.

Clinical examination revealed growth failure with head circumference, weight, and height below the 3rd centile, distinct dysmorphic features in the form of low-set ears, hypertelorism, micrognathia, flat nasal bridge and epicanthal folds were observed. The central nervous system was normal apart from delayed growth motor milestones.

His abdomen was distended, tender and bowel sounds were absent which indicated a possible intestinal obstruction. A plain abdominal X-ray confirmed the presence of gas under the diaphragm together with distended small bowel loops. After resuscitation with fluids, he underwent exploratory laparotomy which revealed perforation of the ascending colon. Peritoneal lavage was performed, and an ileostomy was fixed.

Investigations showed normal full and differential blood count, renal and liver function tests. All cultures including blood, urine, and peritoneal fluids were negative. Serum immunoglobulins analysis showed a low IgM level at 0.22g/L (normal=0.38-2.35), IgA=0.25g/L (normal=0.57-3.18) and normal IgG level at 6.07 g/L (normal=6.6-16.2). Lymphocyte subset analyses and antibodies titer to Pneumococcal and Tetanus were normal.

Cytogenetic and molecular genetics result

Chromosomal analysis of the peripheral blood specimen revealed 46, XY; an apparently normal male karyotype. However, pericentric breaks of chromosome 1 and 16 were observed in most of the metaphasis, which is consistent with ICF syndrome (Figures 2A-2D).

Molecular genetic analysis

Informed consent to perform genetic studies was obtained from the parents. The DNA was isolated from the blood leukocytes of the

patient and his parents. Approximately 37 MB (214,405 EXONS) of the Consensus Coding Sequences were enriched from the genomic DNA by >340,000 probes which were designed against the human genome (Nextera Rapid Capture Exome, Illumina). The generated data was sequenced on an Illumina platform to an average coverage depth of 70-100X. An end to end bioinformatics pipelines including base calling primary filtering of low-quality reads and artifacts and variants annotation were applied. We considered all disease-causing variants already reported in HGMD and also in ClinVar (class 1). Also, a variant with a minor allele frequency of less than 1% in ExAc database was entertained. Whole exome sequencing detected a homozygous variant in the *DNMT3B* gene, c.2506 G>A, (p.Val836Met) (Figure 3). This variant has been observed in both parents in a heterozygous state. It is classified as likely pathogenic (class 2) according to the recommendations of the American College of Medical Genetics (ACMG). This variant has been reported before [9].

Discussion

Up to date, the ICF registry includes 66 patients reported from all over the world [3]. In this paper and for the first time, we describe a patient with ICF presented with colonic perforation. The association of primary immunodeficiency and the gastrointestinal manifestation were well documented; however, intestinal perforation was not previously reported. Previously, 4 cases were reported from Saudi Arabia and included in the ICF registry [9]. All these four patients were females, and like our patient most of them present in infancy with a variable degree of Hypogammaglobulinemia, different clinical symptoms, and all parents were consanguineous.

Like most of the reported patients with ICF syndrome, our patient had delayed growth motor milestones while his intelligence was preserved [3]. Although Hypogammaglobulinemia is a common feature of ICF syndrome which usually affects all three main classes ((IgA, IgM, and IgG); however, our patient had a normal serum level for IgG with reduced IgM and IgA level [3]. This demonstrates that despite having the phenotypically characteristics of ICF syndrome patients may have variable immunoglobulin features. As some patients

with ICF syndrome were shown to have a tendency towards developing malignancies, we screened our patient, and we have not observed this risk. Nevertheless, we plan to continue future surveillance of our patient regarding the development of malignancy.

All reported variants in patients with ICF syndrome were observed in *DNMT3B* and *ZBTB24* genes [3]. In our patient, we identified a homozygous variant in the *DNMT3B* gene, c.2506 G>A, (p.Val836Met) using the whole exome sequencing technique. This missense point mutation has been reported before [3,9]. It results in a nucleotide codon that code for methionine instead of Valine which ultimately affects the protein function.

Like most reported cases with ICF syndrome with the variable range of centromeric instability involving chromosomes 1 and 16, our patient had pericentric breaks of chromosome 1 and 16. This reflects the importance of genetic testing for pediatric patient who present with failure of thrive, and unusual presentation, even though no major dysmorphism is observed.

Conclusion

In conclusion, we report, for the first time, a patient with ICF syndrome presented with colonic perforation. This expands the phenotype of this syndrome. Also, we emphasize that early diagnosis of ICF syndrome is crucial since early treatment with immunoglobulin and possible stem cell transplantation can improve the patient's outcome.

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