Stargazer—A Mouse to Seize!

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The goals of this short review are to familiarize readers with the stargazer mouse and to outline the major functional defects associated with this mutant. The roles of the stargazin protein in calcium channel function and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor trafficking are discussed; focus is placed on studies regarding the thalamus, whence absence seizures potentially originate, and the cerebellum, which is associated with the ataxic phenotype. Finally, two additional alleles of stargazer, waggler and stargazer 3Jackson (3J), illustrate the value of an allelic series for understanding stargazin function.

The Origin of the Stargazer Mouse

Stargazer arose on the A/J mouse inbred strain at The Jackson Laboratory in the 1980s. It was initially detected by its unsteady gait and unusual, repeated head elevations. Breeding studies revealed that stargazer was due to a single, recessive mutation on mouse chromosome 15 (1,2). The first published report on stargazer also described another very important phenomenon—that this mouse had frequent spike–wave discharges (SWDs), characteristic of absence seizures in humans (1).

The three mouse mutants, ducky, lethargic, and tottering, share phenotypic features with stargazer, including ataxic gait, paroxysmal dyskinesia (affecting limbs in ducky, lethargic, and tottering but seen as neck dystonia in stargazer), and absence seizures with SWDs between 5 and 7 Hz (3,4). These mouse mutants have defects in voltage-dependent calcium channel (VDCC) subunit genes: *Cacna2d2* for ducky (5), *Cacnb4* for lethargic (6), and *Cacna1a* for tottering (7).

The mutation in stargazer was identified as a retroviral-like, early transposon insertion in the second intron of the VDCC $\gamma 2$ subunit gene, *Cacng2*. This insertion severely reduced normal *Cacng2* expression (8–10). Several similarities were observed between the previously isolated VDCC γ protein found in muscle (11) and the *Cacng2* product. The proteins shared 25% amino acid identity, and both had a similar secondary structure, including four transmembrane domains with both termini projecting into the cytoplasm. Furthermore, the *Cacng2* protein caused a small hyperpolarizing shift in VDCC steady-state inactivation in vitro (8). The *Cacng2* protein product is referred to interchangeably as stargazin, $\gamma 2$, and CACNG2.

Absence Seizures with Stargazer Are Accompanied by VDCC and T-type Changes

Absence seizures arise from disturbances of the corticothalamic circuitry, including the cortex, thalamus, and thalamic reticular neurons and their interconnecting neuronal pathways (12–15). An oscillatory balance in the inhibitory and excitatory network activities between the cortex and thalamus is maintained in the normal state, but abnormal perturbations within this loop can result in SWDs. For instance, within the thalamus, low-voltage calcium channels (T-type or Cav3.1) act as critical pacemakers in a recurrent cycle with the hyperpolarization-activated cation I_h currents. Aberrant burst firing of the T-type channels results in rhythmic oscillations that generate SWDs (16–18). Alternatively, these SWDs can arise from abnormal neuronal discharges from the pyramidal neurons in the cortex (19). The SWDs exhibit widespread synchronization and rapid generalization, detected by EEG recordings from the cortical surface.

The role of stargazin as a regulator of VDCC activity has been questioned because the in vitro results show marginal changes, at best (20–25). However, the recordings from thalamocortical relay nuclei from slice preparations revealed that both VDCC and low-voltage T-type channels are altered in the stargazer mouse (26). These slices retained the integrity of the tissue and were taken directly from mutant and control mice. The stargazer mice showed both increased VDCC and low-voltage calcium channel activity, with a depolarizing shift in the steady-state inactivation of the T-type current. Furthermore, similar results were observed for the tottering mouse (26).

The $\alpha 1$G subunit is the major component of T-type calcium channels in the thalamocortical relay neurons (27). A mouse $\alpha 1$G knockout (*Cacna1g*^{tm1Hssh}) was generated to explore the functional consequences of deleting this particular channel. No burst-mode firing could be induced in the neurons from the targeted knockout, and the mice were resistant to baclofen-induced absence seizures (28). Moreover, when this $\alpha 1$G knockout mutation was combined with stargazer, lethargic, or tottering mutations, the incidence of absence seizures was severely reduced (29). In summary, the similarities between the phenotypes of these mice, the thalamic slice recordings, and the

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double-mutant studies provide strong evidence that stargazin plays a role in VDCC regulation. Changes in VDCC activity lead to an increase in low-voltage T-type activity within the thalamus that, in turn, initiates aberrant SWDs, the hallmarks of absence seizures.

Stargazin and AMPA-Receptor Trafficking

The ataxic phenotype is most commonly associated with cerebellar defects (30–35). Although the cellular organization within the stargazer cerebellum was grossly normal (1), numerous neurophysiological defects associated with the granule cell layer have been described (36). Granule cells from the cerebellum of stargazer and its allelic partner, waggler, were found to be missing functional α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (37,38). These receptors mediate fast excitatory synaptic transmission in the brain in response to glutamate. They recycle rapidly at the plasma membrane and contribute to the overall synaptic plasticity of the neuronal circuitry.

Following up on this loss of AMPA function, Chen and colleagues (39) determined that the stargazin protein was essential for the trafficking of AMPA receptors from the Golgi complex to the plasma membrane and, furthermore, was required for the ultimate targeting of the receptors to the postsynaptic membrane. Stargazin's critical binding and trafficking domains involved in the migration of the AMPA receptor to the plasma membrane include the first extracellular loop and the intracellular carboxy terminus (40). The final amino acids, trp-trp-pro-val (TTPV), at the carboxy tail of stargazin, are essential for the subsequent binding of the postsynaptic proteins, such as PSD-95, to target the entire complex to its active site at the postsynaptic membrane (39,41,42). Additionally, in vitro studies revealed that stargazin binding enhanced glutamate-induced currents at the synapse (43) and ultrastructural changes in the excitatory synapses within the cerebellum reflect the loss of normal AMPA-receptor trafficking in stargazer (44).

Stargazin and other closely related members of the γ subunit family, including γ3, γ4 and γ8, share a high degree of amino acid conservation, including the TTPV motif. These four proteins are referred to as transmembrane AMPA-receptor regulatory proteins, or TARPs, and all can promote expression of functional AMPA receptors at the postsynaptic membrane (45). TARP members associate independently with AMPA receptors and cocluster with the receptors at the postsynaptic sites. However, in the cerebellar granule cells, only stargazin is expressed significantly (20), explaining why AMPA-receptor localization is noticeably defective in these cells.

Stargazer also lacked brain-derived neurotrophic factor message in its granule cells (46). A reduction in the inhibitory neurotransmitter GABA was observed, and fewer GABAergic synapses were present (47). The $GABA_A$-receptor α6 (an indicator of mature granule cells) and β3 subunits were reduced in granule cells (48). Finally, stargazer mice showed an impaired cerebellum-dependent eye-blink conditioning response (49). The outcome of all these impairments appears to be that, although stargazer cerebellar granule cells retain the ability to migrate correctly, they lack the neurotransmitter and neurotrophic innervations required for their full maturation.

Additional Mutants for Studying Stargazin Function

Waggler, Stargazer 3Jackson (3J), and a γ4 Targeted Mutant

The stargazer mouse has proved to be a complex model with pleiotrophic defects. It can survive despite its severe phenotype, with very reduced *Cacng2* message expression and no detectable protein (9,10). After stargazer, two spontaneous mutants have been found with defects in the same *Cacng2* gene: waggler and stargazer 3J. Surprisingly, all three mutations are caused by similar insertions into *Cacng2* introns (10).

Waggler mice are ataxic but lack the head elevation of stargazer. They also showed no stargazin protein expression but had a variable SWD profile (10). Additionally, wagglers were missing functional AMPA receptors in granule cells and showed similar impairments in granule cell maturation to stargazer (38,50). The waggler mutation arose from an early transposon insertion in the first intron, whereas stargazer 3J, like stargazer, had an early transposon insertion in the second intron at a more distal 3′ position (10).

Stargazer 3J has the mildest phenotype of the three alleles. The mice are ataxic but retain approximately 25% of the normal *Cacng2* message. In contrast to stargazer and waggler, stargazin protein also was detected in this allele (10). Stargazer 3J consistently showed no SWD activity, suggesting that sufficient stargazin exists to overcome the seizure phenotype and head tossing, but not the ataxia.

Recently a targeted mutation was introduced into the VDCC γ4-subunit gene, *Cacng4* (51). The targeted homozygous $Cacng4^{tm1Frk}$ mouse had no discernible phenotypic abnormalities, including no spontaneous absence seizure activity.

Absence Seizures in Double Cacng2;Cacng4 Mutants

Double-mutant studies can provide insight into functional interactions, as illustrated by the studies of Song et al. (29), in which the α1G knockout was combined with VDCC mutants. However, early death can confound full phenotypic analysis—in particular, EEG recording and ataxia, for which the mice must age to about 2 weeks. For example, the double mutant between stargazer and $Cacng4^{tm1Frk}$ rarely survived. However, double mutants between waggler or stargazer 3J and $Cacng4^{tm1Frk}$ were viable. Although neither single mutants had SWDs, the

stargazer 3J; Cacng4^{tm1Frk} double homozygotes proved to be most informative, as the double mutants showed absence seizure activity (51). In summary, the depletion of $\gamma 4$ alone appears to have no effect on the mouse. However, both the duration and recurrence of seizure episodes increased in the double homozygotes, exacerbating the seizures compared with the waggler mutant and introducing seizures into the previously seizure-free stargazer 3J. These results suggest that $\gamma 4$ has a role in seizure susceptibility, but this role is revealed only when expression of stargazin also is compromised.

Are the Functions of Stargazin Interconnected?

One study was performed of VDCC activity in the cerebellum of stargazer mice. Whole-cell measurements from stargazer granule cells showed no differences in VDCC currents compared with wildtype (39), although individual VDCC, including P/Q, N, R, and L types, were not assessed. Notably, increased N- and L-type channels in the cerebellum of the tottering mouse (with a mutation in the P/Q-type channel) are proposed to contribute to tottering's ataxic and dystonic phenotypes (52–54).

Conversely, no reports exist of AMPA-receptor localization or activity in the stargazer mouse cortex and thalamus, although stargazer hippocampal studies indicated that AMPA receptor function is normal (37). Is there less AMPA-receptor activity in the thalamus of stargazer, waggler, or stargazer 3J mice? The double mutants between stargazer 3J and Cacng4^{tm1Frk} may be particularly informative for thalamic studies, as stargazin and $\gamma 4$ constitute the major TARP expression in this region (20,51). If both these functions are indeed altered in the thalamus, the challenge will be to assess the relative contributions of VDCC activation and AMPA-receptor mislocalization to the seizure phenotype.

AMPA-receptor–knockout Mutants and Thalamic Defects

Studies of mouse mutants with knockouts of the AMPA-receptor subunits could reveal an association between AMPA receptors and absence seizures without the conflicting VDCC mutational effects. Four subunits, GLUR1-4, form the heterotetrameric receptor (55), and knockout mice exist (*Gria1-3*) of GLUR 1, GLUR 2, and GLUR 3, respectively (56–60). These mutants have generally been studied for long-term potentiation disorders; only one absence seizure study has been reported on the *Gria2* knockout (61). This mutant, despite having multiple behavioral abnormalities (58,59), proved to be more resistant to absence-seizure induction than were controls (61). Similar studies may be worth pursuing with the Gria2; Gria3 double knockout (60). This particular mutant combination showed a striking reduction in AMPA-receptor activity; more closely resembling the AMPA-receptor defect in stargazer than the single Gria2 mutant.

Last, But Not Least, Stargazin Is Also a Cell-adhesion Molecule

The structural similarities between stargazin and the claudin family led to a recent article describing yet another role for stargazin as a cell-adhesion molecule (62). Furthermore, *Cacng2* message is expressed as early as embryonic day 12 in mouse (51). Thus, stargazin may be involved in forming close cell–cell contacts during neuronal development. Future studies comparing stargazer with control mice should reveal more about stargazin's cell-adhesion function in vivo.

Conclusion

The stargazer mouse has proved to be an exceptionally informative mutant. With the removal of one small stargazin protein from the brain, numerous disorders, including spontaneous absence seizures, ataxia, and head tossing, have materialized. The breadth of research generated from this one mutant underscores the power of mouse genetics. Spontaneous and genetically engineered mouse mutants give researchers insight into individual protein function within the context of the whole animal and provide the mechanistic tools to reveal the pathways that underlie the affected phenotype.

References

1. Noebels JL, Qiao X, Bronson RT, Spencer C, Davisson MT. Stargazer: A new neurological mutant on chromosome 15 in the mouse with prolonged cortical seizures. *Epilepsy Res* 1990;7:129–135.
2. Letts VA, Valenzuela AV, Kirley JP, Sweet HO, Davisson MT, Frankel WN. Genetic and physical maps of the stargazer locus on mouse chromosome 15. *Genomics* 1997;43:62–68.
3. Felix R. Insights from mouse models of absence epilepsy into Ca2+ channel physiology and disease etiology. *Cell Mol Neurobiol* 2002;22:103–120.
4. Noebels JL. The biology of epilepsy genes. *Annu Rev Neurosci* 2003;26:599–625.
5. Barclay J, Balaguero N, Mione M, Ackerman SL, Letts VA, Brodbeck J, Canti C, Meir A, Page KM, Kusumi K, Perez-Reyes E, Lander ES, Frankel WN, Gardiner RM, Dolphin AC, Rees M. Ducky mouse phenotype of epilepsy and ataxia is associated with mutations in the Cacna2d2 gene and decreased calcium channel current in cerebellar Purkinje cells. *J Neurosci* 2001;21:6095–6104.
6. Burgess DL, Jones JM, Meisler MH, Noebels JL. Mutation of the Ca^{2+} channel b subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse. *Cell* 1997;88:385–392.
7. Fletcher CF, Lutz CM, O'Sullivan TN, Shaughnessy JD Jr, Hawkes R, Frankel WN, Copeland NG, Jenkins NA. Absence epilepsy in tottering mutant mice is associated with calcuim channel defects. *Cell* 1996;87:607–617.
8. Letts VA, Felix R, Biddlecome GH, Arikkath J, Manaffey CL, Valenzuela A, Bartlett FS 2nd, Mori Y, Campbell KP, Frankel WN. The mouse stargazer gene encodes a neuronal Ca2+-channel gamma subunit. *Nat Genet* 1998;19:340–347.

9. Sharp AH, Black JL 3rd, Dubel SJ, Sundarraj S, Shen JP, Yunker AM, Copeland TD, McEnery MW. Biochemical and anatomical evidence for specialized voltage-dependent calcium channel gamma isoform expression in the epileptic and ataxic mouse, stargazer. *Neuroscience* 2001;105:599–617.
10. Letts VA, Kang MG, Mahaffey CL, Beyer B, Tenbrink H, Campbell KP, Frankel WN. Phenotypic heterogeneity in the stargazin allelic series. *Mamm Genome* 2003;14:506–513.
11. Jay SD, Ellis SB, McCue AF, Williams ME, Vedvick TS, Harpold MM, Campbell KP. Primary structure of the gamma subunit of the DHP-sensitive calcium channel from skeletal muscle. *Science* 1990;248:490–492.
12. Snead OC. Basic mechanisms of generalized absence seizures. *Ann Neurol* 1995;37:146–157.
13. McCormick DA. Are thalamocortical rhythms the rosetta stone of a subset of neurological disorders? *Nat Med* 1999;5:1349–1351.
14. McCormick DA, Contreras D. On the cellular and network bases of epileptic seizures. *Annu Rev Physiol* 2001;63:815–846.
15. Crunelli V, Leresche N. Childhood absence epilepsy: Genes, channels, neurons and networks. *Nat Rev Neurosci* 2002;3:371–382.
16. Yunker AM, McEnery MW. Low-voltage-activated ("T-Type") calcium channels in review. *J Bioenerg Biomembr* 2003;35:533–575.
17. Luthi A, McCormick DA. Modulation of a pacemaker current through Ca(2+)-induced stimulation of cAMP production. *Nat Neurosci* 1999;2:634–641.
18. Ludwig A, Budde T, Stieber J, Moosmang S, Wahl C, Holthoff K, Langebartels A, Wotjak C, Munsch T, Zong X, Feil S, Feil R, Lancel M, Chien KR, Konnerth A, Pape HC, Biel M, Hofmann F. Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. *EMBO J* 2003;22:216–224.
19. Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A. Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. *Arch Neurol* 2005;62:371–376.
20. Klugbauer N, Dai S, Specht V, Lacinova L, Marais E, Bohn G, Hofmann F. A family of gamma-like calcium channel subunits. *FEBS Lett* 2000;470:189–197.
21. Rousset M, Cens T, Restituito S, Barrere C, Black JL 3rd, McEnery MW, Charnet P. Functional roles of gamma2, gamma3 and gamma4, three new Ca2+ channel subunits, in P/Q-type Ca2+ channel expressed in *Xenopus* oocytes. *J Physiol* 2001;532:583–593.
22. Green PJ, Warre R, Hayes PD, McNaughton NC, Medhurst AD, Pangalos M, Duckworth DM, Randall AD. Kinetic modification of the alpha(1I) subunit-mediated T-type Ca(2+) channel by a human neuronal Ca(2+) channel gamma subunit. *J Physiol* 2001;533:467–478.
23. Kang MG, Chen CC, Felix R, Letts VA, Frankel WN, Mori Y, Campbell KP. Biochemical and biophysical evidence for gamma 2 subunit association with neuronal voltage-activated Ca2+ channels. *J Biol Chem* 2001;276:32917–32924.
24. Moss FJ, Dolphin AC, Clare JJ. Human neuronal stargazin-like proteins, gamma2, gamma3 and gamma4; an investigation of their specific localization in human brain and their influence on CaV2.1 voltage-dependent calcium channels expressed in Xenopus oocytes. *BMC Neurosci* 2003;4:1–23.
25. Black JL 3rd. The voltage-gated calcium channel gamma subunits: A review of the literature. *J Bioenerg Biomembr* 2003;35:649–660.
26. Zhang Y, Mori M, Burgess DL, Noebels JL. Mutations in high-voltage-activated calcium channel genes stimulate low-voltage-activated currents in mouse thalamic relay neurons. *J Neurosci* 2002;22:6362–6371.
27. Talley EM, Cribbs LL, Lee JH, Daud A, Perez-Reyes E, Bayliss DA. Differential distribution of three members of a gene family encoding low voltage-activated (T-type) calcium channels. *J Neurosci* 1999;19:1895–1911.
28. Kim D, Song I, Keum S, Lee T, Jeong MJ, Kim SS, McEnery MW, Shin HS. Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha(1G) T-type Ca(2+) channels. *Neuron* 2001;31:35–45.
29. Song I, Kim D, Choi S, Sun M, Kim Y, Shin HS. Role of the alpha1G T-type calcium channel in spontaneous absence seizures in mutant mice. *J Neurosci* 2004;24:5249–5257.
30. Herrup K, Wilczynski SL. Cerebellar cell degeneration in the leaner mutant mouse. *Neuroscience* 1982;7:2185–2196.
31. Maricich SM, Soha J, Trenkner E, Herrup K. Failed cell migration and death of Purkinje cells and deep nuclear neurons in the weaver cerebellum. *J Neurosci* 1997;17:3675–3683.
32. Sonmez E, Herrup K. Role of staggerer gene in determining cell number in cerebellar cortex. II. Granule cell death and persistence of the external granule cell layer in young mouse chimeras. *Brain Res* 1984;314:271–283.
33. Park C, Finger JH, Cooper JA, Ackerman SL. The cerebellar deficient folia (cdf) gene acts intrinsically in Purkinje cell migrations. *Genesis* 2002;32:32–41.
34. Sausbier M, Hu H, Arntz C, Feil S, Kamm S, Adelsberger H, Sausbier U, Sailer CA, Feil R, Hofmann F, Korth M, Shipston MJ, Knaus HG, Wolfer DP, Pedroarena CM, Storm JF, Ruth P. Cerebellar ataxia and Purkinje cell dysfunction caused by Ca2+-activated K+ channel deficiency. *Proc Natl Acad Sci U S A* 2004;101:9474–9478.
35. Duchala CS, Shick HE, Garcia J, Deweese DM, Sun X, Stewart VJ, Macklin WB. The toppler mouse: A novel mutant exhibiting loss of Purkinje cells. *J Comp Neurol* 2004;476:113–129.
36. Qiao X, Meng H. Nonchannel functions of the calcium channel gamma subunit: insight from research on the stargazer mutant. *J Bioenerg Biomembr* 2003;35:661–670.
37. Hashimoto K, Fukaya M, Qiao X, Sakimura K, Watanabe M, Kano M. Impairment of AMPA receptor function in cerebellar granule cells of ataxic mutant mouse stargazer. *J Neurosci* 1999;19:6027–6036.
38. Chen L, Bao S, Qiao X, Thompson RF. Impaired cerebellar synapse maturation in waggler, a mutant mouse with a disrupted neuronal calcium channel gamma subunit. *Proc Natl Acad Sci U S A* 1999;96:12132–12137.
39. Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Bredt DS, Nicholl RA. Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. *Nature* 2000;408:936–943.
40. Tomita S, Fukata M, Nicoll RA, Bredt DS. Dynamic interaction of stargazin-like TARPs with cycling AMPA receptors at synapses. *Science* 2004;303:1508–1511.
41. Dakoji S, Tomita S, Karimzadegan S, Nicoll RA, Bredt DS. Interaction of transmembrane AMPA receptor regulatory proteins with multiple membrane associated guanylate kinases. *Neuropharmacology* 2003;45:849–856.
42. Schnell E, Sizemore M, Karimzadegan S, Chen L, Bredt DS, Nicoll RA. Direct interactions between PSD-95 and stargazin

control synaptic AMPA receptor number. *Proc Natl Acad Sci U S A* 2002;99:13902–13907.
43. Yamazaki M, Ohno-Shosaku T, Fukaya M, Kano M, Watanabe M, Sakimura K. A novel action of stargazin as an enhancer of AMPA receptor activity. *Neurosci Res* 2004;50:369–374.
44. Richardson CA, Leitch B. Phenotype of cerebellar glutamatergic neurons is altered in stargazer mutant mice lacking brain-derived neurotrophic factor mRNA expression. *J Comp Neurol* 2005;481:145–159.
45. Tomita S, Chen L, Kawasaki Y, Petralia RS, Wenthold RJ, Nicholl RA, Bredt DS. Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins. *J Cell Biol* 2003;161:805–816.
46. Qiao X, Hefti F, Knusel B, Noebels JL. Selective failure of brain-derived neurotrophic factor mRNA expression in the cerebellum of stargazer, a mutant mouse with ataxia. *J Neurosci* 1996;16:640–648.
47. Richardson CA, Leitch B. Cerebellar Golgi, Purkinje, and basket cells have reduced gamma-aminobutyric acid immunoreactivity in stargazer mutant mice. *J Comp Neurol* 2002;453:85–99.
48. Thompson CL, Tehrani MH, Barnes EM Jr, Stephenson FA. Decreased expression of GABAA receptor alpha6 and beta3 subunits in stargazer mutant mice: A possible role for brain-derived neurotrophic factor in the regulation of cerebellar GABAA receptor expression? *Brain Res Mol Brain Res* 1998;60:282–290.
49. Qiao X, Chen L, Gao H, Bao S, Hefti F, Thompson RF, Knusel B. Cerebellar brain-derived neurotrophic factor-TrkB defect associated with impairment of eyeblink conditioning in Stargazer mutant mice. *J Neurosci* 1998;18:6990–6999.
50. Bao S, Chen L, Qiao X, Knusel B, Thompson RF. Impaired eyeblink conditioning in waggler, a mutant mouse with cerebellar BDNF deficiency. *Learn Mem* 1998;5:355–364.
51. Letts VA, Mahaffey CL, Beyer B, Frankel WN. A targeted mutation in Cacng4 exacerbates spike-wave seizures in stargazer (Cacng2) mice. *Proc Natl Acad Sci U S A* 2005;102:2123–2128.
52. Campbell DB, Hess EJ. L-type calcium channels contribute to the tottering mouse dystonic episodes. *Mol Pharmacol* 1999;55:23–31.
53. Fletcher CF, Tottene A, Lennon VA, Wilson SM, Dubel SJ, Paylor R, Hosford DA, Tessarollo L, McEnery MW, Pietrobon D, Copeland NG, Jenkins NA. Dystonia and cerebellar atrophy in Cacna1a null mice lacking P/Q calcium channel activity. *FASEB J* 2001;15:1288–1290.
54. Zhou YD, Turner TJ, Dunlap K. Enhanced G protein-dependent modulation of excitatory synaptic transmission in the cerebellum of the Ca2+ channel-mutant mouse, tottering. *J Physiol* 2003;547:497–507.
55. Nakagawa T, Cheng Y, Ramm E, Sheng M, Walz T. Structure and different conformational states of native AMPA receptor complexes. *Nature* 2005;433:545–549.
56. Jensen V, Kaiser KM, Borchardt T, Adelmann G, Rozov A, Burnashev N, Brix C, Frotscher M, Andersen P, Hvalby O, Sakmann B, Seeburg PH, Sprengel R. A juvenile form of postsynaptic hippocampal long-term potentiation in mice deficient for the AMPA receptor subunit GluR-A. *J Physiol* 2003;553:843–856.
57. Bannerman DM, Deacon RM, Seeburg PH, Rawlins JN. GluR-A-deficient mice display normal acquisition of a hippocampus-dependent spatial reference memory task but are impaired during spatial reversal. *Behav Neurosci* 2003;117:866–870.
58. Jia Z, Agopyan N, Miu P, Xiong Z, Henderson J, Gerlai R, Taverna FA, Velumian A, MacDonald J, Carlen P, Abramo-Newerly W, Roder J. Enhanced LTP in mice deficient in the AMPA receptor GluR2. *Neuron* 1996;17:945–956.
59. Gerlai R, Henderson JT, Roder JC, Jia Z. Multiple behavioral anomalies in GluR2 mutant mice exhibiting enhanced LTP. *Behav Brain Res* 1998;95:37–45.
60. Meng Y, Zhang Y, Jia Z. Synaptic transmission and plasticity in the absence of AMPA glutamate receptor GluR2 and GluR3. *Neuron* 2003;39:163–176.
61. Hu RQ, Cortez MA, Man HY, Roder J, Jia Z, Wang YT, Snead OC 3rd. Gamma-hydroxybutyric acid-induced absence seizures in GluR2 null mutant mice. *Brain Res* 2001;897:27–35.
62. Price MG, Davis CF, Deng F, Burgess DL. The alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptor trafficking regulator stargazin is related to the claudin family of proteins by its ability to mediate cell-cell adhesion. *J Biol Chem* 2005;280:19711–19720.