The Genetic Basis of Spondyloarthritis: SPARTAN/IGAS 2009

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ABSTRACT. A joint meeting was held in July 2009 in Houston, Texas, of members of the Spondyloarthritis Research and Therapy Network (SPARTAN), founded in 2003 to promote research, education, and treatment of ankylosing spondylitis (AS) and related forms of spondyloarthritis (SpA), and members of International Genetics of AS (IGAS), founded in 2003 to encourage and coordinate studies internationally in the genetics of AS. The general topic was the genetic basis of SpA, with presentations on the future of human genetic studies; microbes, SpA, and innate immunity; susceptibility of AS to the major histocompatibility complex (MHC) and non-MHC; and individual discussions of the genetics of psoriasis and psoriatic arthritis, uveitis, inflammatory bowel disease, and enteropathic arthritis. Summaries of those discussions are presented. (J Rheumatol 2010;37:2626–31; doi:3899/jrheum.100892)

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A joint meeting was held in July 2009 in Houston, Texas, USA, of members of the Spondyloarthritis Research and Therapy Network (SPARTAN), founded in 2003 to promote research, education, and treatment of ankylosing spondylitis (AS) and related forms of spondyloarthritis (SpA), and members of International Genetics of AS (IGAS), founded in 2002 to encourage and coordinate studies internationally in the genetics of AS. The general topic was the genetic basis of SpA, with presentations on the future of human genetic studies; microbes, SpA, and innate immunity; susceptibility of AS to the major histocompatibility complex (MHC) and non-MHC; and individual discussions of the genetics of psoriasis and psoriatic arthritis (PsA), uveitis, inflammatory bowel disease (IBD) and enteropathic arthritis.

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Future of Human Genetic Studies

David M. Evans, PhD (University of Bristol, Bristol, UK) first explained that genetic mapping studies of complex diseases had not met with success until very recently, generally because sample sizes were insufficient and coverage of common genetic variation in the genome was inadequate[1]. Then 3 developments made genome-wide association studies (GWAS) a reality: large cohorts, high throughput genotyping, and the haplotype map (HapMap; International HapMap Project)[2]. Dr. Evans briefly reviewed current knowledge of the genetics of AS, and suggested that important next steps would be fine mapping to better localize the variants involved, as well as *in vitro* and animal studies to identify the functional variants involved.

Dr. Evans discussed the possibility of genetic testing in complex diseases, noting difficulty because the effects of individual variants were so small; however, if several predisposing genetic and environmental factors were considered, it might be possible to predict disease risk in conditions like AS where there exists a variant of large effect (i.e., HLA-B27).

He noted that although the current paradigm in diagnostic testing was to test only variants known to affect disease risk, extra information might be gathered by genotyping individuals across their genome and constructing a risk score based on thousands of putative genetic variants. He showed that constructing a genome-wide score did increase the degree to which individuals with and without disease could be discriminated[3].

Dr. Evans briefly discussed how new findings from GWAS could be used to inform classical observational epidemiology through a technique called Mendelian randomization. Because randomized clinical trials are not always possible or ethical, Mendelian randomization could be used

as an alternative to investigate whether an exposure-disease association reflects an underlying causal relationship. The approach is based on Mendel's law of independent assortment (i.e., inheritance of a trait is independent with respect to other traits) so that individuals are in essence randomized into 3 "exposures" according to their genotype, and that their genotype at this locus should be random (under certain assumptions) with respect to other confounding factors. As an example, he showed how a variant in the nicotinic receptor could be used as a proxy for smoking status (a modifiable environmental exposure) and how this could then be related to functional impairment on the Bath AS Functional Index (BASFI). If the variant in the nicotinic receptor was associated with functional impairment, then it suggests that smoking affects severity of AS, whereas if there was no correlation between the variant and BASFI, then it would suggest that the relationship between smoking and severity is correlational only.

The MHC and AS Susceptibility

John D. Reveille, MD (University of Texas, Houston, TX, USA) displayed a schematic of the MHC, which contains over 220 genes divided into 3 classes of molecules and which has the greatest single effect on susceptibility to AS — particularly HLA-B27. The arthritogenic peptide hypothesis suggests that disease results from the ability of HLA-B27 to bind a unique peptide or a set of antigenic peptides, and HLA-B27 misfolding generates the proinflammatory unfolded protein response. Over 62 HLA-B27 subtypes have evolved and migrated along ethnogeographic lines, with HLA-B*2705, the parent subtype, being the most common throughout the world, and small numbers of most other subtypes centered in particular areas of the globe (such as B*2703 in Africa; B*2707 in the Middle East; B*2702 in Europe; B*2704 in East Asia; and B*2706 in Southeast Asia).

Although numerous HLA-B27 subtypes exist, only HLA-B*2705, B*2702, B*2704, and B*2707 have been definitely shown to be associated with AS. HLA-B*2706 and B*2709 are not associated with AS, and in fact may be protective, which some have attributed to the last Asp at position 116. However, AS-associated HLA-B*2707 also lacks Asp116 and shows preference for peptides with nonpolar C-terminal residues. Examination of the relationships between the peptide specificity of B*2707 and those of the disease-associated B*2705 and the non-associated subtypes found that the B*2707-bound repertoire was as different from that of B*2705 as from those of B*2706, B*2709, or the 2 latter subtypes from each other[4].

HLA-B27 can adopt novel conformations, resulting in differential accessibility of cysteine residues, which can explain the propensity to homodimerize. The cysteine exposure in the HLA-B27 heavy chain is also affected by residues within the 114 and 116 regions, thereby possibly providing a potential biochemical basis for the association of HLA-B27 subtypes with AS[5].

Dr. Reveille reminded the group that while less than 5% of HLA-B27-positive people develop SpA, 20% of HLA-B27-positive relatives of AS patients will develop SpA. And although family studies suggest that HLA-B27 forms only about 16%–40% of the overall risk for SpA, the entire effect of the MHC is about 50%. Other HLA-B alleles that have been implicated in AS susceptibility include B*4001 (B60; White and Asian cohorts)[6] and B*1403 (West Africa)[7].

Non-MHC and AS Susceptibility

Matthew Brown, MBBS, MD, FRACP (Diamantina Institute, University of Queensland, Brisbane, Australia) began with an update of the Australo-Anglo-American Spondylitis Consortium (TASC) GWAS, introduced briefly elsewhere in this supplement[8]. In the study in question, several previously unknown loci were newly identified. Three markers for the 2p15 "gene desert" achieved genome-wide significance in the discovery set [rs10865331 ($p = 6.1 \times 10^{-15}$), rs10865332 ($p = 3.5 \times 10^{-10}$), and rs4672503 ($p = 9.3 \times 10^{-10}$)] and 2 were genotyped in the confirmation set [rs4672495 ($p = 8.4 \times 10^{-4}$), rs10865331 ($p = 5.5 \times 10^{-6}$)]; the combined association was very strong for rs4672495 ($p = 3.2 \times 10^{-9}$) and rs10865331 ($p = 1.9 \times 10^{-19}$). Of note, 2p15 has not been associated previously with any disease.

Three markers for the 21q22 gene desert also achieved genome-wide significance in the discovery set [rs2242944 ($p = 2.7 \times 10^{-14}$), rs2836878 ($p = 4.9 \times 10^{-12}$), rs378108 ($p = 6.1 \times 10^{-11}$)] and one was genotyped in the confirmation set [rs2242944 ($p = 5.6 \times 10^{-7}$)], with a strong combined association for rs2242944 ($p = 8.3 \times 10^{-20}$). 21q22 had been associated previously with pediatric IBD[9]; however, the association did not change with exclusion of IBD cases in our study [n = 1159 cases; rs2242944 ($p = 1.3 \times 10^{-9}$)].

The peak association for the known loci ERAP1 (endoplasmic reticulum aminopeptidase) lies in a 4.6 kb region between rs27529 to rs469758, achieving $p < 10^{-11}$. Two noncoding single-nucleotide polymorphisms (SNP) also lie in this region, including rs31087. ERAP1 has 2 known functions: it cleaves cytokine receptors (e.g., TNFR1, IL1R2, IL6Rα) from the cell surface; and it trims peptides before presentation by HLA Class 1 molecules.

The strongest associated SNP for the known locus IL23R is rs11209026 ($p = 9.1 \times 10^{-14}$). Strong association also was observed with rs11465817 ($p = 1.2 \times 10^{-10}$), compared with rs11209026 ($p = 2.3 \times 10^{-9}$). Among East Asians, IL23R is not associated with Crohn's disease (CD) in Japanese[10], nor with psoriasis in Han Chinese[11] or AS in Koreans[12] or Han Chinese[13].

The strongest associations for IL1R2 were with genotyped markers at rs2310173 ($p = 8.3 \times 10^{-6}$) and imputed markers at rs10185424 ($p = 5.4 \times 10^{-6}$); rs2310173 also was

associated with AS in the replication study ($p = 0.018$) and overall ($p = 4.8 \times 10^{-7}$). For ANTXR2, rs4333130 was associated with AS in both the discovery cohort ($p = 7.5 \times 10^{-7}$) and replication cohort ($p = 0.029$), and overall ($p = 9.3 \times 10^{-8}$).

Several other genes (TNFR1, TRADD, CARD9, STAT3, TNFSF15) have shown moderate associations that have not been fully established. In most GWAS studies, study power remains limited and further work must be done.

Genetics of Psoriasis and Psoriatic Arthritis

Vinod Chandran, MBBS, MD, DM, on behalf of Dafna D. Gladman, MD, FRCPC (University of Toronto, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, Toronto, Canada), outlined the systematic approach to identifying genetic factors in disease[14]; showed that the recurrence risk ratio is increased in psoriasis and psoriatic arthritis (PsA)[15,16]; and presented a summary of results from linkage studies in psoriasis that have identified 10 psoriasis susceptibility loci, as well as the result of a single linkage study in PsA[17,18]. He summarized association studies in psoriasis and PsA and described the largest GWAS survey in psoriasis that revealed an association with Th17 and nuclear factor- B (NF-κB) pathways, in addition to confirming the strong association with HLA-Cw6[19]. Associations of genomic copy number variants with psoriasis (ß-defensin, late cornified envelope LCE3B and LCE3C genes) were discussed.

Among several environmental factors that appear to affect development of disease, smoking reportedly has a major effect: the time to development of PsA decreases with smoking prior to psoriasis onset, but increases with smoking after psoriasis onset[20]. Also, the association between IL13 polymorphisms and PsA is modified by smoking[21].

Moreover, the risk allele, HLA-Cw*0602, is reportedly associated with early onset psoriasis, higher incidence of guttate or streptococcal-induced flares, koebnerization, and a more severe disease course[22]. In PsA, HLA alleles associated with patterns of joint involvement as well as joint damage progression and protection were discussed[23].

Dr. Chandran concluded by suggesting that genetic studies have the potential to help us understand disease pathogenesis and identify pharmacologic targets, and may help predict disease course and response to therapy.

Genetics of Uveitis

Tammy M. Martin, PhD (Department of Ophthalmology, Oregon Health and Science University, Portland, OR, USA) began with a discussion of Mendelian uveitic disease: studying the genotype/phenotype relationships of rare autosomal dominant forms of uveitis can provide insights into the disease, and different variations in the same gene can lead to dominant as well as complex disease phenotypes. She noted that several NOD-like receptors (nucleotide-binding oligomerization domain) have been implicated in diseases such as IBD, asthma, CD, and Blau syndrome, and said that in a cohort of Blau syndrome patients with NOD2 mutation, ocular involvement was the most relevant morbidity[24]. The discovery of NOD2 mutations in Blau syndrome has led to ongoing studies in animal models.

Dr. Martin reviewed several strong MHC Class I associations [HLA-A29, birdshot retinochoroidopathy; HLA-B15 and HLA-B51, Behçet's disease; HLA-B27, acute anterior uveitis (AAU)] before discussing the challenges of uveitis genetic studies: clinical descriptors are variably used; subjects are not followed longitudinally; and the same uveitis phenotype may be present in the absence or presence of systemic disease, and may be episodic. Uveitis nomenclature for reporting clinical trial data was standardized following an international workshop in 2005[25].

Linkage mapping was used in the first genome-wide scan for AAU[26], in which regions with linkage to AAU [chromosomes 6p (MHC) and 1q] also were found to have linkage to AS; a gene on chromosome 9q may be uniquely implicated in AAU. In a candidate-gene analysis, the relationship of IL23R SNP to genetic risk in uveitis was studied because of the well established clinical association of uveitis with IBD, psoriasis, and AS; 6 of 11 IL23R SNP were associated with AAU. Two ERAP1 SNP, previously identified for AS susceptibility, have also been associated with AAU; however, a larger cohort is needed to verify this finding.

Dr. Martin presented interesting work with KIR, which are expressed on natural killer cells and some T cells and transmit activating (aKIR) or inhibitory (iKIR) signals to these cells. In a study of 143 AAU patients and 429 controls, there were no differences in KIR gene frequencies or genotypes between AAU and controls; however, a trend was noted toward decreased aKIR genes in AAU with SpA compared to controls[27].

In a GWAS survey of uveitis patients versus AS patients with/without uveitis, no differences were noted at known AS loci (MHC, IL23R, ERAP1, 2p15, 21q22, IL1R2, ANTXR2); however, some positive associations indicate that we can detect uveitis-specific genetic factors. Alternative comparisons and further research is needed.

Genetics of Inflammatory Bowel Disease

Dermot McGovern, MD, PhD, MRCP (Cedars-Sinai Medical Center, Los Angeles, CA, USA) summarized the recent advances in IBD, CD, and ulcerative colitis (UC) genetics and how these novel insights help us not only to better understand the pathogenesis of IBD but also may lead to a more sophisticated molecular classification of the heterogeneous conditions within IBD as well as highlighting novel pathways for future therapeutic intervention in IBD.

Variants of the NOD2 gene and the 5q31 cytokine cluster were associated with CD in the pre-GWAS era[28,29], and after several GWAS studies and a metaanalysis, a total of 32

loci had been confirmed as CD susceptibility regions[30,31,32,33]. These findings highlighted novel pathogenic pathways including autophagy and the IL23R/Th17 pathway[32]. Dr. McGovern also discussed a GWAS in patients with UC, where UC loci were identified at chromosomes 1p36 and 12q15[34].

After summarizing IBD-associated genetic findings organized by cellular immune mechanisms, Dr. McGovern emphasized that additional studies are required following identification of loci in GWAS studies. These include both more detailed haplotypic analysis of the individual loci as well as appropriate pathway analyses such as have been performed with IL23R itself[33] and the extended IL23/IL17 pathway[35]. Further, "functional" studies are also necessary to determine how these loci alter disease susceptibility; one recent example of such a study demonstrated that TL1A (encoded by the IBD gene TNFSF15) is expressed differentially by haplotype, ethnic background, and antibody response[36].

Future genetic work in IBD should include characterizing the complete extent and causative SNP of loci, conducting larger and smarter GWAS studies, and analyzing both gene-environment and gene-gene interactions.

Genetics of Enteropathic Arthritis

Paul Wordsworth, MA, MB, FRCP (University of Oxford, Headington, UK) reminded the group that the presentation of AS is highly variable and often insidious, which contributes to diagnostic delay. Unsurprisingly, where coexistent active IBD is observed, involvement of the axial skeleton may be missed. In his series of over 3000 subjects with AS, about 6% also have IBD, and many patients with IBD have peripheral and/or axial arthritis[37]. The prevalence of peripheral arthritis was reviewed among patients with IBD (n = 976 with UC, and n = 483 with CD) attending the Oxford (UK) IBD clinic. Type 1 arthropathy (typically oligoarticular and self-limiting) affects about 3.6% of those with UC and 6% of those with CD; Type 2 arthropathy (typically polyarticular and persistent) affects about 2.5% of those with UC and 4% of those with CD[38]. Further, these 2 clinically distinct forms of arthropathy had distinctive immunogenetic associations (Type 1 with HLA-B27, -B35, and –DRB1*0103; Type 2 with HLA-B44[39]). In a subgroup of patients with CD of at least 5 years' duration, suggestive magnetic resonance image (MRI) evidence of sacroiliitis was observed in over one-third of patients. HLA-B27 correlated better with the presence of clinical AS than with MRI sacroiliitis alone[40]. The relevance of these findings should be tested in longitudinal studies.

Prof. Wordsworth reviewed results from the Wellcome Trust Case-Control Consortium (WTCCC) GWAS, particularly the involvement of ERAP1 (also know as ARTS 1) and IL23R with AS[41]. The Oxford Spondyloarthropathy Research Group extended the WTCCC study of IL23R to 730 further AS cases and combined their results in a meta-analysis, which confirmed the association with AS (rs11209026; OR = 0.61, $p < 10^{-10}$)[42]. This association is robust to stratification on the presence of IBD and/or psoriasis, indicating that the association with this coding SNP is likely to be the primary association with AS[42]. Other genes that are associated with both IBD and AS include CARD9, an important component of the innate immune system, linking infection and NF-κB activation[43]. The number of genetic associations common to both IBD and AS is likely to increase with the imminent release of further GWAS data in both conditions, highlighting the likely common genetic background to these disorders, which also show substantial clinical overlap.

Microbes, Spondyloarthritis, and Innate Immunity

Robert D. Inman, MD, FRCPC, FACP, FRCP (Toronto Western Hospital, Toronto, Canada) spoke of SpA as an interplay of genes and germs, citing 2 studies: target-tissue injury in the postinfectious sequelae of Salmonella in reactive arthritis (ReA) that suggested a pathogen-host interaction[44]; and a study of host determinants of severity in experimental Chlamydia-induced arthritis[45]. Further, a genetically defined early host immune response to an arthritogenic pathogen may result in either transient inflammation or chronic joint injury, showing results from a study of interferon-γ dysregulation in patients with AS[46]. In a study of the Rac gene in neutrophils and Toll-like receptor 4 (TLR4) in mice, Rac deficiency was associated with a decrease in severity of acute Chlamydia-induced arthritis and an increase in severity of chronic Chlamydia-induced arthritis, indicating that innate immunity, the first line of host defense against pathogens, sets the stage for ReA. The data also demonstrated that Chlamydia upregulation of TLR4 in neutrophils depends on Rac[47].

Two separate studies in mice were discussed: one where pathogen-derived TLR2 ligands promoted proliferation of dysfunctional Tregs (regulatory T lymphocytes) paralleled by temporarily abrogated suppression, thus failing to suppress an immune response to acute infection[48]; and a second where TLR2 deficiency was associated with increased arthritis severity and a TLR4 deficiency with decreased arthritis severity[49]. He also discussed a study of 592 people who developed acute gastroenteritis following an outbreak of Salmonella in Ontario in 2005: of 104 people who responded to the survey, 62 reported extraintestinal symptoms consistent with ReA. Genotyping of patients and controls demonstrated that TRL2 polymorphisms are associated with acute ReA[50].

Recognizing the plasticity of the immune response (genetically defined or not) is important because environmental exposure can reverse an inherent resistance to ReA, resulting in a susceptible phenotype[51]. In an individual who is B27-positive, or who has certain allelic variants of the

ERAP1 or IL23R genes, the immune stage is set for the development of SpA. Ongoing research into gene-environment interactions in SpA should look broadly at genetic susceptibility and at potential environmental factors.

Future Plans of SPARTAN and IGAS

SPARTAN and IGAS will continue to support clinical research projects in SpA. SPARTAN's next Annual Research and Education meeting will be held July 23–24, 2010, in Houston, TX (see www.spartangroup.org). The next meeting of IGAS will be held Shanghai in March 2011, to be organized by Prof. Huji Xu.

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