Gene Corner

A novel mutation of the *SLC39A4* gene causing acrodermatitis enteropathica

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Acrodermatitis enteropathica (AE, OMIM 201100) is an autosomal recessive disease characterized by skin findings caused by defective intestinal zinc absorption. The skin lesions include erythema, erosions and small blisters in the perioral and perianal regions, hands and feet, which develop soon after weaning.[1] The AE gene has recently been identified as *SLC39A4*.[2] This gene, located on chromosomal region 8q24.3, encodes a novel zinc transporter protein belonging to the ZIP (zinc/iron-regulated transporter-like protein) family.[3] It was found mutated in several distinct families with AE coming from Europe, North Africa, Japan and the Middle East.[4–6]

We report a 23-month-old boy with AE who exhibits a new mutation in exon 11 of the *SLC39A4* gene. This is the first report on the screening of *SLC39A4* mutations from Turkey.

Case and methods

A 23-month-old boy, who was born to first-degree consanguineous parents, presented with vesicular and crusted lesions together with well-defined, erythematous, moist plaques on perioral, perigenital and perianal regions that he had had since 15 months of age. He had intermittent diarrhoea, recurrent respiratory tract infections and a 2-month history of irritability. He had been weaned from breast feeding at 8 months of age.

On admission, his weight was 11 kg and his height was 83 cm (both 5th percentile). He had vesicobullous and erythematous crusted lesions on his face, napkin area and extremities (Fig. 1a,b) associated with alopecia universalis. Laboratory investigations, including a full blood count, liver and kidney function tests, serum albumin levels and stool examination, were normal. Serum IgG and IgM levels were low, while IgA level was normal. The lymphocyte subsets were within normal limits while antibody response to tetanus vaccine was low. Serum zinc level was 35 μg dL^{-1} (normal 70–127) and alkaline phosphatase level was 24 U L^{-1} (normal 37–147). Histopathological examination of a specimen taken from a bullous lesion on the left gluteal region disclosed intracellular oedema of epidermal keratinocytes and a perivascular lymphocytic infiltrate.

Given the symptoms pathognomonic of AE, we performed a mutation analysis of the *SLC39A4* gene in our patient. Written informed consent was obtained from the parents. Genomic DNA was extracted from a venous blood sample and used for direct sequencing of the coding and flanking intronic regions of *SLC39A4*; primers and conditions were described previously.[4]

Results and discussion

We observed, in exon 11, the homozygous replacement of a guanine by a thymine at position 1784 of the mRNA sequence NM_130849 (c.1784 G→T) (Fig. 2). This transversion leads to the protein modification p.Gly595Val. To exclude the possibility of a polymorphism, we screened exon 11 of 103 healthy Turkish controls for the mutation found in our

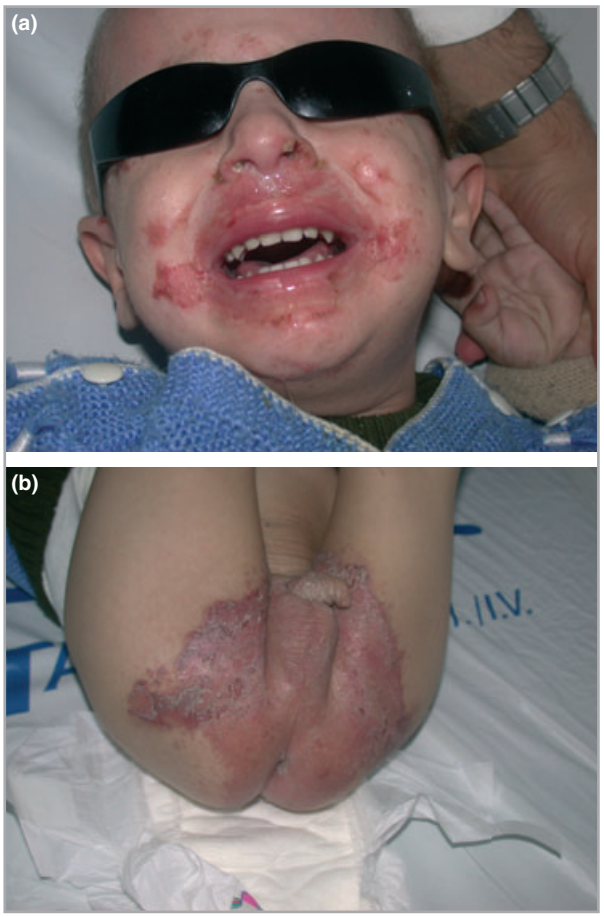

Fig 1. (a, b) Characteristic pustular and erythematous periorificial and anogenital skin lesions.

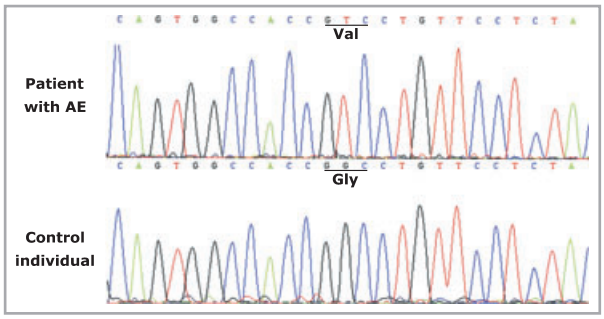

Fig 2. Mutation analysis of the gene *SLC39A4*. The upper sequence electropherogram shows the homozygous mutation c.1784 G→T (p.Gly595Val) found in exon 11 of the study patient. The lower electropherogram corresponds to the same region of *SLC39A4* sequenced in a Turkish control individual unaffected with acrodermatitis enteropathica (AE).

patient. None of the 103 control individuals was found to carry the mutation c.1784 G→T, either in a homozygous or a heterozygous state. Therefore, we assumed that the novel mutation c.1784 G→T caused the AE in our patient.

The diagnosis of AE was followed by therapy with oral zinc sulphate 1·5 mg kg^{-1} daily. After 3 weeks of therapy, the cutaneous lesions had completely disappeared. Serum zinc and alkaline phosphatase levels had returned to normal at the end of the fourth week. Over the following 2 years, the patient still continued to require oral zinc supplementation (1 mg kg^{-1} daily). Recurrent respiratory tract infections or episodes of diarrhoea were not observed during this period.

The mechanisms behind the immunostimulating action of zinc are complex, although thymic hormone (of which zinc is an essential cofactor) stimulation seems to be most important. Zinc deficiency affects primarily T cells, resulting in a decreased number of T cells and disruption of their functions.[7] Immunoglobulin production that requires T-cell help is reduced in zinc deficiency. Zinc deficiency results in a reduced antibody formation, in particular in response to neoantigens, because naive B cells are more affected by zinc deprivation than memory B cells.[8] We detected humoral immunodeficiency characterized by reduced response to tetanus vaccine and low IgG and IgM levels which caused recurrent respiratory tract infections in our patient.

The *SLC39A4* gene is expressed in tissues involved in zinc absorption, including the stomach, small intestine, colon and kidney.[1,3] In our study, the homozygous mutation c.1784 G→T induces the substitution of a glycine by a valine at position 595 of the protein sequence (p.Gly595Val), i.e. an amino acid residue that is very conserved across species. According to bioinformatic programs predicting protein secondary structure (THMM, TMPRED, Chou-Fasman, MEMSTAT), this mutation occurs within the seventh transmembrane domain of the protein, thereby changing an α-helix to a β-sheet. It is therefore very likely that this mutation alters the zinc absorption function of SlC39A4 protein and causes zinc deficiency.

We report here a novel mutation of the gene *SLC39A4* which caused AE in a Turkish boy. This case highlights the effects of high-dose zinc supplementation, which resulted in reversal of the zinc deficiency and improvement of the clinical findings of AE.

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[Correction added after online publication 27th June 2007: Author name changed from S. Sebnem Kilic to S. S. Kilic]

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Conflicts of interest: none declared.

