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Solute Carrier Family 11 Member A1 Gene Polymorphisms in Reactive Arthritis

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To investigate the role of *SLC 11A1* polymorphisms in the development of reactive arthritis, 91 patients with reactive arthritis and 163 healthy controls were enrolled in this study. The *SLC 11A1* polymorphisms were determined by the method of polymerase chain reaction/restriction fragment length polymorphism. The genotype distributions of *SLC 11A1* 274, 823, 1703, and 1729 + 55 del 4 were significantly different between the patients with reactive arthritis and controls. The genotype frequency of *SLC 11A1* 274C/C was significantly decreased in the patients with reactive arthritis when compared with that of the controls. In contrast, the *SLC 11A1* 274C/T showed a significant association with reactive arthritis. The patients with reactive arthritis have a significantly higher frequency of *SLC 11A1* 823C/C than the controls. However, *SLC 11A1* 823T/T was resistant to the development of reactive arthritis. The allele frequencies of *SLC 11A1* 274T and 823C were significantly increased in the patients with reactive arthritis in comparison with those of the controls, independent of HLA-B27. On the contrary, the allele frequencies of *SLC 11A1* 274C and 823T were significantly decreased in the patients with reactive arthritis. The estimated haplotype frequency of *SLC 11A1* 274C 823T 1703G 1729 + 55del 4 TGTG + was significantly decreased in the patients with reactive arthritis when compared with that of the controls. In contrast, the estimated haplotype frequency of *SLC 11A1* 274T 823C 1703G 1729 + 55 del 4 TGTG + was significantly increased in the patients with reactive arthritis. This study shows that the *SLC 11A1* 274T and 823C alleles are associated with susceptibility to reactive arthritis independently of HLA-B27 in Taiwan. The *SLC 11A1* 274T 823C 1703G 1729 + 55 del 4 TGTG + haplotype is associated with the development of reactive arthritis in Taiwan. In contrast, the *SLC 11A1* 274C 823T 1703G 1729 + 55 del 4 TGTG + haplotype may be a protective factor.

KEY WORDS: Reactive arthritis; *SLC 11A1*; NRAMP1; *chlamydia*.

INTRODUCTION

Reactive arthritis is a form of arthritis occurring after genitourinary or gastrointestinal tract infections caused by certain pathogens including *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Chlamydia trachomatis*. Several other pathogens may also be involved. Reactive arthritis typically occurs acutely 1–4 weeks after infection, and the genitourinary tract infection is frequently asymptomatic. Reactive arthritis is usually asymmetric and oligoarticular. Most patients with reactive arthritis run a self-limited course. However, about 15% of patients continue to have chronic, destructive, and disabling arthritis or enthesitis. In addition, some patients have extra-articular manifestations including keratoderma blennorhagicum, circinate balanitis, uveitis, and aortitis (1, 2).

Chlamydia trachomatis is a major pathogen of genitourinary tract infection in reactive arthritis. However, only a minor proportion of patients with *Chlamydia trachomatis* infection develop reactive arthritis (3), the reason for which is still unknown. Genetic factors may play a role in the development of this disease. *HLA-B27* is related to the increased disease susceptibility and influences disease severity and expression (4–6). Tuokko *et al*. also showed that *TNFc1* might be a new susceptibility marker for reactive arthritis independent of *HLA-B27* (7). Our recent study also revealed associations of cytochrome p450 1A1 and manganese superoxide dismutase genes with reactive arthritis following *Chlamydial* infection (8).

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Solute carrier family 11 member A1 (SLC 11A1), also called natural resistance-associated macrophage protein 1, is involved in killing intracellular pathogens (9). *Chlamydia trachomatis* is an intracellular pathogen. Therefore, SLC 11A1 may be related to the reactive arthritis following *Chlamydial* infection. The *SLC 11A1* polymorphisms may have different effects on the killing of these pathogens, and then influence the development and severity of reactive arthritis.

A study on the association of *SLC 11A1* with reactive arthritis is still unavailable in the literature. This is the first study of *SLC 11A1* polymorphisms in reactive arthritis, the purpose of which is to investigate the role of *SLC 11A1* polymorphisms in the development and clinical manifestations of reactive arthritis.

MATERIALS AND METHODS

The diagnosis of reactive arthritis is made according to the criteria proposed in the Third International Workshop on Reactive Arthritis (10). Only reactive arthritis patients with active *Chlamydial* infection were enrolled in this study, as confirmed by an indirect immunoperoxidase assay with either antichlamydial IgG-Ab $\geq$ 1:128 or both antichlamydial IgG-Ab $\geq$ 1:64 and IgA-Ab $\geq$ 1:16 (IPAzyme Chlamydia kit, Savyon Diagnostics Ltd., Israel). Ninety-one patients (48 males, 43 females) with reactive arthritis following urogenital *Chlamydial* infection and 163 age- and sex-matched healthy controls (83 males, 80 females) were enrolled in this study. All the patients and controls are Taiwanese. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital.

SLC 11A1 polymorphisms were determined by the polymerase chain reaction/ restriction fragment length polymorphism method, including 274 C/T (at codon 66 in exon 3), 469 + 14 G/C (at nucleotide + 14 of intron 4), 577–18 G/A (at nucleotide − 18 of intron 5), 823 C/T (at codon 249 or nucleotide 823 in exon 8), A318V (at codon 318 in exon 9; C or T at nucleotide 1029), 1465–85 G/A (at nucleotide − 85 of intron 13), D543N (at codon 543 in exon 15; G or A at nucleotide 1703), and 1729 + 55 del 4 (deletion of TGTG in the 3′-UTR; 55 nucleotides 3′ to the last codon in exon 15). The sequences of primers and restriction enzymes are given in Table I.

The chi-square test or Fisher's exact test was used for statistical analysis. Odds ratio (OR) and its 95% confidence interval (CI) were calculated by the SPSS statistical program. The Haldane method was used to calculate OR if the value of any cell is 0 (11). The delta values (Δ) were calculated to evaluate the linkage disequilibrium. To calculate the estimated haplotype frequencies, the EH program was used (Web Resources of Genetic Linkage Analysis). The Mantel–Haenszel test was used in a statistic with stratification.

RESULTS

The genotypes of *SLC 11A1* in the controls appeared to be in Hardy–Weinberg equilibrium. The genotype distributions of *SLC 11A1* 274C/T, 823C/T, 1703G/A (D543N), and 1729–55 del4 TGTG/-polymorphisms were significantly different between the patients with *Chlamydia*-induced reactive arthritis and the healthy controls (Table II). The patients with reactive arthritis have a significantly lower genotype frequency of *SLC 11A1*

Table I. The Sequences of Primers and Restriction Enzymes in Determining *SLC 11A1* Polymorphisms

SLC 11A1	Primers	Restriction enzymes
274 C/T	5′-TGCCACCATCCCTATACCCAG-3′ 5′-CTTCAACACTTAGCCTGGTCAC-3′	Mnl I
469 + 14G/C	5′-TCTCTGGCTGAAGGCCTCTCC-3′ 5′-TGTGCTATCAGTTTGAGCCTC-3′	Apa I
577–18G/A	5′-CTGGACCAGGCTGGGCTGAC-3′ 5′-CCACCACTCCCCTATGAGGTG-3′	Msp I
823 C/T	5′-CTTGTCCTGACCAGGCTCCT-3′ 5′-CATGGCTCCGACTGAGTGAG-3′	Nar I
A318V (1029C/T)	5′-TCCCTTTGATCTTCGTAGTCTC-3′ 5′-GGCTTACAGGACATGAGTAC-3′	BstU I
1465–85G/A	5′-GCAAGTTGAGGAGCCAAGAC-3′ 5′-ACCTGCATCAACTCCTCTTC-3′	Bsr I
D543N (1703G/A)	5′-GCATCTCCCCAATTCATGGT-3 5′-AACTGTCCCACTCTATCCTG-3′	Ava II
1729 + 55 del 4 TGTG + /del	5′-GCATCTCCCCAATTCATGGT-3 5′-AACTGTCCCACTCTATCCTG-3′	BstF5 I

Table II. Genotype Frequencies of *SLC 11A1* Polymorphisms in the Patients with Reactive Arthritis and Controls

SLC 11A1 genotypes	Reactive arthritis $n = 91$ (%)	Controls $n = 163$ (%)	p Value (for overall genotype frequency)	p Value (for individual genotype frequency)	OR (95% CI)
274					
C/C	69 (75.8)*	145 (88.9)	0.02		1
C/T	21 (23.1)	17 (10.4)		0.006	2.6 (1.3–5.2)
T/T	1 (1.1)	1 (0.6)			
469 + 14					
G/G	72 (79.1)	144 (88.3)	NS		
G/C	18 (19.8)	17 (10.4)			
C/C	1 (1.1)	2 (1.2)			
577–18					
G/G	84 (92.3)	148 (90.8)	NS		
G/A	6 (6.6)	14 (8.6)			
A/A	1 (0)	1 (0.6)			
823					
C/C	76 (83.5)#	106 (65.0)	0.002		1
C/T	15 (16.5)	45 (27.6)			
T/T	0 (0)	12 (7.4)		0.004	0.06 (0.01–0.4)
1029 (A318V)					
C/C (A/A)	91 (100.0)	161 (98.8)	NS		
C/T (A/V)	0 (0)	2 (1.2)			
T/T (V/V)	0 (0)	0 (0)			
1465-85					
G/G	41 (45.1)	76 (46.6)	NS		
G/A	47 (51.6)	78 (47.9)			
A/A	3 (3.3)	9 (5.5)			
1703 (D543N)					
G/G (D/D)	69 (75.8)	108 (66.3)	0.04		
G/A (D/N)	19 (20.9)	54 (33.1)			
A/A (N/N)	3 (3.3)	1 (0.6)			
1729 + 55del 4					
TGTG +/+	69 (75.8)	106 (65.0)	0.03		
TGTG +/del	19 (20.9)	56 (34.4)			
TGTG del/del	3 (3.3)	1 (0.6)			

Note. NS, not significant.
*Reactive arthritis versus Controls: $p = 0.006$, OR = 0.4, 95% CI = 0.2–0.8.
#Reactive arthritis versus Controls: $p = 0.002$, OR = 2.7, 95% CI = 1.4–5.2.

274C/C than the controls ($p = 0.006$, OR = 0.4, 95% CI = 0.2–0.8). In comparison with *SLC 11A1* 274 C/C, the patients with reactive arthritis have a significantly higher frequency of *SLC 11A1 274 C/T* than the controls ($p = 0.006$, OR = 2.6, 95% CI = 1.3–5.2). We also found that the genotype frequency of *SLC 11A1* 823C/C was significantly increased in the patients with reactive arthritis when compared with that of the controls ($p = 0.002$, OR = 2.7, 95% CI = 1.4–5.2). In comparison with *SLC 11A1* 823 C/C, the patients with reactive arthritis have a significantly lower genotype frequency of *SLC 11A1* 823T/T than the controls ($p = 0.004$, OR = 0.06, 95% CI = 0.01–0.4).

The allele frequency of *SLC 11A1* 274T was significantly higher in patients with reactive arthritis than that of the controls (Table III, $p = 0.008$, OR = 2.3, 95% CI = 1.2–4.4). A similar finding could also be found in *SLC 11A1* 823C. The patients with reactive arthritis have a significantly higher allele frequency of *SLC 11A1* 823C than the controls (Table III, $p < 0.001$, OR = 3.0, 95% CI = 1.7–5.4). However, the patients with reactive arthritis have significantly lower allele frequencies of *SLC 11A1* 274C and 823T than the controls ($p = 0.008$, OR = 0.4, 95% CI = 0.2–0.8, and $p < 0.001$, OR = 0.3, 95% CI = 0.2–0.6, respectively).

The haplotype frequency of *SLC 11A1* 274C 823T 1703G 1729 + 55 del 4 TGTG + was significantly decreased in the patients with reactive arthritis when compared with that of the controls (Table IV, $p < 0.001$, OR = 0.02, 95% CI = 0–0.2). In contrast, the patients with reactive arthritis have a significantly higher haplotype frequency of *SLC 11A1* 274T 823C 1703G 1729 + 55 del 4 TGTG + than the controls ($p = 0.004$, OR = 2.4, 95% CI = 1.2–4.6).

This study also revealed that *HLA-B27* was associated with the development of reactive arthritis (positive *HLA-B27*: patients vs. controls = 34.1% vs. 6.7%, $p < 0.001$, OR = 7.1, 95% CI = 3.4–15.1, data not shown). To

Table III. Allele Frequencies of *SLC 11A1* Polymorphisms in the Patients with Reactive Arthritis and Controls

SLC 11A1 allele frequencies	Reactive arthritis $2n = 182$ (%)	Controls $2n = 326$ (%)	p	OR (95% CI)
274				
C	159 (87.4)	307 (94.2)	0.008	0.4 (0.2–0.8)
T	23 (12.6)	19 (5.8)	0.008	2.3 (1.2–4.4)
469 + 14				
G	162 (89.0)	305 (93.6)	NS	
C	20 (11.0)	21 (6.4)		
577-18				
G	174 (95.6)	310 (95.1)	NS	
A	8 (4.4)	16 (4.9)		
823				
C	167 (91.8)	257 (78.8)	<0.001	3.0 (1.7–5.4)
T	15 (8.2)	69 (21.2)	<0.001	0.3 (0.2–0.6)
1029				
C (318 A)	182 (100.0)	324 (99.4)	NS	
T (318 V)	0 (0)	2 (0.6)		
1465–85				
G	129 (70.9)	230 (70.6)	NS	
A	53 (29.1)	96 (29.4)		
1703				
G (543D)	157 (86.3)	270 (82.8)	NS	
A (543N)	25 (13.7)	56 (17.2)		
1729 + 55 del 4				
TGTG +	157 (86.3)	268 (82.2)	NS	
TGTG del	25 (13.7)	58 (17.8)		

Note. OR, odds ratio.

clarify the role of *SLC 11A1* in the pathogenesis of reactive arthritis, the allele frequencies of *SLC 11A1* polymorphisms were stratified with *HLA-B27* (Table V). The Mantel–Haenszel test was used for statistical analysis. It showed that the association of *SLC 11A1* 274T with reactive arthritis was independent of *HLA-B27* ($p = 0.03$, adjusted OR = 2.2, 95% CI = 1.1–4.4). The association between *SLC 11A1* 823C and reactive arthritis was also independent of *HLA-B27* ($p = 0.001$, adjusted OR = 3.1, 95% CI = 1.6–5.9). In contrast, *SLC 11A1* 274C and 823T resist the development of reactive arthritis independently of HLA-B27 ($p = 0.03$, OR = 0.5, 95% CI = 0.2–0.9, and $p = 0.001$, OR = 0.3, 95% CI = 0.2–0.6, respectively).

DISCUSSION

This study has demonstrated that *SLC 11A1* 274T and 823C are associated with the development of reactive arthritis. The *SLC 11A1* 274T 823C 1703G 1729 + 55 del 4 TGTG + haplotype is related to susceptibility to reactive arthritis, while the *SLC 11A1* 274C 823T 1703G 1729 + 55 del 4 TGTG + haplotype is a protective factor.

Table IV. Estimated Haplotype Frequencies of *SLC 11A1* Polymorphisms in the Patients with Reactive Arthritis and Controls

Haplotype of *SLC 11A1*	Reactive arthritis	Controls	p	OR (95% CI)
274C 823C 1703G 1729 + 55 del 4 TGTG +	0.743	0.670	NS	
274C 823C 1703A 1729 + 55 del 4 TGTG del	0.058	0.060	NS	
274C 823T 1703G 1729 + 55 del 4 TGTG +	0	0.099	<0.001	0.02 (0–0.2)
274C 823T 1703G 1729 + 55 del 4 TGTG del	0	0.006	NS	
274C 823T 1703A 1729 + 55 del 4 TGTG del	0.078	0.101	NS	
274T 823C 1703G 1729 + 55 del 4 TGTG +	0.114	0.05	0.004	2.4 (1.2–4.6)
274T 823C 1703A 1729 + 55 del 4 TGTG del	0.002	0.007	NS	
274T 823T 1703G 1729 + 55 del 4 TGTG +	0	0.006	NS	
274T 823T 1703A 1729 + 55 del 4 TGTG del	0.005	0	NS	

Note. OR, odds ratio.

Table V. Allele Frequencies of *SLC 11A1* Polymorphisms Stratified by *HLA-B27* in the Patients with Reactive Arthritis and Controls

	HLA-B27(+)		*HLA-B27*(−)			
	Reactive A	Controls	Reactive A	Controls		
SLC 11A1	$2n = 62$(%)	$2n = 22$(%)	$2n = 120$(%)	$2n = 304$(%)	*P*	Adjusted OR (95% CI)
274T	12 (19.4)	0 (0)	11 (9.2)	19 (6.3)	0.03	2.2 (1.1–4.4)
823C	56 (90.3)	18 (81.8)	111 (92.5)	239 (78.6)	0.001	3.1 (1.6–5.9)
274C	50 (80.6)	22 (100)	109 (90.8)	285 (93.8)	0.03	0.5 (0.2–0.9)
823T	6 (9.7)	4 (18.2)	9 (7.5)	65 (21.4)	0.001	0.3 (0.2–0.6)

Note. The Mantel–Haenszel test was used for statistical analysis. Reactive A, reactive arthritis.

SLC 11A1 has pleiotropic effects on macrophage functions, including antimicrobial activity, tumoricidal activity, and upregulation of chemokine/cytokine gene, tumor necrosis factor α (TNFα), interleukin 1 β(IL-1β), inducible nitric oxide synthase (iNOS), as well as major histocompatibility complex expression (12–15). These effects are involved in resistance to infection and may also be involved in induction and maintenance of autoimmune disease (12). Our previous study also showed that *SLC 11A1* was related to the susceptibility and clinical manifestation of rheumatoid arthritis (16).

SLC 11A1 is located on chromosome 2q35. *SLC 11A1* expression is primarily in tertiary granules of polymorphonuclear cells and macrophages. Then, it is recruited from tertiary granules to the phagosomal membrane on phagocytosis (17). *SLC 11A1* is a proton/divalent cationic (Fe^{2+}, Zn^{2+}, Co^{2+}, Mn^{2+}, and Mg^{2+}) antiporter (18–20), which fluxes divalent cations in either direction depending on the PH on either side of the membrane (21). In late endosomes/lysosomes, *SLC 11A1* delivers divalent cations from the cytosole to this acidic compartment. The Fenton reaction uses ferrous iron to generate toxic hydroxyl radicals, which are associated with killing intracellular pathogens (9). The expression of iNOS and generation of toxic NO may be influenced by the polymorphisms of *SLC 11A1* (22, 23). Mutation of *SLC 11A1* also impairs phagosomal acidification, which is related to intracellular infection (24). Vidal showed that a mutation at amino acid 169 of *SLC 11A1* made mice more susceptible to infection by many pathogens (25). *SLC 11A1* polymorphisms are also related to many human infectious diseases, including pulmonary tuberculosis (TB), leprosy, human immunodeficiency virus infection, visceral leishmaniasis, and meningococcal meningitis (26–30). The associations of *SLC 11A1* polymorphisms with TB infection are still controversial. However, the polymorphisms at different sites may be associated with TB susceptibility or resistance in different ethnic groups (31).

In addition to killing intracellular pathogens, *SLC 11A1* also upregulates the expression of TNFα and IL-1β by macrophages. TNFα and IL-1β play important roles in inflammation and tissue destruction of inflammatory arthritis including reactive arthritis (32). Therefore, *SLC 11A1* may be related to the pathogenesis of reactive arthritis. Smit showed that *SLC 11A1* might provide a link between the genetic background, the bacterial environmental, and the development of allergic diseases (33). A similar condition may also be present in reactive arthritis.

This study has demonstrated the associations between *SLC 11A1* polymorphisms and development of reactive arthritis. *SLC 11A1* 274T and 823C are related to susceptibility to reactive arthritis independently of *HLA-B27*. On the contrary, *SLC 11A1* 274C and 823T prevent the development of reactive arthritis. A linkage disequilibrium is present between *SLC 11A1* 1703G and 1729 + 55 del 4 TGTG + ($p < 0.0001$, $\Delta = 0.18$, data not shown). The *SLC 11A1* 274T 823C 1703G 1729 + 55 del 4 TGTG + haplotype is a precipitating factor for reactive arthritis. In contrast, the *SLC 11A1* 274C 823T 1703G 1729 + 55 del 4 TGTG + haplotype is a protective factor. This study also reveals that the *SLC 11A1* 274C/T, 823C/T, 1703G/A, and 1729 + 55 del 4 TGTG + /del polymorphisms are not related to clinical manifestations of reactive arthritis including conjunctivitis, uveitis, oral ulcer, circinate balanitis, keratoderma blenorrhagica, and enthesopathy (data not shown).

The associations of *SLC 11A1* with immune-mediated diseases, including rheumatoid arthritis, juvenile rheumatoid arthritis, type 1 diabetes, multiple sclerosis, and Crohn's disease, have also been demonstrated (34–39).

In summary, *SLC 11A1* 274T and 823C are risk factors for the development of reactive arthritis independent of *HLA-B27*. The *SLC 11A1* 274T 823C 1703G 1729 + 55 del 4 TGTG + haplotype is associated with susceptibility to reactive arthritis in Taiwan, and the *SLC 11A1* 274C 823T 1703G 1729 + 55 del 4 TGTG + haplotype is associated with resistance to reactive arthritis.

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REFERENCES

1. Khan MA, van der Linden SJ: Reactive arthritis. *In* Arthritis and Allied Conditions, Vol 1. WJ Koopman, ML Tremblay (eds). Philadelphia, Lippincott Williams & Wilkins, 2005, pp 1335–1355
2. Flores D, Marquez J, Garza M, Espinoza LR: Reactive arthritis: Newer developments. Rheum Dis Clin North Am 29(1):37–59, vi, 2003
3. Kvien TK, Glennas A, Melby K, Granfors K, Andrup O, Karstensen B, Thoen JE: Reactive arthritis: Incidence, triggering agents and clinical presentation. J Rheumatol 21(1):115–122, 1994
4. Linssen A: B27 + disease versus B27 − disease. Scand J Rheumatol 87(Suppl):111–118; discussion 118–119, 1990
5. Moller P: Seronegative arthritis—etiology and diagnosis. Scand J Rheumatol 66(Suppl):119–127, 1987
6. Yu D, Kuipers JG: Role of bacteria and HLA-B27 in the pathogenesis of reactive arthritis. Rheum Dis Clin North Am 29(1):21–36, v–vi, 2003
7. Tuokko J, Koskinen S, Westman P, Yli-Kerttula U, Toivanen A, Ilonen J: Tumour necrosis factor microsatellites in reactive arthritis. Br J Rheumatol 37(11):1203–1206, 1998
8. Yen JH, Tsai WC, Lin CH, Ou TT, Hu CJ, Liu HW: Cytochrome P450 1A1 and manganese superoxide dismutase genes polymorphisms in reactive arthritis. Immunol Lett 90(2–3):151–154, 2003
9. Blackwell JM, Goswami T, Evans CA, Sibthorpe D, Papo N, White JK, Searle S, Miller EN, Peacock CS, Mohammed H, Ibrahim M: SLC11A1 (formerly NRAMP1) and disease resistance. Cell Microbiol 3(12):773–784, 2001
10. Kingsley G, Sieper J: Third International Workshop on Reactive Arthritis. 23–26 September 1995, Berlin, Germany. Report and abstracts. Ann Rheum Dis 55(8):564–584, 1996
11. Haldane JB: The estimation and significance of the logarithm of a ratio of frequencies. Ann Hum Genet 20(4):309–311, 1956
12. Blackwell JM: Structure and function of the natural-resistance-associated macrophage protein (Nramp1), a candidate protein for infectious and autoimmune disease susceptibility. Mol Med Today 2(5):205–211, 1996
13. Blackwell JM, Barton CH, White JK, Roach TI, Shaw MA, Whitehead SH, Mock BA, Searle S, Williams H, Baker AM: Genetic regulation of leishmanial and mycobacterial infections: The Lsh/Ity/Bcg gene story continues. Immunol Lett 43(1–2):99–107, 1994
14. Blackwell JM, Roach TI, Atkinson SE, Ajioka JW, Barton CH, Shaw MA: Genetic regulation of macrophage priming/activation: The Lsh gene story. Immunol Lett 30(2):241–248, 1991
15. Karupiah G, Hunt NH, King NJ, Chaudhri G: NADPH oxidase, Nramp1 and nitric oxide synthase 2 in the host antimicrobial response. Rev Immunogenet 2(3):387–415, 2000
16. Yen JH, Lin CH, Tsai WC, Ou TT, Wu CC, Hu CJ, Liu HW: Natural resistance-associated macrophage protein 1 gene polymorphisms in rheumatoid arthritis. Immunol Lett 102(1):91–97, 2006
17. Canonne-Hergaux F, Calafat J, Richer E, Cellier M, Grinstein S, Borregaard N, Gros P: Expression and subcellular localization of NRAMP1 in human neutrophil granules. Blood 100(1):268–275, 2002
18. Blackwell JM, Searle S: Genetic regulation of macrophage activation: Understanding the function of Nramp1 (= Ity/Lsh/Bcg). Immunol Lett 65(1–2):73–80, 1999
19. Forbes JR, Gros P: Iron, manganese, and cobalt transport by Nramp1 (Slc11a1) and Nramp2 (Slc11a2) expressed at the plasma membrane. Blood 102(5):1884–1892, 2003
20. Wyllie S, Seu P, Goss JA: The natural resistance-associated macrophage protein 1 Slc11a1 (formerly Nramp1) and iron metabolism in macrophages. Microbes Infect 4(3):351–359, 2002
21. Jabado N, Jankowski A, Dougaparsad S, Picard V, Grinstein S, Gros P: Natural resistance to intracellular infections: Natural resistance-associated macrophage protein 1 (Nramp1) functions as a pH-dependent manganese transporter at the phagosomal membrane. J Exp Med 192(9):1237–1248, 2000
22. Roach TI, Kiderlen AF, Blackwell JM: Role of inorganic nitrogen oxides and tumor necrosis factor alpha in killing Leishmania donovani amastigotes in gamma interferon-lipopolysaccharide-activated macrophages from Lshs and Lshr congenic mouse strains. Infect Immun 59(11):3935–3944, 1991
23. Arias M, Rojas M, Zabaleta J, Rodriguez JI, Paris SC, Barrera LF, Garcia LF: Inhibition of virulent *Mycobacterium tuberculosis* by Bcg(r) and Bcg(s) macrophages correlates with nitric oxide production. J Infect Dis 176(6):1552–1558, 1997
24. Hackam DJ, Rotstein OD, Zhang W, Gruenheid S, Gros P, Grinstein S: Host resistance to intracellular infection: Mutation of natural resistance-associated macrophage protein 1 (Nramp1) impairs phagosomal acidification. J Exp Med 188(2):351–364, 1998
25. Vidal S, Tremblay ML, Govoni G, Gauthier S, Sebastiani G, Malo D, Skamene E, Olivier M, Jothy S, Gros P: The Ity/Lsh/Bcg locus: Natural resistance to infection with intracellular parasites is abrogated by disruption of the Nramp1 gene. J Exp Med 182(3):655–666, 1995
26. Blackwell JM, Searle S, Mohamed H, White JK: Divalent cation transport and susceptibility to infectious and autoimmune disease: Continuation of the Ity/Lsh/Bcg/Nramp1/Slc11a1 gene story. Immunol Lett 85(2):197–203, 2003
27. Abe T, Iinuma Y, Ando M, Yokoyama T, Yamamoto T, Nakashima K, Takagi N, Baba H, Hasegawa Y, Shimokata K: NRAMP1 polymorphisms, susceptibility and clinical features of tuberculosis. J Infect 46(4):215–220, 2003
28. Shaw MA, Collins A, Peacock CS, Miller EN, Black GF, Sibthorpe D, Lins-Lainson Z, Shaw JJ, Ramos F, Silveira F, Blackwell JM: Evidence that genetic susceptibility to *Mycobacterium tuberculosis* in a Brazilian population is under oligogenic control: Linkage study of the candidate genes NRAMP1 and TNFA. Tuberc Lung Dis 78(1):35–45, 1997
29. Abel L, Sanchez FO, Oberti J, Thuc NV, Hoa LV, Lap VD, Skamene E, Lagrange PH, Schurr E: Susceptibility to leprosy is linked to the human NRAMP1 gene. J Infect Dis 177(1):133–145, 1998
30. Bellamy R: Susceptibility to mycobacterial infections: The importance of host genetics. Genes Immun 4(1):4–11, 2003
31. Delgado JC, Baena A, Thim S, Goldfeld AE: Ethnic-specific genetic associations with pulmonary tuberculosis. J Infect Dis 186(10):1463–1468, 2002
32. Jendro MC, Raum E, Schnarr S, Kohler L, Zeidler H, Kuipers JG, Martin M: Cytokine profile in serum and synovial fluid of arthritis patients with *Chlamydia trachomatis* infection. Rheumatol Int 25(1):37–41, 2005
33. Smit JJ, Folkerts G, Nijkamp FP: Ramp-ing up allergies: Nramp1 (Slc11a1), macrophages and the hygiene hypothesis. Trends Immunol 25(7):342–347, 2004

34. Sanjeevi CB, Miller EN, Dabadghao P, Rumba I, Shtauvere A, Denisova A, Clayton D, Blackwell JM: Polymorphism at NRAMP1 and D2S1471 loci associated with juvenile rheumatoid arthritis. Arthritis Rheum 43(6):1397–1404, 2000
35. Bassuny WM, Ihara K, Matsuura N, Ahmed S, Kohno H, Kuromaru R, Miyako K, Hara T: Association study of the NRAMP1 gene promoter polymorphism and early-onset type 1 diabetes. Immunogenetics 54(4):282–285, 2002
36. Hofmeister A, Neibergs HL, Pokorny RM, Galandiuk S: The natural resistance-associated macrophage protein gene is associated with Crohn's disease. Surgery 122(2):173–178; discussion 178–179, 1997
37. Kotze MJ, de Villiers JN, Rooney RN, Grobbelaar JJ, Mansvelt EP, Bouwens CS, Carr J, Stander I, du Plessis L: Analysis of the NRAMP1 gene implicated in iron transport: Association with multiple sclerosis and age effects. Blood Cells Mol Dis 27(1):44–53, 2001
38. Takahashi K, Satoh J, Kojima Y, Negoro K, Hirai M, Hinokio Y, Kinouchi Y, Suzuki S, Matsuura N, Shimosegawa T, Oka Y: Promoter polymorphism of SLC11A1 (formerly NRAMP1) confers susceptibility to autoimmune type 1 diabetes mellitus in Japanese. Tissue Antigens 63(3):231–236, 2004
39. Runstadler JA, Saila H, Savolainen A, Leirisalo-Repo M, Aho K, Tuomilehto-Wolf E, Tuomilehto J, Seldin MF: Association of SLC11A1 (NRAMP1) with persistent oligoarticular and polyarticular rheumatoid factor-negative juvenile idiopathic arthritis in Finnish patients: Haplotype analysis in Finnish families. Arthritis Rheum 52(1):247–256, 2005