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Control of Homeostasis of CD8$^+$ Memory T Cells by Opposing Cytokines

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Memory T cells maintain their numbers for long periods after antigen exposure. Here we show that CD8$^+$ T cells of memory phenotype divide slowly in animals. This division requires interleukin-15 and is markedly increased by inhibition of interleukin-2 (IL-2). Therefore, the numbers of CD8$^+$ memory T cells in animals are controlled by a balance between IL-15 and IL-2.

Although persistent antigen may help preserve memory T cell numbers (*1*), it is now clear that antigen is not needed for memory T cell survival (*2*, *3*). Thus, memory T cells might not need external stimuli for survival. However, memory T cells and T cells with memory phenotype continue to divide, albeit slowly, in the absence of antigen (*3*, *4*). This suggests that memory T cells might depend on some constantly available factor(s) to preserve themselves.

To investigate the causes of memory T cell division, we characterized the cells and established a system in which we could study the phenomenon. Memory T cells bear high levels of CD44 (*5*) and high levels of IL-2 receptor β (IL-2Rβ), a polypeptide that is shared by the receptors for IL-2 and IL-15 (*6*, *7*). To confirm this phenotype, we measured the levels of IL-2Rβ on CD44^{low} and CD44^{high} CD8$^+$ T cells from normal young or old mice or on antigen-primed T cells bearing a transgenic T cell receptor (TCR) specific for K^b bound to a peptide from ovalbumin (*8*). Almost all of the CD8$^+$ cells that bear high levels of CD44 also bear high levels of IL-2Rβ and vice versa (Fig. 1). Also, as expected, the proportion of CD8$^+$ T cells that were IL-2Rβ^{high}, CD44^{high} increased as the animals aged (*9*). In young mice, exposure to antigen-converted CD44^{low}, IL-2Rβ^{low} TCR transgenic CD8$^+$ T cells into CD44^{high}, IL-2Rβ^{high} cells. These experiments confirmed that both environmentally created and deliberately primed memory CD8$^+$ T cells were CD44^{high} and IL-2Rβ^{high}.

Memory T cells are thought to divide slowly in animals (*3*). To confirm this, we gave mice bromodeoxyuridine (BrdU) in their drinking water for 28 days. CD8$^+$ T cells from the mice were then analyzed for incorporation of BrdU into their DNA, an indication of cell division. The data in Fig. 2, A and B, show that more of the IL-2Rβ^{high} CD8$^+$ T cells had divided than the IL-2Rβ^{low} cells. To find out how frequently the cells were dividing, we sorted IL-2Rβ^{high} or IL-2Rβ^{low} or CD44^{high} or CD44^{low} CD8$^+$ T cells, labeled them with 5-carboxyfluorescein diacetate succininyl ester (CFSE), and transferred them into normal recipients. Many more of the IL-2Rβ^{high} or CD44^{high} cells divided than did their IL-2Rβ^{low} or CD44^{low} counterparts, as demonstrated by dilution of their CFSE stain (Fig. 2, C to F). These experiments confirm that, in animals, CD8$^+$ T cells of memory phenotype divide slowly. Previous experiments by others and our own data suggest that this division is antigen-independent because it occurs in β_2 microglobulin-deficient (β2MKO) mice (*3*, *10*) (see below).

To investigate the idea that cytokines might be driving this proliferation, we tested a number of antibodies against cytokines and cytokine receptors for their ability to affect the process. The combination of antibody to IL-7 (anti–IL-7) and IL-7 receptor α (anti–IL-7Rα) was used to block IL-7 signaling. Anti–IL-2Rβ was used to block signaling by IL-2 and/or IL-15 because the receptors for these cytokines share the IL-2Rβ chain (*7*). To distinguish between the effects of IL-2 and IL-15, we compared the results with anti–IL-2Rβ with those with anti–IL-2 (sometimes combined with anti–IL-2Rα), which blocks IL-2 but not IL-15. These are all rat antibodies so normal rat immunoglobulin G (IgG) was used as a control. To prevent Fc-mediated effects of the antibodies to receptor, we converted them to F(ab′)$_2$'s (*11*). Because the recipients would eventually respond to the rat antibodies, we limited the duration of the experiment to 7 to 9 days. Examples of these

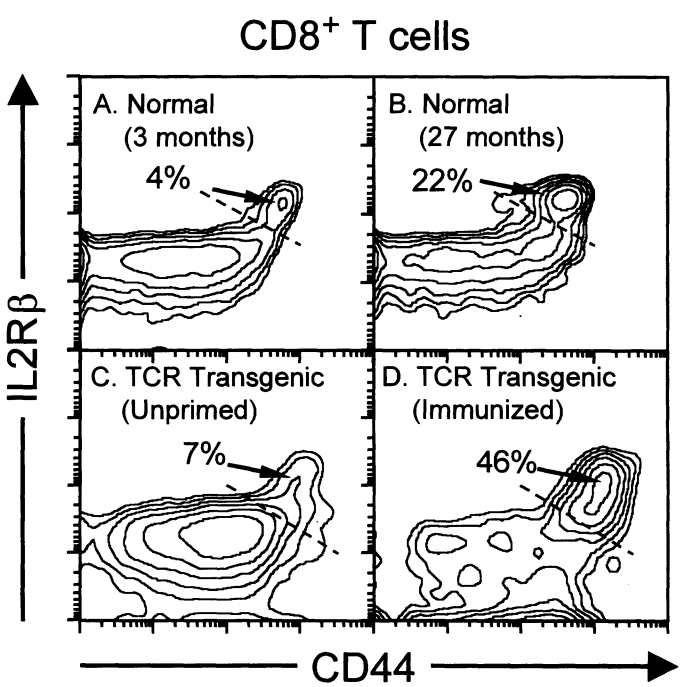

Fig. 1. Memory CD8$^+$ T cells bear high levels of CD44 and IL-2Rβ. (**A** and **B**) Peripheral blood lymphocytes were isolated from C57BL/6 mice, stained with anti-CD8, anti–IL-2Rβ, and anti-CD44, and analyzed (*22*). The data shown are gated on live CD8$^+$ T cells. (**C** and **D**) C57BL/6 mice transgenic for the OT1 TCR (*8*) were untreated (C) or infected with vaccinia virus modified to express chicken ovalbumin (D). Forty-seven days later, T cells were purified by passage over nylon wool, stained, and analyzed as described above, except that cells were also gated to be Vα2$^+$.

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experiments are shown in Figs. 3 and 4, and the results are summarized in Table 1.

In Fig. 3, unseparated CFSE-labeled T cells were transferred and analyzed. In the short time of the experiment, proliferation was modest in control mice, but effects of the antibodies could still be seen. Anti–IL-2Rβ consistently inhibited proliferation of the transferred cells. This was due to effects on IL-15, rather than on IL-2 because anti–IL-2, with or without anti–IL-2Rα, markedly increased the numbers of dividing cells. This was not due to cross-linking of the IL-2R by anti–IL-2Rα because anti–IL-2 was effective alone. Anti–IL-2 was sometimes not as effective as the combination of anti–IL-2 plus anti–IL-2Rα probably because of less efficient blocking of IL-2. The results of a number of experiments of this type are summarized in Table 1. Anti–IL-2 with or without anti–IL-2Rα always substantially increased the number of proliferating $CD8^+$ T cells, whereas anti–IL-2Rβ decreased the number. None of these treatments increased expression of IL-2Rα or CD69 on the transferred cells.

The effects of blocking IL-7 were less clear. In a few experiments, modest inhibition of proliferation was seen with anti–IL-7 plus anti–IL-7Rα (Fig. 3A and Table 1), but sometimes the treatment had no effect (Figs. 3B and 4). Further experiments will be needed to uncover the reasons for this variability. In preliminary experiments, simultaneous blocking of IL-7 and IL-15 had no additive effect.

Because most of the proliferating cells were of memory phenotype (Fig. 2), it was likely that these were the cells affected by the antibody treatments. To demonstrate this directly, we transferred purified populations of naïve and memory phenotype cells (Fig. 4A) or gated on naïve versus memory phenotype cells at the time of analysis (Fig. 4B). In both cases, most of the proliferating cells were of memory phenotype. Recovery of these proliferating memory phenotype cells was greatly stimulated by anti–IL-2 and greatly inhibited by anti–IL-2Rβ. Similar effects have been seen in preliminary experiments with memory T cells produced by deliberate priming with antigen.

To confirm the previous report that this proliferation by $CD8^+$ memory T cells was not driven by antigen, in a preliminary experiment we developed β2MKO T cells in β2M sufficient chimeras, primed them with vaccinia virus, labeled them with CFSE, and transferred them to β2MKO nonirradiated hosts. The hosts were then treated with control rat Ig or anti–IL-2. Seven days after transfer, 9.4% of the transferred $CD8^+$, IL-$2R\beta^{high}$ cells had divided in the rat Ig-treated host, whereas an average of 59.6% of the transferred CD8+, IL-$2R\beta^{high}$ cells had divided in anti–IL-2–treated recipients.

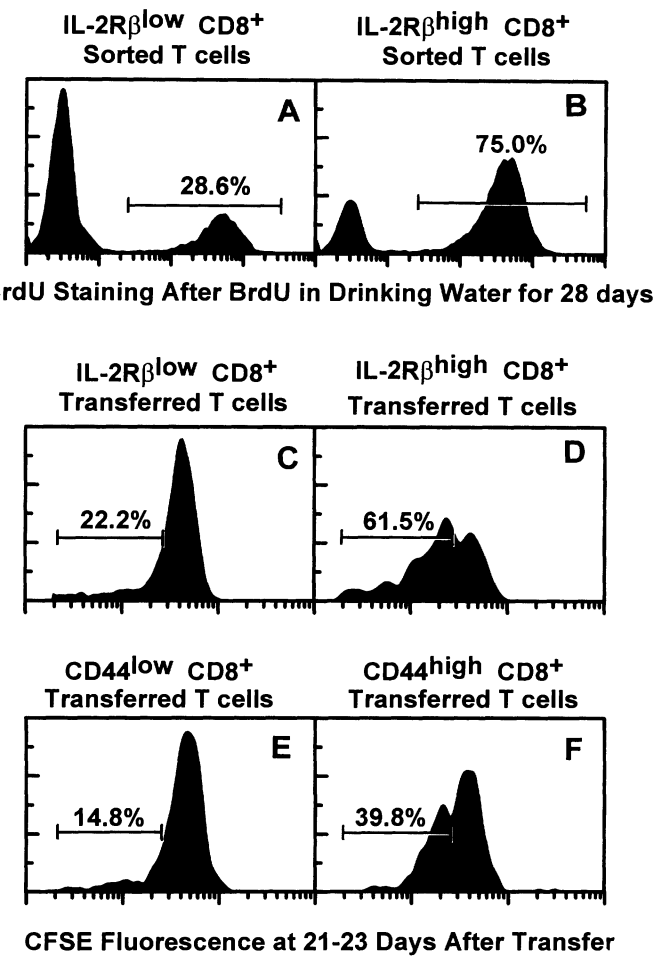

Fig. 2. T cells with memory phenotype divide slowly in animals. (**A** and **B**) C57BL/10 mice were thymectomized when they were 8 weeks old. Five weeks later, BrdU (0.8 mg/ml) was added to their drinking water for 28 days. Their T cells were then purified, stained with anti–IL-2Rβ and anti-CD8, and sorted into $CD8^+$ populations bearing low or high amounts of IL-2Rβ. The sorted cells were stained with anti-BrdU (*22*). Anti-BrdU staining of the cells bearing low (A) and high (B) amounts of IL-2Rβ is shown. (**C** to **F**) T cells were isolated from 10-month-old C57BL/6 mice, stained with anti–IL-2Rβ and anti-CD8, and sorted into $CD8^+$ cells bearing low or high amounts of IL-2Rβ or CD44. The sorted populations were stained with CFSE and transferred into nonirradiated, 12-week-old syngeneic recipients. Twenty-one to 23 days later, T cells were purified from the recipients and analyzed for CFSE staining. Data shown are for transferred $CD8^+$ cells, which were IL-$2R\beta^{low}$ (C), IL-$2R\beta^{high}$ (D), $CD44^{low}$ (E), or $CD44^{high}$ (F).

Whether the cells were transferred into normal or β2MKO recipients, little proliferation by naïve cells was observed (Fig. 4) (*12*). This small amount of proliferation was marginally stimulated by anti–IL-2 and blocked by anti–IL-2Rβ, results consistent with a small contamination of the naïve cells by memory cells.

To find out if these treatments affected the

Table 1. The rate of appearance of dividing $CD8^+$ T cells is increased by IL-15 and reduced by IL-2. The experiments were performed as described in Fig. 3, (*22*), and the text. Cells analyzed were alive, $CFSE^+$, and $CD8^+$. The percentages of recovered, transferred T cells that had divided during the course of the experiments in mice receiving control antibody ranged from 11.6 to 37.3%. The percentage of control proliferation of transferred cells in experimental mice was calculated as the percentage of the surviving, transferred T cells that divided in mice treated with the indicated antibodies divided by the percentage of the surviving, transferred T cells that divided in mice treated with control antibody.

Donor age (months)	% of control proliferation of transferred cells in mice treated with			
	Anti–IL-2	Anti–IL-2 + Anti–IL-2Rα	Anti–IL-2Rβ	Anti–IL-7 + Anti–IL-7Rα
3	458			
3	469			
6	337			
10	189			
10	187			
12	354	505.2	51.7	59.5
			47.4	
12		476.9	36.8	67.5
18	177.5		25.5	93.4

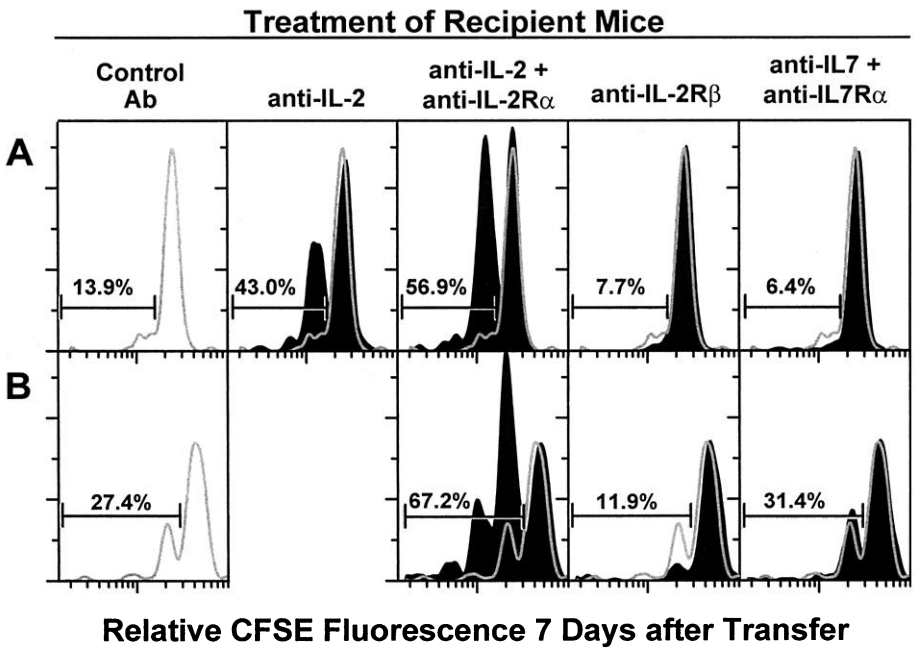

Fig. 3. The appearance of proliferating $CD8^+$ memory phenotype cells is stimulated by IL-15 and inhibited by IL-2. T cells were isolated from the lymph nodes and spleens of (**A**) a 12-month-old adult thymectomized and (**B**) a 26-month-old C57BL/6 mouse, labeled with CFSE, and transferred into nonirradiated, 8-week-old, syngeneic animals. On days 2 to 6 after transfer, the animals were injected intraperitoneally with the indicated antibodies and $F(ab')_2$'s (1 mg/day) (*11*). Seven days after transfer, T cells were isolated from the recipients, stained with anti-CD8 and anti-TCR Cβ or antibody to the Vβ expressed on large $CD8^+$ clones known to be in the mice, and analyzed. Data shown are for the $C\beta^+$, $CD8^+$, $CFSE^+$ cells or, if the mice were >12 months old, for $CD8^+$, $CFSE^+$ cells excluding large $CD8^+$ clones. The light line represents the CFSE staining of cells from mice treated with control antibody. The shaded areas represent the CFSE profiles of T cells from animals treated with the indicated antibodies. Percentages on the figure represent the percentages of the surviving CFSE-labeled cells that had divided.

total numbers of cells, we calculated the numbers of transferred $CD8^+$ T cells of memory phenotype recovered per mouse from animals treated with the various antibodies. In this experiment, anti–IL-7 plus anti–IL-7Rα had little effect on the yields of dividing or nondividing cells (Table 2). In contrast, anti–IL-2Rβ markedly reduced the numbers of cells that had divided and had no effect on the numbers of cells that had not divided. Conversely, anti–IL-2 treatment increased the yield of dividing cells tremendously and had a modest effect on the yield of nondividing cells. These results show that IL-15 drives the proliferation of memory $CD8^+$ T cells and that IL-2 causes the death of the dividing cells rather than inhibition of division of the precursors. Altogether, these data show that IL-15 and IL-2 have a profound effect on the total numbers of $CD8^+$ memory phenotype cells in the animals. Even in the short term of this experiment, lack of IL-15 caused a drop by one-third in the total numbers of transferred $CD8^+$ memory phenotype cells, and lack of IL-2 caused an increase of more than 10-fold in the size of this same population.

IL-15 is constitutively produced in animals (*4*, *13*, *14*). Although IL-2 is not constitutively produced in animals, recent evidence suggests that it is present, even in young pathogen-free mice, retained on the extracellular matrix (*15*). Perhaps this is the source of the IL-2 that is functioning in the experiments reported here.

Interleukin-2 can induce activated T cells to die (*16*) and/or, as illustrated by the experiments reported here, kill proliferating $CD8^+$ memory phenotype cells [but see (*17*)]. IL-2– or IL-2Rα–deficient mice suffer from lymphoproliferative diseases, especially if infected (*18*). We suggest that this is because lack of IL-2 allows unchecked proliferation of memory T cells in response to IL-15 in these animals.

Mice deficient in IL-15Rα lack $CD8^+$ memory phenotype T cells (*19*), and IL-15, induced by poly inosinic–poly cytidilic acid or interferon, makes $CD8^+$ T cells of memory phenotype divide (*4*, *20*). However, the experiments described here suggest that the slow division of memory phenotype $CD8^+$ T cells in specific pathogen-free mice is caused by the same cytokine. Competition for IL-15

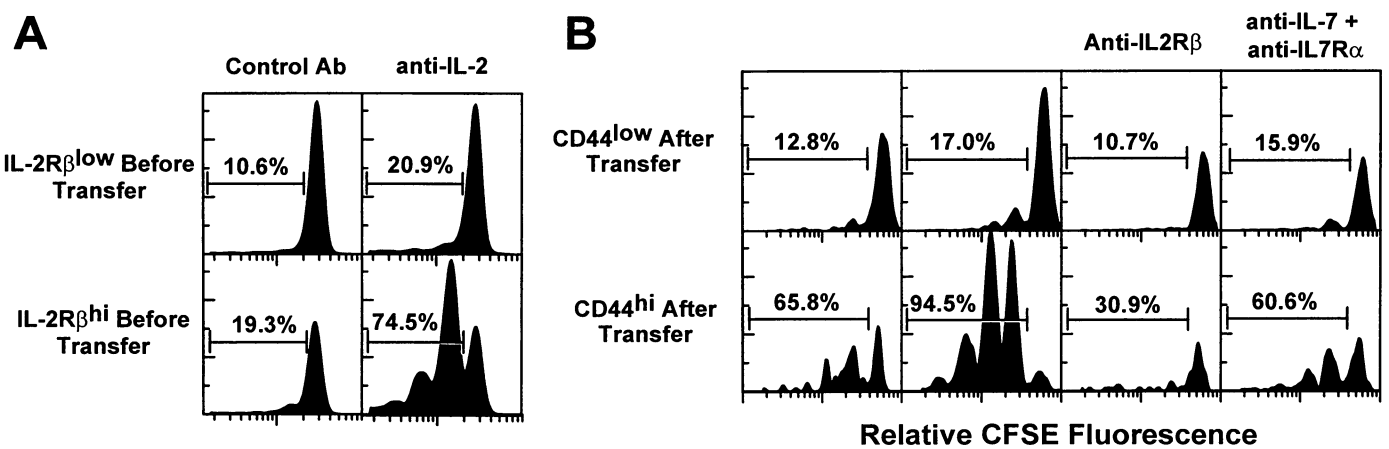

Fig. 4. The $CD8^+$ T cells stimulated to divide by inhibition of IL-2 are of memory phenotype. (**A**) T cells from 12-week-old C57BL/10 mice were purified, stained with anti-CD8 and anti–IL-2Rβ, sorted into $CD8^+$, $IL\text{-}2R\beta^{low}$ and $CD8^+$, $IL\text{-}2R\beta^{high}$ populations, and transferred into 12-week-old, nonirradiated syngeneic recipients. The recipients were treated with antibody as described for Fig. 3. Seven days after transfer, T cells were isolated, stained, and analyzed as described for Fig. 3. (**B**) T cells from 18-month-old thymectomized C57BL/6 mice were treated as described in Fig. 3, except that they were transferred into 12-week-old recipients. Mice were given antibodies for 7 days and killed 9 days after cell transfer. Cells were stained with anti-CD44, and $CD44^{low}$ and $CD44^{high}$ cells were analyzed separately. Ab, antibody.

Table 2. IL-15 increases and IL-2 decreases the total numbers of memory phenotype $CD8^+$ T cells in animals by affecting dividing cells. Transfer and analyses were done as described in Fig. 4B. Cell numbers are for $CD44^{high}$, $CD8^+$ T cells in the spleens and inguinal, axillary, brachial, superficial cervical, mesenteric, lumbar, and caudal lymph nodes of recipients.

	Numbers of donor memory phenotype $CD8^+$ T cells per recipient $\times 10^{-3}$ (% control)		
	Dividing	Nondividing	Total
Control	8.0 (100)	8.1 (100)	16.1 (100)
Anti–IL-2	170 (2125)	22 (275)	192 (1193)
Anti–IL-2Rβ	2.4 (30)	8.9 (111)	11.3 (70)
Anti–IL-7 + Anti–IL-7Rα	10.3 (129)	8.4 (105)	18.7 (116)

may, in fact, limit the total number of $CD8^+$ memory $CD8^+$ T cells that the animal can sustain (*21*). Conversely, production of IL-2 during an immune response may check otherwise uncontrolled responses by bystander $CD8^+$ memory T cells induced by increased levels of IL-15.

In immune responses, the stimulatory effects of one process are frequently counterbalanced by the inhibitory effects of another. Such contrary effects allow the immune system to respond vigorously but not uncontrollably to infections. The opposing effects of IL-15 and IL-2 reported here represent another example of the checks and balances inherent in the mechanisms of immunity.

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Location of a Major Susceptibility Locus for Familial Schizophrenia on Chromosome 1q21-q22

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Schizophrenia is a complex disorder, and there is substantial evidence supporting a genetic etiology. Despite this, prior attempts to localize susceptibility loci have produced predominantly suggestive findings. A genome-wide scan for schizophrenia susceptibility loci in 22 extended families with high rates of schizophrenia provided highly significant evidence of linkage to chromosome 1 (1q21-q22), with a maximum heterogeneity logarithm of the likelihood of linkage (lod) score of 6.50. This linkage result should provide sufficient power to allow the positional cloning of the underlying susceptibility gene.

Schizophrenia is a serious neuropsychiatric illness affecting ~1% of the general population. Family, twin, and adoption studies have demonstrated that schizophrenia is predominantly genetic, with a high heritability (*1*). Segregation analyses have failed to clearly support a single model of inheritance, with the suggestion of several, possibly interacting, susceptibility loci (*2*). The existence of a spectrum of related psychiatric disorders has led to uncertainty over the most appropriate phenotype for use in genetic studies. The complex genetics, unclear role of environmental interactions, and phenotypic uncertainty have led to the view that significant genetic linkage will not be easily obtained (*3*). Of the complete genome scans for schizophrenia susceptibility loci published to date (*4–14*), only one (*8*) has reported a significant linkage result, to chromosome 13q32, which was recently confirmed in our independent sample of families (*15*). Suggestive (although not significant) results have been obtained to many other chromosomal regions, but the multitude of these findings and the broad regions involved limit their