REVIEW

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Innate immunity and genetic determinants of urinary tract infection susceptibility

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Purpose of review
Urinary tract infections (UTIs) are common, dangerous and interesting. Susceptible individuals experience multiple, often clustered episodes, and in a subset of patients, infections progress to acute pyelonephritis (APN), sometimes accompanied by uro-sepsis. Others develop asymptomatic bacteriuria (ABU). Here, we review the molecular basis for these differences, with the intention to distinguish exaggerated host responses that drive disease from attenuated responses that favour protection and to highlight the genetic basis for these extremes, based on knock-out mice and clinical studies.

Recent findings
The susceptibility to UTI is controlled by specific innate immune signalling and by promoter polymorphisms and transcription factors that modulate the expression of genes controlling these pathways. Gene deletions that disturb innate immune activation either favour asymptomatic bacteriuria or create acute morbidity and disease. Promoter polymorphisms and transcription factor variants affecting those genes are associated with susceptibility in UTI-prone patients.

Summary
It is time to start using genetics in UTI-prone patients, to improve diagnosis and to assess the risk for chronic sequels such as renal malfunction, hypertension, spontaneous abortions, dialysis and transplantation. Furthermore, the majority of UTI patients do not need follow-up, but for lack of molecular markers, they are unnecessarily investigated.

Keywords
genetics, innate immunity, urinary tract infection susceptibility

INTRODUCTION

The susceptibility to infection varies greatly, depending on the pathogen, exposure rate and individual. Genetic predisposition is essential, not just for rare monogenetic disorders but for common infections such as urinary tract infection (UTI), wherein disease-associated genetic variants primarily control the expression of genes involved in the antibacterial defense. Genetic determinants of UTI susceptibility work in concert with social and behavioural risk factors, structural or functional abnormalities, catheters, foreign bodies or surgery, all of which modify the penetrance of susceptibility genes. As the vast majority of UTI-prone patients lack such risk factors, genetic predisposition is a major determinant of UTI morbidity [1,2].

UTI susceptibility runs in families and UTI-prone individuals experience recurrent, often clustered infections with potentially severe complications, depending on the site of infection and type of UTI. In three-generation family pedigrees, an increased frequency of acute pyelonephritis (APN) was detected in both male and female family members of APN-prone children, compared with children without UTI [3]. There was no evidence of increased cystitis morbidity in those families, suggesting that different genetic mechanisms control APN and cystitis susceptibility. Several studies have associated personal and family histories of UTI with an increased risk of acute cystitis, and in one study, 42% of family members were cystitis-prone, compared with 11% of controls. The risk increased

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KEY POINTS

- The urinary tract is defended against UTI by a rapid and efficient innate immune response that clears the infection while maintaining tissue homeostasis.
- Most known UTI-associated genes control the innate immune response to infection and UTI susceptibility is inherited with distinct patterns for APN and acute cystitis.
- UTI susceptibility is controlled by specific innate signalling pathways and by promoter polymorphisms and transcription factors that control the expression of genes in these pathways.
- Innate immune dysregulation alters UTI susceptibility, by enhancing beneficial or destructive aspects of the host defence.
- It is time to start validating genes or gene combinations with optimal predictive power in the different UTI-prone patient groups.

with the number of affected individuals, especially if a sister, mother or daughter had a history of UTI and the influence of behavioural factors was increased [4,5], consistent with a combined effect of genetics and exposure variables.

INNATE IMMUNITY AND MOLECULAR MECHANISMS

Most known UTI-associated genes control the innate immune response to infection [1]. Studies in mice carrying single gene deletions have demonstrated that the loss of specific innate immune functions creates strong phenotypes. Innate immune attenuation results in asymptomatic bacteriuria, while exaggerated, dysregulated responses drive disease ('good' versus 'bad' inflammation).

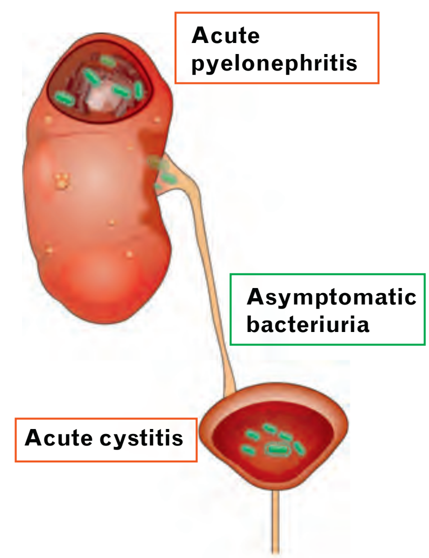
UTIs elicit a rapid innate immune response that has been extensively characterized [1,6,7]. The mucosa provides an efficient protective barrier against bacterial attack, but uropathogenic *Escherichia coli* (UPEC) are equipped to target the surface layer of epithelial cells, through specific adhesive interactions and then engage additional tissue compartments through a variety of toxic perturbations of the mucosa, sometimes followed by invasion [8]. Specific molecular recognition mechanisms determine the flavour of the innate immune response by activating different signalling pathways and effector functions [1,6,7]. For example, P-fimbriated *E. coli,* which account for 70–100% of febrile infections in patients with normal urinary tracts, are recognized by glycosphingolipid receptors [9]. Through the release of ceramide, Toll-like receptor 4 (TLR4) signalling is activated, through the TIR-domain-containing adapter-inducing interferon-β/TRIF-related adapter molecule (TRIF/TRAM) (where TIR is Toll/interleukin-1 receptor) adaptors, mitogen-activated protein kinases (MAPKs) and cAMP response element-binding protein 1 (CREB-1) phosphorylation and transcription factor activation [10,11]. The TRIF/TRAM or MyD88/TIR domain-containing adaptor protein (TIRAP) adaptor proteins that control the two main arms of TLR4 signalling [12] are differentially activated by UPEC, depending on their fimbrial expression profile. FimH may initiate TLR4 signalling through lipopolysaccharide (LPS), activating the MyD88 and TIRAP adaptors [12] and nuclear factor kappa B (NF-κB) transcription through MyD88 and TIRAP [13▪]. Flagella activate TLR5 signalling [14] and numerous additional recognition and signalling mechanisms are being explored [15▪,16▪].

As a result of these interactions, infection activates an innate cascade, allowing antibacterial effector mechanisms to clear infection while maintaining tissue homeostasis [17▪▪]. UPEC alter the expression of more than 1000 genes in human kidney cells, and in genetically competent mice, kidney or bladder infection modifies the expression of at least 500 genes, depending on the bacterial strain. These include well known responses such as chemokines and receptors for inflammatory cells, and cytokines [18,19], inflammasome and acute phase response genes, type I interferon (IFN), growth factors and antibacterial peptides [20▪,21]. In addition, UTIs modify a large number of genes that have not yet been identified as determinants of resistance against infection, predicting that there are new categories of cellular and tissue responses to be explored.

GENETIC CONTROL OF URINARY TRACT INFECTION IN THE MURINE MODEL

Here, we discuss genetic control of innate immunity following the approximate order of activation by UPEC infection (Fig. 1). Gene deletions that prevent innate immune activation favour long-term bacteriuria without inflammation or disease. The early innate immune response to UTI is therefore low or absent in *Tlr4*$^{-/-}$ mice and in C3H/HeJ mice [22,23], carrying an inactivating mutation of the Toll/interleukin-1 receptor (TIR) homology domain of TLR4 [22,24–27]. As the antibacterial effector functions are suppressed, *Tlr4*$^{-/-}$ mice develop a state of asymptomatic bacteriuria (ABU) [28]. Infected *Trif*$^{-/-}$ or *Myd88*$^{-/-}$ mice develop a similar phenotype, with a low innate immune response and prolonged bacterial carriage [29]. Cytokine and neutrophil responses are virtually undetectable

(a)



(b)

APN, sepsis or renal scarring

Genotype	Ref	Genotype	Ref
mCxcr2−/−	[33, 36, 37]	*Camp−/−*	[39]
Irf3−/−	[11]	*Thp−/−*	[45]
Ifnb1−/−	[11]	*Tlr11−/−*	[41]

Asymptomatic bacteriuria

Genotype	Ref	Genotype	Ref
C3H/HeJ *Tlr4* mutant	[23, 26, 28, 30, 33]	*Tram−/−*	[30]
Tlr4−/−	[30]	*Myd88−/−*	[30]
Trif−/−	[30]		

*Bladder infection**

Genotype	Ref	Genotype	Ref
Car2−/−	[42]	*Tlr5−*	[47]
Cox2−/−	[46]		

(c)

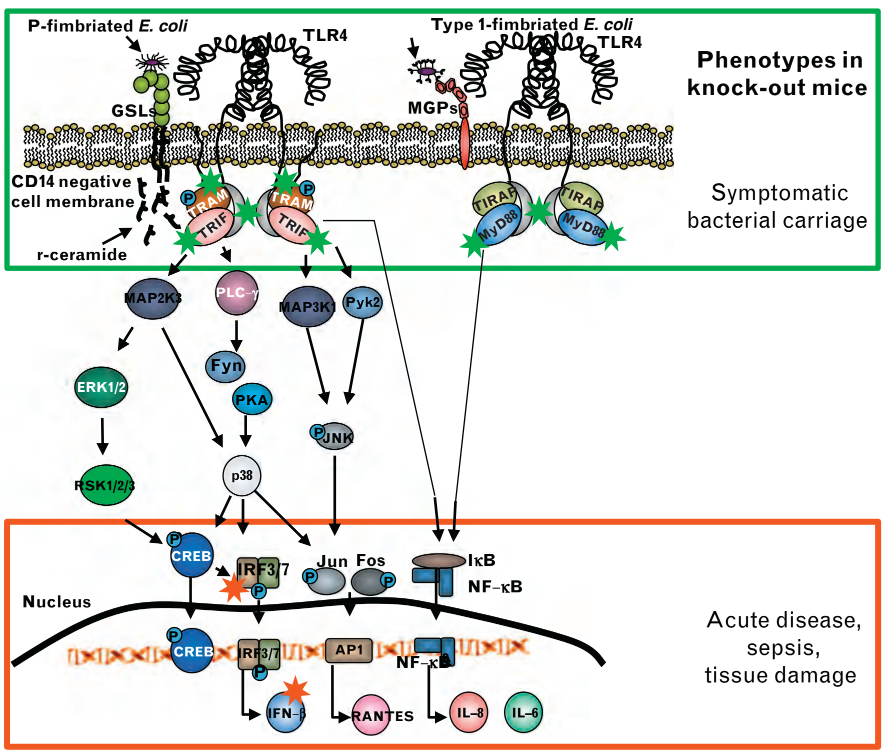


FIGURE 1. Genetic determinants of urinary tract infection susceptibility in the murine and human urinary tract infection model. (a) Infections of the urinary tract give rise to acute pyelonephritis, acute cystitis or asymptomatic bacteriuria. (b) Genetic control at the proximal level of the TLR4 signalling cascade (green) determines whether an innate immune response will be activated by infection. Gene deletions (*Tlr4, MyD88, Trif, Tram*) abrogate response, as well as symptoms and disease, thus protecting the infected host from acute disease and tissue damage. Genetic control at the distal level of the TLR4 signalling cascade (red) determines the efficiency of the antibacterial defense. Gene deletions (*Irf3, Ifnb1*) cause acute pyelonephritis and renal tissue damage. In addition, perturbations of neutrophil recruitment and function drastically increase the susceptibility to APN and renal scarring (*mCxcr2*). (c) Genes associated with UTI susceptibility in the murine UTI model. *IL-1 and inflammasome genes [48].

in *Tlr4*$^{-/-}$ and *Myd88*$^{-/-}$ mice and low in *Trif* mutant mice and there is no evidence of tissue disease in those mice [29,30].

Gene deletions that disturb the effector phase of the innate immune response increase the susceptibility to infection by decreasing the efficiency of bacterial clearance. In addition, an imbalance of transcriptional control may cause exaggerated inflammation, resulting in bladder or kidney disease. Gene deletions driving disease include both transcription factors and specific structural genes [1,2].

Transcription is differentially regulated by virulence factors and signalling pathways. P-fimbriated *E. coli* activates IRF-3 and IRF-7, which regulate type I IFN responses and associated antibacterial effector mechanisms. IRF-3 also works in concert with the AP-1 transcription factor, formed by c-Fos and c-Jun heterodimers, and triggers the acute phase response, neutrophil migration, adhesion and activation [11,17■■]. *Irf3*$^{-/-}$ mice are highly UTI-prone defined by acute and chronic morbidity. APN and urosepsis are followed by massive renal abscess formation, 1 week after infection. Kidneys from *Irf3*$^{-/-}$ and *Ifnb1*$^{-/-}$ mice show an exaggerated, destructive neutrophil infiltrate. A similar phenotype occurs in *Ifnb1*$^{-/-}$ mice, illustrating the importance of IRF-3-dependent transcription, which regulates *Ifnb1* expression and IFN-β dependent genes involved in bacterial clearance [11,31].

The importance of the neutrophil-dependent innate immune response is further highlighted in *mCxcr2*$^{-/-}$ mice. Mice lack CXCL8 [interleukin (IL)-8], but express several chemokine ligands for the murine receptor CXCR2, including CXCL2/3 [macrophage inflammatory protein 2 (MIP 2)], CXCL1 [keratinocyte chemoattractant (KC)] and CXCL5 [epithelial neutrophil activating peptide-78 (ENA-78)]. An *mCxcr2* deletion inactivates neutrophil recruitment virtually completely, and neutrophil activation is reduced [32]. *mCxcr2*$^{-/-}$ mice develop severe APN with urosepsis, and surviving mice remain chronically infected, with signs of kidney disease, resembling renal scarring in humans [32–35] (Fischer *et al.*, in preparation). Long-term studies revealed no alleviation of the damage process by macrophages forming foam cells or specific immune cells, including T-lymphocytes and plasma cells [36].

Antibacterial peptides contribute to UTI resistance, but in contrast to humans, only one cathelicidin is expressed in the murine urinary tract [37]. *Camp*$^{-/-}$ mice, deficient for the cathelin-related antimicrobial peptide (CRAMP), show elevated bacterial numbers [38], increased sepsis-associated mortality and elevated kidney size compared with wild-type mice [37,39]. In mice, TLR11 is strongly expressed in the kidneys and influences renal infection in the murine UTI model. Kidneys from *Tlr11*$^{-/-}$ mice are massively infected compared with wild-type mice, with defective neutrophil infiltration [40]. Carbonic anhydrase 2 deficient mice have metabolic acidosis, impaired urine acidification and decreased renal bacterial clearance. *Car2*$^{-/-}$ mice had increased baseline neutrophil-gelatinase-associated lipocalin mRNA and protein but a decreased response to infection [41■■].

Additional genes have been suggested to affect UTI susceptibility especially in the urinary bladder, but their importance for acute cystitis pathogenesis remains unclear. Tamm–Horsfall protein (THP) or uromodulin acts as a receptor for type 1 fimbriae on the bladder mucosa [42,43], but *Thp*$^{-/-}$ mice showed higher bacterial numbers in the bladders [44] with no effect on kidney infection [44]. *Thp* mRNA expression was reduced in *Cox2*$^{-/-}$, cyclooxygenase-2 deficient mice, which showed increased susceptibility to type 1 fimbriated *E. coli* [45]. TLR5 is expressed in the urinary tract mucosa and *Tlr5*$^{-/-}$ mice show a gradual increase in bacterial numbers in the bladder, with superficial bacterial micro-abscesses in parallel with submucosal oedema [46]. Recently, a mechanistic and genetic basis for acute cystitis susceptibility was proposed, involving the activation of IL-1β and downstream genes, dysregulation of the inflammasome and activation of cytotoxic enzymatic pathways [47].

GENETICS OF HUMAN URINARY TRACT INFECTION SUSCEPTIBILITY

Clinical studies clearly distinguish genetic repertoires of patients prone to APN from those who preferentially develop ABU, consistent with the dichotomy of genetic control in the murine UTI model (Fig. 1 and Table 1) [48–55].

It may seem counterintuitively that low TLR4 expression reduces the risk for symptomatic infection, but TLR4 expression is lower in children with ABU than in age-matched controls or APN patients [48]. The *TLR4* promoter is highly polymorphic and *TLR4* promoter genotypes with reduced function are common in children with ABU [49]. In contrast, structural *TLR4* gene polymorphisms are relatively rare [56] and their functional contribution to human disease susceptibility remains unclear. In association studies, Hawn *et al.* [50] suggested that TLR4 Asp299Gly protected from recurrent cystitis in adults, but this was not seen in children. They also associated *TLR5* +1174C/T with cystitis risk and *TLR1* +1805G/T with protection from pyelonephritis [50]. The *TLR4* +896 G allele had a higher

Table 1. Genetic determinants of human urinary tract infection susceptibility

Genetic variants	Function	References
Asymptomatic bacteriuria		
	Reduced TLR4 expression.	[48]
TLR4; (−2570A>G, −2081G>A, −2016A>G, genotype pattern VII, X, XX; 896A>G, 1196C>T)	Reduced promoter activity, low TLR4 expression, PMN number and cytokine response to infection	[49]
TLR1; (1805G>T)	NA	[50]
TLR2, (2258G>A)	NA	[50,51]
CXCR1; (92T>G, 1003C>T, 11069A>G)	NA	[50]
CXCR2; (768C>T, 136339T>C)	NA	[50]
Acute pyelonephritis		
	Low CXCR1 expression	[33]
CXCR1; (217G>C, 3081C>T, 3082G>A, 3665G>A, 2608G>C)	Reduced promoter activity, increased 3′-mRNA processing,	[52]
CXCL8; (−251A>T, 2767A>G)	NA	[53]
IRF3; (−925A>A, −776C>C)	Reduced promoter activity	[11]
CCL5 (RANTES); (−403G>A)	NA	[54]
	No reduction in TLR4 expression	[48]
TLR4; (−2604G>A, −2570A>G,−2081G>A)		[49]
VEGF; (−1154G>A)	Activating variant	[55]

Genes predicted to affect the susceptibility to ABU or APN susceptibility, through effects on the innate immune response. Early clinical studies identifying changes in protein expression levels (TLR4 and CXCR1) are indicated. Identified genetic variants affecting gene expression and with functional effects validated in reporter assays are shown and gene associations without functional data are listed, separately. For further detail, see Ragnarsdottir *et al.* [1].

prevalence in UTI patients and *TLR4* expression in monocytes was significantly lower in chronic cystitis patients than in controls. In addition, patients carrying the TLR2 Arg753Gln allele had a higher risk of UTI with gram-positive pathogens [51].

Consistent with the APN phenotype in $Irf3^{-/-}$ mice, polymorphisms affecting transcription factor expression have also been associated with susceptibility in APN-prone patients. *IRF3* promoter polymorphisms -925A/G and -776C/T are strongly associated with human APN susceptibility, occurring in about 70% of APN-prone patients [11]. This association was confirmed in two separate, APN-prone populations. The minor allele frequency was decreased in APN compared with primary ABU and paediatric controls [11]. APN-prone children have also reduced *CXCR1* expression levels compared with paediatric controls and reduced CXCR1 expression was detected in family members of the APN-prone children [52]. Sequencing revealed two heterozygous polymorphisms and three unique mutations in 32% of the patients compared with 8% of controls, which were predicted to reduce CXCR1 expression. The frequency of disease-associated *CXCR1* polymorphisms was 54%, when reflux was excluded.

In association studies, a *CXCR1* polymorphism +2608G/C and *CXCL8* (*IL8*) gene polymorphisms −251A/T and +2767A/G were not APN associated [53], but the −251 TT *CXCL8* genotype was significantly more frequent in children with dimercaptosuccinic acid (DMSA) scan negative APN. *CCL2* (MCP-1) and *CCL5* regulated on activation, normal T cell expressed and secreted (RANTES)] polymorphisms and their receptors, *CCR2* and *CCR5*, have been investigated and the *CCL5* −403 G allele was significantly associated with UTI risk [54]. Finally, *SELE* (E-selectin), *ICAM1*, *PECAM1* and ITGAM (CD11b) polymorphisms were investigated. The *ICAM1* exon 4(G/A) polymorphism was less common in patients who developed renal scars than in controls, possibly as a result of reduced leucocyte infiltration and tissue damage [57]. The functional importance of those associations remains to be defined.

VEGFA and *TGFB1* polymorphisms predispose to progressive renal disease [55,58,59]. The *VEGFA* -460T/C polymorphism and *TGFB1* −800G/A and −509C/T polymorphisms are associated with UTI and vesicoureteral reflux (VUR) in children [59] and the *VEGFA* −460C allele increased basal promoter activity by 71% compared with the wild-type sequence [60]. The *TGFB1* +869 CC genotype was more common in patients with renal scarring [61]. In a meta-analysis, the *ACE* I/D and T allele of *TGFB1* -509C/T polymorphisms were associated with renal scarring, although with a high degree of variability [62].

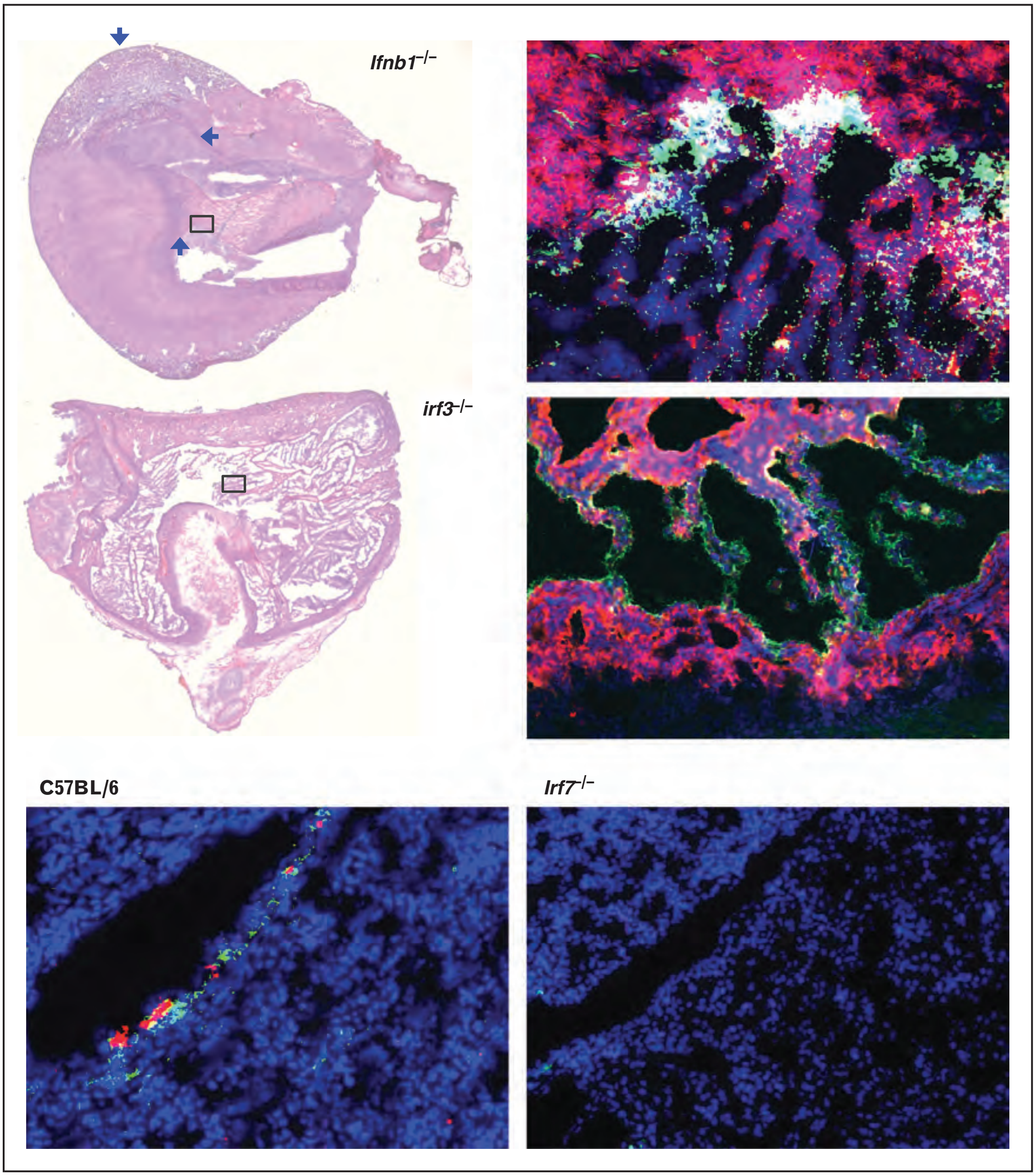


FIGURE 2. Innate immune dysregulation damages renal tissue, reduces bacterial clearance and augments neutrophil infiltration into the kidneys of infected mice. Kidneys were obtained from immune-competent C57BL/6 mice, highly susceptible *Irf3*$^{-/-}$ or *Ifnb1*$^{-/-}$ deficient mice or resistant *Irf7*$^{-/-}$ mice, 7 days after intra-vesical infection with the uropathogenic *E. coli* strain CFT073. Bacteria (green) and neutrophils (red) were detected by immunohistochemistry, using specific antibodies. Kidney morphology was visualized by Htx-eosin staining. *Irf3*$^{-/-}$ and *Ifnb1*$^{-/-}$ mice showed extensive kidney pathology with abscess formation and loss of tissue structure (blue arrows). Specific antibodies detected invasive bacterial growth and massive neutrophil accumulation along the mucosa and in the collecting ducts of the renal papilla. The renal pelvic mucosa remained intact in C57BL/6 and *Irf7*$^{-/-}$ mice, with weak or negative superficial staining for bacteria and neutrophils (Images by M. Puthia and D. Butler).

The susceptibility to UTI is also influenced by the repertoire of host cell receptors for bacterial adhesins and by soluble, antiadhesive molecules [63]. Due to P blood group dependent variation in receptor expression [63–65], individuals of blood group P_1 have an approximately 17-fold increased risk for APN and have an increased carriage of P-fimbriated *E. coli* in their intestinal flora [63–65]. In contrast, individuals of blood group P lack the Gb_3 glucosyl-transferase and fail to express functional receptors for P fimbriae [9]. Epithelial receptor expression is also influenced by the ABO blood group and secretor state [4] and individuals expressing globo-A are preferentially infected by *E. coli* expressing the prsG adhesin, which uses group A as a receptor [66]. By predicting the mucosal receptor repertoire, the P blood group is therefore a risk marker in APN.

BACTERIAL MODULATION OF INNATE IMMUNITY

Bacteria manipulate the innate immune response in the human urinary tract. A secreted TIR domain homologue inhibits MyD88 and inflammasome activation [67]. ABU strains modulate host gene expression, by suppressing RNA polymerase II in patients with ABU [17■■]. As a result of mutual adaptive strategies, bacteria adjust to individual hosts. During long-term ABU, *E. coli* 83972 reisolates showed host-specific reproducible genome alterations, suggesting that the evolution of fitness for the urinary tract is 'personal' [68].

URINARY TRACT INFECTION SUSCEPTIBILITY AND FUTURE RISK

Assessing UTI susceptibility and selecting appropriate therapeutic interventions is essential, in view of the high prevalence of UTIs and their significance to health and society. UTIs are common, encountered at all levels of healthcare whether primary or tertiary and consume considerable healthcare costs. It is estimated that 40–50% of women and 5% of men worldwide will develop UTI at least once in their lifetime, and UTIs account for more than 1 million hospitalizations and $1.6 billion in medical expenses annually, in the USA. UTIs also cause premature delivery and perinatal mortality, chronic renal disease and renal failure, unless properly treated. UTIs have an incidence of 5% in children less than 12 years old. Up to 30% of children with APN developed renal scars following UTI and this process is associated with long-term morbidity such as hypertension, complications of pregnancy and renal failure if scarring is extensive. Thus, the disease burden of UTI is significant, if not optimally managed.

Yet, the management of these patients remains unsatisfactory. Despite the urgent need, molecular tools are not used routinely to identify individuals at risk, resulting in a worldwide lack of consensus and uniform tools. Selection criteria for further radiological imaging and invasive fluoroscopy will thus remain unclear, guided only by best practices. The genes discussed above are biomarkers of UTI susceptibility or resistance. It is time to start including genetic markers in the daily risk assessment in UTI-prone patients to validate genes or gene combinations with optimal predictive power in the different UTI-prone patient groups.

CONCLUSION

UTI susceptibility is influenced by the genetic make up of the host, especially by genes that regulate the innate immune response to infection. Functionally relevant genes are regulatory rather than structural, suggesting that control of gene expression is essential. Thus, unlike the rare, monogenetic disorders defined by gene loss, UTI susceptibility is defined by the efficiency of the host defense. Furthermore, emerging data suggest that different molecular response pathways and genes characterize patients with APN, acute cystitis or ABU. To further validate the power of genetic variants in UTI risk assessment, clinical study criteria should be coordinated between study centres.

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Conflicts of interest

There are no conflicts of interest.

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■■ of outstanding interest

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