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EDITORIAL

Looking back and looking forward

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As we enter the new year and the start of a new volume, it is again time to reflect briefly and provide some perspective on the future of our journal. In many ways, it is hard to imagine that we are already starting Volume 4. We believe that *Genes and Immunity* has emerged as an important venue for functional genomic studies of immune system genes. The journal has continued to publish valuable studies that focus on the genetic factors that determine variability in the propensity and severity of human immune-mediated diseases. Prominently, these manuscripts include efforts to unravel the genetics of host response to infectious disease as well as the genetics of autoimmune diseases.

Our standing among other journals has improved as attested by our most recent ISI impact factor of 3.7. This reflects our progress in attracting and publishing noteworthy studies and reviews. The journal now ranks as a leader in the field of immunogenetics as we enter our fourth year. Manuscripts in the journal are frequently featured in Nature.com in the Immunology and Genetics Subject areas. Our E-mail alert on Table of Contents now has over 11 000 subscribers!

During the last year, we have had a marked increase in the manuscript submission rate. This was particularly true for high-quality manuscripts. Several of these manuscripts published in Volume 3 have provided new insight that will drive the cutting edge of our field. Many of these are highlighted below. These include a study suggesting that the receptor for advanced glycation end products (RAGE) that has been implicated in the amplification of the immune response may be an important susceptibility gene in rheumatoid arthritis (RA).[1] This study showed that a specific variant in the ligand-binding domain enhanced ligand binding and subsequent cytokine and metalloproteinase generation. The data also indicated that this variant was associated with RA. Although an effect independent of the DRB1*0401 allele, in strong linkage disequilibrium with RAGE, could not be demonstrated, it might help explain why some shared epitope alleles have a stronger association with RA than other shared epitope alleles. This report was accompanied by an important guest editorial.[2]

A number of potentially important linkage studies were presented in the journal. These included two large genome-wide linkage screens for multiple sclerosis susceptibility genes,[3,4] and a genome-wide analysis of orchard grass-sensitive allergic rhinitis.[5] Importantly, the latter study showed several loci concordant with those previously implicated in either asthma or atopy.

Many detailed linkage and association studies of both specific candidate chromosomal regions and candidate genes have been published during the last year. These include a manuscript providing the strongest evidence to date for a type I diabetes gene in the IgH region of human chromosome 14,[6] the association of a functional promoter polymorphism in the MIF gene with RA severity,[7] an IL-10 regulatory region dinucleotide repeat with systemic lupus erythematosus (SLE),[8] IL-1B and IL-6 polymorphisms with development of recurrent aphthous stomatitis,[9] IL-11 polymorphism with ulcerative colitis[10] and IL-1ra in both ulcerative colitis and Crohn's disease.[11]

Other association studies have examined candidate genes that may modify the host response to infectious agents. These include genotypic analyses suggesting that myeloperoxidase is important in the progression of hepatic fibrosis in chronic hepatitis C provided in one such study[12] and the association of low-density lipoprotein receptor polymorphism and outcome of hepatitis C infection in another.[13] Another report contained provocative preliminary evidence that a promoter polymorphism in CD40L can provide protection from severe malaria.[14] Of additional note is a study that found a striking correlation of an IL-12B polymorphism with mortality from cerebral malaria.[15] This polymorphism is also associated with decreased IL-12 secretion (see below for additional studies of the relation of this mutation to IL-12 secretion).

The effect of gene/environment interactions was also examined in several studies. These include the association of an SLC11A1 (NRAMP1) linked polymorphism and atopy in BCG vaccinated children[16] and studies of periodontal disease implicating complex relations between risk for disease dependent on smoking and genetic factors including polymorphisms of myeloperoxidase and a plasminogen-activator-inhibitor-1 promoter.[17,18]

Potentially important associations between specific allelic variants and gene regulation have been suggested by several studies published during the last year. In addition to the RAGE study,[1] these include the association of potentially regulatory cis-polymorphisms for the levels of C-reactive protein (CRP),[19] IL-4 production[20] and IFN-gamma gene transcription.[21] The latter study demonstrated that an SNP in the proximal promoter of the IFN-γ gene altered the control of gene transcription and was associated with an allele-specific DNA-binding protein complex. Another study intriguingly indicates a strong association of a polymorphism in the IL-12 p40 (IL-12B) gene with altered secretion of the IL-12 p70 gene but not IL-12 p40.[22] Although the mechanisms responsible for the observation remain to be elucidated, the evidence suggesting this complex regulation appears convincing. Interestingly, an IL-12B polymorphism was also linked to IL-12 expression in studies of NOD and other autoimmune mice in another manuscript published in the journal.[23]

Volume 3 has also featured multiple studies using mouse models to advance our understanding of complex genetic interactions. Quantitative trait loci (QTL) analysis provided evidence for several NZB genes that modify the NZB/SWR mouse model of autoimmunity,[24] and another study provided evidence for three QTLs that determine CD4/CD8 T cell subset ratios.[25] Other studies examined

mouse crosses for host genes controlling response to infection. These included evidence for and mapping of multiple genes controlling IgE levels in Leishmania major infected mice[26] as well as a study implicating SLC11A1 (NRAMP1) in the persistence of Salmonella infection in mice.[27] Another provocative study linked a gp130 gene 'knock-in' with susceptibility to Listeria infection.[28] This gene, which is a critical subunit of IL-6 family genes, is within the critical region for a QTL identified in other studies of Listeria mouse infection. However, the effects of background genes in the knock-out could not be excluded. This report was accompanied by a guest editorial reviewing the complex genetics of Listeria infection in the mouse.[29]

Of special note, the last volume included several high-impact reviews in the field and this will be a continuing feature of future editions. These included a series of state-of-the-art presentations of efforts to understand the genetics of host response to infectious agents that was organized by Philipe Gros. These reviews detailed both the progress and approaches towards positional cloning identification of QTL controlling susceptibility genes for Plasmodium infection in mice,[30] insightful prospects of integrating human studies with those in mouse for malaria,[31] the genetic basis for leprosy susceptibility,[32] the regulation of host gene responses to Salmonella infection,[33] and the role of innate immunity in cytomegalovirus infection.[34] The journal has also included timely reviews of progress in elucidating the genetics of type I diabetes[35] and systemic lupus erythematosus (SLE),[36] each contributed by leaders in the field. The reviews have also included the second supplement on cytokine polymorphism in human disease. This feature is an important resource for many in the field.[37]

Also of special note, Volume 3 has also included a Special Supplementary issue 'Lupus—Progress with a Complex Genetic Phenotype' that was coedited by our colleague John Harley. This Special Supplement contained substantial studies examining the genetic etiology of SLE, many of which were presented at the Lupus Genetics Conference. Included in this supplement was the development of an approach to increasing the power of linkage studies by applying a novel covariate analysis to a genome-wide screen of affected relative pairs.[38] This method showed promise in the lupus study and suggested new linkage relations as well as strengthening others. The issue also included studies suggesting the importance of several candidate genes in lupus[39,40] and two papers defining new chromosomal regions of interest by application of a phenotypic stratification strategy.[41–43]

What do we see in the future for *Genes and Immunity*? The continued explosion of genomic information and technology will undoubtedly drive progress in the field and change the content of our journal. Current efforts will provide a more comprehensive knowledge of sequence diversity and suggest a vast array of potentially biologically important variations. This information, including which SNPs are likely to be most useful in genetic analyses, is soon to be part of our informatics armamentarium. This coupled with improved technology for assessing the polymorphisms will lead to more sophisticated studies examining reasonably comprehensive haplotypes that may be associated with critical functional elements.

In addition, the progress in examining and interpreting large-scale gene expression studies may begin to provide insight into novel gene pathways and unravel the complex events that regulate different aspects of the immune response in a variety of diseases. Indeed, the coming months will see studies in the journal that contain detailed haplotypic analyses and others utilizing gene array expression data to provide some novel clues into the pathogenesis of several immunologically mediated diseases.

The near quixotic search for definitive information that links sequence variation in non-Mendelian disease to plausible mechanisms will continue to occupy many in the field and is likely to keep our pages full. The journal will continue to encourage the contribution of studies that define sequence/function relations. More journal pages are likely to be occupied by studies that provide such insight. These are certain to include targeted mutations in mouse and *in vitro* studies providing support for the functional role of specific allelic variants of cytokine and other genes that modify the inflammatory response. We also will continue to encourage and solicit timely reviews of developments in the field. Notably, the current issue contains two such reviews.[44,45] We anticipate an exciting Volume 4 and advances in our quest to understand *Genes and Immunity*.

Some acknowledgements are in order. The visibility of our journal both within the Nature Group as well as in the scientific community has continued to grow. This is, in large part, the work of our publication staff and in particular our Executive Editor Nick Campbell. We also have our editorial and publishing staff to thank for the smooth conversion to our online submission process and the continued efficient processing of manuscripts. Many kudos to Yolanda Figueroa, Jennifer Kimball, Pauline Cripps, Denise Taylor and Trevor Barton. We also offer a hardy thanks to our Editorial Board that has continued to provide critical input and service and deserves much of the credit for the journal's success. Last and most importantly, our journal is dependent on the hard work of those who contribute manuscripts and serve as referees. We thank you for your efforts during the last year and continued support of the journal.

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