Inherited Susceptibility to Acute Pyelonephritis: A Family Study of Urinary Tract Infection

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Background. Urinary tract infections (UTIs) are important causes of morbidity and death. The present study investigated whether genetic factors influence susceptibility to acute pyelonephritis (APN). CXCR1 expression was investigated as a factor predisposing to APN, because low CXCR1 expression has been associated with disease susceptibility in mice and disease-prone children.

Methods. The families of APN-prone children (n = 130) and of age-matched control subjects without UTI (n = 101) were studied. Three-generation pedigrees of UTI-associated morbidity were established by means of structured interviews of the families. CXCR1 expression was quantified by flow cytometric analysis of peripheral blood neutrophils obtained from family members and control subjects.

Results. APN was significantly more common in the family members of the APN-prone children (20 [15%] of 130 family members) than in the relatives of the control subjects (3 [3%] of 101 family members) (P < .002). Acute cystitis, in contrast, occurred with equal frequency in both groups (19%; P = 1.0). Some families included many affected individuals, consistent with a dominant pattern of inheritance, whereas other families showed a recessive pattern of disease susceptibility. CXCR1 expression was significantly lower in the APN-prone children and in their relatives than in pediatric and adult control subjects (P < .0001).

Conclusions. Our results suggest that susceptibility to APN is inherited and that low CXCR1 expression might predispose to disease.

The large intraindividual differences in the frequency and severity of urinary tract infection (UTI) are consistent with a genetic predisposition among disease-prone individuals, but inherited defects in the defense against UTI have not been identified. Structural defects and social and environmental factors influence disease susceptibility [1, 2], and we, as well as other investigators, have shown that an intact innate immune system is required for a functional defense against UTI [3–6]. In an attempt to characterize the critical mechanisms and gene(s), we have studied “knockout” mice and have shown that innate immune-response genes strongly influence susceptibility to UTI and, especially, acute pyelonephritis (APN) [7–9]. Specific immunity and Mendelian immunodeficiencies, in contrast, do not appear to predispose to UTI, and attempts to associate the HLA antigen type with UTI have failed [10]. The experimental studies suggested that susceptibility to clinical APN is genetically controlled and that disease might vary with the expression of specific, innate, host response molecules.

The contribution of genetics to infections of the lower urinary tract (hereafter known as “lower UTIs”) has been discussed elsewhere [11, 12], because such infections appear to be clustered in certain families. Hopkins et al. [13] found evidence of a familial predisposition to recurrent lower UTI in female family members. However, because control families were not included in the study, there was no accounting for the frequency of sporadic cases of UTI among relatives. Such controls are necessary, because sporadic infections in the grandmother, mother, and daughter may occur without necessarily involving genetics. Factors predis-
posing to lower UTI were investigated in a large, population-based study [14], and a high frequency of cystitis was detected in female relatives, suggesting an element of predisposition. In a separate study, relatives of patients with APN were shown to have a history of UTI, but the type of infection was not specified [15]. Stauffer et al. [16] found that 42% of girls with recurrent UTI had a positive family history, compared with 11% of control subjects. Like Scholes et al. [14, 15], they emphasized a combination of family history, sexual practices, and behavioral factors as a cause of UTI susceptibility. Genetic factors predisposing to UTI were not examined, except in a study of patients with early rheumatoid arthritis, in whom lower UTI was associated with tumor necrosis factor, lymphotoxin-α, and Fcγ receptor A polymorphisms and in whom there was a strong correlation between nonsevere UTIs and the number of risk alleles [17].

We studied the molecular basis of resistance in a murine UTI model and identified genes that control the innate immune response [7, 9]. Remarkably, mice lacking the murine interleukin (IL)-8 receptor homologue (mIL-8Rh) developed APN with bacteremia and renal scarring, whereas mice with an intact mIL-8Rh gene were resistant to infection [8, 9, 18]. The susceptibility in the knockout mice was caused by a neutrophil activation defect, and the tissue pathologic finding was caused by subepithelial neutrophil entrapment resulting from impaired transepithelial migration [19]. In recent clinical studies, we found significantly reduced expression of the human IL-8 receptor CXCR1 among APN-prone children, compared with age-matched control subjects without UTI [9]. CXCR2 expression did not vary with APN susceptibility, however, suggesting that the reduction in chemokine receptor function is specific for CXCR1 [9]. Heterozygous IL-8 receptor (CXCR1) polymorphisms were found in 38% of those children, compared with 4% of control subjects (A.–C.L., S. McCarthy, M. Gustafsson, G. Godaly, U. Jodal, D.K., I.L., C. Lindén, J. Martinell, B.R., M. Samuelsson, L. Truedsson, B.A., C.S., unpublished data), suggesting that inherited genetic variants may predispose to infection. The present study investigated whether susceptibility to APN might be inherited and also examined whether disease susceptibility is related to the level of CXCR1 expression.

**MATERIALS AND METHODS**

**Subjects.** The study enrolled 10 children with a history of APN and recurrent UTI, as well as their families. Four patients (in pedigrees A, C, E, and I in figure 1A) had recurrent episodes of APN, and 4 had an initial episode of APN, followed by episodes of acute cystitis (pedigrees G, H and J in figure 1A) or asymptomatic bacteriuria (pedigree F in figure 1A). Two children had a single episode of APN without a recurrence (pedigrees B and D in figure 1A). Most (9 of 10) of the children were girls, because recurrent UTI predominantly occurs in females; however, 1 boy was included in the study. The patients had been monitored for several years at the pediatric nephrology unit at Lund University Hospital (Lund, Sweden). The patients were <1 to 5 years of age (median age, 2.25 years) at the time of the first infection and were 1–12 years of age (median age, 6.5 years) at the time of the study. 99mTc-dimercapto-succinic acid scintigraphy (DMSA) revealed that all of the children had renal polar uptake defects typical of previous APN and that 7 children had renal scars. All of the children were investigated by means of voiding cystourethrography, which showed that 6 children had reflux.

Age-matched children without a history of UTI, as well as their families, were enrolled as control subjects. The 15 control children (7 boys and 8 girls) attended the pediatric outpatient clinic or had been admitted for elective surgery. They were <1 to 11 years of age (median age, 5 years) at the time of the study. Females living in the same geographic area were enrolled as adult control subjects. The women did not have a history of APN or episodes of acute cystitis requiring treatment, but an occasional acute cystitis episode could not be excluded. The study was approved by the medical ethics committee of Lund University, and informed consent was obtained from the patients, the control subjects, and/or their parents, as well as from their family members.

**Family study design.** The families of the patients and control subjects were contacted, and a questionnaire was distributed by mail. Questions concerning the history of UTI, the age at first infection, the recurrence rate, and the symptoms noted, including fever. Furthermore, the questionnaire addressed whether antibiotic treatment had been used, whether the patients had been hospitalized, and whether they had undergone radiological examinations. The research nurse then contacted the families and obtained replies to the questionnaire by use of a standardized protocol.

**Diagnostic criteria.** Significant bacteriuria was defined by growth of a single strain (>10^5 cfu/mL) in a midstream urine sample or by any growth noted in a suprapubic bladder aspirate. In the index case patients, pyelonephritis was defined by a febrile infection (temperature, ≥38.5°C) with significant bacteriuria, a C-reactive protein level >20 g/L, and a lack of symptoms associated with other infections. Asymptomatic bacteriuria was defined by >10^3 cfu/mL in 3 consecutive urine samples obtained from an asymptomatic individual. Acute cystitis was defined by symptoms associated with lower UTI (e.g., dysuria and frequency) and a temperature <38.0°C.

The history of UTI in the family members was obtained by interview. APN was defined as a febrile UTI episode with general malaise, and patients had either been hospitalized or recalled receiving antibiotics. Some individuals also had flank pain. Acute cystitis was defined as an episode of UTI with frequent voiding, dysuria, and either low-grade or no fever, and
some individuals had hematuria. Recurrent UTI was defined as ≥1 episode of UTI. Medical records were not available.

**Blood samples.** Heparinized blood was obtained from patients during an infection-free interval, as well as from 49 of 130 of their family members, in connection with the interviews. Samples were also obtained from the age-matched control subjects and from 46 adult females from the same geographic area who had no history of UTI.

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**Figure 1.** Pedigrees showing the history of acute pyelonephritis (APN; red symbols), acute cystitis (gray symbols) or other urinary tract infection (UTI)–associated morbidity. Roman numerals denote the generations. A, Children with APN. B, Age-matched control subjects without UTI. The index child in families A, C, D–F, and I had reflux. Roman numerals denote generations. Arrows denote the index child in each family. n.i., no information was available. *Post partum.
**CXCR1 receptor expression.** Polymorphonuclear granulocytes were purified on a Polymorphprep density gradient (Axis-Shield PoC AS). The samples contained $>97\%$ neutrophils (as determined by Wright's Giemsa stain) with $98\%$ viability (as determined by trypan blue exclusion). CXCR1 surface expression was quantified by flow cytometry performed with the use of fluorescein isothiocyanate (FITC)–conjugated mouse IgG1 as a negative control. Instrumental settings were calibrated using Flow-Set FITC-conjugated plastic beads (Coulter). The receptor expression of each individual was related to an adult standard run at the same time [9], and values were expressed as the percentage of the standard.

**Statistical analysis.** Data were analyzed using GraphPad Instat 3 software for Macintosh (version 3.0b; GraphPad Software). A 2-tailed Fisher's exact test was used to compare UTI frequencies. The Mann-Whitney U test (2-tailed) and the Kruskal-Wallis test (a nonparametric analysis of variance [ANOVA]) were used to examine levels of CXCR1 expression.

**RESULTS**

For APN-prone patients, pedigrees showing the history of UTI or other urinary tract–associated morbidity are shown in figure 1A. Information was obtained for 130 relatives of the APN-prone children, representing 3 generations; 122 individuals were alive, and 100 were interviewed. A close relative provided information for 22 living and 8 deceased family members. For the control families, information was obtained from 101 individuals representing 3 generations; 100 individuals were alive, and 92 were interviewed (see pedigrees in figure 1B). A close relative provided information for 8 living and 1 deceased relative. Seven relatives of the control children either could not be reached or declined to participate. The case-selection criteria did not involve knowledge of family history.

**Difference in APN-associated morbidity between patient and control families.** There was a marked difference in APN-associated morbidity between relatives of the APN-prone patients and relatives of the control subjects (20 [15\%] of 130 relatives vs. 3 [3\%] of 101 relatives; $P<.002$ (table 1)). There was $\geq 1$ relative with APN in 9 of 10 families of the APN-prone children, compared with 3 of 15 families of control subjects. The number of individuals with recurrent UTI was also higher in the APN-prone families (26 [20\%] of 130 relatives) than in the control families (10 [10\%] of 101 relatives). In contrast, between families of APN-prone and control children, there was no difference in acute cystitis–associated morbidity (19\% [not significant [NS]]) (table 1), and because of the high frequency of cystitis in the control subjects, there was no difference in overall UTI-associated morbidity between the families of the APN-prone children (36 [28\%] of 130 relatives) and the families of the control subjects (21 [21\%] of 101 relatives). The UTI episodes in the control families were mainly restricted to women, with $\sim$15\% of episodes related to pregnancy.

To avoid sex bias resulting from the selection of the control subjects, the frequency of APN was compared between the families of the female patients and pediatric control subjects. The difference in APN-associated morbidity remained highly significant ($P<.03$) (table 1). The number of men with APN was too small for a similar analysis to be conducted. The first episode of APN occurred before 5 years of age in 22\% of the relatives, between 6 and 15 years of age in 17\%, between 16 and 20 years of age in 28\%, and after 21 years of age in 33\% of the relatives. There was no evidence of clustering of cases of APN in the families. The frequency of cases of APN was 15\% (5 of 34 relatives) among relatives of children without reflux and 20\% (15 of 75 relatives) among relatives of children with reflux ($P>.05$).

**Complex urinary tract disease.** Renal stones (in families C and G), renal cancer (in family G), prostate cancer (in family E), and prostate hyperplasia (in family B) were more common in the APN-prone families than in the control families, when all of those conditions were evaluated as a group ($P<.02$). An association between childhood UTI and the development of renal stones in adult life has been proposed [20], but the males with renal stones in the present study had no known history of UTI. The related males in family E all had prostate cancer, but APN was restricted to the females.

**APN in men and women.** All forms of UTI were more common among females than males ($P<.0001$) (table 2). The difference in APN-associated morbidity between the APN-prone and control families remained highly significant when men and women were analyzed separately (table 3). Half of the women in the APN-prone families had a history of UTI (31 [50\%] of 62 women), and 15 (24\%) of 62 women had a history of APN. In the control families, 20 (37\% [NS]) of 54 women had a history of UTI-associated morbidity, and 3 (6%;

**Table 1. History of urinary tract infection (UTI) in relatives of acute pyelonephritis (APN)–prone children and control subjects.**

<table>
<thead>
<tr>
<th>Relatives, UTI</th>
<th>Of children with APN</th>
<th>Of control subjects</th>
<th>$P^{a}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n = 130$)</td>
<td>($n = 101$)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>36 (28)</td>
<td>21 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>APN</td>
<td>20$^{b}$ (15)</td>
<td>3$^{c}$ (3)</td>
<td>$&lt;.002$</td>
</tr>
<tr>
<td>Cystitis</td>
<td>25$^{b}$ (19)</td>
<td>19$^{a}$ (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Females</td>
<td>31 (24)</td>
<td>20 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>APN</td>
<td>15 (12)</td>
<td>3 (3)</td>
<td>$&lt;.03$</td>
</tr>
<tr>
<td>Cystitis</td>
<td>25 (19)</td>
<td>18 (18)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** NS, not significant.

$\text{a}$ Two-tailed (Fisher's exact test).

$\text{b}$ Nine family members had both APN and cystitis.

$\text{c}$ One family member had both APN and cystitis.
P < .01) of 54 women had a history of APN (P < .01 [NS]). UTI-associated morbidity was also high among the men in the APN-prone families (5 [7%] of 68 men), compared with that among men in the control families (1 [2%] of 47 men) (NS).  

Pattern of inheritance. The pedigrees suggested that >1 gene may be involved in the inheritance of UTI susceptibility, but that the transmission in each family may be restricted to 1 gene. Susceptibility was transmitted vertically, on both the maternal and paternal side of the families, and, in some cases, both sides of the family appeared to be involved. Family A had an extensive history of disease, beginning with the great-grandmother and affecting 8 females and 1 male in the main lineage. APN occurred in 23% of the children in generation II but in none of the children in generation I, possibly because all individuals were males, in whom the penetrance of UTI is low. The transmission pattern suggested that the predisposition could be a dominant trait with a female-associated penetrance. The inheritance of APN showed similar, seemingly dominant patterns in families B and C, but here the transmission of inheritance was observed in both females and males (B III2 and C3, I4). Inheritance was observed in both females and males (B III2 and C3, I4).

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CXCR1 receptor expression. CXCR1 receptor expression was quantified by flow cytometric analysis of neutrophils isolated from peripheral blood (figure 2). Samples were obtained from each index case patient and from 49 relatives. Control samples were obtained from 14 age-matched control children, and CXCR1 expression among adults in the background population was determined by analysis of neutrophils from 46 adult female control subjects.

CXCR1 expression was significantly lower in the patients and their family members, compared with the pediatric or adult control subjects (P < .0001, by ANOVA) (figure 2A and table 4). For the female relatives of the APN-prone children, mean expression (denoted as the percentage of a standard) was 84% (range, 45%–166%), whereas, for female adult control subjects, mean expression was 98% (range, 23%–168%) (P = .0153). Among the girls with APN (n = 9), mean CXCR1 expression was 73% (range, 42%–96%), whereas, for girls who were control subjects (n = 8), mean expression was 96% (range, 77%–165%) (P = .0149, 2-tailed Mann-Whitney U test).

The difference in levels of CXCR1 expression is illustrated in figure 2B for the patient and control who had the median CXCR1 expression values in their respective group. Most of the family members (47%) had CXCR1 expression levels that were <80% of the control standard, and 80% had levels lower

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**Table 2. Urinary tract infection (UTI) in female and male relatives.**

<table>
<thead>
<tr>
<th>Family, UTI</th>
<th>Relatives with a history of UTI, no. (%)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Male</td>
</tr>
<tr>
<td>APN prone</td>
<td>n = 62</td>
<td>n = 68</td>
</tr>
<tr>
<td>APN</td>
<td>31 (50)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>25 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Control</td>
<td>n = 54</td>
<td>n = 47</td>
</tr>
<tr>
<td>APN</td>
<td>3 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>18 (33)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

**NOTE.** APN, acute pyelonephritis; NS, not significant.

<sup>a</sup> Nine females in the APN-prone families and 1 female in the control families had both APN and cystitis.

<sup>b</sup> Two-sided (Fisher’s exact test).

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**Table 3. History of urinary tract infection (UTI) in relation to sex.**

<table>
<thead>
<tr>
<th>Sex of relative, UTI</th>
<th>Of children with APN (n = 130)</th>
<th>Of control subjects (n = 101)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>n = 62</td>
<td>n = 54</td>
<td></td>
</tr>
<tr>
<td>APN</td>
<td>15 (24)</td>
<td>3 (6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cystitis</td>
<td>25 (40)</td>
<td>18 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>31 (50)</td>
<td>20 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>n = 68</td>
<td>n = 47</td>
<td></td>
</tr>
<tr>
<td>APN</td>
<td>5 (7)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Cystitis</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>5 (7)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** APN, acute pyelonephritis; NS, not significant.

<sup>a</sup> Two-tailed (Fisher’s exact test).
than the control standard (figure 2C). There was no difference in CXCR1 expression related to their history of UTI, however. The family members with a history of APN had a median CXCR1 expression level (denoted as a percentage of a standard) of 79% (range, 42%–166%), whereas family members with a history of acute cystitis had a median expression level of 90% (range, 56%–109%), and those without a UTI had a median expression level of 76% (range, 45%–163%) (NS). There was no difference in CXCR1 expression between females and males (NS) (figure 2D) or between the families of children with or without reflux (data not shown).

**DISCUSSION**

The present study investigated whether the susceptibility to UTI is influenced by genetic factors, by use of a family study protocol. The results strongly indicate that susceptibility to APN is inherited. There was marked familial clustering of cases of APN among the relatives of APN-prone children, and the frequency of APN was remarkably high in those families, compared with the control families and with reported frequencies [1, 21]. There was no general increase in UTI-associated morbidity, however, because acute cystitis occurred with similar frequency in both the APN-prone and control families. Analysis of the pedigrees showed that susceptibility was inherited from both the paternal and maternal sides of the family, and that although disease penetrance was higher in women, frequency of APN was also increased in male family members. This is the first evidence that susceptibility to APN may be inherited.

The present study selected children with a history of APN as index case patients and also investigated their families [9] (A.-C.L., S. McCarthy, M. Gustafsson, G. Godaly, U. Jodal, D.K., I.L., C. Lindén, J. Martinell, B.R., M. Samuelsson, L. Truédsson, B.A., C.S., unpublished data). The family histories of patients and control subjects were obtained by means of structured interviews that included several generations in each family. Of importance, the control subjects were carefully age matched, and a history of UTI was excluded by interviews and through review of medical records. This selection method was chosen to identify the susceptible individuals and their families with high accuracy. If susceptibility were inherited, the relatives of susceptible individuals would be expected to have APN more often than the relatives of children without such susceptibility.

**Figure 2.** Levels of CXCR1 expression. A, Acute pyelonephritis (APN)–prone children and their relatives, compared with pediatric and adult control subjects. B, Flow cytometric curve showing the median CXCR1 expression values in respective groups. The patient (white peak), the control subject (black peak), and the negative antibody (gray peak). C, Letters A–J denote family designations, as shown in the pedigrees. Index case patients are denoted by an asterisk. Red symbols denote individuals with APN, gray symbols denote those with acute cystitis, and blue symbols denote those with urinary tract infection. D, Relatives of the APN-prone children. Males (blue symbols) were compared with females (pink symbols).
This was indeed the case, among both male and female family members. However, in contrast to previous investigators, we did not find an increase in susceptibility to cystitis among the relatives of APN-prone children. The results thus suggest that different risk factors might influence susceptibility to APN and acute cystitis. Mechanistic studies in the murine UTI model have suggested that antibacterial peptides play an important role in the bladder mucosa [6, 22, 23], whereas neutrophils are essential for clearance of bacteria from the renal tissue [4, 5, 8]. The genetic element might be stronger in APN, which is the most severe and least frequent form of UTI.

It is clear from our results that susceptibility to APN is inherited in the families of patients. Several individuals in >1 generation had APN, and this was not the case in the control families. Some APN-prone families contained few affected individuals and possible contributions from different branches of the pedigree, whereas others showed a higher frequency of affected individuals. The latter finding is more consistent with a dominant pattern of inheritance, whereas the former finding suggests a recessive pattern. The large proportion of affected individuals in some of these families indicates that a small number of genes, possibly even only one, may be involved in each family. The penetrance of UTI is further influenced by social and environmental factors and by the virulence of the Escherichia coli strains that infect each host, and those variables add complexity to the genetic analysis. Still, future studies might make it possible to identify relevant genes in addition to CXCR1, as well as the genetic variants associated with susceptibility to APN, and to better understand the host defense mechanisms that are influenced by genetic variation.

Several studies have suggested that uropathogenic E. coli (UPEC) strains can be transmitted to susceptible children either from the neonatal ward or from family members [24, 25]; however, this was not investigated in the present study. The patterns of infection did not suggest that the acquisition of a specific UPEC strain was the cause of outbreaks of APN in the disease-prone families, because the APN episodes often were separated in time by several years. This does not exclude the possibility that infection-prone family members may have an increased tendency for intestinal carriage of UPEC strains, which might add to the penetrance of infection among susceptible family members. Furthermore, severe reflux is a risk factor that predisposes to APN by facilitating bacterial ascent into the kidneys [26, 27]. However, the role of reflux in APN has been debated, because the majority of children who develop renal scars after APN do not have dilations or reflux [27–30]. Six of the index children in this study and 1 brother with APN had reflux, but information on the inheritance of reflux could not be generated, because family members without APN do not undergo reflux investigations.

CXCR1 expression levels were investigated, on the basis of data from the animal model and a clinical pilot study [9]. The family members had reduced CXCR1 expression levels, but low CXCR1 expression was not restricted to the family members with a history of APN, and the levels were not directly linked to disease susceptibility. This was expected in view of the many factors that influence the pathogenesis of APN and the variable disease penetrance among susceptible individuals. We propose that low CXCR1 expression is inherited and is one of the factors predisposing to APN. To our knowledge, this is the first attempt to associate susceptibility to APN with an identified host defense gene, on the basis of the assumption that the attenuation of the encoded phenotype would be detrimental for the host.

There is a great, unmet clinical need to identify children at risk for recurrent APN and renal scarring. Current risk assessment involves renal imaging with DMSA scans and detection of mechanical defects and reflux, but parameters that quantify the antibacterial defense are not in use. Such methods might make it possible to identify those children who need more-intense follow-up and therapy to avoid renal scarring and other effects of recurrent APN. CXCR1 expression might be quantified when children present with their first episode of febrile UTI, but when relevant genes and mutations have been identified, genotyping methodology might prove to be more efficient. Similar approaches have been used—for example, in children with a suspected diagnosis of cystic fibrosis, for which multiple mutations may cause the dysfunctional phenotype [31]. So far, CXCR1 polymorphisms have been detected in ~38% of children with low CXCR1 expression and APN (A.-C.L., S. McCarthy, M. Gustafsson, G. Godaly, U. Jodal, D.K., I.L., C. Lindén, J. Martinell, B.R., M. Samuelsson, L. Truedsson, B.A., C.S., unpublished data), but it is not clear whether these polymorphisms are responsible for the low CXCR1 expression.

### Table 4. Reduced CXCR1 expression levels in patients and their relatives.

<table>
<thead>
<tr>
<th>Group</th>
<th>CXCR1 expression, median % (range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index patients</td>
<td>70 (42–96)</td>
<td>.0006</td>
</tr>
<tr>
<td>Pediatric control subjects</td>
<td>100 (77–165)</td>
<td></td>
</tr>
<tr>
<td>Girls with APN</td>
<td>73 (42–96)</td>
<td>.0149</td>
</tr>
<tr>
<td>Female control subjects</td>
<td>96 (77–165)</td>
<td></td>
</tr>
<tr>
<td>Relatives of APN-prone children</td>
<td>80 (45–166)</td>
<td>.0041</td>
</tr>
<tr>
<td>Adult control subjects</td>
<td>98 (23–168)</td>
<td></td>
</tr>
<tr>
<td>Female relatives of APN-prone children</td>
<td>84 (45–166)</td>
<td>.0153</td>
</tr>
<tr>
<td>Female control subjects</td>
<td>98 (23–168)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Test (analysis of variance).

a Individual values are given as the percentage of a standard. Nos. denote the mean fluorescence intensities as determined by flow cytometry.

b Two-tailed Mann-Whitney U test (P < .0001) was used to analyze the differences between 2 groups, and the Kruskal-Wallis test (analysis of variance) was used to analyze the variation between all groups.
and disease susceptibility or whether other mechanisms are involved.

Acknowledgments

We thank the patients, controls, and families for taking part in this study.

References