BACKGROUND & AIMS: Homozygous loss of function mutations in interleukin-10 (IL10) and interleukin-10 receptors (IL10R) cause severe infantile (very early onset) inflammatory bowel disease (IBD). Allogeneic hematopoietic stem cell transplantation (HSCT) was reported to induce sustained remission in 1 patient with IL-10R deficiency. We investigated heterogeneity among patients with very early onset IBD, its mechanisms, and the use of allogeneic HSCT to treat this disorder.

METHODS: We analyzed 66 patients with early onset IBD (younger than 5 years of age) for mutations in the genes encoding IL-10, IL-10R1, and IL-10R2. IL-10R deficiency was confirmed by functional assays on peripheral blood mononuclear cells (immunoblot and enzyme-linked immunosorbent assay analyses). We assessed the therapeutic effects of standard allogeneic HSCT.

RESULTS: Using a candidate gene sequencing approach, we identified 16 patients with IL-10 or IL-10R deficiency: 3 patients had mutations in IL-10, 5 had mutations in IL-10R1, and 8 had mutations in IL-10R2. Refractory colitis became manifest in all patients within the first 3 months of life and was associated with perianal disease (16 of 16 patients). Extraintestinal symptoms included folliculitis (11 of 16) and arthritis (4 of 16). Allogeneic HSCT was performed in 5 patients and induced sustained clinical remission with a median follow-up time of 2 years. In vitro experiments confirmed reconstitution of IL-10R-mediated signaling in all patients who received the transplant.

CONCLUSIONS: We identified loss of function mutations in IL-10 and IL-10R in patients with very early onset IBD. These findings indicate that infantile IBD patients with peri-anal disease should be screened for IL-10 and IL-10R deficiency and that allogeneic HSCT can induce remission in those with IL-10R deficiency.

Keywords: Children; Genetic Defect; Immunodeficiency; Intestinal Inflammation.
leukin-10 (IL10) genes. IL-10 represents a potent anti-inflammatory and immunosuppressive cytokine that mediates its pleiotropic effects on different immune cells through the transmembrane heterotetrameric complex composed of 2 IL-10R1 and IL-10R2 chains. Although IL-10R1 is specific to IL-10, IL-10R2 is a shared cytokine receptor subunit mediating signals via IL-10, IL-22, IL-26, and interferon-α. Because IL-10 acts predominantly on hematopoietic and immune cells, transplantation of allogeneic hematopoietic stem cells might be considered as curative therapeutic approach. In fact, proof-of-concept could be demonstrated in one IL-10R−deficient patient. Here, we analyzed a cohort of 66 patients with infantile (very early onset) IBD for mutations in the IL-10−related genes and describe our experience of standardized allogeneic hematopoietic stem transplantation (HSCT) in 5 patients with IL-10R deficiency.

Materials and Methods

Patients and DNA Sanger Sequencing

We collected blood samples from 66 early-onset IBD patients with clinical onset at younger than 5 years of age (subgroup of the A1a entity according to the Paris classification1), a severe course of disease, and different ethnic background. DNA Sanger sequencing of genes encoding for IL-10R1, IL-10R2, and IL-10 was performed upon parental written informed consent. The respective primer sequences are specified in Supplementary Table 1. Clinical information on IL-10− and IL-10R−deficient patients was collected by their attending physicians. The study was approved by the Institutional Review Board at Hannover Medical School, Germany.

Western Blot Analysis and Enzyme-Linked Immunosorbent Assay

Whenever potentially disease-causing mutations were identified, we performed additional functional studies to validate IL-10R deficiency. Experimental details have previously been published. In brief, peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll density gradient centrifugation and were stimulated with recombinant human IL-10 (25 ng/mL; PeproTech, Hamburg, Germany) for various time periods, followed by Western blot analysis of signal transducer and activator of transcription 3 phosphorylation at the residue tyrosine 705 (Tyr705, Cell Signaling; Danvers, MA), a crucial downstream event of IL-10 signal transduction. In addition, to exemplify defective IL-10−mediated anti-inflammatory cytokine response, we harvested supernatants of lipopolysaccharide (LPS)-stimulated PBMCs (100 ng/mL; Sigma-Aldrich, Munich, Germany) and quantified tumor necrosis factor−α (TNF−α) secretion upon costimulation with IL-10 (25 ng/mL) using a commercially available OptEIA ELISA kit according to manufacturer’s instructions (BD Bioscience, San Jose, CA).

To assess the functional impact of the identified IL-10 mutations, we followed a previously published protocol. In brief, we synthesized wild-type and mutant IL-10 by lentiviral-mediated overexpression of respective complementary DNA sequences in 293T cells, quantified the concentration of secreted IL-10 in the supernatants by enzyme-linked immunosorbent assay, and analyzed the suppression of TNF-α secretion in PBMCs.

Allogeneic HSCT

Allogeneic HSCT was considered in patients with confirmed diagnosis of IL-10R deficiency (mutational analysis, functional studies). To date, 5 patients with a severe and refractory course unresponsive to treatment with steroids, immunosuppressive agents, and surgery were treated by allogeneic HSCT after a standardized protocol. Patients had a conditioning regimen including alemtuzumab (1 mg/kg body weight), fludarabine (180 mg/m2 body surface area), treosulfan (42 g/m2 body surface area), and thiotepa (10 mg/kg body weight). Strict gut decolonization was performed with the use of colistin, amphotericin B (oral), ciprofloxacin, metronidazole, vancomycin (oral), fluconazole, and total parenteral nutrition during the peritransplantation period. Graft-versus-host disease (GVHD) prophylaxis included ciclosporin and mycophenolate mofetil. Infection prophylaxis was intensified with additional aciclovir and itraconazole substituting fluconazole on day 3 after HSCT. Tapering of the immunosuppressive medication was started at day +100 in the absence of GVHD and included withdrawal of mycophenolate mofetil and dose reduction of ciclosporin by 10% every week. Hematopoietic chimera was determined using restriction fragment length polymorphism. The reconstitution of IL-10−mediated signal transduction in PBMCs from transplanted IL-10R−deficient patients was validated by Western blot analysis and enzyme-linked immunosorbent assay as described.

Results

Genetic Analysis

We sequenced the genes encoding for IL-10R1, IL-10R2, and IL-10 in 66 patients with early onset IBD (younger than 5 years of age). We identified 16 patients with mutations in IL-10−related genes: 5 patients had mutations in the IL10RA gene, 8 patients had mutations in the IL10RB gene, and 3 patients had mutations in the IL10 gene. Of those, 9 mutations had not been previously documented in IBD (1 stop codon mutation, 4 amino acid substitutions, 2 compound heterozygous mutations, 1 3'UTR mutation, and 1 deletion). Results of this mutational screening are summarized in Table 1. Molecular details are displayed in Supplementary Figures 1A-C. In silico analysis using PolyPhen17 predicted that all identified mutations with amino acid substitution are either probably or, in the case of patient 12, possibly damaging with respect to protein structure and function. In contrast, SIFT18 analysis predicted tolerated protein function in IL-10RAArg117Arg/Cys (patient 7) and IL-10RAIle169Thr (patient 12) mutations. Bioinformatic studies on the 3'UTR mutation suggested that this sequence variation targets a putative SR-protein binding site.

Characterization of IL-10- and IL-10R-Deficient Patients

All patients with mutations in IL10 and IL10R genes presented with severe and progressive colitis in the first 3 months of life, fulfilling the criteria of infantile (very early onset) IBD. Colitis was associated with failure to thrive (15 of 16), recurrent fever and infections (15 of 16), bloody diarrhea (16 of 16), abscesses (15 of 16), perianal fistula (13 of 16), oral aphthous lesions (4 of 16),
Table 1. Summary of Demographic, Molecular, and Clinical Information on IL-10- and IL-10R-deficient patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Ethnicity, country of origin</th>
<th>Consanguinity</th>
<th>Age of diagnosis</th>
<th>Mutation (gene; genotype)</th>
<th>Age of onset, month(s)</th>
<th>Disease location/behavior</th>
<th>Extraintestinal manifestations</th>
<th>Enteral/parenteral nutrition</th>
<th>Anti-inflammatory/immunosuppressive drugs</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Kurdish, Turkey</td>
<td>Yes</td>
<td>9 y 5 mo</td>
<td>IL10RB, Ex 4: c.G477A, p.Trp159X</td>
<td>30</td>
<td>L2, B2B3p</td>
<td>Folliculitis, gonorarthritis</td>
<td>PN (p)</td>
<td>CS (g), ETN (n), IFX (n), MTX (n), CS (g), IFX (g)</td>
<td>ileocolostomy, colectomy (3 mo, p)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Kurdish, Turkey</td>
<td>Yes</td>
<td>6 y 9 mo</td>
<td>IL10RB, Ex 4: c.G477A, p.Trp159X</td>
<td>49</td>
<td>L2, B2B3p</td>
<td>Folliculitis, granarthritis, renal abscesses</td>
<td>None</td>
<td>CS (g), IFX (g)</td>
<td>ileostomy, colectomy (2 mo, p)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Arab, Lebanon</td>
<td>Yes</td>
<td>13 y 3 mo</td>
<td>IL10RA, Ex 4: c.G421A, p.Gly141Arg</td>
<td>7</td>
<td>L2, B2B3p</td>
<td>Folliculitis, STH deficiency</td>
<td>None</td>
<td>CS (g), IFX (nt)</td>
<td>Colostomy, bowel resection (3 mo, p), colectomy (33 mo, p)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Caucasian, Germany</td>
<td>Yes</td>
<td>7 mo</td>
<td>IL10RA, Ex 3: c.C251T, p.Trp159X</td>
<td>13</td>
<td>L2, B1p</td>
<td>Folliculitis</td>
<td>PN (p)</td>
<td>AZA (p), CS (p), CsA (p), ETN (g), IFX (n), MTX (n)</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Turkish, Turkey</td>
<td>Yes</td>
<td>7 y 9 mo</td>
<td>IL10RA, Ex 3: c.C301T, p.Trp159X</td>
<td>7</td>
<td>L2, B2B3p</td>
<td>Folliculitis</td>
<td>None</td>
<td>AZA (n), CS (n)</td>
<td>Colectomy (44 mo, p)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Kurdish-Turkish, East Turkey</td>
<td>Yes</td>
<td>4 y 11 mo</td>
<td>IL10RA, Ex 4: c.G477A, p.Trp159X</td>
<td>60</td>
<td>L3L4a, B2B3p</td>
<td>Autoimmune hepatitis, folliculitis</td>
<td>None</td>
<td>CS (g), IFX (nt), MP (g), MTX (n)</td>
<td>Colostomy, bowel resection (28 mo, p)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Latin American, Brazil</td>
<td>No</td>
<td>2 y 2 mo</td>
<td>IL10RA, Ex 2: c.A170A/G, p.Tyr57Tyr/Cys</td>
<td>41</td>
<td>L2, B1p</td>
<td>Arthralgia/arthritis (lower limbs), Kawasaki disease</td>
<td>None</td>
<td>CS (g), IFX (nt), MP (g), MTX (n)</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>South Asian, Bangladesh</td>
<td>Yes</td>
<td>9 mo</td>
<td>IL10RB, Ex 3: c.G197A, p.Cys66Tyr</td>
<td>45</td>
<td>L2, B1p</td>
<td>Folliculitis</td>
<td>EN (p), PN (p)</td>
<td>ADA (n), mesalamine (n), Aza (p), CS (n), IFX (n), TAC (n)</td>
<td>ileostomy (6 mo, p)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Arab, Israel</td>
<td>Yes</td>
<td>6 mo</td>
<td>IL10RB, 3'UTR: c.*C52T</td>
<td>90</td>
<td>L2, B1p</td>
<td>Arthritis (large joints), folliculitis</td>
<td>PN (g)</td>
<td>Mesalamine (n), Aza (n), CS (p), ETN (g), IFX (nt), MP (n), MTX (n)</td>
<td>ileostomy (6 mo, g)</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Caucasian, Germany</td>
<td>No</td>
<td>1 y 5 mo</td>
<td>IL10RB, Ex 5: c.G611G/A, p.Tyr57Tyr/Cys</td>
<td>21</td>
<td>L2L4a, B1p</td>
<td>Dermatitis, folliculitis</td>
<td>PN (g)</td>
<td>Mesalamine (n), Aza (p), IFX (p)</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Caucasian, Poland</td>
<td>Unknown</td>
<td>5 y 4 mo</td>
<td>IL10RB, Ex 5: c.G611G/A, p.Tyr57Tyr/Cys</td>
<td>29</td>
<td>L2L4a, B3p</td>
<td>Folliculitis</td>
<td>PN (p)</td>
<td>Mesalamine (n), Aza (p), CS (n), IFX (g)</td>
<td>ileostomy (16 mo, p)</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>Black, Pacific Island</td>
<td>Yes</td>
<td>11 y 3 mo</td>
<td>IL10RB, Ex 5: c.T506G, p.Nec169Thr</td>
<td>7</td>
<td>L3L4a, B2B3p</td>
<td>Atopic dermatitis, folliculitis</td>
<td>EN (p), PN (n)</td>
<td>ADA (n), Aza (n), CS (n), IFX (n), MTX (n)</td>
<td>PEG/ileostomy/colostomy (1 y, p), stricture-plasty (11 y), rectal stricture dilatations (12 y)</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>Arab, Kuwait</td>
<td>Yes</td>
<td>26</td>
<td>IL10, Ex 5: c.G458A, p.Gly153Asp</td>
<td>26</td>
<td>L2, B1p</td>
<td>None</td>
<td>None</td>
<td>Mesalamine (n), g., CS (g)</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Arab, Kuwait</td>
<td>Yes</td>
<td>31</td>
<td>IL10, Ex 5: c.G458A, p.Gly153Asp</td>
<td>31</td>
<td>L2, B1p</td>
<td>None</td>
<td>None</td>
<td>Mesalamine (n), p., CS (g)</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>Arab, Kuwait</td>
<td>Yes</td>
<td>34</td>
<td>IL10, Ex 5: c.G458A, p.Gly153Asp</td>
<td>34</td>
<td>L2, B3p</td>
<td>None</td>
<td>None</td>
<td>Mesalamine (n), p., CS (g)</td>
<td>Fistula/abscesses</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>Turkish, Turkey</td>
<td>Yes</td>
<td>65</td>
<td>IL10RB, Ex 5: c.331 + 907,574del</td>
<td>65</td>
<td>L2L4a, B2B3p</td>
<td>Folliculitis</td>
<td>PN (p)</td>
<td>Aza (p), CS (g), IFX (p), CS (p)</td>
<td>Colostomy (g)</td>
</tr>
</tbody>
</table>

ADA, adalimumab; AZA, azathioprine; CS, corticosteroids; CsA, cyclosporin; EN, enteral nutrition; ETN, etanercept; F, female; g, good; IFX, infliximab; M, male; MP, mercaptopurine; MTX, methotrexate; n, none; nt, not tolerated; p, partial; PN, parenteral nutrition; TAC, tacrolimus.

*Patients have been reported previously by Glocker et al.12
*Diagnosis is defined as IL-10 or IL-10R deficiency.
*Defined as first symptoms of IBD.
*According to the Paris classification.16
*Patient died due to traffic accident.
*Patient died due to sepsis.
foliculitis (11 of 16), and arthritis (4 of 16). Of note, all 16 patients had perianal disease. Immunological workup revealed normal numbers of B and T cells and normal proliferative responses of T cells. Analysis of serum immunoglobulins revealed in some patients elevated IgG, IgA, and IgM levels, but IgE levels were within normal range. All IL-10R−deficient patients developed specific antibodies in response to vaccination and displayed normal neutrophil reduced nicotinamide adenine dinucleotide phosphate-oxidase activity (data not shown). Colonoscopy demonstrated moderate to severe discontinuous colitis with deep ulcerations and pseudo-polyps (Figure 1A). Histological analysis of colonic biopsies revealed unspecific acute colitis with multiple ulcerations and dense polymorphic infiltrations (Figure 1B, C), reminiscent of Crohn’s disease. All patients had multimodal therapy, including exclusive enteral nutrition, anti-inflammatory and/or immunomodulatory agents. Most patients underwent ileostomy, colostomy, and/or surgical intestinal resection. Despite complex multimodal therapy approaches, none of the patients had a sustained response. Detailed information on demographics, clinical phenotype, and treatment of individual IL-10/IL-10R−deficient patients is provided in Table 1.

We assessed the functional consequences of the mutations and assayed IL-10R−dependent signaling in primary PBMCs from 10 patients. As shown in Figure 1D and Supplementary Figure 2A, deleterious mutations in IL10R genes abrogate IL-10−mediated signaling resulting in deficient phosphorylation of signal transducer and activator of transcription 3 at the Tyr705 residue, an essential downstream target for the physiological anti-inflammatory response of IL-10. As a consequence, IL-10R−deficient primary cells are unresponsive to IL-10−dependent negative feedback regulation and secrete high amounts of TNF-α upon costimulation with LPS and IL-10 (Figure 1E, F and Supplementary Figure 2B). To analyze the functional impact of the IL-10<sup>Gly153Asp</sup> mutation, we quantified the inhibition of TNF-α release in LPS-stimulated PBMCs from healthy donors upon stimulation with letriviroplase overexpressed and secreted wild-type or mutant IL-10 (Figure 2). Wild-type IL-10 induced suppression of TNF-α secretion comparable with recombinant human IL-10. In contrast, mutant IL-10 failed to exert anti-inflammatory effects.

**Allogeneic HSCT**

Based on our previous observation, we performed allogeneic HSCT in 5 IL-10R−deficient patients unresponsive to immunosuppressive medication and surgical intervention. We used an immunosuppressive and myeloablative conditioning regimen consisting of alemtuzumab, fludarabine, treosulfan, and thiotepa (Figure 3). Cyclosporin and mycophenolate mofetil were administered for GVHD prophylaxis. Age at transplantation...
Donor-derived hematopoiesis post transplantation is displayed over time in Supplementary Figure 3. After rejection of first graft from a 9 of 10 matched unrelated donor, patient 4 was subjected to retransplantation from another 9 of 10 matched unrelated donor resulting in a prompt and durable engraftment. To prevent disease recurrence after the development of mixed hematopoietic chimerism patient 5 received one donor lymphocyte infusion (1 × 10^6 CD3^pos^ cells/kg body weight, day +235) and the mixed chimerism remained stable (80%–82%, day +248 to 416) without any overt clinical symptoms. Furthermore, no hospitalization was required since day 60 after HSCT. Antiviral ganciclovir or cidofovir therapy of human herpes virus 6 infection in patient 6 was associated with partial bone marrow suppression resulting in red blood cell and platelet deficiency. He was treated with a stem cell boost on day +260 and recovered with his bone marrow leading to substantial clinical improvement of colitis.

All transplanted patients had viral infections or reactivations after HSCT (cytomegalovirus, adenovirus, rotavirus, human herpes virus 6) and some required antiviral treatment (cidofovir, ganciclovir, foscarnet, and aciclovir). Viral infections could be controlled in all patients without any long-term side effects. Patients 1, 4, and 6 developed acute GVHD responding to a short-term course of prednisone therapy. Patient 4 developed limited chronic skin GVHD without sclerosis or ulcers requiring treatment with steroids and tacrolimus.

To date, 4 patients achieved fast and sustained complete clinical remission at a median follow-up of 2 years after HSCT. Improvement of the clinical status was furthermore evidenced by ameliorated wound healing, accelerated growth, and reduced need for hospitalization. Importantly, colonoscopy (Figure 4A) and histopathological examination (Figure 4B, C) of ileal and colonic biopsies revealed no evidence of active inflammation at 6 months after HSCT. Furthermore, functional studies on PBMCs isolated from transplanted IL-10R− deficient patients showed phosphorylation of signal transducer and activator of transcription 3 at Tyr705 upon stimulation with IL-10 comparable to healthy donors (Figure 4D and Supplementary Figure 4A). In addition, we could detect a

![Graph](image-url)
substantial inhibition of TNF-α secretion in LPS/IL-10−co stimulated PBMCs from transplanted patients (Figure 4E, F and Supplementary Figure 4B). Taken together, the clinical data and functional studies suggest reconstitution of the IL-10R−mediated signal transduction in IL-10R−deficient patients after allogeneic HSCT.

Discussion

We here provide a systematic study on the genetic etiology and a tailored therapy approach using allogeneic HSCT in children with IL-10R deficiency. Analyzing 66 early onset IBD patients, we identified 16 patients with loss-of-function mutations in IL10 or IL10R genes. A variety of mutations were discovered. Most patients were born to consanguineous parents and had homozygous biallelic mutations (point mutations or deletions). However, some patients also presented with compound heterozygous mutations.

Clinically, all patients with documented IL-10 or IL-10R deficiency presented in their first 3 months of life. However, our results do not exclude that patients with first presentation of symptoms later during infancy or early childhood may have defects in the IL-10−mediated signaling. Our study suggests that patients with clinical history of severe refractory course of infantile IBD should be genotyped for mutations in IL10 and IL10R genes. We could not observe clear genotype–phenotype correlations in our cohort of IL10- and IL10R−deficient patients. For example, patient 1 and patient 2 (siblings sharing the same homozygous IL10RB mutation) had a remarkably distinct level of disease severity, suggesting that the phenotypic manifestation is dependent on other intrinsic or extrinsic factors that remain presently unknown.

Very-early-onset IBD represents a rare variant within the pediatric IBD population. In a prospective European registry including 2054 unslected newly diagnosed pediatric IBD patients (EuroKids19), only 21 (1%) of 2022 informative patients manifested their bowel disease during infancy and, of those, only 5 (0.25%) within the first 3 months of life (de Bie CL & Escher JC, personal communication). Our cohort of 66 patients is prone to bias with respect to ethnic background and predominance of genetic factors in the pathogenesis of IBD. Nevertheless, mutations in IL-10−related genes were only discovered in approximately one third of the patients with onset in the first year of life, indicating that infantile IBD is heterogeneous. Other monogenic conditions associated with IBD must be taken into consideration. For example, mutations in XIAP20,21 NCF1 (p47-phox),22 and PIK3R123 can present with early onset IBD. We expect that additional monogenic defects contributing to the pathogenesis of early-onset IBD will be discovered in the near future.

Current therapeutic strategies for pediatric IBD include the use of exclusive enteral nutrition, corticosteroids, mesalazine, sulfasalazine, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and anti−TNF-α antibodies.24 Knowledge of the underlying genetic etiol-
Figure 4. Clinical phenotype and reconstitution of the IL-10–mediated signal transduction in IL-10–deficient patients after allogeneic HSCT. (A) Representative colonoscopy of patient 4 demonstrates normal intestinal mucosa without evidence of inflammatory processes 13 months after HSCT. (B, C) Histopathological examination of colon biopsies after 13 months of HSCT revealed almost complete reduction of glandular distortion and an inconspicuous, sparse leukocytic infiltration within the lamina propria mucosa. (D) Representative Western blot analysis of signal transducer and activator of transcription 3 phosphorylation at Tyr705 residue demonstrating reconstitution of IL-10R–mediated signal transduction in patient 4 following 1 year of HSCT. (E) Representative enzyme-linked immunosorbent assay showing substantial inhibition of TNF-α secretion in LPS-stimulated PBMCs upon costimulation with IL-10 in patient 4 after 1 year of HSCT. Healthy donor, black bars; patient, gray bars. (F) Grouped column scatter graph showing reconstituted inhibition of TNF-α secretion in PBMCs from the cohort of transplanted IL-10R–deficient patients upon stimulation with LPS and IL-10.

In summary, our study highlights that IL-10 and IL-10R deficiencies represent a defined subgroup of pediatric IBD patients, manifesting within the first 3 months of life. This condition is characterized by a severe and progressive course of colitis associated with perianal disease and variable extraintestinal manifestations, such as folliculitis and arthritis. We conclude that infantile IBD pa-
tients with perianal disease should be genotyped for mutations in IL10 and IL10R genes. Furthermore, our results suggest that allogeneic HSCT can induce sustained remission of IL-10R deficiency without undue toxicities or severe GVHD.

### Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at http://dx.doi.org/10.1053/j.gastro.2012.04.045.

### References


Received November 11, 2011. Accepted April 18, 2012.

Reprint requests
Address requests for reprints to: Christoph Klein, MD, PhD, University Children’s Hospital Münich, Dr von Hauner Children’s Hospital, Ludwig Maximilian University Munich, Lindwurmstr 4, D-80337 Munich, Germany. e-mail: christoph.klein@med.uni-muenchen.de; fax: +49-(0)89-5160-7702.

Acknowledgments
We gratefully acknowledge all members of the interdisciplinary clinical and scientific teams, in particular P. Bufler, MD, M. Szczepanski, MD, S. Bielack, MD, C. L. de Bie, MD, J. C. Escher, MD and N. Waespe, MD. Further, we thank R. Adam, MD, M. Baran, MD, A. Daukszewicz, MD, S. Kolaček, MD, A. Krahl, MD, L. W. Seah, MD, and R. Shaoul, MD for providing us with clinical information on early onset IBD patients without IL-10 or IL-10R deficiency. Chimerism data were generated by Wolfgang Kühnau at the Institute of Human Genetics from Hannover Medical School, Germany (Head: Prof. Dr. med. J. Schmidtke).

Drs Kotlarz, Beier, and Murugan contributed equally to this work and should be considered aequo loco.

Conflicts of interest
The authors disclose no conflicts.

Funding
The study was supported by grants from DFG (SFB621, Gottfried-Wilhelm-Leibniz Program), the Deutsche José Carreras Leukämie-Stiftung e. V. (fellowship to Dr. Kotlarz), the BMBF (E-RARE), and the Care-for-Rare Foundation.