

Letter to the Editor

Severe phenotype of severe combined immunodeficiency caused by adenosine deaminase deficiency in a patient with a homozygous mutation due to uniparental disomy

To the Editor:

Severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID) commonly presents with a phenotype consisting of life-threatening infections, chronic persistent diarrhea, and failure to thrive in the first months of life.¹ In patients with ADA-SCID, toxic metabolites will destroy the lymphocytes and lead to absent or decreased numbers of B, T, and natural killer cells. Patients with ADA-SCID not only have an immunodeficiency but also other organs might be affected if increased concentrations of the metabolite persist.² ADA-SCID is autosomal recessively inherited through mutations in the *ADA* gene, which is located on chromosome 20q13.12.

We present a patient with a severe phenotype of ADA-SCID. She was the second child of healthy unrelated Dutch parents and prematurely born (35⁺2 weeks gestation) by means of emergency cesarean section because of lack of fetal movement and abnormal heart rate. Apgar scores were 6/9/9. Immediately after birth, dysmorphic facial features (including a broad nasal tip, epicanthal folds, large low-set ears, and microretrognathia), microcephaly, erythroderma, and thermolability were noted. A skin biopsy specimen did not show any indicative abnormalities. During the neonatal period, she had a urinary tract infection with *Klebsiella* species, paronychia of the fingers on both hands, and multiple episodes of cellulitis associated with intravenous catheters for which she received intravenous antibiotic treatments and surgical incisions. She had hypotonia, absent reflexes, blindness and deafness, and an abnormal breathing pattern.

Because of the erythroderma and infectious problems combined with lymphocytopenia in peripheral blood, a primary immunodeficiency was suspected. Flow cytometry showed no B, T, or natural killer cells ($<0.02 \times 10^9$ cells/L per subpopulation). IgA and IgM levels were not measurable (both <0.07 g/L), and the concentration of IgG decreased over time (2.9 g/L on day 26). The diagnosis of severe combined immunodeficiency (SCID) was made. Biochemical analysis demonstrated a complete deficiency of adenosine deaminase (ADA) activity in the erythrocytes.

At day 26, she had respiratory insufficiency requiring artificial ventilation. She had a lower airway infection and symptoms of acute respiratory distress syndrome. After 4 days of intensive treatment and artificial ventilation, further medical treatment was withdrawn because of the very limited treatment options, the prognosis of the ADA-SCID itself, and the irreversible neurologic condition.

Sequence analysis of our patient demonstrated homozygosity for a 5-bp deletion (c.956_960delAAGAG) in exon 10 of the *ADA* gene. This frameshift mutation leads to a premature stop codon, resulting in a truncated protein. Analysis of the parental DNA showed that only the father was a heterozygous carrier for this deletion. Considering the autosomal recessive inheritance of ADA-SCID, this did not match with the homozygous occurrence in our patient. 250K Nsp SNP Array (Affymetrix, Santa Clara, Calif) analysis of the patient-parent trio was performed to examine the scenario of either a maternal deletion within the *ADA* gene or a

paternal uniparental disomy of chromosome 20 (UPD[20]). The patient data showed a large approximately 50-Mb region of homozygosity on chromosome 20 (p13q13.2 from 0.85 to 51.71 Mb) encompassing hundreds of genes, including the *ADA* gene (located at approximately 42.25 Mb). On the basis of the single nucleotide polymorphism data, we could determine that both entire chromosomes 20 of our patient were of paternal origin. They contained 2 terminal heterodisomic regions (that contain the 2 different paternal alleles) and an isodisomic region (containing 2 identical paternal alleles), leading to homozygosity of the pathogenic 5-bp deletion in *ADA*. This phenomenon is called a UPD and is the result of a rescue of trisomy 20 in very early embryonic development (Fig 1). UPD is a rare causative mechanism of autosomal recessive disease and has never been described for patients with ADA-SCID. Understanding the mechanism of inheritance is very important, especially for determining the risk of recurrence.

The mutation has been described before in patients with ADA-SCID.³⁻⁵ Because our patient has a homozygous mutation with a truncated nonfunctional protein, a severe phenotype can be expected.⁶

Because the molecular defect in patients with ADA-SCID is not only present in hematopoietic cells, metabolic problems can also occur in other tissues.² Our patient demonstrated dysmorphic features and erythroderma. Erythroderma, as seen in patients with Omenn syndrome, has been described before in patients with ADA-SCID with residual ADA activity.⁷ Activated oligoclonal T cells are thought to be the cause of erythroderma in patients with Omenn syndrome, but these cells were not detected in our patient. On the other hand, the erythroderma might reflect an aberrant inflammatory condition associated with SCID caused by multiple genetic defects.⁸

Whether the dysmorphic features result from the specific deletion is unclear. One possibility is that the additional features are caused by the UPD(20) for chromosome 20 itself. Several patients with UPD(20) have been described and share features like microcephaly, prenatal and postnatal growth retardation, and mild dysmorphism.⁹ Another possibility is the presence of a mosaicism for trisomy 20 as a “leftover” of the rescue mechanism very early in life. Full trisomy 20 has not been described in a live-born patient and is expected to be incompatible with life. Trisomy 20 mosaicism has rarely been described and is usually associated with a mild phenotype. A CytoScan HD array (Affymetrix) did not show any sign of trisomy 20 in the DNA derived from a skin biopsy specimen, making this possibility highly unlikely.¹⁰ Other more sensitive techniques to detect mosaicism, such as fluorescence *in situ* hybridization analysis, could not be performed because no suitable material was available. A final possibility is homozygosity for a mutation in one of the other genes (>100) in the UPD region.

The recurrence risk of UPD without chromosomal disturbances in parents is low ($<1\%$). Because the recurrence risk would be 25% when both parents are a carrier of the mutation, this indicates how important understanding the mechanism of inheritance is for correct counseling of the parents.

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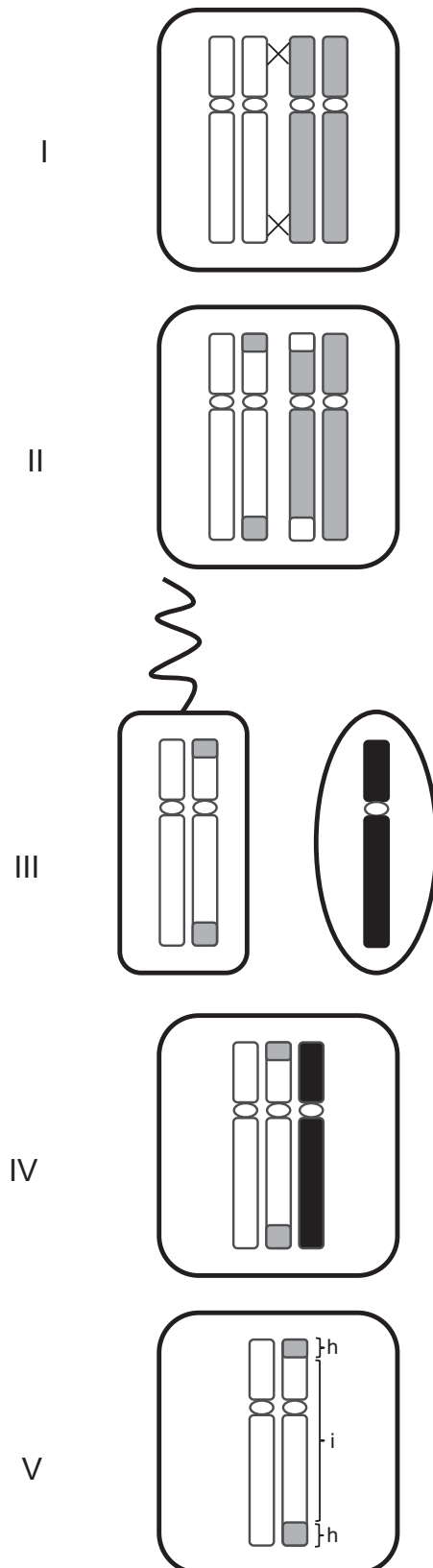


FIG 1. Schematic overview of the cause of UPD(20). *I*, A chromosome 20 pair will occur in meiosis prophase-I when crossing over between chromosome/chromatid pairs. Crossover positions are indicated by X. *II*, The chromosome 20 pair after crossing over. The exchange of genetic material is visible. *III*, A gamete (in this case, sperm cell) that is disomic for chromosome 20

because of a meiotic nondisjunction error. The *oval* represents the maternal gamete (oocyte) that contributes another chromosome 20. *IV*, The result of the fertilization of the egg and sperm cell of stage III, which has resulted in a zygote with a trisomy of chromosome 20. *V*, The result of a "trisomy rescue" during which (in this case) the maternal chromosome 20 is lost, resulting in 2 chromosomes of paternal origin (a paternal uniparental disomy). In this particular case this has resulted in a UPD(20) in which both terminal parts of chromosome 20 are heterodisomic (2 different paternal alleles, indicated with *h*) and an interstitial isodisomic stretch (2 identical paternal alleles, indicated with *i*). The border positions between the isodisomic and heterodisomic regions represent the original meiotic crossover breakpoints.