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Association between Susceptibility to Theiler's Virus-Induced Demyelination and T-Cell Receptor *Jβ1-Cβ1* Polymorphism rather than *Vβ* Deletion

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Theiler's murine encephalomyelitis virus (TMEV) induces demyelinating disease in susceptible mouse strains after intracerebral inoculation. The clinical symptoms and histopathology of the central nervous system appear to be similar to those of human multiple sclerosis (MS), and thus, this system provides an excellent infectious animal model for studying MS. The virus-induced demyelination is immune mediated, and the genes involved in the immune response such as those for the T-cell receptor β-chain and major histocompatibility complex (MHC) haplotypes are known to influence disease susceptibility. To define whether the T-cell receptor *Jβ-Cβ* or *Vβ* genes are associated with susceptibility, we have analyzed F_2 mice from crosses of susceptible SJL/J ($V\beta^a$-$JC\beta^a$) mice and resistant C57L ($V\beta^a$-$JC\beta^b$) mice. Our results indicate that susceptibility to TMEV-induced demyelination is associated with restriction fragment length polymorphism reflecting the T-cell receptor *Jβ1-Cβ1* region rather than the *Vβ* polymorphism. This association becomes stronger when the MHC haplotype is considered in the linkage analysis. However, differences in the T-cell receptor α-chain haplotype have no significant influence on the pathogenesis of TMEV-induced demyelination.

Intracerebral inoculation of Theiler's murine encephalomyelitis virus (TMEV) into susceptible strains of mice induces a chronic inflammatory demyelinating disease which is similar to human multiple sclerosis (MS) (9, 28). The clinical signs of this virally induced demyelination include a spastic waddling gait, extensor spasms, and incontinence (9, 21). As with human MS, the pathogenesis of TMEV-induced demyelinating disease (TMEV-IDD) appears to be T lymphocyte mediated, based on immunologic, histopathologic, and genetic evidence (7, 21, 22, 24, 28, 29). Previously, it has been shown that susceptibility to TMEV-IDD is associated with genes coding for the major histocompatibility complex (MHC) (7, 29) and the constant region of the T-cell receptor (TCR) β-chain (24), although these genes may cooperate with each other and/or override other gene effects (19). The genetics of TMEV-IDD is similar to that of human MS. The first significant candidate gene locus conferring susceptibility to MS is apparently the MHC (8, 11, 16, 23, 34). TCR β-chain (2, 8) and α-chain (11) genotypes have also been linked to increased incidence of MS, although the significance of this association with the TCR alone has been challenged (11, 18, 36). However, some of the difficulties in these studies may be due to the potential complex interactions of multiple gene products which are involved in the induction and/or progression of MS (16).

To elucidate the relationship between susceptibility to TMEV-IDD and the genes involved in T-cell antigen recognition, the distribution of the MHC and TCR genes was correlated with susceptibility. Strains of mice were chosen to address whether the deletion of *Vβ* genes or the restriction fragment length polymorphism (RFLP) in the *Cβ1* region was involved in influencing susceptibility. This is particularly important in light of many studies indicating that T-cell populations involved in MS (27, 37) and experimental autoimmune encephalomyelitis (4, 40) may preferentially use a certain set of TCR *Vβ* and/or *Vα* genes. We generated crosses between resistant C57L ($H\text{-}2^b$) and susceptible SJL/J ($H\text{-}2^s$) strains. Both C57L mice and SJL mice carry identical sets of the *Vβ* genes ($V\beta^a$ haplotype) representing a nearly 50% deletion of *Vβ* genes in the genome compared to that ($V\beta^b$) of the majority of other mouse strains (1, 3, 33). However, these strains differ from each other in the *Cβ* RFLP pattern (12). The difference in *Cβ1* RFLP extends to the *Jβ1-Cβ1* region. On the other hand, the SJL/J mouse has a *Jβ1-Cβ1* RFLP identical to that of two other inbred strains (SWR and RIIIS/J) which are susceptible to TMEV-IDD (6, 12, 19, 30). Thus, we have utilized a combination of the above mice differing in the *Vβ* and *Jβ-Cβ* genes to elucidate the potential genetic association of susceptibility to viral demyelination with the genes involved in T-cell antigen recognition. For convenience of discussion, we designated the genotype of the SJL/J-type *Jβ1-Cβ1* RFLP "$JC\beta1^a$" and that of the C57L or C57BL/6 mice "$JC\beta1^b$" (Fig. 1 and Table 2).

C57L mice with a Vβ deletion exhibit resistance to TMEV-IDD. Table 1 shows the genotypes of the MHC, TCR β-chains, and TCR α-chains, as well as susceptibility to TMEV-IDD in the parental and the F_1 mice. SJL/J mice bearing homozygous $H\text{-}2^s$, $V\beta^a$-$JC\beta1^a$, and $V\alpha^c$ are susceptible to TMEV-IDD (97%). On the other hand, C57L mice expressing homozygous $H\text{-}2^b$, $V\beta^a$-$JC\beta1^b$, and $V\alpha^b$ are resistant (21%) to disease. F_1 mice from crosses between SJL/J and C57L mice are susceptible (86%), suggesting that $JC\beta1^a$ may be a dominant trait of susceptibility in this combination. These results are consistent with our previous report (20). Therefore, the potential association between the TCR β-chain genes and susceptibility to TMEV-IDD previously observed in congenic mice or crosses between BALB/c ($H\text{-}2^d$, $V\beta^b$-$JC\beta1^b$) and SJL ($H\text{-}2^s$, $V\beta^a$-$JC\beta1^a$) mice (19, 24) may reflect the *JCβ1* genotype differences rather than the deletion of *Vβ* genes ($V\beta^a$). However, this result cannot rule out the possibility that either TCR *Vα* or

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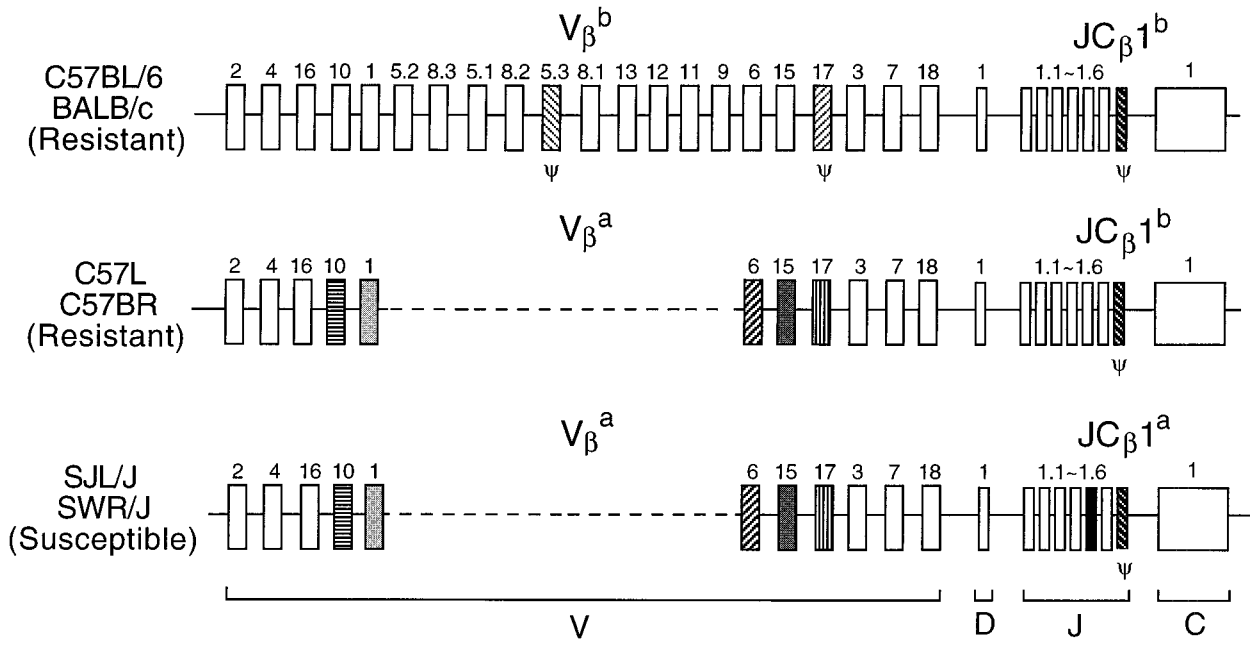

FIG. 1. Schematic diagram of genomic organization and polymorphism of the TCR β-chain genes in various mouse strains.

MHC may exert a dominant influence on susceptibility to TMEV-IDD.

***Jβ1-Cβ1* polymorphism is associated with susceptibility of (SJL/J × C57L)F_2 mice to TMEV-IDD.** To correlate these MHC and TCR genes with susceptibility to TMEV-IDD, we have analyzed gene segregation and susceptibility in F_2 mice derived from susceptible SJL/J and resistant C57L mice. Table 2 shows the relationship between the *Jβ1-Cβ1* polymorphism and susceptibility to TMEV-IDD in (SJL/J × C57L)F_2 mice. Mice (85%) with the homozygous $JC\beta1^a/JC\beta1^a$ genotype of susceptible SJL mice, even without considering the MHC haplotypes, were significantly ($P < 0.002$) more susceptible than mice (46%) with the homozygous $JC\beta1^b/JC\beta1^b$ genotype of resistant C57L mice (Table 2). We believe that this is the first report on F_2 analyses using TCR and MHC markers. Interestingly, RIIIS/J mice which carry the same *Jβ1-Cβ1* ($JC\beta1^a$) polymorphism as susceptible SJL/J mice (17) were also susceptible to TMEV-IDD: all eight (five females and three males) of the RIIIS/J mice developed clinical disease with a mean day of onset at day 71 with the BeAn 8386 strain (data not shown). Rodriguez et al. (30) have concluded that an increased susceptibility to TMEV-IDD by the DA strain is associated with an additional deletion in the *V*β region ($V\beta^c$) using the F_1 backcross and F_2 mice derived from RIIIS/J ($V\beta^c$-$JC\beta1^a$) and C57BR ($V\beta^a$-$JC\beta1^b$) mice. However, these results are also compatible with our hypothesis that the increased susceptibil-

TABLE 1. TCR, MHC, and susceptibility to TMEV-IDD of parental strains and the F_1 mice

Mice	Genotype				TMEV-IDD[a] (%)
	H-2	*V*β	*JC*β*1*	*V*α	
SJL/J	ss	aa	aa	cc	84/87 (97)
C57L	bb	aa	bb	bb	11/52 (21)
(SJL × C57L)F_1	sb	aa	ab	cb	32/37 (86)

[a] Number of mice with clinical disease/total number infected. BeAn 8386 stock (173R at 2×10^5 PFU in 30 μl of Dulbecco modified Eagle medium) was injected intracerebrally into each mouse (20). Clinical signs of spastic waddling gait and extensor spasms were tested on a skid-free surface. Mice were graded weekly for at least 140 days postinfection for clinical signs of disease. When a few mice were randomly examined for verification, the clinical signs were well correlated with the histopathology of demyelination (9). $P < 0.01$ for SJL/J versus C57L as well as for C57L versus (SJL/J × C57L)F_1. The InStat program (GraphPAD Software, San Diago, Calif.) was used to calculate the two-tailed *P* value by Fisher's exact 2×2 test as recommended for the analysis of small sample sizes. This was used in all statistical analyses.

TABLE 2. Relationship between susceptibility to TMEV-IDD and segregation of the TCR β-chain and *H-2* MHC type in (SJL/J × C57L)F_2 mice

H-2[a]	No. of mice with the following *JC*β genotype[b]:			Total (%)[c]
	aa	ab	bb	
ss	9/9[d]	9/11	2/3	20/23 (87)
sb	17/18[e,f]	17/30	5/13	39/61 (61)
bb	3/7	6/10	4/8	13/25 (52)
Total (%)	29/34[g,h] (85)	32/51[i] (63)	11/24 (46)	72/109 (66)

[a] In the early experiments, the *H-2* type of mice was determined by an antibody-mediated complement-dependent microcytotoxicity assay as described previously (20). In subsequent experiments, we used a method based on PCRs to simply the typing. The *Eco*RI-digested genomic DNAs were amplified by using the I-A specific primer sets. *H-2*[s]: forward, 5′-TGCTACTTCACCAACGGGACG-3′; reverse, 5′-CAGGTACTGCTTATTGTAGTA-3′. *H-2*[b]: forward, 5′-TGCTACTTCACCAACGGGACG-3′; reverse, 5′-CAGGATCTCCGGCTGGCTGTT-3′.

[b] TCR β-chain genotype: SJL/J = $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^a$; C57L = $V\beta^a$-$JC\beta1^b/V\beta^a$-$JC\beta1^b$. TCR typing was performed as described previously (19) by using standard Southern hybridization with TCR β-chain (Cβ1A and/or Vβ8.3) and TCR α-chain (Vα7 and Vα8.3) probes.

[c] Number of mice with clinical disease/total number infected.

[d] $P = 0.00004$ for one boxed set of data versus the other.

[e] $P = 0.008$ for $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^a$ versus $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^b$.

[f] $P = 0.001$ for $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^a$ versus $V\beta^a$-$JC\beta1^b/V\beta^a$-$JC\beta1^b$.

[g] $P = 0.028$ for $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^a$ versus $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^b$.

[h] $P = 0.00189$ for $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^a$ versus $V\beta^a$-$JC\beta^b/V\beta1^a$-$JC\beta1^b$.

[i] $P = 0.33$ for $V\beta^a$-$JC\beta1^a/V\beta^a$-$JC\beta1^b$ versus $V\beta^a$-$JC\beta1^b/V\beta^a$-$JC\beta1^b$.

ity in mice with *Vβ*^{c}-*JCβ1*^{a} may reflect the effect of *JCβ1*^{a} rather than that of *Vβ*^{c}.

To exclude the potential influence by MHC, F_2 mice with heterozygous MHC (*H-2*^{s}/*H-2*^{b}) were also analyzed. Again, there were significant differences in susceptibility between mice ($P = 0.001$) with homozygous *JCβ1*^{a}/*JCβ1*^{a} and *JCβ1*^{b}/*JCβ1*^{b} as well as between mice ($P = 0.028$) with homozygous *JCβ1*^{a}/*JCβ1*^{a} and heterozygous *JCβ1*^{a}/*JCβ1*^{b} (Table 2). However, there was no significant difference ($P = 0.33$) between F_2 mice with heterozygous *JCβ1*^{a}/*JCβ1*^{b} and homozygous *JCβ1*^{b}/*JCβ1*^{b}, indicating that the resistance effect associated with *JCβ1*^{b} functions in a dominant fashion. This is different from the susceptibility pattern in the F_1 mice, where susceptibility appears to be dominant. Therefore, the TCR polymorphism representing the *Jβ1-Cβ1* region, but not the *Vβ* deletion, may exert the susceptible-gene effect in concert with other, unknown gene products as well. When the homozygous *H-2*^{b}/*H-2*^{b}-bearing mice were excluded from the SJL/J-type *JCβ1*^{a} group and the homozygous *H-2*^{s}/*H-2*^{s} mice were excluded from the C57L-type *JCβ1*^{b} group in order to reduce the counteracting effect of MHC, the significance of the differences in susceptibility increased to an impressive level ($P = 0.00004$): the F_2 mice carrying a combination of homozygous *JCβ1*^{a}/*JCβ1*^{a} and susceptible *H-2*^{s} haplotypes (heterozygous or homozygous) were much more susceptible than those with homozygous *JCβ1*^{b}/*JCβ1*^{b} and resistant *H-2*^{b} haplotypes. These results clearly indicate that the difference in the *JCβ1* region is strongly associated with susceptibility to TMEV-IDD in combination with the MHC loci.

It is not yet clear how the difference in the *Jβ1-Cβ1* TCR gene RFLP influences susceptibility to disease in combination with MHC genes. One possibility is that a gene located in close proximity to *Jβ1-Cβ1* rather than *Jβ1-Cβ1* itself is involved in controlling susceptibility to TMEV-IDD. However, collectively these MHC and TCR genes are known to be involved in the establishment of the TCR repertoire toward specific antigens by restricting available regions of viral proteins to be recognized by TCR (38, 39). Susceptible mice may preferentially stimulate a set of T cells that secrete cytokines manifesting the disease. In addition, T cells may also be able to recognize a separate set of viral epitopes involved in immune-mediated pathogenesis. Alternatively, different specificities of virus-reactive cytotoxic T lymphocytes may be generated by the combinations of the gene products. These T cells may be more efficient in controlling viral persistence, which is likely a prerequisite for the immune-mediated pathogenicity of demyelination. To understand the mechanism of TMEV-induced demyelination, examination of TCRs specific for the disease process may be necessary.

The TCR α-chain haplotype difference is not associated with susceptibility to TMEV-IDD. In contrast to the genetic association between the *Jβ1-Cβ1* region and susceptibility to TMEV-IDD, TCR α-chain (32) segregation (Table 3) was not significantly associated with susceptibility ($P > 0.09$) among F_2 mice with *Vα*^{c}/*Vα*^{c}, *Vα*^{c}/*Vα*^{b}, or *Vα*^{b}/*Vα*^{b}. Even when the segregation of the TCR α-chain was combined with the MHC haplotype, there was no significant relationship between the TCR α-chain genotype and susceptibility to TMEV-IDD ($P = 0.16$ between mice with *Vα*^{c}/*Vα*^{c} and *H-2*^{s}/*H-2*^{s} or *H-2*^{s}/*H-2*^{b} and those with *Vα*^{b}/*Vα*^{b} and *H-2*^{b}/*H-2*^{b} or *H-2*^{b}/*H-2*^{s}). When the TCR α-chain genotype is similarly combined with TCR β-chain genotype (*JCβ1*), the susceptibility is again clearly controlled by the β-chain genotype but not by the α-chain genotype (data not shown). The lack of strong influence of a TCR α-chain genotype on TMEV-IDD was also found in the CxJ RI strains (19). However, previous reports have shown an association between some human TCR α- or β-chain genotypes and MS incidence (2, 26), although the association with the TCR α-chain is controversial (18). Therefore, it is conceivable that the lack of *Vα* genotype influence on susceptibility to TMEV-IDD is limited to particular strain combinations. Alternatively, this genotype difference may not critically affect the T-cell repertoire development involved in the pathogenicity of demyelination.

TABLE 3. Relationship between susceptibility to TMEV-IDD and segregation of the TCR α-chain and H-2 MHC type in (SJL/J × C57L)F_2 mice

H-2	No. of mice with the following α-chain genotype[a]:			Total[b] (%)
	cc	cb	bb	
ss	2/4 [c]	3/5	5/5	10/14 (71)
sb	7/13[d,e]	15/27[f]	3/13	25/53 (47)
bb	2/4	4/9	1/4	7/17 (41)
Total (%)	11/21[g] (52)	22/51 (43)	9/22 (41)	42/84 (50)

[a] TCR genotypes: SJL/J = *Vα*^{c}/*Vα*^{c}, C57L = *Vα*^{b}/*Vα*^{b}.
[b] Number of mice with clinical disease/total number infected.
[c] $P = 0.16$ for one boxed set of data versus the other.
[d] $P = 1.0$ for *Vα*^{c}/*Vα*^{c} versus *Vα*^{c}/*Vα*^{b}.
[e] $P = 0.11$ for *Vα*^{c}/*Vα*^{c} versus *Vα*^{b}/*Vα*^{b}.
[f] $P = 0.09$ for *Vα*^{c}/*Vα*^{b} versus *Vα*^{b}/*Vα*^{b}.
[g] $P = 0.55$ for *Vα*^{c}/*Vα*^{c} versus *Vα*^{b}/*Vα*^{b}.

Genomic DNA sequence analysis of the *Dβ1.1-Jβ1.6* region in SJL/J mice. It has been well established that *Jβ* is extremely important for antigen recognition by participating in the formation of the third complementary determinant region (CDR3) of the TCR β-chain (1, 14, 15) and that certain *Jβ1* usage in SJL/J mice is severely restricted (5, 25). To elucidate the relationship between the *Jβ1-Cβ1* polymorphism and susceptibility to TMEV-IDD, we cloned the *Dβ1-Jβ1* region (*JCβ1*^{a}) of the SJL/J mouse strain and compared it with the previously published mouse genomic *JCβ1*^{b} (B10.A) sequence (15). The *Jβ1-Cβ1* polymorphism represented mainly the scattered nucleotide substitutions throughout the noncoding regions between the *Jβ1.1* and *Jβ1.6* regions, without extensively clustered substitutions or deletions (GenBank database accession no. U77843). A single silent nucleotide substitution was found in the *Jβ1.4* coding region, and one additional as well as two substitutional variations were found in the *Jβ1.5* coding region (from Gln-Pro-Ala-Pro-Pro to Asn-Gln-Ala-Gln-His in the sequence of the first five amino acid). In addition, a variation was also identified in the nonamer recombinase recognition sequence (CCATATTCG→CCATATTAG) for *Jβ1.2* (data not shown) (GenBank accession no. U77843).

Collectively, our results indicate that the gene(s) coding for the *Jβ1* region is associated with resistance (or susceptibility) to TMEV-IDD in the strain combinations of susceptible SJL and resistant C57L mice, and this appears to function in concert with other genes including MHC haplotypes. The effect of the *Vβ* difference may not be critical in determining susceptibility to TMEV-IDD because C57BL/6 mice expressing a full set of *Vβ*'s with the identical *H-2*^{b} and *JCβ*^{b} yielded a level of resistance similar to that for C57L mice (29) (data not shown). Since a similar association of the resistance effect with the *JCβ*^{b} gene was also seen with other strain combinations such as SJL and BALB/c mice (19, 24), such association of susceptibility with the *Jβ1* RFLP is not likely restricted to this particular strain combination of SJL and C57L mice. Furthermore, our parallel experiments with (SJL × C57L)F_1 mice (Table 1) indicated that (SJL × C57BL/6)F_1 mice are similarly suscep-

tible (77% [data not shown]), in contrast to reports that (SJL × C57BL/6)F_1 mice are resistant (22). Differences in the substrains (sources) of mice and/or virus stocks may have caused the differences in susceptibility to TMEV-IDD in the F_1 mice. Preferential expression of specific TCR *V*β in central nervous system T cells compared to that in spleen cells of mice was not detectable (25, 31), and yet certain *Jβ1* usage is markedly skewed in susceptible SJL mice (5, 25). It has been suggested that this skewed usage of *Jβ1* is partially due to recombination mechanics and partially due to selection forces (5). It is known that Jβ is extremely important for antigen recognition by participating in the formation of the CDR3 region of the TCR β-chain (1, 14, 15). Therefore, these genes are most likely involved in shaping the T-cell repertoire, which may influence the manifestation of demyelinating disease as shown in identical twins with MS (35). Although direct correlation between the nucleotide sequence variations in the *JCβ1*^{a} genotype and the skewed usage of *Jβ1* is not yet available, we speculate that these variations in the JCβ1 regions may have an effect on the recognition by and/or function of factors involved in the recombinatory process. In fact, recent studies indicated that variations either in the introns upstream of J coding regions (13) or in the nonamer/heptamer sequences (10) can significantly influence the function of Rag-1 and -2, which are involved in the joining of V(D)J. Alternatively, an unknown gene(s) downstream of the TCR *JCβ1* region may be responsible for controlling susceptibility to TMEV-IDD. Ultimately, extensive analysis of *Jβ1* usage among T cells specific for TMEV epitopes during the development of demyelination may provide a critical clue as to whether the differences in the *J*β genes are directly involved in determining susceptibility to this disease.

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REFERENCES

1. **Barth, R. K., B. S. Kim, N. Lan, T. Hunkerpiller, N. Sobieck, A. Winoto, H. Gershenfeld, C. Okada, I. L. Weissman, and L. Hood.** 1985. The murine T-cell receptor uses a limited repertoire of expressed Vβ gene segments. Nature **316:**517–523.
2. **Beall, S. S., P. Concannon, P. Charmley, H. F. McFarland, R. A. Gatti, L. E. Hood, D. E. McFarlin, and W. E. Biddison.** 1989. The germline repertoire of T-cell receptor β-chain genes in patients with chronic progressive multiple sclerosis. J. Neuroimmunol. **21:**59–66.
3. **Behlke, M. H., H. Chou, K. Huppi, and D. Y. Loh.** 1986. Murine T-cell receptor mutants with deletions of β-chain variable region genes. Proc. Natl. Acad. Sci. USA **83:**767–771.
4. **Burns, F. R., X. B. Li, N. Shen, H. Offner, Y. K. Chou, A. A. Vandenbark, and E. Heber-Katz.** 1989. Both rat and mouse T cell receptors specific for the encephalitogenic determinant of myelin basic protein use similar Vα and Vβ chain genes even though the major histocompatibility complex and encephalitogenic determinants being recognized are different. J. Exp. Med. **169:**27–39.
5. **Candeias, S., C. Waltzinger, C. Benoist, and D. Mathis.** 1991. The Vβ17+ T cell repertoire: skewed Jβ usage after thymic selection; dissimilar CDR3s in $CD4^+$ versus $CD8^+$ cells. J. Exp. Med. **74:**989–1000.
6. **Clatch, R. J., H. L. Lipton, and S. D. Miller.** 1987. Class II-restricted T cell responses in Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease. II. Survey of host immune responses and central nervous system virus titers in bred mouse strains. Microb. Pathog. **3:**327–337.
7. **Clatch, R. J., R. W. Melvold, S. D. Miller, and H. L. Lipton.** 1985. Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease in mice is influenced by H-2D region: correlation with TMEV-specific delayed-type hypersensitivity. J. Immunol. **135:**1408–1414.
8. **Compston, D. A. S., H. Kellar Wood, N. Robertson, S. Sawcer, and N. W. Wood.** 1995. Genes and susceptibility to multiple sclerosis. Acta Neurol. Scand. Suppl. **161:**43–51.
9. **Dal Canto, M. C., and H. L. Lipton.** 1976. Primary demyelination in Theiler's virus infection. An ultrastructural study. Lab. Invest. **33:**626–637.
10. **Eastman, Q. E., T. M. J. Leu, and D. G. Schatz.** 1996. Initiation of V(D)J recombination in vitro obeying the 12/23 rule. Nature **380:**85–88.
11. **Ebers, G. C., K. Kukay, D. E. Bulman, A. D. Sadovnick, G. Rice, C. Andreson, H. Armstrong, K. Cousin, R. B. Bell, W. Hader, D. W. Paty, S. Hashimoto, J. Oger, P. Duquette, S. Warren, T. Gray, P. O'Connor, A. Nath, A. Auty, L. Metz, G. Francis, J. E. Paulseth, T. John Murray, W. Pryse-phillips, R. Nelson, M. Freedman, D. Brunet, J.-P. Bouchard, D. Hinds, and N. Risch.** 1996. A full genome search in multiple sclerosis. Nat. Genet. **13:**472–476.
12. **Epstein, R., N. Roehm, P. Marrack, J. Kappler, M. Davis, S. Hedrick, and M. Cohn.** 1985. Genetic markers of the antigen-specific T cell receptor locus. J. Exp. Med. **161:**1219–1224.
13. **Ferradini, L., H. Gu, A. DeSmet, K. Rajewsky, C.-A. Reynaud, and J.-C. Weill.** 1996. Rearrangement-enhancing element upstream of the mouse immunoglobulin kappa chain J cluster. Science **271:**1416–1420.
14. **Garcia, K. C., M. Degano, R. L. Stanfield, A. Brunmark, M. R. Jackson, D. A. Peterson, L. Teyton, and I. A. Wilson.** 1996. A αβ T cell receptor structure at 2.5Å and its orientation in TCR-MHC complex. Science **274:**209–219.
15. **Gascoigne, N. R. J., Y.-H. Chien, D. M. Becker, J. Kavaler, and M. M. Davis.** 1984. Genomic organization and sequence of T-cell receptor β-chain constant- and joining-region genes. Nature **310:**387–391.
16. **Haines, J. L., M. Ter-Minassian, A. Bazyk, J. F. Gusella, D. J. Kim, H. Terwedow, M. A. Pericak-Vance, J. B. Rimmier, C. S. Haynes, A. D. Roses, A. Lee, B. Shaner, M. Menold, E. Seboun, R.-P. Fitoussi, C. Gartioux, C. Reyes, F. Ribbierre, G. Gyapay, J. Weissenbach, S. L. Hauser, D. E. Goodkin, R. Lincoln, K. Usuku, A. Garcia-Merino, N. Gatto, S. Young, and J. R. Oksenberg.** 1996. A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. Nat. Genet. **13:**469–471.
17. **Haqqi, T. M., S. Banerjee, G. D. Anderson, and C. S. David.** 1989. RIIIS/J (H-2^r). An inbred mouse strain with a massive deletion of the T-cell receptor Vβ genes. J. Exp. Med. **169:**1903–1909.
18. **Hashimoto, L. L., T. W. Mak, and G. C. Ebers.** 1992. T cell receptor α-chain polymorphisms in multiple sclerosis. J. Neuroimmunol. **40:**41–48.
19. **Kappel, C. A., M. C. Dal Canto, R. W. Melvold, and B. S. Kim.** 1991. Hierarchy of effects of the MHC and T cell receptor β-chain genes in susceptibility to Theiler's murine encephalomyelitis virus-induced demyelinating disease. J. Immunol. **147:**4322–4326.
20. **Kappel, C. A., R. W. Melvold, and B. S. Kim.** 1990. Influence of sex on susceptibility in the Theiler's murine encephalomyelitis virus model for multiple sclerosis. J. Neuroimmunol. **29:**15–19.
21. **Lehrich, J. R., B. G. Arnason, and F. H. Hochberg.** 1976. Demyelinative myelopathy in mice induced by DA virus. J. Neurol. Sci. **29:**149–160.
22. **Lipton, H. L., and R. Melvold.** 1984. Genetic analysis of susceptibility to Theiler's virus-induced demyelinating disease in mice. J. Immunol. **132:**1821–1825.
23. **Marrosu, M. G., F. Muntoni, M. R. Murru.** 1992. HLA-DQB1 genotype in Sardinian multiple sclerosis: evidence for a key role of DQB1.0201 and DQB1.0302 alleles. Neurology **42:**883–886.
24. **Melvold, R. W., D. M. Jokinen, R. L. Knobler, and H. L. Lipton.** 1987. Variations of genetic control of susceptibility to Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease. I. Differences between susceptible SJL/J and resistant BALB/c strains map near the T-cell β-chain constant gene on chromosome 6. J. Immunol. **138:**1429–1433.
25. **Musette, P., J. F. Bureau, G. Gachelin, P. Kourilsky, and M. Brahic.** 1995. T lymphocyte repertoire in Theiler's virus encephalomyelitis: the nonspecific infiltration of the central nervous system of infected SJL/J mice is associated with a selective local T cell expansion. Eur. J. Immunol. **25:**1589–1593.
26. **Oksenberg, J. R., M. Sherritt, A. B. Begovich, H. A. Erlich, C. C. Bernard, L. L. Cavalli-Sforza, and L. Steinman.** 1989. T-cell receptor Vα and Cα alleles associated with multiple sclerosis and myasthenia gravis. Proc. Natl. Acad. Sci. USA **86:**988–992.
27. **Oksenberg, J. R., S. Stuart, A. B. Begovich, R. B. Bell, H. A. Erlich, L. Steinman, and C. C. Bernard.** 1990. Limited heterogeneity of rearranged T-cell receptor Vα transcripts in brains of multiple sclerosis patients. Nature **345:**344–346.
28. **Oleszak, E. L., J. Kuzmak, R. A. Good, and C. D. Platsoucas.** 1995. Immunology of Theiler's murine encephalomyelitis virus infection. Immunol. Res. **14:**13–33.
29. **Rodriguez, M., and C. S. David.** 1985. Demyelination induced by Theiler's virus: influence of the H-2 haplotype. J. Immunol. **135:**2145–2148.
30. **Rodriguez, M., A. K. Patick, L. R. Pease, and C. S. David.** 1992. Role of T cell receptor Vβ genes in Theiler's virus-induced demyelination of mice. J. Immunol. **148:**921–927.
31. **Rodriguez, M., N. Prayoonwiwat, P. Zhou, and C. David.** 1993. Expression of T cell receptor Vβ transcripts in central nervous system of mice susceptible and resistant to Theiler's virus-induced demyelination. J. Neuroimmunol. **47:**95–100.
32. **Singer, P. A., R. J. McEvilly, R. S. Baleras, F. J. Dixon, and A. N. Theofilopoulos.** 1988. T-cell receptor α-chain variable-region haplotypes of normal and autoimmune laboratory mouse strains. Proc. Natl. Acad. Sci. USA **85:**7729–7733.
33. **Smith, L. R., A. Plaza, P. A. Singer, and A. N. Theofilopoulos.** 1990. Coding sequence polymorphisms among Vβ T cell receptor genes. J. Immunol. **144:**3234–3327.
34. **Stewart, G. J., and R. L. Kirk.** 1989. The genetics of multiple sclerosis: the HLA system and other genetic markers, p. 97. *In* J. F. Hallpike, C. W. M.

Adams, and W. W. Tourtellotte (ed.), Multiple sclerosis. The Williams & Wilkins Co., Baltimore, Md.
35. **Utz, U., W. E. Biddison, H. F. McFarland, D. E. McFarlin, M. Flerlage, and R. Martin.** 1993. Skewed T-cell receptor repertoire in genetically identical twins correlates with multiple sclerosis. Nature **364:**243–247.
36. **Wood, N. W., S. J. Sawcer, H. F. Kellar-Wood, P. Holmans, D. Clayton, N. Robertson, and D. A. S. Compston.** 1995. The T-cell receptor β locus and susceptibility to multiple sclerosis. Neurology **45:**1859–1863.
37. **Wucherpfennig, K. W., K. Ota, N. Endo, J. G. Seidman, A. Rosenzweig, H. L. Weiner, and D. A. Hafler.** 1990. Shared human T-cell receptor Vβ usage to immunodominant regions of myelin basic protein. Science **248:**1016–1019.
38. **Yauch, R. L., and B. S. Kim.** 1994. A predominant viral epitope recognized by T cells from the periphery and demyelinating lesions of SJL/J mice infected with Theiler's virus is located within VP-1 (233–244). J. Immunol. **153:**4508–4519.
39. **Yauch, R. L., K. Kerekes, K. Saujani, and B. S. Kim.** 1995. Identification of a major T-cell epitope within VP3 amino acid residues 24 to 37 of Theiler's virus in demyelination-susceptible SJL/J mice. J. Virol. **69:**7315–7318.
40. **Zamvil, S. S., D. J. Mitchell, N. E. Lee, A. C. Moore, M. K. Waldor, K. Sakai, J. B. Rothbard, H. O. McDevitt, L. Steinman, and H. Archa-Orbea.** 1988. Predominant expression of a T-cell receptor Vβ gene family in autoimmune encephalomyelitis. J. Exp. Med. **167:**1586–1596.