ITGB2 mutation combined with deleted ring 21 chromosome in a child with leukocyte adhesion deficiency

To the Editor:

Leukocyte adhesion deficiency type 1 (LAD-1, MIM: 116920) is a rare, autosomal-recessive primary immunodeficiency disorder caused by defects in ITGB2, a gene mapping on chromosome 21q22.31-3 and encoding for the β2-integrins subunit, CD18.4,5 LAD-1 is characterized by extreme elevation of blood neutrophil counts, recurrent fungal and bacterial infections, slow wound healing, and dystrophic scars from skin injuries. The severity of symptoms is correlated with the level of CD11/CD18 expression. Generally, patients with less than 1% expression of CD11/CD18 are susceptible to frequent and life-threatening systemic infections and require hematopoietic stem cell transplantation (HSCT).

Ring 21 (r(21)), is a rare chromosomal abnormality6 whose classic phenotype includes hypertonia, prominent nasal bridge, downward slanting palpebral fissures, protuberant occiput, and large ears. Microcephaly, sparse curly hair, prominent forehead, long eye lashes, broad antverted nasal tip, long philtrum, thin upper lip, small mouth, and retrognathia are also commonly seen.7,8 Other manifestations include the consistent features of prenatal and postnatal growth retardation, hematologic disorder, a distinctive facies, and cognitive impairment.

We report on a child with LAD-1, dysmorphic features, and growth retardation caused by a combination of a point mutation in ITGB2 and a gross deletion resulting in r(21).

The patient is the only child of nonconsanguineous parents. Delivered at 36 weeks after labor induction for suspected intrauterine growth retardation, his birth weight was 1785 g (<3rd percentile), length 42 cm (<3rd percentile) and head circumference 30 cm (<3rd percentile). Perinatality was characterized by delayed umbilical cord separation. During workup for herniotomy, a subvalvular aortic stenosis was discovered, and postoperatively slow wound healing was noted. Because of persistent anemia and leukocytosis (52 × 10⁹/L), he was referred to our...
center with a suspicion of primary immunodeficiency disorder. On admission, microcephaly, prominent forehead, flat nasal bridge, downward slanting palpebral fissures, and large ears were noted. He had sparse, thin hair, long eye lashes, broad anteverted nasal tip, long philtrum, a small mouth with thin lips, and micrognathia. A holosystolic murmur (4/6) was audible, and the hypoplastic scrotum harbored only the right testicle (volume 1 mL). Swabs from the umbilicus and the surgical wound grew *E. faecalis* and *C. parapsilosis*. Immunologic workup revealed normal lymphocyte subpopulations with good proliferative response to mitogens, normal IgG and IgM, and low IgA serum levels. Lack of CD11b and CD18 expression on the surface of polymorphonuclear leukocytes and lymphocytes prompted a diagnosis of LAD-1.

The boy was isolated in a laminar air flow regimen, and HSCT was performed at 7 months of age from a matched unrelated donor. At 2 years after HSCT, >99% of the patients’ neutrophils and lymphocytes expressed normal levels of CD18. The patient is currently awaiting cardiac surgery to correct the subvalvular aortic stenosis.

Sequencing of the *ITGB2* cDNA of the patient revealed a homozygous nonsense mutation in exon 3 (NM_000211.3: c.79A > T; NP_000202.2: p.Lys27X). The same mutation was detected in heterozygosis in the mother, but not in the father (Fig 1). Once paternity was confirmed, the presence of a gross deletion spanning the entire *ITGB2* gene on the paternally derived allele was hypothesized.

Cytogenetic analysis on fibroblasts from a skin biopsy and performed using QFQ banding with ≥450 band resolution revealed the presence of 1 normal chromosome 21 and a ring of the second 21 (Fig 2, A).

![FIG 2](image)

**FIG 2.** Cytogenetic and single nucleotide polymorphism array analyses. A, Patient’s G-banding (arrow). B, FISH painting of chromosome 21 shows signal on 2 chromosomes, including the ring chromosome (arrow). C, FISH using BAC clone RP11-15F6 reveals lack of signal on 1 of the 2 chromosomes 21 (arrow). D, Copy number state of chromosome 21 probes inferred by CNAG and reported as logarithm to the base 2 of the intensity ratio between proband and controls set. The arrow points to the deleted region.
Fluorescent in situ hybridization (FISH) with painting probe (WCP) of chromosome 21 confirmed that the ring was derived from chromosome 21, whereas FISH performed by using a 21q-specific telomere probe and BAC clone RP11-15F6, containing the \textit{ITGB2} sequence, showed a complete lack of signals on the r(21) chromosome (Fig 2, B and C). On the basis of these findings, we determined the karyotype to be 46, XY, ish r(21) (WCP+, 21qter-, RP11-15F6-) \textsuperscript{9}. Conventionnal chromosomal and FISH analysis with the same probes revealed normal results in both parents.

The Whole Genome Analysis of the trio with the Affymetrix GeneChip Human Mapping 250 K NspI array (Affymetrix, Santa Clara, Calif) confirmed the presence in the proband of a heterozygous \textit{de novo} deletion in the chromosome region 21q22.3-qter (Fig 2, D). According to CNAT4 software (Affymetrix), the deletion breakpoint mapped between SNP_A-2020087 (42,346,671 bp) and SNP_A-4209155 (42,365,654 bp), whereas, according to CNAG software (Affymetrix), the breakpoint was included between 42,374,607 bp and 42,389,446 bp. The deletion spanned 4.6 Mb and, besides the \textit{ITGB2} gene, included 69 additional genes, among which were the \textit{ADARB1} gene encoding for the enzyme responsible for pre-mRNA editing of the glutamate receptor subunit B, and \textit{COL1A1}, \textit{COL1A2}, \textit{COL6A1}, and \textit{COL6A2} genes encoding for members of the collagen superfamily.

These results confirm that most often different pathologies occurring in the same person can be related to 1 common cause, and emphasize the importance of including cytogenetic analysis in patients with complex clinical phenotypes.

The boy we have reported, besides the typical features of r(21), also had the characteristic findings of LAD-1. Typically, the loss of 1 allele of \textit{ITGB2} does not lead to a clinical immunodeficiency because this disease is inherited as an autosomal-recessive trait; however, in our patient, the LAD-1 phenotype was disclosed by an \textit{ITGB2} nonsense mutation that he inherited from the heterozygous mother. CD18 is expressed on blood leukocytes, and hence, donor stem cell engraftment leads to correction of the LAD-1 phenotype. Although LAD-1 can be cured by HSCT, this is not the case for the other r(21)-associated clinical features. Indeed, at 18 months of age, although he has no evidence of immune deficiency, he remains beneath the third percentile for height, weight, and cranial circumference, and also shows signs of neurodevelopmental delay.

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REFERENCES


Placental transfer of allergen-specific IgG but not IgE from a specific immunotherapy-treated mother

To the Editor:

Several reports suggest that allergic sensitization can be influenced already \textit{in utero}. Some studies indicate that allergic sensitization can occur \textit{in utero} by transfer of allergens via the placenta to the child, whereas others have argued against this possibility and suggest that allergen-specific IgE in cord blood does not reflect intrauterine sensitization but rather is the result of a transfer of maternal IgE to the fetus. However, whether IgE and in particular allergen-specific IgE can be transferred via the placenta to the child represents a controversial issue. The presence of allergen-specific IgE antibodies in children with specificities similar to those of their mothers has been reported in 2 studies, whereas others suggested that the placenta represents a barrier for IgE antibodies.

We had the opportunity to study the antibody reactivity profiles in serum samples from a mother with birch and grass pollen allergy (IgE levels before specific immunotherapy: 18.50 kilo units [kU]/L total IgE, 1.8 kUA/L recombinant [r] Bet v 1, 2.48 kUA/L rPhl p 1 + rPhl p 5) who had received subcutaneous injection immunotherapy with birch and grass pollen extracts (Alutard SQ; ALK-Abelló, Hørsholm, Denmark) for 2 years before she became pregnant and delivered her baby as well as in the corresponding cord blood sample of her child using an array of purified allergen molecules. To the best of our knowledge, this is the first detailed analysis of allergen-specific IgE (Fig 1), IgG\textsubscript{A}, and IgG\textsubscript{A} antibodies (Fig 2) to purified allergen molecules from several different