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Review

Comparative immunogenetics of autism and schizophrenia

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Autism and schizophrenia are highly heritable neurodevelopmental disorders, each mediated by a diverse suite of genetic and environmental risk factors. Comorbidity and familial aggregation of such neurodevelopmental disorders with other disease-related conditions can provide important insights into their etiology. Epidemiological studies have documented reduced rates of rheumatoid arthritis, a systemic autoimmune condition, in schizophrenia, and recent work has shown increased rates of rheumatoid arthritis in first-degree relatives of autistic individuals, especially mothers. Advances in understanding the genetic basis of rheumatoid arthritis have shown that much of the genetic liability to this condition is due to risk and protective alleles at the HLA *DRB1* locus. These data allow robust testing of the hypotheses that allelic variation at *DRB1* pleiotropically modulates risk of rheumatoid arthritis, autism and schizophrenia. Systematic review of the literature indicates that reported associations of *DRB1* variants with these three conditions are congruent with a pleiotropic model: *DRB1*04* alleles have been associated with increased risk of rheumatoid arthritis and autism but decreased risk of schizophrenia, and *DRB1*13* alleles have been associated with protection from rheumatoid arthritis and autism but higher risk of schizophrenia. These convergent findings from genetics and epidemiology imply that a subset of autism and schizophrenia cases may be underlain by genetically based neuroimmune alterations, and that analyses of the causes of risk and protective effects from *DRB1* variants may provide new approaches to therapy.

Keywords: autism, HLA *DRB1*, immune, neurodevelopment, rheumatoid arthritis, schizophrenia

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Autism and schizophrenia are each highly heritable neurodevelopmental disorders mediated by genetic risk factors ranging from rare, single-gene mutations and copy-number variants to common single nucleotide polymorphisms of small effect (Abrahams & Geschwind 2010; Happé *et al*. 2006; Stefansson *et al*. 2009). Given the complex genetic architecture of each of these conditions, recent approaches to understanding etiology and developing rational therapies have focused on identifying subsets of cases that share phenotypes, genetic risk factors and alterations to particular neurodevelopmental and neurological function pathways (Bourgeron 2009; Ehninger *et al*. 2008; Kalkman 2006).

Alterations to aspects of the immune system have been recognized as correlates of neurodevelopmental disorders for many years, based predominantly on patterns of cytokine imbalance, the presence of brain autoantibodies in some patients, comorbidities and familial associations with autoimmune diseases, and functional roles of the neuroimmune system in brain development (Ashwood *et al*. 2006, 2011; Goldsmith & Rogers 2008; Müller & Schwarz 2006; Patterson 2009; Schwartz & Shechter 2010; Theoharides *et al*. 2009). Such findings have been additionally supported by recent genome-wide association studies that show human leukocyte antigen (HLA) loci among the strongest known common-variant risk factors for schizophrenia (International Schizophrenia Consortium 2008; Shi *et al*. 2009; Stefansson *et al*. 2009) and gene expression studies that have documented differential expression of *DRB1* (or its paralog *DRB4*) in schizophrenia (Glatt *et al*. 2005) and autism (Ghahramani Seno *et al*. 2011; Lintas *et al*. in press). Gene network analyses have also reported enrichment of schizophrenia risk genes in immunological pathways in general and rheumatoid arthritis-related genes in particular (Guilloux *et al*. 2010; Sun *et al*. 2010). In autism, analysis of genes and gene pathways convergently dysregulated in autism spectrum disorder, Rett syndrome and Down syndrome has similarly identified immune functions as the strongest molecular commonality among the three conditions (Lintas *et al*. in press).

A useful approach to elucidating causes of association between immune-related processes and neurodevelopmental disorders is the analysis of epidemiological data that link immune-related disorders with autism or schizophrenia. One of the best-replicated immunological correlates of schizophrenia is an apparent reduced incidence of the autoimmune condition rheumatoid arthritis in individuals with schizophrenia (Gilvarry *et al*. 1996; Gorwood *et al*. 2004; Oken & Schulzer 1999). Diverse hypotheses have been proposed to explain this strong, inverse epidemiological

association (Torrey & Yolken 2001), but robust tests of the hypotheses have thus far been precluded due to limitations in understanding the genetic bases of schizophrenia, autism and rheumatoid arthritis and how they might be related. These constraints have recently been partly alleviated due to progress in understanding the genetic basis of rheumatoid arthritis (Imboden 2009; Orozco & Barton 2010). Recent studies have also shown elevated rates of rheumatoid arthritis in mothers of offspring with autism (Atladóttir *et al*. 2009) and genetic links of autism with the immune system locus, *DRB1*, that is most closely associated with genetically based risk of rheumatoid arthritis (Johnson *et al*. 2009).

The purpose of this review is to evaluate the hypothesis that epidemiological associations of schizophrenia, and autism, with rheumatoid arthritis are mediated, in part, by pleiotropic effects of genetic variation at the *DRB1* locus. This hypothesis makes specific predictions regarding five independent lines of evidence: (1) genetic associations of rheumatoid arthritis with *DRB1* alleles, (2) genetic associations of autism with *DRB1* alleles, (3) genetic associations of schizophrenia with *DRB1* alleles, (4) epidemiological associations of autism with rheumatoid arthritis and (5) epidemiological associations of schizophrenia with rheumatoid arthritis. To the extent that these sources of evidence yield concordant results, subsets of cases of autism and schizophrenia should be recognizable as mediated in part by neuroimmune etiologies due to variation at the *DRB1* locus.

Methods

To evaluate the evidence for epidemiological associations of rheumatoid arthritis with autism and schizophrenia, and the *DRB1* locus with these three conditions, PubMed and Web of Science were searched using combinations of the terms 'rheumatoid arthritis', 'autism', 'schizophrenia', 'HLA', 'DRB1*04', 'DRB1*13' and 'genetic'.

Results

We first provide a brief overview of the human *DRB1* locus, followed by relevant background on rheumatoid arthritis and how genetic variation at *DRB1* affects risk of, and protection from, this condition. Next, we review the genetic association data regarding *DRB1* in autism risk and schizophrenia risk, with a focus on the sets of alleles known to mediate the etiology of rheumatoid arthritis. Finally, we present the epidemiological data that relate rheumatoid arthritis with autism and schizophrenia.

HLA DRB1 locus

The HLA locus spans about 4 Mb at chromosome 6, cytoband p21.31 and includes over 160 known protein-coding genes (Shiina *et al*. 2009; Traherne 2008). The class II region gene *DRB1* encodes the beta subunit of the heterodimeric HLA-DR protein that presents peptides, derived from extracellular proteins, to immune system cells that elicit or suppress the production of antibodies. This locus harbors over 450 alleles and has evolved very rapidly in the human lineage (Hohjoh *et al*. 2003; von Salomé *et al*. 2007). High density of genes and single nucleotide polymorphisms (SNP) in the HLA region, complex patterns of gene copy-number variation (variation among individuals in numbers of copies of specific gene regions) and extensive long-range linkage disequilibrium between variants complicate the assignment of phenotypic effects to particular loci or alleles (Blomhoff *et al*. 2006; McEvoy *et al*. 2009; Traherne 2008). Copy-number variation may be largely responsible for the inadequate coverage of the HLA region on standard commercial SNP arrays, and although some common HLA alleles can be tagged with a small number of genetic markers (Leslie *et al*. 2008), it is currently problematic to predict HLA alleles via SNP-based tagging alone (de Bakker *et al*. 2006; Mayilyan *et al*. 2008) unless this region is specifically targeted for detailed analysis.

Phenotypic effects and selective pressures associated with the HLA region in general and the *DRB1* locus in particular include infectious disease resistance (Apanius *et al*. 1997; Blackwell *et al*. 2009), autoimmune disease risk (Fernando *et al*. 2008; Price *et al*. 1999; Reveille 2006), mate choice (Chaix *et al*. 2008), recurrent spontaneous abortion (Hviid & Christiansen 2005; Kruse *et al*. 2004), segregation distortion (Alper *et al*. 1986; Awdeh *et al*. 1983; Crouau-Roy & Clayton 2002), maternal–fetal conflicts (Haig 1997, 2004) and birth weight variation (Aroviita *et al*. 2004; Capittini *et al*. 2009; Hviid 2004). Moreover, as described in more detail below, effects of *DRB1* genotype on autoimmune disease susceptibility have been shown to depend on not just the genotype of the patient, but also on the noninherited genotype present in the mother, which has been considered in only a small subset of analyses (Johnson *et al*. 2009).

DRB1 haplotypes are designated by generic type (e.g. *DRB1*04*) or through fine-scale genotyping, by hierarchically nested subtype (e.g. *DRB1*0401*). Genetic studies of rheumatoid arthritis include *DRB1* subtype information, but most genetic studies of *DRB1* haplotypes in relation to autism or schizophrenia risk do not.

HLA DRB1 and rheumatoid arthritis

Rheumatoid arthritis is a chronic, systemic inflammatory autoimmune disease, with 30–50% of the overall genetic susceptibility ascribed to genetic variation at the HLA locus, predominantly *DRB1* (Holoshitz 2010; Imboden 2009; Stahl *et al*. 2010). Risk of rheumatoid arthritis due to *DRB1* variants is largely a function of the amino acids at hypervariable positions 70–74 in the HLA-DR molecule, whose identity determines the shape of the peptide-binding groove that interacts with both antigenic peptides and the T-cell receptor that stimulates immune responses (de Vries *et al*. 2011; Imboden 2009). *DRB1* variants coding for Q-K-R-A-A, K-K-R-A-A or Q-Q-R-A-A at these two positions – the so-called shared epitope in the rheumatoid arthritis literature (de Vries *et al*. 2011) – are associated with well-replicated, greatly increased risk and severity of this disease, with odds ratios of 3–4.5 from bearing one such allele and 7–13 from bearing two (Tables 1 and 2 in Imboden 2009). Such high risk of rheumatoid arthritis from the presence of Q-K-R-A-A, K-K-R-A-A or Q-Q-R-A-A at residues 70–74 is due predominantly to the *DRB1* alleles *0401, *0404 and *0101, which are present

at much higher frequencies in European populations than the other risk alleles (De Almeida *et al*. in press; Imboden 2009). In contrast to such high-risk variants, one set of amino acids at these residues, D-E-R-A-A, is associated with an approximately twofold reduction in rheumatoid arthritis risk, compared to variants with no measurable effect, which harbor other combinations of amino acids at these positions (de Vries *et al*. 2006, 2011; Feitsma *et al*. 2008; Lundström *et al*. 2009). Such protection from rheumatoid arthritis is conferred mainly through the *1301 and *1302 haplotypes, which are about 10-fold more common in Europeans than other haplotypes coding for the D-E-R-A-A combination. The mechanisms whereby the *DRB1*-shared epitope generates increased or decreased rheumatoid arthritis remain unknown, but appear to involve activation or deletion of autoreactive T cells, and, for protective effects, stimulation of regulatory T cells (Taneja *et al*. 2008).

Increased or reduced risk of rheumatoid arthritis due to amino acid variation at positions 70–74 in *DRB1* is mediated not just by the genotype of the focal individual, but also by the genotype of their mother (Feitsma *et al*. 2007, 2008; Guthrie *et al*. 2009; Harney *et al*. 2003), with the two sources of risk or protection appearing to be of comparable magnitude (de Vries *et al*. 2011; Feitsma *et al*. 2008). Modulation of risk thus depends in part on an individual's noninherited maternal antigen, the *DRB1* allele present in the mother but not inherited. Noninherited maternal antigens influence immune system function in the offspring due to trafficking of cells at the placental interface during pregnancy, which leads to maternal microchimerism – the long-term persistence of maternally derived cells in diverse tissues of the offspring (Kaplan & Land 2005; Klonisch & Drouin 2009). Transfer of the rheumatoid arthritis-shared epitope via maternal microchimerism has recently been documented directly (Rak *et al*. 2009; Yan *et al*. in press), and maternal microchimerism appears to represent a general mechanism for modulation of autoimmune disease risk, as well as risk of transplant rejection, in human populations (Stevens *et al*. 2009; von Rood & Claas 2000).

Amino acid variation at residues 70–74 confers risk or protection with regard to the main form of rheumatoid arthritis (at least 70% of cases), which involves production of autoantibodies to proteins that are citrullinated – post-translationally modified via conversion of arginine to citrulline (Alivernini *et al*. 2008; de Vries *et al*. 2011; Holoshitz 2010; Taneja & David 2010; van Gaalen *et al*. 2005). The genetic basis of rheumatoid arthritis cases not characterized by anti-citrullinated protein antibodies is less well understood, but increased risk of this form of the disease has been linked with a large HLA haplotype, referred to as the 8.1 ancestral haplotype, that is common (with frequencies of 5–10%) in northern Europeans (Gregersen 2003; Plenge 2009).

Autism risk and HLA DRB1

Evaluation of autism risk with regard to *DRB1* variants has focused predominantly on *DRB1*04* (also known as DR4) and the extended haplotypes that bear *DRB1*04* alleles, as these variants were shown to mediate risk in the initial series of studies. Warren *et al*. (1991) showed that autistic individuals ($N = 38$) and their mothers, but not their fathers, exhibited a significantly higher frequency than controls ($N = 62$) of the *C4B* null allele ($P = 0.03$ for autistic subjects, $P = 0.01$ for mothers). The *C4B* null allele forms part of the ancestral HLA haplotype 44.1 (B44-SC30-DRB1*0401-DQ7) (Warren *et al*. 1996a; Windsor *et al*. 2005). This finding was replicated in Warren *et al*. (1992) ($N = 21$ cases and 62 controls, $P = 0.0035$ for autistic subjects, $P = 0.016$ for mothers) and Daniels *et al*. (1995) ($N = 45$ cases + parents, and 64 controls; $P < 0.001$ for autistic subjects and mothers). Using case–control studies, a significantly higher frequency of the *C4B* null allele in autistics compared to controls was also reported by Odell *et al*. (2005) ($N = 85$ cases and 69 controls; odds ratio 4.33, $P = 0.00006$) and Mostafa and Shehab (2010) ($N = 80$ cases and 80 controls; odds ratio 6.26, $P < 0.001$).

Warren *et al*. (1996b) found significantly higher frequencies of two haplotypes, B44-SC30-DR4 and B62-SC33-DR4, both of which bear the *DRB1*0401* allele, in autistic individuals ($N = 50$) compared to controls ($N = 79$), with relative risk of autism increasing 19.8-fold for individuals with Q-K-R-A-A at amino acid positions 70–74 ($P < 0.001$). Warren *et al*. (1996b) also found suggestive evidence for higher risk from *DRB1*0401* as the noninherited maternal haplotype, with nine mothers of autistic children but no fathers, bearing Q-K-R-A-A. The presence of *DRB1*0401* on either of the maternal chromosomes (inherited or not) may thus increase risk of autism in offspring. An apparent association of the shared epitope Q-K-R-A-A or Q-R-R-A-A with higher risk of both autism and rheumatoid arthritis was also described by Warren *et al*. (1996b) as evidence for autoimmune etiology in a subset of autism cases. All these studies involved northern Europeans and several of them (Daniels *et al*. 1995; Warren *et al*. 1991, 1992, 1996a,b) used partially overlapping samples of autistic individuals, and thus cannot be considered as independent. By contrast, the Odell *et al*. (2005) study described above used a fully separate set of cases and controls.

Torres *et al*. (2002) found evidence for involvement of both *DRB1*04* and *DRB1*13* alleles in risk of autism, using samples from 103 families of northern Europeans that apparently overlap in part with those from previous studies from the same laboratory group (Daniels *et al*. 2005; Warren *et al*. 1991, 1992, 1996). Torres *et al*. (2002), however, analyzed family-structured data and showed a higher frequency of the *DRB1*04* allele ($P = 0.007$) and a lower frequency of the *DRB1*13* pooled with *DRB1*14* ($P = 0.003$) in autistics compared to controls. *DRB1*13*, the 'protective' allele was also inherited less frequently than expected from mothers ($P = 0.006$), and the risk allele *DRB1*04* was inherited more frequently than expected from fathers ($P = 0.026$). These findings are consistent with a dominant protective effect from the noninherited maternal allele *DRB1*13* in mothers and increased risk from both inherited and noninherited DRB1*04 alleles in mothers, although this hypothesis was not evaluated directly. Similar parent-specific effects of *DRB1* variants on risk and protection have also been reported for type 1 diabetes (Akesson *et al*. 2009; Feitsma *et al*. 2007).

Lee *et al*. (2006) studied HLA variants in autism for one population in Tennessee (16 families) and one set of AGRE samples (33 families) from diverse localities across the USA. For the Tennessee population they reported higher

frequencies of the *DRB1*0401* and *DRB1*0404* alleles in autistics (odds ratio 4.2, $P < 0.05$) and their mothers (odds ratio 5.5, $P < 0.05$) but not fathers; by contrast, the AGRE sample showed no differences. These authors also noted that 'unlike autism, in schizophrenia *DRB1*04* is less common in patients and mothers and therefore appears to be protective against the disease', citing Wright *et al*. (1996a).

Guerini *et al*. (2006, 2009) tested for associations of HLA markers with autism in a population of 37 families in Sardinia. In both studies, they found no differences between autistics and controls in *DRB1* genotype ($P > 0.40$ by TDT tests). Data on the haplotype structure of regions bearing these alleles are required to evaluate such data further, especially given the highly unusual genetic structure of human populations in Sardinia (Marrosu *et al*. 2001). Guerini *et al*. (2011) also tested for associations of HLA markers with autism using an Italian population (without Sardinian ancestry) including 76 children with autism spectrum disorder, their siblings and parents, compared to published HLA data in controls. Case–control and TDT tests did not show any significant associations with class II HLA markers, including *DRB1* (results not shown in original paper).

In a recent study of *DRB1* alleles in autism risk, Johnson *et al*. (2009) used 31 families from New Jersey, mainly Caucasians, and showed that significant transmission disequilibrium of *DRB1*04* was seen only for transmissions from maternal grandmothers to mothers of autistic children (odds ratio 4.67, $P = 0.008$) and not from mothers or parents to autistic offspring. These results provide evidence that *DRB1*04* in mothers increases risk of autism in offspring, apparently via effects on the fetus during pregnancy (Johnson 2003) (Fig. 1).

Synthesis

Studies of five independent populations, (1) one population in Warren *et al*. (1991, 1992, 1996b) and Daniels *et al*. (1995) from Utah and Oregon, (2) one population in Odell *et al*. (2005) from Utah and Oregon, (3) one population in Tennessee (Lee *et al*. 2008), (4) one population in New Jersey (Johnson *et al*. 2009), and (5) one population in Egypt (Mostafa & Shehab 2010), have yielded evidence for *DRB1*04* alleles, in probands, their mothers or both, as risk factors in the etiology of autism. Moreover, two of these studies (Torres *et al*. 2002; Warren *et al*. 1996b) showed patterns consistent with effects of noninherited maternal alleles at *DRB1*, involving increased risk (via *DRB1*04*) or protection (via *DRB1*13*). These results are consistent with a simple model (Fig. 1) whereby the presence of *DRB1*04* on either of the maternal chromosomes confers increased risk of autism in offspring, whereas *DRB1*13* on either of the maternal chromosomes confers protection, as for rheumatoid arthritis. Data from Johnson *et al*. (2009) are consistent with a lack of effect on risk from *DRB1*04* in offspring themselves, but robust interpretation of these results regarding maternal and offspring risk and protection alleles requires additional studies.

In contrast to these results, four studies, two of Sardinians (Guerini et 2006, 2009), one of Italians (Guerini *et al*. 2011) and one of a geographically diverse population (Lee *et al*. 2006), found no associations of *DRB1* alleles with autism.

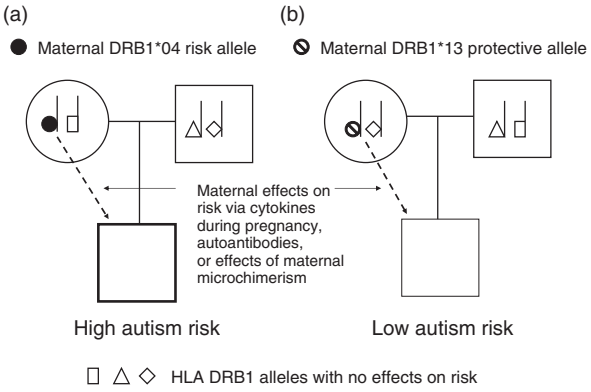

Figure 1: Model for maternal risk and protective alleles of *DRB1* modulating risk of autism in offspring. (a) The *DRB1*04* allele in mothers may lead to increased autism risk in offspring via effects of fetal cytokine exposure, autoantibodies or microchimerism, whether or not the risk allele is inherited by the offspring. (b) The *DRB1*13* allele may protect against autism by similar mechanisms. To the extent that offspring autism risk is mediated by such maternal effects, offspring genotype itself need not directly influence risk. However, case–control studies may still show significant effects on autism risk from *DRB1*04* and *DRB1*13* alleles, due to their distributions within and among families. This model is based predominantly on data in Warren *et al*. (1991, 1996), Li *et al*. (2001), Torres *et al*. (2002), Lee *et al*. (2006) and Johnson *et al*. (2009). Offspring sex is arbitrary. Maternal effects from *HLA DRB1* alleles are also involved in the inheritance of rheumatoid arthritis risk and may be involved in inheritance of schizophrenia risk, as described in the text.

The primary limitations to interpretation of these positive and negative studies are small sample sizes, population-specific effects given high geographic variation in HLA haplotypes, lack of fine-scale *DRB1* genotyping and analysis of locus-specific and extended haplotypes via conditioned analyses and the absence of systematic testing for noninherited maternal antigen effects or effects on risk or protection parallel to those found for rheumatoid arthritis.

Schizophrenia risk and HLA-DRB1

Wright *et al*. (2001) review studies of HLA loci in schizophrenia, reporting evidence of replicated associations for three loci with specific typing or subtyping: *DRB1*01* (four studies), *DQB*0602* (three studies) and *DRB1*04* (two studies). Odds ratios were similar for the two studies involving *DRB1*04*: (1) a study of Caucasians (Wright *et al*. 1996a; $N = 94$ schizophrenia patients, 92 of their mothers and 177 controls, $P = 0.004$, odds ratio 0.46 comparing patients with controls, $P = 0.002$, odds ratio 0.42 comparing mothers with controls) and 0.63 in a study of Japanese (Arinami *et al*. 1998, with 266 patients and 281 controls, $P = 0.02$) for whom *DRB1*0405* is the most common allelic subtype. Multiple studies did not further replicate these three HLA associations with regard to *DRB1*04* (Akaho *et al*. 2000 with 45 patients and 117 controls, $P > 0.10$; Li *et al*. 2001 with TDT tests on 165 families, $P > 0.10$; Nunes *et al*. 2005 with 50 patients

and 48 controls, $P > 0.50$; see also Wright *et al*. 2001 for details on earlier studies). Several additional lines of evidence salient to effects of *DRB1*04* in schizophrenia include: (1) consistency of the results with those of Blackwood *et al*. (1996), who reported a nominally significant association (odds ratio 0.58, $P = 0.04$) that did not survive adjustment for multiple tests, (2) a nonsignificant trend toward preferential nontransmission of *DRB1*04* from heterozygous parents to schizophrenic offspring ($N = 23$ pedigrees with 187 individuals, $P = 0.06$) (Wright *et al*. 1998), (3) a reduced frequency of *DQA1*0301/2* alleles, which are in tight linkage with *DRB1*04* (Fernando *et al*. 2008), in schizophrenics ($N = 94$ patients, 177 controls, odds ratio 0.52, $P = 0.01$) and their mothers (92 mothers, 177 controls, odds ratio $= 0.38$, $P = 0.0004$) (Wright *et al*. 1997), (4) a significant protective effect in the analysis of three pooled Japanese case–control samples ($N = 181$ patients and 825 controls, $P = 0.005$) (Sasaki *et al*. 1999) and (5) a lack of effects from *DRB1*04* genotype in a set of studies conducted prior to 2001 (reviewed in Wright *et al*. 2001), including work by Hawi *et al*. (1999) and Gibson *et al*. (1999) suggesting that some positive results from Wright *et al*. (1996a) may have been confounded by population stratification.

One study noted preferential transmission in TDT tests, for a Chinese population, of the *DRB1*13* allele in schizophrenia (Li *et al*. 2001, 165 families, $P = 0.041$), such that this allele is positively associated with the disorder. This result has not been replicated, but data in Nunes *et al*. (2005), comparing the frequencies of *DRB1*13* between controls (1, 2% of 48) and schizophrenia patients (6, 12% of 50), yielded a marginally nonsignificant result (Fisher's exact test, $P = 0.062$), also suggesting a higher frequency of this allele in schizophrenia.

Three recent genome-wide association studies have reported associations of SNPs in the HLA region, including SNPs at the *DRB1* locus (Shi *et al*. 2009), with risk of schizophrenia (Nöthen *et al*. 2010). These findings are difficult to evaluate directly in the context of the hypotheses addressed here, because the studies did not directly consider the *DRB1*04* or *DRB1*13* haplotypes or the efficiency of tagging *DRB1* alleles. One of the strongest results from these studies was apparent protective effects from the *DRB1*0301* allele (which is a component of the HLA 8.1 extended haplotype) (Baschal *et al*. 2009) on risk of schizophrenia (International Schizophrenia Consortium 2008). This finding is concordant with a higher incidence of autoimmune diseases in individuals with the 8.1 extended haplotype (Candore *et al*. 2002), but this haplotype is associated only with the anti-citrullinated antibody-negative form of rheumatoid arthritis (Plenge 2009). This form of rheumatoid arthritis is genetically and etiologically distinct from the most common form of rheumatoid arthritis (the anti-citrullinated antibody-positive form), which is mediated by the shared epitope and other residues at the hypervariable region of *DRB1*. An alternative hypothesis for the mechanism of a protective effect from *DRB1*0301* (and the 8.1 haplotype) in schizophrenia risk is the higher birth weight of individuals with this haplotype (Aroviita *et al*. 2004; Capittini *et al*. 2009), given that higher birth weight has been shown to protect against schizophrenia (Abel *et al*. 2010).

Synthesis

Multiple lines of evidence support a negative association of *DRB1*04* with schizophrenia risk. However, transmission disequilibrium tests, using large samples of families and HLA genotyping focusing on rheumatoid arthritis risk and protective alleles (Imboden 2009), are required for more conclusive tests of such protective effects and tests for increased susceptibility from *DRB1*13*.

Epidemiological associations of rheumatoid arthritis with autism

Money *et al*. (1971) first suggested an autoimmune etiology for some cases of autism, based on comorbidity and familial aggregation of autoimmune conditions and autism in one family. Anecdotal accounts from Sullivan (1975) describe a notable prevalence of rheumatoid arthritis in particular in families with autistic children, an apparent pattern also reported by Raiten and Massaro (1986), who found that 5 of the 15 mothers of autistic children in their sample had rheumatoid arthritis.

Comi *et al*. (1999) analyzed familial clustering of autoimmune disorders in autism (using families of 61 autistic patients and 46 controls), finding that across seven such conditions, only combined adult and juvenile rheumatoid arthritis exhibited a significant difference between autism (46% of family members) and controls (26%) (odds ratio 2.4, $P < 0.05$). Juvenile rheumatoid arthritis represents a heterogeneous set of rheumatoid conditions showing partial overlap with adult rheumatoid arthritis with regard to the role of *DRB1*04* (Garavito *et al*. 2004). The difference between autism (39%) and controls (24%) for adult rheumatoid arthritis considered separately was nonsignificant (odds ratio 2.1, $P = 0.095$). Comi *et al*. (1999) also reported a higher combined incidence of autoimmune diseases in mothers of autistics compared to controls (odds ratio 8.8, $P < 0.05$), with considerably lower odds ratios for other family members and combinations thereof.

Using a study design similar to that of Comi *et al*. (1999), but also including individuals with pervasive developmental disorder not otherwise specified (PDD-NOS), Sweeten *et al*. (2003) reported an overall higher incidence of autoimmune conditions in families of individuals with PDD-NOS than in controls ($N = 101$ families for each), especially with regard to mothers, but data on the incidence of rheumatoid arthritis are not presented and can be inferred to be nonsignificant. Croen *et al*. (2005) found a lack of difference in the incidence of rheumatoid arthritis, in the 4-year period surrounding pregnancy, between mothers of children with autism (0.2%; $N = 333$) and control mothers (0.3%; $N = 1709$).

Molloy *et al*. (2006) evaluated the role of autoimmune factors in autism spectrum disorders with, and without, a history of regression in the phenotypic manifestation of autism. These authors found a higher rate of autoimmune conditions in family members (especially maternal relatives) of individuals with regression; no difference was found for rheumatoid arthritis considered separately (39, 25% of 155 families with regression; 28, 20% of 144 without regression), and these rates were not compared with those of controls. By contrast, a comparable study by Valicenti-McDermott

et al. (2006) reported threefold higher rates (33%, 8 of 24) of rheumatoid arthritis in first- and second-degree family members of autistic individuals with language regression, compared to autistic individuals without language regression (11%, 8 of 71; $P = 0.02$).

Mostafa *et al*. (2008), Mostafa and Kitchener (2009), and Mostafa and Shehab (2010) reported significantly higher rates of autoimmune conditions (most commonly rheumatoid arthritis, but also including type 1 diabetes, systemic lupus erythematosus, rheumatic fever and type 1 diabetes) in first- and second-degree relatives of children with autism than in controls ($P < 0.001$ in each study). Data on the incidence of autoimmune conditions among mothers in particular, described in Mostafa and Kitchener (2009), provide evidence for a higher incidence of rheumatoid arthritis in mothers of children with autism (6 of 80), compared to controls (none of 80; Fisher's exact test, $P = 0.014$); comparable test results for other autoimmune conditions were nonsignificant.

The largest, most comprehensive study of autoimmunity in relation to autism spectrum disorders was conducted by Atladóttir *et al*. (2009), who used Danish Registry data (1993–2004) to test for higher rates of autoimmune conditions in parents and siblings of individuals with autism spectrum disorders ($N = 3325$) compared to controls ($N = 685\,871$). Significantly higher risk of autism spectrum disorders was reported for children of mothers with rheumatoid arthritis (incidence rate ratio 1.70, $P < 0.05$) and celiac disease, and higher risk of infantile autism was found in children with a family history of type 1 diabetes.

Keil *et al*. (2010) used data from 1968 to 2003, from the Swedish Registry systems to quantify rates of autoimmune diseases in parents of children with autism spectrum disorders ($N = 1227$) compared to controls ($N = 30\,693$). They found weakly but significantly higher rates of autoimmune disorders in mothers (odds ratio 1.6, 95% CI 1.1–2.2, $P < 0.05$) and fathers (odds ratio 1.4, 95% CI 1.0–2.0, $P < 0.05$) of children with ASD. Rheumatoid arthritis was not included in their set of autoimmune conditions.

Synthesis

Multiple studies show higher incidence of autoimmune conditions in relatives, especially maternal relatives, of individuals with autism spectrum conditions, although high heterogeneity among studies in populations and methods, and small sample sizes in most studies, limit the generality of inferences. However, evidence from the most recent studies, with comparatively large samples (Atladóttir *et al*. 2009; Mostafa & Kitchener 2009), shows a significantly higher incidence of rheumatoid arthritis in mothers of children with autism.

Epidemiological associations of rheumatoid arthritis with schizophrenia

Low rates of comorbidity between schizophrenia and rheumatoid arthritis were initially reported by Nissen and Spencer (1936), and the first large-scale review found reduced rates of rheumatoid arthritis in schizophrenics across 12 of 14 studies (Eaton *et al*. 1992). A formal meta-analysis was conducted by Oken & Schulzer (1999), who computed an overall relative risk for rheumatoid arthritis, in schizophrenics compared to individuals with other psychiatric diagnoses, of 0.288 ($P < 0.0001$, 95% CI 0.22–0.38), from nine independent studies; they also estimated that the relative risk in schizophrenics, compared to the general population, may be as low as one-third of this value.

Mors *et al*. (1999) reported odds ratios for rheumatoid arthritis in schizophrenic individuals of 0.46 for females and 0.44 for males and females combined ($P < 0.05$ for each; $N = 20\,495$ schizophrenia patients and 204 912 controls), but similarly reduced odds for several musculoskeletal conditions; these authors suggested that ascertainment bias, due to underreporting of pain in schizophrenia, may partially account for the negative association of the two conditions. Lack of association of rheumatoid arthritis with schizophrenia or nonaffective psychosis (in individuals or first-order relatives) was reported by Eaton *et al*. (2006) ($N = 7704$ schizophrenia patients and 192 590 controls) and Eaton *et al*. (2010) ($N = 20{,}317$ schizophrenia cases and 39 076 cases of nonaffective psychosis in a population sample of 2 901 158) using study designs that required rheumatoid arthritis to have appeared before the patient was diagnosed with schizophrenia or nonaffective psychosis, which is relatively unlikely given the usual earlier onset of these psychiatric conditions than rheumatoid arthritis.

Gorwood *et al*. (2004) tested for an inverse relationship between schizophrenia-related psychological phenotypes and rheumatoid arthritis, by scoring rheumatoid arthritis patients ($N = 220$), schizophrenics ($N = 44$), individuals with psoriatic arthritis ($N = 88$) and additional controls ($N = 196$) with nonspecific medical conditions, on measures of paranoid ideation and psychoticism. They found 25% lower levels of paranoid ideation in patients with rheumatoid arthritis than in controls ($P = 0.005$) after controlling for age, gender and disease severity; they also found the expected highly elevated levels of psychoticism and paranoid ideation in schizophrenics. Gorwood *et al*. (2004) also noted that low rates of comorbidity between rheumatoid arthritis and schizophrenia appear to represent a robust finding, given that the relationship has been found: (1) in multiple countries, (2) in large samples of schizophrenics specifically assessed for rheumatoid arthritis, (3) using control populations of individuals with other psychiatric diagnoses, as well as population-based controls, (4) with various means of assessment for the relationship of the two conditions and (5) via their analysis at a dimensional level.

Four studies have provided data on rates of rheumatoid arthritis in first-degree relatives of schizophrenics. McLaughlin (1977) and Gilvarry *et al*. (1996) reported lower rates of rheumatoid arthritis in mothers of schizophrenics (but not, in the latter study, across all first-degree relatives), Wright *et al*. (1996b) found similar rates in first-degree relatives and in mothers of schizophrenia patients ($N = 121$) compared to controls ($N = 116$) and Eaton *et al*. (2006) reported significantly higher rates of rheumatoid arthritis in parents of schizophrenia patients, in a study (described above) that required rheumatoid arthritis to have appeared before schizophrenia was diagnosed.

Synthesis

The meta-analysis by Oken and Schilzer (1999) and dimensional analysis by Gorwood *et al*. (2004) provide clear evidence for an inverse relationship between schizophrenia and rheumatoid arthritis. Additional data on rates of rheumatoid arthritis in mothers of schizophrenics are required for robust interpretation, and such information would be especially useful if combined with data on *DRB1* genotypes.

Discussion

The primary finding of this review is that the genetic and epidemiological evidence available to date are largely concordant with a simple model of pleiotropic effects from *DRB1* alleles on risk of rheumatoid arthritis, autism and schizophrenia (Fig. 2). By this model, *DRB1*04* mediates increased risk of both rheumatoid arthritis and autism, but decreased risk of schizophrenia; by contrast, the *DRB1*13* allele tends to protect against rheumatoid arthritis and autism, but may increase risk of schizophrenia. Although some of the genetic or epidemiological associations between these three conditions remain weak, the five independent lines of evidence evaluated here provide convergent support for the model, which can serve as a simple working hypothesis for targeted tests. Of particular note is the data showing effects from the mother's *DRB1* haplotype on disease risk in the offspring, for rheumatoid arthritis, autism and schizophrenia. These results, in conjunction with other studies showing effects of maternal genotype at other loci on risk or severity of autism or schizophrenia in offspring (Cohen *et al*. 2011; James *et al*. 2010; Kistner-Griffin *et al*. 2011; Williams *et al*. 2007; Zhang *et al*. 2010), suggest that some proportion of the 'missing' heritability for neurodevelopmental disorders may reside in genetically based maternal effects on risk (Johnson 1999), which have seldom been addressed even in family-based studies.

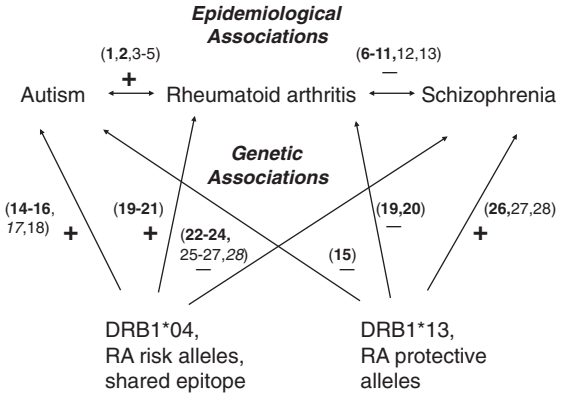

Figure 2: Depiction of the primary evidence for and against epidemiological and genetic associations involving autism, rheumatoid arthritis, schizophrenia, and *DRB1* alleles. A '+' refers to positive associations that are supported by statistically significant evidence from one or more studies (citations below), and '−' refers to negative associations that are supported by statistically significant evidence in one or more studies. Boldface numbers refer to articles that describe statistical support for the association, non-boldface numbers refer to studies that tested for the association and found nonsignificant results and italicized numbers refer to studies that report a mixture of significant and nonsignificant results. (1) Atladóttir *et al*. (2009); (2) Mostafa *et al*. (2008), Mostafa and Kitchener (2009) and Mostafa and Shehab (2010); (3) Comi *et al*. (1999); (4) Sweeten *et al*. (2003); (5) Croen *et al*. (2005); (6) Eaton *et al*. (1992); (7) Mors *et al*. (1999); (8) Oken and Schilzer (1999); (9) Gorwood *et al*. (2004); (10) McLaughlin (1977); (11) Gilvarry *et al*. (1996); (12) Wright *et al*. (1996b); (13) Eaton *et al*. (2006, 2010); (14) Warren *et al*. (1996b); (15) Torres *et al*. (2002); (16) Johnson *et al*. (2009); (17) Lee *et al*. (2006); (18) Guerini *et al*. (2006, 2009, 2011); (19) Feitsma *et al*. (2008); (20) Imboden *et al*. (2009); (21) Holoshitz (2010); (22) Wright *et al*. (1996a); (23) Arinami *et al*. (1998); (24) Sasaki *et al*. (1999); (25) Akaho *et al*. (2000); (26) Li *et al*. (2001); (27) Nunes *et al*. (2005); (28) Wright *et al*. (2001) (review summarizing results prior to 2001).

Several candidate mechanisms may help to explain pleiotropic associations of *DRB1* haplotypes with risk of rheumatoid arthritis, autism and schizophrenia. First, cytokines pleiotropically regulate both immune system inflammatory reactions and central aspects of neurodevelopment (Deverman and Patterson 2009; Jonakait 2007; Meyer *et al*. 2011), with major alterations in levels of inflammatory cytokines such as IL-6 and TNFα reported in schizophrenia and autism (Ashwood *et al*. 2011; Watanabe *et al*. 2010) as well as rheumatoid arthritis (Brennan and McInnes 2008). In particular, inflammation during pregnancy due to infection represents a well-documented risk factor for schizophrenia and autism (Meyer *et al*. 2011; Patterson 2009); by contrast, pregnancy ameliorates inflammatory symptoms of rheumatoid arthritis in about two-thirds of females (de Man *et al*. 2008; Østensen and Villiger 2007). Roles for *DRB1* haplotypes in cytokine mediation of neurodevelopmental conditions, via effects during pregnancy and later in development, have yet to be investigated.

Second, the nitric oxide (NO) signaling system has been implicated in risk and etiology of both rheumatoid arthritis and neurodevelopmental disorders. NO, a highly diffusible gas, is produced in neurons and immune system cells such as macrophages and endothelial cells, via NO synthases that convert arginine to citrulline. In rheumatoid arthritis, NO signaling appears to be triggered by the presence of the shared epitope, higher NO levels are positively correlated with inflammatory markers of rheumatoid arthritis, and anti-RA agents suppress NO production (Holoshitz 2010; Holoshitz *et al*. 2007; Taneja & David 2010) (Fig. 3a). Autoantibodies against citrullinated proteins, associated with overactive NO signaling, may play a role in the etiology of rheumatoid arthritis, although the mechanisms involved remain to be fully elucidated Alivernini *et al*. 2008; Ling & Holoshitz 2007; Nagy *et al*. 2007).

In the brain, calcium influx via *N*-methyl-D-aspartate (NMDA) receptor activation represents a key trigger for NO production, and NO is an important modulator of neuronal activity via the glutamatergic and dopaminergic systems (Hoque *et al*. 2010; Rodrigo & Felipo 2007; Vincent 2010) (Fig. 3b). Allelic variants of nitric oxide synthase genes have been associated with risk of autism (Kim *et al*. 2009) and

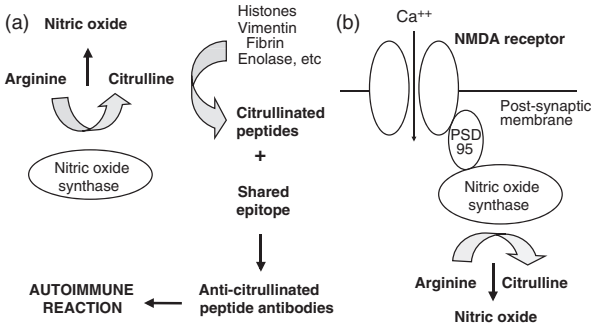

Figure 3: Models for the role of nitric oxide in rheumatoid arthritis and neurodevelopmental disorders. (a) Hypothesis for development of autoimmunity to citrullinated proteins in rheumatoid arthritis, after Alivernini *et al*. (2008, Fig. 1). Nitric oxide signaling is mediated by citrullination, and citrullinated peptides interact with the *HLA DRB1* shared epitope to generate autoantibodies. (b) Nitric oxide signaling in neurons, adapted from Greener (2004, Fig. 1). Post-synaptic calcium influx via NMDA receptors activates neuronal nitric oxide synthase, which diffuses to nitrosylate cysteine residues on protein targets. CAPON, the protein product of the schizophrenia-associated gene *NOS1AP* (Kremeyer *et al*. 2009; Wratten *et al*. 2009) also competes with PSD95 for binding with nNOS, to activate Dexras1 (not shown).

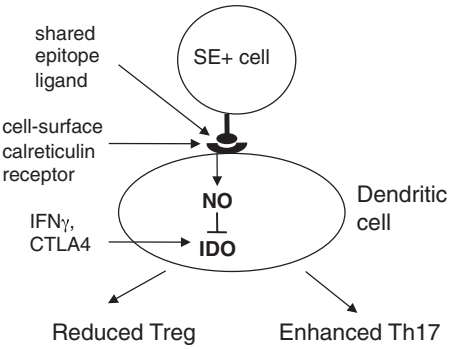

Figure 4: Proposed model for effects of *HLA DRB1* shared epitope on NO signaling and Treg/Th17 balance in risk of rheumatoid arthritis, adapted from Holoshitz *et al*. (2010, Fig. 3). Interaction of the shared epitope with the calreticulin receptor stimulates NO production, which inhibits activity of IDO. This inhibition results in a decrease in tryptophan metabolites and reduced generation of Treg cells, concomitant to excessive Th17 polarization that mediates the autoimmune response.

schizophrenia (Bernstein *et al*. 2005; O'Donovan 2008; Tang 2008), and levels of plasma NO (or NO metabolites) have been reported as increased in autism (Sweeten *et al*. 2004) and decreased in schizophrenia (Lee & Kim 2008; Nakano *et al*. 2010; Reif *et al*. in press). Risperidone has also been reported to increase NO activity (Nakano *et al*. 2010), and in mice, phencyclidine-induced schizophrenic symptoms can be blocked by pretreatment with NO synthase inhibitors (Wass *et al*. 2009). These findings suggest roles for NO alterations in autism and schizophrenia risk that involve changes to activation of NMDA receptors and related systems of glutamatergic and dopaminergic signaling (Blaylock & Strunecka 2009; Kantrowitz & Javitt 2010). Given, however, that NO synthase is generally overexpressed in inflammatory conditions (Kobayashi 2010), the degree to which altered NO signaling in rheumatoid arthritis, schizophrenia and autism indicates pleiotropic effects due in part to variation at the *DRB1* locus remains unclear.

Third, the presence of autoantibodies targeting brain proteins has been reported in autism (Dantzer & Kelley 2008; Gupta *et al*. in press). Such autoantibodies may be maternally derived via the placenta, from mothers subject to autoimmune conditions or other causes of immune activation (Braunschweig *et al*. 2008; Goines *et al*. 2011). These findings may help to explain higher rates of some autoimmune disorders (including rheumatoid arthritis) in mothers of children with autism. Brain autoantibodies generated via citrullination (Kidd *et al*. 2008) represent a potential mechanism that would link autoantibodies in autism with effects from *DRB1*-shared epitope alleles.

Fourth, *DRB1* locus effects on rheumatoid arthritis and autoimmune-associated risks of autism and schizophrenia may be mediated not by self-peptide presentation, but by cell-surface calreticulin acting as a signal-transducing receptor for the shared epitope (De Almeida *et al*. 2010, in press; Holoshitz *et al*. 2010). By this mechanism, the shared epitope acts as an allele-specific signal-transducing ligand that activates NO signaling and polarizes T-cell differentiation toward Th17 cells and away from development of autoimmune-suppressing Treg cells (Fig. 4). Calreticulin has also been implicated in glutamatergic signaling via the NMDA receptor (Hossain *et al*. 2000) and in genetic risk of schizophrenia itself (Farokhashtiani *et al*. 2011), as have two other genes underlying central components of this pathway, *IFN-α* and *CTLA4* (Jones *et al*. 2009; Paul-Samojedny *et al*. 2011). Schizophrenia risk may also be influenced through this pathway by effects from alterations to indoleamine 2,3 dioxygenase (IDO) and IFN-α activity on kynurenine metabolism (Müller & Schwarz 2010), such that IDO activity is increased in schizophrenia (Müller *et al*. 2011), in contrast to its inhibition by increased NO in rheumatoid arthritis (De Almeida *et al*. 2010). This hypothesis predicts alterations to calreticulin and NO signaling, as well as Treg/Th17 (regulatory T cell/helper T cell 17) balance, in rheumatoid arthritis and some subset of individuals with autism or schizophrenia. An animal model of maternal infection during pregnancy has shown preferential development of Th17 cells, which is associated with increased inflammatory responses, autoimmunity and alterations to fetal neurodevelopment (Mandal *et al*. 2011). In schizophrenia, serum levels of IL17 (a Th17-associated cytokine) have been shown to be significantly and substantially increased (Schwarz *et al*. in press, Table 2), but the functional significance of this alteration has yet to be investigated. Schwarz *et al*. (in press) also showed serum biomarker discrimination between autism (Asperger syndrome) and schizophrenia with sensitivity and specificity of 0.96, partially on the basis of cytokine-level differences.

Finally, maternal microchimerism effects, whereby maternal cells enter the offspring via the placenta, persist for

many years, and modulate immune system development and function, have been shown to mediate liability to rheumatoid arthritis and other autoimmune conditions (Feitsma *et al*. 2008; Gammill & Nelson 2010; Miech 2010; Nelson *et al*. 2007; Rak *et al*. 2009; Yan *et al*. 2011). Maternal microchimerism provides a possible explanation for association of autism risk in offspring with mother's *DRB1* genotype (Johnson *et al*. 2009) and rheumatoid arthritis status (Altadóttir *et al*. 2009), via alterations to immune system development, production of autoantibodies or other processes.

The main implication of this review is that a subset of cases of autism (Sacco *et al*. 2010) and schizophrenia (Sun *et al*. 2010) appear to be mediated, more or less directly, by immune system alterations that involve *DRB1* alleles in patients and mothers. Such subsets of cases may be recognizable via fine-scale genotyping of this locus (Leslie *et al*. 2008) that focuses on shared epitope vs protective alleles, in conjunction with functional studies designed to differentiate between the models depicted in Figs 3 and 4 and to evaluate possible roles for maternal microchimerism in pathogenesis. Established therapies that modulate inflammatory signaling pathways in rheumatoid arthritis and other conditions (Benicky *et al*. 2011) may usefully be investigated as treatments for such subsets of patients (Careaga *et al*. 2010).

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