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Variation in experimental autoimmune encephalomyelitis scores in a mouse model of multiple sclerosis

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Core tip: Multiple sclerosis (MS) is a common demyelinating central nervous system disease associated with progressive physical impairment. Experimental autoimmune encephalomyelitis (EAE) is often used as an animal model to study MS. EAE can be induced in various species by introducing specific antigens, and the severity of the paralysis is indicated using the EAE score. The score is simple and easy to use, however, its application varies between laboratories, and the scoring is dependent on the subjective bias of the researchers. We described the criteria used for the EAE scoring systems in various laboratories, to facilitate the study of MS.

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Abstract

Multiple sclerosis (MS) is a common demyelinating central nervous system disease associated with progressive physical impairment. To study the mechanism underlying disease pathogenesis and develop potential treatments, experimental autoimmune encephalomyelitis (EAE) is often used as an animal model. EAE can be induced in various species by introducing specific antigens, which ultimately result in motor dysfunction. Although the severity of the paralysis is indicated using the EAE score, there is no standard scoring system for EAE signs, and there is variability between research groups with regard to the exact EAE scoring system utilized. Here, we describe the criteria used for EAE scoring systems in various laboratories and suggest combining EAE score with another quantitative index to evaluate paralysis, such as the traveled distance, with the goal of facilitating the study of the mechanisms and treatment of MS.

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the brain and spinal cord. More than 100 years have passed since the clinical and pathological characteristics of MS were first described in the medical literature[1]. Despite extensive research since then, the pathogenesis underlying MS is still not fully understood. There are more than 2500000 patients with MS worldwide, and the prevalence is approximately 4 to 150 per 100000 in the population[2,3]. The incidence of MS varies across the world; it is quite high in northern Europe but lower in Asian and African countries[3,4]. MS typically manifests in young adulthood, primarily between the late twenties and early forties. Although the clinical course and prognosis of the disease demonstrate individual dif-

ferences, 50% of patients need help walking, or in some cases require a wheelchair within 15 years of the initial disease onset[4]. The demyelinating lesion of MS has been described as "disseminated in time and space"[5]. The clinical course of the disease is characterized by four major subtypes: relapse-remitting, secondary progressive, primary progressive, and progressive-relapsing MS[1,4,6]. Approximately 80% of all patients initially manifest with relapsing-remitting type MS. Symptoms and signs typically become aggravated over a period of several days, and the condition then gradually stabilizes. Patients often improve spontaneously or in response to treatment within weeks. Eventually, approximately 65% of patients with relapsing-remitting MS enter the secondary progressive phase[4]. Moreover, in 20% of all patients, the illness gradually worsens after onset, which is defined as primary progressive MS[1,4]. There is no consensus definition in progressive-relapsing MS[6].

Because the opportunity to obtain central nervous system tissue from individual patients is rare, animal models of MS have been developed to investigate the pathogenesis and treatment of the disease. Experimental autoimmune encephalomyelitis (EAE) is the most popular animal model of MS[7-11]. EAE is characterized by inflammatory infiltrates consisting of T-lymphocytes, B-lymphocytes, macrophages, and focal demyelinating plaques in the CNS; these features are also observed in MS. EAE is induced in various species, including rodents and primates, either by active immunization using a myelin antigen in adjuvant (active EAE) or by the adoptive transfer of encephalitogenic T cells (passive EAE)[10,11]. In addition, T cell receptor transgenic mice have been generated as a spontaneous EAE model. The characteristics of these mice are variable, and thus, most of the spontaneous EAE mice are also defined as atypical EAE[8,12,13].

Commonly used murine EAE models manifest motor dysfunction as ascending flaccid paralysis, beginning with a flaccid or limp tail[7,10,11]. The paralysis progresses from the hind limbs to the fore limbs and is occasionally followed by urinary incontinence and fecal impaction (classical EAE models)[7,10]. Lesions are predominantly localized to the spinal cord in classical EAE. The standard EAE mouse model is induced using myelin proteolipid protein (PLP) peptide (amino acids 139-151), which causes relapse-remitting EAE in SJL mice. In addition, the myelin oligodendrocyte glycoprotein (MOG) peptide (amino acids 35-55) causes monophasic EAE with an incomplete recovery in C57BL/6 mice[8]. Several reports have demonstrated real primary progressive or secondary progressive EAE, in which mice die as a result of disease progression[14]. However, variations from the classical EAE phenotype, such as ataxia or the head rolling phenomenon rather than limb paralysis, have been described and are referred to as atypical EAE[15-17]. The clinical signs observed in atypical EAE models reflect an increase in inflammation in the brain compared to classical EAE models. The characteristics of spontaneous EAE mice are also defined as atypical EAE.

In the active EAE model, the mice are immunized by subcutaneous injection of the myelin antigen with complete Freund's adjuvant (that is, the antigen is emulsified in paraffin oil containing inactive *Mycobacterium tuberculosis*). Intravenous or intraperitoneal injection of pertussis toxin is required to increase the incidence of EAE induction. Although the signs of motor dysfunction depend on the type of EAE model, paralysis usually begins within 9 to 14 d after sensitization[10]. Passive induction of EAE in naïve mice is achieved by the adoptive transfer of T cells isolated from active EAE mice that have been primed with myelin antigens. The day of onset of visible EAE signs varies, and depends on the model; however, signs usually appear between 10 and 15 d after induction[11].

In this review, unless otherwise noted, we describe the development of the signs of classical EAE and the evaluating system used by researchers. Many researchers misuse terms for evaluating EAE signs; for example, "EAE symptom" or "clinical assessment of EAE." The term "symptom" and "clinical" should only be used in the context of humans; and thus, the term "signs" must be used instead of "symptom." In addition, "clinical" must not be used in EAE studies. The severity of EAE is generally evaluated using an EAE score (occasionally referred to as the EAE scale or grade). Mice are scored daily after the day of sensitization to precisely detect the time of disease onset and to investigate the progression of EAE. The commonly used EAE scores are 0 to 5 or 0 to 6 point scales (Tables 1-3)[10,18-29]; however, there are problems using this method. First, each laboratory has its own method for evaluating the severity of EAE; these methods have not been standardized between laboratories. In most laboratories, a loss of tail tone is recognized as a score of 1, which is designated as a "loss of tail tonicity"[18,20,23,26,29], "flaccid tail"[19,22], "limp tail"[25,28], "tail weakness"[24] and "tail atony"[27]. In particular, a complete loss of tone has been required in previous studies[25-29]. In contrast, Sobel *et al*[21] described a score of 1 as "decreased tail tone or slightly clumsy gait". A score of 2 is identified by symptoms of paralysis/weakness of the hind limbs, impairment of the righting reflex (the mice have difficulty turning over after being laid down on their back, but there are no observed locomotor difficulties), tail paralysis and gait disturbance. The term "paralysis" indicates a complete or partial loss of voluntary movement. The prefix "para" means "both" and "plegia" means severe weakness. The term "paraplegia" is defined as a severe symmetrical muscle weakness of both lower limbs. "Paraparesis" commonly means slight or partial paralysis of both lower limbs; however, the definition of these terms is subjective and indistinct. These symptoms have been described as "mild hind limb or unilateral paralysis"[19,22,26,28] or "hind limb weakness"[18,27], "impaired or poor righting reflex"[20,21,29] or "loss of the righting reflex"[25], "tail atony or paralysis"[21,24] or "flaccid tail"[23], and "moderately clumsy gait"[21] or "abnormal gait"[29]. Most laboratories define a score of 3 as hind limb paralysis[18-20,23,25-29] or weakness[21,22]; however, Pollak *et al*[24] included "loss of

Table 1 Commonly used classical experimental autoimmune encephalomyelitis score

Score	EAE signs	Observation
0	No signs of EAE	Hind legs are extended; tail extends up and moves; tail wraps around cylindrical object; normal gait
0.5	Partially limp tail	Hind legs are extended; tip of tail droops and/or does not wrap around cylindrical object; normal gait
1	Paralyzed tail	Hind legs are extended; tail droops and does not wrap around cylindrical object; normal gait
2	Loss in coordinated movement; hind limb paralysis	Hind legs contract when held at the base of tail; mouse walks with uncoordinated movement; hind limbs reflex when toes are pinched; limp tail
2.5	One hind limb paralysis	Mouse drags one hind limb; one hind limb does not respond to pinch; limp tail
3	Both hind limbs paralysis	Mouse drags both hind limbs; both hind limbs do not respond to toe pinch; limp tail
3.5	Hind limb paralysis; weakness in forelimbs	Mouse drags hind limbs but has difficulty using forelimbs to pull body; forelimbs respond to toe pinch; limp tail
4	Forelimbs paralysis	Mouse cannot move; forelimbs do not respond to toe pinch; limp tail
5	Moribund	No movement; cold to the touch; altered breathing

Note there are no scores denoted 1.5 and 4.5. The data available from reference 10. EAE: Experimental autoimmune encephalomyelitis.

Table 2 Differences in experimental autoimmune encephalomyelitis scores among researchers

	Swanborg[18]	Matsumoto *et al*[19]	Yamamura *et al*[20]	Sobel *et al*[21]	Kalyvas *et al*[22]	Mendel *et al*[23]	Pollak *et al*[24]	Takeuchi *et al*[25]
Strain	Lewis rat	Lewis rat	C57BL/6J mice	SJL/J mice	C57BL/6J mice	C57BL/6J mice	SLJ/J mice	C57BL/6J mice
Antigen	MBP	MBP	MOG_{35-55}	$PLP_{131-151}$	MOG_{35-55}	MOG	$PLP_{131-151}$	MOG_{35-55}
0	ND	ND	No clinical signs	No disease	Normal	No clinical signs	No neurological signs	No detectable signs of paralysis
1	Loss of tail tonicity	Flaccid tail	Loss of tail tonicity	Decreased tail tone or slightly clumsy gait	Flaccid tail	Loss of tail tonicity	Tail weakness	Completely limp tail
2	Definite hind quarter weakness	Mild paraparesis	Impaired righting reflex	Tail atony and/or moderately clumsy gait and/or poor righting ability	Mild hindlimb paralysis	Flaccid tail	Tail paralysis	Loss of the righting reflex
3	Hind leg paralysis	Severe paraparesis	Partial hindlimb paralysis	Limb weakness	Severe hindlimb weakness	Hind leg paralysis	Loss of righting reflex	Partial hind limb paralysis
4	ND	Moribund condition	Total hindlimb paralysis	Limb paralysis	Hindlimb paralysis	Hind leg paralysis with hind body paresis	Hind limb paresis/paralysis	Complete hind limb paralysis
5	ND	ND	ND	Moribund	Hindlimb paralysis and forelimb weakness or moribund	Hind and fore leg paralysis	Quadriplegia (immobility)	Total paralysis of allfour limbs
6	ND	ND	ND	ND	ND	Death	Death	Death

ND: Not defined.

the righting reflex". Thus, the same EAE score may indicate different conditions in the EAE mice. Furthermore, the score is not a quantitative analysis. Some researchers use "in-between" scores (0.5 point) when the symptom lies between the two defined scores (Table 3). Tsunoda *et al*[26] and Storch *et al*[27] only showed an in-between score of between 0 and 1 (0.5 score) but not between other intervals. In contrast, there were in-between scores for all intervals except for a score of 4.5 in a method used by Greter *et al*[28]. Most researchers judge the statistical significance of EAE signs by comparing the scores of two groups of EAE mice: *i.e.*, wild type EAE mice and genetically modified EAE mice, or treated EAE mice and non-treated EAE mice. Furthermore, the method of assessing an EAE score depends on subjective observation. For example, researchers hold the base of the mouse tail to judge tail limpness. In addition, they touch or perform a toe pinch to evaluate the gait condition of the mice[10,11]. Finally, designation of the sign as "mild" or "severe" is ill-defined; thus, we need to eliminate the observer bias in the judgment of EAE scores. In addition, the cumulative score is obtained by the sum of the daily EAE score using previously described methods.

Not only is a standard behavior scoring system for EAE needed, but a different method for evaluating EAE progression is also required. After sensitization, in general, the mice are weighed regularly and scored for EAE signs. Body weight loss is a common feature of EAE that

Table 3 Experimental autoimmune encephalomyelitis scores using the 0.5 point scale

	Tsunoda *et al*[26]	Storch *et al*[27]	Greter *et al*[28]	Kihara *et al*[29]
Strain	SJL/J mice	BN and DA rat	C57/BL mice	C57/BL mice
Antigen	PLP	MOG_{1-125}	MOG_{35-55}	MOG_{35-55}
0	No clinical disease	ND	No detectable signs of EAE	No signs
0.5	Loss of tonicity of the distal half of the tail	Partial loss of tail tone	Distal limp tail	Mild loss of tail tone
1	Complete loss of tail tonicity	Complete tail atony	Complete limp tail	Complete loss of tail tone
1.5	ND	ND	Limp tail and distal limb weakness	Mildly impaired righting reflex
2	Mild hind leg paresis	Hind limb weakness	Unilateral partial limb paralysis	Abnormal gait and/or impaired righting reflex
2.5	ND	ND	Bilateral partial hind limb paralysis	Hind limb paresis
3	Moderate hind leg paralysis	Hind limb paralysis	Complete bilateral hind limb paralysis	Hind limbs paralysis
3.5	ND	ND	Complete bilateral hind limb paralysis and unilateral forelimb paralysis	Hind limb paralysis with hind body paresis
4	Complete paraplegia	Tetraplegy, moribund state	Total paralysis of fore and hind limbs	Hind and fore limb paralysis
4.5	ND	ND	ND	Moribund
5	quadriplegia, moribund state or death	Death	Death	Death
5.5	ND	ND	ND	ND
6	ND	ND	ND	ND

ND: Not defined.

usually precedes paralysis, and low body weight remains during the recovery phase[12,30,31]. Body weight begins to increase during the chronic phase of the disease; thus, weight loss is an important sign during the acute stage of EAE. Jones *et al*[32] observed the relationship between the EAE score and rotarod performance, the grip strength test of both the fore limbs and hind limbs, and the open field test. In the open field test, gait and rearing events of natural exploratory behavior could be detected. A drawback of this method is that severe (and, in some cases, moderate) paralysis prevents animals from performing the rotarod and grip strength tests. The Basso, Beattie, and Bresnahan (BBB) score is a well-established technique for evaluating spinal cord injury in animal models[33,34]; thus, this score may also be used in EAE studies[35,36]. To determine the BBB score, mice are placed in an open field area with two observing researchers. The BBB sub-components include limb movement, trunk position, paw placement, walking, predominant paw position, trunk instability and tail position. BBB is rated on a scale from 0 (no observable hind limb movements) to 21 (consistent coordinated gait, consistent toe clearance, predominant paw position is parallel at initial contact and lift-off, tail consistently up, and consistent trunk stability), which represents the sequential recovery of spinal cord injury[33]. Kerschensteiner *et al*[36] reported that the BBB score is predictive of the site and extent of the pathological lesion and is more sensitive for assessing the development of EAE than are EAE scores. However, the BBB score must be determined in precisely 21 stages by two proficient observers. Thus, a simple, universal and clear-cut method is needed for evaluating motor dysfunction in EAE. Our recent study suggests that the traveled distance is a sensitive and accurate marker of motor dysfunction in a MS mouse model (unpublished).

In conclusion, the EAE score is simple and easy to use; however, its application varies between laboratories, and scoring is dependent on the subjective bias of the researchers. To achieve the standard scoring system in EAE, it is necessary to define the terms for signs and to clarify the criteria for the signs in the EAE score. Furthermore, ambiguous representation, *e.g.*, weak or strong weakness of the hind limb, must be eliminated. We suggest that a standardized EAE scoring system should be implemented and combined with another quantitative index, such as the distance traveled in the open field test, which would provide a substantial advantage over the current conventional EAE scoring methods.

REFERENCES

1 **Noseworthy JH**, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000; **343**: 938-952 [PMID: 11006371 DOI: 10.1056/NEJM200009283431307]

2 **Rosati G**. The prevalence of multiple sclerosis in the world: an update. *Neurol Sci* 2001; **22**: 117-139 [PMID: 11603614 DOI: 10.1007/s100720170011]

3 **Alonso A**, Hernán MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology* 2008; **71**: 129-135 [PMID: 18606967 DOI: 10.1212/01.wnl.0000316802.35974.34]

4 **Compston A**, Coles A. Multiple sclerosis. *Lancet*

2008; **372**: 1502-1517 [PMID: 18970977 DOI: 10.1016/S0140-6736(08)61620-7]
5 **Polman CH**, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; **69**: 292-302 [PMID: 21387374 DOI: 10.1002/ana.22366]
6 **Lublin FD**, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996; **46**: 907-911 [PMID: 8780061 DOI: 10.1212/WNL.46.4.907]
7 **Baxter AG**. The origin and application of experimental autoimmune encephalomyelitis. *Nat Rev Immunol* 2007; **7**: 904-912 [PMID: 17917672 DOI: 10.1038/nri2190]
8 **Gold R**, Linington C, Lassmann H. Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. *Brain* 2006; **129**: 1953-1971 [PMID: 16632554 DOI: 10.1093/brain/awl075]
9 **Steinman L**, Zamvil SS. How to successfully apply animal studies in experimental allergic encephalomyelitis to research on multiple sclerosis. *Ann Neurol* 2006; **60**: 12-21 [PMID: 16802293 DOI: 10.1002/ana.20913]
10 **Stromnes IM**, Goverman JM. Active induction of experimental allergic encephalomyelitis. *Nat Protoc* 2006; **1**: 1810-1819 [PMID: 17487163 DOI: 10.1038/nprot.2006.285]
11 **Stromnes IM**, Goverman JM. Passive induction of experimental allergic encephalomyelitis. *Nat Protoc* 2006; **1**: 1952-1960 [PMID: 17487182 DOI: 10.1038/nprot.2006.284]
12 **Bettelli E**, Pagany M, Weiner HL, Linington C, Sobel RA, Kuchroo VK. Myelin oligodendrocyte glycoprotein-specific T cell receptor transgenic mice develop spontaneous autoimmune optic neuritis. *J Exp Med* 2003; **197**: 1073-1081 [PMID: 12732654 DOI: 10.1084/jem.20021603]
13 **Krishnamoorthy G**, Lassmann H, Wekerle H, Holz A. Spontaneous opticospinal encephalomyelitis in a double-transgenic mouse model of autoimmune T cell/B cell cooperation. *J Clin Invest* 2006; **116**: 2385-2392 [PMID: 16955140 DOI: 10.1172/JCI28330.]
14 **Tsunoda I**, Kuang LQ, Theil DJ, Fujinami RS. Antibody association with a novel model for primary progressive multiple sclerosis: induction of relapsing-remitting and progressive forms of EAE in H2s mouse strains. *Brain Pathol* 2000; **10**: 402-418 [PMID: 10885659 DOI: 10.1111/j.1750-3639.2000.tb00272.x]
15 **Endoh M**, Tabira T, Kunishita T, Sakai K, Yamamura T, Taketomi T. DM-20, a proteolipid apoprotein, is an encephalitogen of acute and relapsing autoimmune encephalomyelitis in mice. *J Immunol* 1986; **137**: 3832-3835 [PMID: 3491150]
16 **Kawamura K**, Yamamura T, Yokoyama K, Chui DH, Fukui Y, Sasazuki T, Inoko H, David CS, Tabira T. Hla-DR2-restricted responses to proteolipid protein 95-116 peptide cause autoimmune encephalitis in transgenic mice. *J Clin Invest* 2000; **105**: 977-984 [PMID: 10841661 DOI: 10.1172/JCI8407]
17 **Sobel RA**. Genetic and epigenetic influence on EAE phenotypes induced with different encephalitogenic peptides. *J Neuroimmunol* 2000; **108**: 45-52 [PMID: 10900336 DOI: 10.1016/S0165-5728(99)00270-2]
18 **Swanborg RH**. Experimental allergic encephalomyelitis. *Methods Enzymol* 1988; **162**: 413-421 [PMID: 2465480 DOI: 10.1016/0076-6879(88)62095-7]
19 **Matsumoto Y**, Fujiwara M. The immunopathology of adoptively transferred experimental allergic encephalomyelitis (EAE) in Lewis rats. Part 1. Immunohistochemical examination of developing lesions of EAE. *J Neurol Sci* 1987; **77**: 35-47 [PMID: 2433404 DOI: http:]
20 **Croxford JL**, Miyake S, Huang YY, Shimamura M, Yamamura T. Invariant V(alpha)19i T cells regulate autoimmune inflammation. *Nat Immunol* 2006; **7**: 987-994 [PMID: 16878136 DOI: 10.1038/ni1370]
21 **Sobel RA**, Tuohy VK, Lu ZJ, Laursen RA, Lees MB. Acute experimental allergic encephalomyelitis in SJL/J mice induced by a synthetic peptide of myelin proteolipid protein. *J Neuropathol Exp Neurol* 1990; **49**: 468-479 [PMID: 2273404 DOI: 10.1097/00005072-199009000-00002]
22 **Kalyvas A**, David S. Cytosolic phospholipase A2 plays a key role in the pathogenesis of multiple sclerosis-like disease. *Neuron* 2004; **41**: 323-335 [PMID: 14766173 DOI: 10.1016/S0896-6273(04)00003-0]
23 **Mendel I**, Kerlero de Rosbo N, Ben-Nun A. A myelin oligodendrocyte glycoprotein peptide induces typical chronic experimental autoimmune encephalomyelitis in H-2b mice: fine specificity and T cell receptor V beta expression of encephalitogenic T cells. *Eur J Immunol* 1995; **25**: 1951-1959 [PMID: 7621871 DOI: 10.1002/eji.1830250723]
24 **Pollak Y**, Ovadia H, Orion E, Yirmiya R. The EAE-associated behavioral syndrome: II. Modulation by anti-inflammatory treatments. *J Neuroimmunol* 2003; **137**: 100-108 [PMID: 12667653 DOI: 10.1016/s0165-5728(03)00073-0]
25 **Takeuchi C**, Matsumoto Y, Kohyama K, Uematsu S, Akira S, Yamagata K, Takemiya T. Microsomal prostaglandin E synthase-1 aggravates inflammation and demyelination in a mouse model of multiple sclerosis. *Neurochem Int* 2013; **62**: 271-280 [PMID: 23266396 DOI: 10.1016/j.neuint.2012.12.007]
26 **Tsunoda I**, Kuang LQ, Tolley ND, Whitton JL, Fujinami RS. Enhancement of experimental allergic encephalomyelitis (EAE) by DNA immunization with myelin proteolipid protein (PLP) plasmid DNA. *J Neuropathol Exp Neurol* 1998; **57**: 758-767 [PMID: 9720491 DOI: 10.1097/00005072-199808000-00005]
27 **Storch MK**, Stefferl A, Brehm U, Weissert R, Wallström E, Kerschensteiner M, Olsson T, Linington C, Lassmann H. Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. *Brain Pathol* 1998; **8**: 681-694 [PMID: 9804377 DOI: 10.1111/j.1750-3639.1998.tb00194.x]
28 **Greter M**, Heppner FL, Lemos MP, Odermatt BM, Goebels N, Laufer T, Noelle RJ, Becher B. Dendritic cells permit immune invasion of the CNS in an animal model of multiple sclerosis. *Nat Med* 2005; **11**: 328-334 [PMID: 15735653 DOI: 10.1038/nm1197]
29 **Kihara Y**, Matsushita T, Kita Y, Uematsu S, Akira S, Kira J, Ishii S, Shimizu T. Targeted lipidomics reveals mPGES-1-PGE2 as a therapeutic target for multiple sclerosis. *Proc Natl Acad Sci U S A* 2009; **106**: 21807-21812 [PMID: 19995978 DOI: 10.1073/pnas.0906891106]
30 **Encinas JA**, Lees MB, Sobel RA, Symonowicz C, Weiner HL, Seidman CE, Seidman JG, Kuchroo VK. Identification of genetic loci associated with paralysis, inflammation and weight loss in mouse experimental autoimmune encephalomyelitis. *Int Immunol* 2001; **13**: 257-264 [PMID: 11222494 DOI: 10.1093/intimm/13.3.257]
31 **Becanovic K**, Wallstrom E, Kornek B, Glaser A, Broman KW, Dahlman I, Olofsson P, Holmdahl R, Luthman H, Lassmann H, Olsson T. New loci regulating rat myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis. *J Immunol* 2003; **170**: 1062-1069 [PMID: 12517974]
32 **Jones MV**, Nguyen TT, Deboy CA, Griffin JW, Whartenby KA, Kerr DA, Calabresi PA. Behavioral and pathological outcomes in MOG 35-55 experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2008; **199**: 83-93 [PMID: 18582952 DOI: 10.1016/j.jneuroim.2008.05.013]
33 **Basso DM**, Beattie MS, Bresnahan JC, Anderson DK, Faden AI, Gruner JA, Holford TR, Hsu CY, Noble LJ, Nockels R, Perot PL, Salzman SK, Young W. MASCIS evaluation of open field locomotor scores: effects of experience and teamwork on reliability. Multicenter Animal Spinal Cord Injury

Study. *J Neurotrauma* 1996; **13**: 343-359 [PMID: 8863191 DOI: 10.1089/neu.1996.13.343]

34 **Scheff SW**, Saucier DA, Cain ME. A statistical method for analyzing rating scale data: the BBB locomotor score. *J Neurotrauma* 2002; **19**: 1251-1260 [PMID: 12427332 DOI: 10.1089/08977150260338038]

35 **All AH**, Agrawal G, Walczak P, Maybhate A, Bulte JW, Kerr DA. Evoked potential and behavioral outcomes for experimental autoimmune encephalomyelitis in Lewis rats. *Neurol Sci* 2010; **31**: 595-601 [PMID: 20508959 DOI: 10.1007/s10072-010-0329-y]

36 **Kerschensteiner M**, Stadelmann C, Buddeberg BS, Merkler D, Bareyre FM, Anthony DC, Linington C, Brück W, Schwab ME. Targeting experimental autoimmune encephalomyelitis lesions to a predetermined axonal tract system allows for refined behavioral testing in an animal model of multiple sclerosis. *Am J Pathol* 2004; **164**: 1455-1469 [PMID: 15039233 DOI: 10.1016/S0002-9440(10)63232-4]

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