Mice with Impaired Met Tyrosine Kinase Signaling Demonstrate Characteristics Relevant to Autism

Jacob M. Smith¹, Elizabeth M. Powell¹²³*

¹Program in Neuroscience, University of Maryland Graduate School, Baltimore, MD, USA
²Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA
³Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Variants of MET, a receptor tyrosine kinase which binds the ligand Hepatocyte growth factor (HGF), have been linked to elevated risk for developing autism spectrum disorders (ASD) in humans. Though best known as a proto-oncogene, MET also plays important roles during normal development, including the development of the central nervous system. Recent studies in several mouse lines have shown that mice with reduced HGF-Met signaling have altered profiles of interneurons in the cortex, striatum, and hippocampus. Alterations in neuronal development, particularly in the cerebral cortex, may contribute to the pathology of developmental disorders, including autism. Other studies have shown changes in excitatory signaling in the Met-deficient cortex. Interestingly, mice with deficient Met signaling also show behavioral alterations characteristic of autism. Here we review anatomical and behavioral findings in mice with altered HGF - Met signaling.

Keywords: HGF; MET; Interneuron; Forebrain; Attentional set-shifting; Reversal learning; Seizure; Plaur

Abbreviations

ADI-R
Autism Diagnostic Interview, Revised

ADOS
Autism Diagnostic Observation Schedule

ASD
Autism Spectrum Disorder

CA1
Cornu Ammonis 1

CA3
Cornu Ammonis 3

CR
Calretinin

Dlx5/6
Distal-less homeobox 5/6

EEG
Electroencephalogram

Emx1
Empty spiracles homeobox 1

EN2
Engrailed 2

EPSC
Excitatory postsynaptic potential

GABA
Gamma aminobutyric acid

Gad67
Glutamic acid decarboxylase 67

GE
Ganglionic eminence

HGF
Hepatocyte growth factor

HOXA1
Homeobox A1

MSN
Medium spiny neuron

NFI
Neurofibromin 1

NrCAM
Neuronal cell adhesion molecule

OFC
Orbital frontal cortex

PV
Parvalbumin

PI3K
Phosphoinositol 3 kinase

PLCγ
Phospholipase C gamma

RAS
Rat sarcoma

Six3
Sine oculis-related homeobox 3

SNP
Single nucleotide polymorphism

SRS
Social Responsiveness Scale

SST
Somatostatin

tPA
Tissue-type plasminogen activator

uPA
Urokinase plasminogen activator

uPAR/PLAUR
Urokinase plasminogen activator receptor protein/gene

WT
Wild type

Introduction

Met is a tyrosine kinase receptor which binds the high-affinity ligand Hepatocyte growth factor (HGF) [1]. Both Met and HGF are initially produced as single-chain pro-proteins, which are subsequently processed into their mature forms by proteolytic cleavage [2]. In the case of HGF, this is accomplished by enzymes such as matriptase [3], HGF activator [4], tissue-type plasminogen activator (tPA, gene: Plat) [5] or urokinase-type plasminogen activator (uPA, gene: Plau) [6]. The proteolytic activity of uPA is increased upon binding to its receptor (uPAR, gene: Plaur) [7]. Upon binding to HGF, Met auto-phosphorylates creating a multi-substrate docking site for a number of adaptor proteins [8]. Downstream targets of HGF-Met signaling include PI3K, RAS, and PLCγ [8]. Potentially owing to this diverse array of downstream targets, Met signaling has been implicated in cellular processes as varied as

*Corresponding author: Elizabeth M. Powell, HSF II S251, 20 Penn St., Baltimore, MD 21201, USA.Tel: 410-706-8189; Fax: 410-706-2512; E-mail: epowe001@umaryland.edu

Received August 30, 2012; Accepted September 10, 2012; Published September 13, 2012

Citation: Smith JM, Powell EM (2012) Mice with impaired Met Tyrosine Kinase Signaling demonstrate characteristics relevant to autism. Autism S1:002. doi:10.4172/2165-7890.S1-002

Copyright: © 2012 Smith JM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
proliferation, migration, survival, the formation of neuronal processes [9-19].

Both Met and HGF are expressed in the developing brain in rodents [19-25] as well as primates [26, 27]. In mice, HGF and Met expression are detectable as early as E11.5. Expression of both HGF and Met is found in the cortical ventricular zone, and later in the cortical plate [15]. HGF is also expressed in the proliferative zone of the ganglionic eminence [15]. Met expression remains high from late embryonic through early post-natal development in the mouse [24,25,28] and at the corresponding ages in primate [27]. At late embryonic and early post-natal stages, Met transcript is also found in the amygdala, septum, and hippocampus [24]. Expression of both HGF and Met persists in the adult brain, albeit at reduced levels [19-22,24,29]. HGF-Met signaling may therefore participate in multiple phases of neurodevelopment. Furthermore, HGF and Met expression are found in multiple areas thought to be affected in autism spectrum disorders (ASD).

**Genetic Association of Autism with the Met Signaling Pathway**

ASD is characterized by language and communication deficits as well as restricted interests and repetitive or stereotyped behaviors. Multiple neuroanatomical abnormalities have been observed in the brains of autistic patients [32-38]. Genetics are thought to play a role in the etiology of ASDs, as they are highly heritable [39-44], although environmental influences could also play important roles [43,45].

A number of genetic syndromes include autistic-like features or are associated with an increased risk of ASD, including Prader-Willi [46,47], Fragile X [48,49], and Rett syndromes [50], as well as tuberous sclerosis [51]. While multiple genomic regions have been linked with autism risk, a particularly strong candidate is a region on chromosome 7q [52], which contains putative autism susceptibility genes such as EN2, HOXA1, WNT2, and NRCAM [53-58]. Chromosome 7q also contains the MET gene, located at 7q31 [59], as well as HGF, located at 7q21 [60]. Several MET variants have been shown to increase risk for ASDs [61-66]. One SNP in particular, rs1858830, has been found to be associated with the co-occurrence of autism with gastrointestinal conditions [63]. Another gene involved in HGF signaling, PLAUR (which encodes uPAR, and is found on chromosome 19q13) [67], has also been associated with autism. The T allele of the PLAUR promoter variant rs344781 is associated with a 1.93 relative risk for ASD [62].

While some studies examining MET association with autism have failed to replicate the association of individual SNPs [64], evidence for the association of the gene as a whole is strong, especially when combined with the association of related genes.

In addition to genetic association, a number of MET variants have been shown to be functionally significant. The C allele of rs1858830 has been shown to reduce MET promoter activity [61]. MET protein levels are also reduced post-mortem in temporal cortex from autistic patients compared to controls [68]. A few MET variants have even been shown to have functional consequences at the level of behavior. The C allele of rs1858830 is also associated with social and communication scores on the ADI-R, ADOS, and SRS [69]. The C allele of rs2237717 and the G allele of rs42336 have been associated with altered facial emotion perception [70], which is altered in ASD. Given the repeated association of MET with autism, and the potential association of other genes in the pathway, it is highly likely that dysregulation of HGF-MET signaling could contribute to the pathology of ASD, in at least a subset of affected individuals.

**Consequences of Altered Met Signaling**

While MET is well validated as a risk gene for autism [61,63,70-72], only a few studies have examined the effects of loss of Met function in animals. This is likely due at least in part to the embryonic lethality of constitutive knockouts. Met function appears to be required for proper placental [73] and liver development [74], and therefore global Met knockout mice die early during gestation. In order to avoid this, groups have used Cre-loxP recombination strategies to inactivate Met specifically in cells expressing Cre recombinase [19,23,75,76].

The Dlx5/6-Cre driver inactivates Met (Met<sup>loxP/Dlx<sup>cre</sup></sup>) mice in post-mitotic GABAergic neurons originating in the Ganglionic Emination (GE). GABAergic neurons from the GE become the inhibitory interneurons of the cerebral cortex, hippocampus, amygdala, and striatum, as well as the medium spiny neurons of the striatum [77]. The Met<sup>loxP/Dlx<sup>cre</sup></sup> mice show increased numbers of parvalbumin (PV) and somatostatin (SST) positive interneurons in the striatum, as well as a reduction in PV interneuron numbers in the sensorimotor and orbitofrontal cortex, but not in visual cortex [19]. Furthermore, at more caudal levels of the striatum, a greater percentage of the population of PV positive interneurons was found in medial (associative), and fewer in lateral (sensorimotor) regions of the striatum than in control mice. Loss of Met function in embryonic interneurons therefore seems to affect the migration of GABAergic interneurons both within the striatum and between the embryonic striatum and cortex.

Hippocampal interneurons are also generated from the ganglionic eminence and appear to be affected by loss of Met signaling. Fewer PV and calretinin (CR) positive interneurons were found in the CA3 region of the hippocampus in Met<sup>loxP/Dlx<sup>cre</sup></sup> mice than in controls. Mice in which Met was inactivated in the proliferative zones of the ganglionic eminence using a Six3-Cre driver (Met<sup>loxP/Six3<sup>cre</sup></sup>) mice showed a similar loss of PV and CR cells in CA3, but further showed a loss of CR interneurons throughout the hippocampus, and an increase in PV interneurons in the dentate gyrus [23]. Alterations in the number of interneurons in the hippocampus of Met<sup>loxP/Dlx<sup>cre</sup></sup> mice are likely due to a migration defect similar to that seen for cortical and striatal interneurons in these animals. Deficits in the Met<sup>loxP/Six3<sup>cre</sup></sup> mice could also be due to changes in the specification of different subtypes of interneuron. It is unlikely that the deficit in the Met<sup>loxP/Six3<sup>cre</sup></sup> mice is due to decreased proliferation of interneurons, as similar a similar pattern of GABA staining found in the hippocampus [23].

In order to examine the functions of Met in the developing cortex, a similar system has been employed using Cre recombinase expressed under the control of the Emx1 promoter to inactivate Met in excitatory neurons and glia of the cerebral cortex and hippocampus. Notably, this system does not directly ablate Met function in cortical GABAergic interneurons, which originate in the ganglionic eminence [76,78] found that pyramidal neurons in layers 2 and 3 of the anterior cingulate cortex of Met<sup>loxP/Emx1<sup>cre</sup></sup> mice showed significant alterations in dendritic arbor. Met<sup>loxP/Emx1<sup>cre</sup></sup> neurons showed reduced apical dendritic arbor length distal to the cell body, and increased basal dendritic arbor length proximal to the cell body. These differences appear to be primarily due to changes in branching complexity. Since the distal apical dendritic arbor of pyramidal neurons receives distinct synaptic inputs from the basal and proximal apical arbor [79], this could result in changes in synaptic connectivity. No difference was found in the number of dendritic spines between Met<sup>loxP/Emx1<sup>cre</sup></sup> and control mice, but an increase in the volume of spine heads was observed [80]. Interestingly, striatal medium spiny neurons (MSNs), were also found to show increases in both dendritic arbor length and spine head volume. Alterations in
MSNs would suggest that loss of Met signaling in cortical pyramidal neurons may have effects on cells targeted by cortical efferents, as striatal MSNs are not targeted by the Emx1-Cre driver [78]. As spine structure is closely related to function, and spines are the main target of glutamatergic synapses, alterations in spine head volume could produce changes in excitatory neurotransmission [81]. Indeed, alterations in excitatory neurotransmission have been shown in the cortex of Met+/−/Emx1−/− mice. In the anterior cingulate cortex of Met+/−/Emx1−/− mice, stimulation layer 2/3 pyramidal neurons produced stronger excitatory post-synaptic potentials (EPSCs) in layer 5B corticostriatal projection neurons [82]. While changes in EPSC amplitude in this population could be due to either presynaptic or postsynaptic alterations, no difference was found in paired pulse ratios between Met+/−/Emx1−/− mice and controls, suggesting that at least some presynaptic parameters (i.e. release probability) are unaltered by loss of Met signaling. In contrast, no changes in EPSCs were found in corticopontine projection neurons after stimulation in layer 2/3 [82], further suggesting that the increased connection strength in corticostriatal neurons is likely due to post-synaptic mechanisms.

Alterations in cortical connectivity in Met+/−/Emx1−/− mice reflect some changes seen in ASD. Altered cortical connectivity is thought to play a role in the etiology of ASD [83], including local hyperconnectivity (as demonstrated in Met+/−/Emx1−/− mice) as well as long-range hyperconnectivity. That hyperconnectivity in the Met+/−/Emx1−/− mice appears specific to corticostriatal projection neurons is significant, as both corticostriatal structural [84] and functional connectivity [85,86] have been shown to be altered in ASD. Furthermore, there is some evidence of an association between changes in striatal functional connectivity and repetitive behavior in children with ASD [86].

Unlike Met−/− or Hgf−/− mice which die before embryonic day 12 [74,87], Plaur−/− mice live to adulthood [88]. These mice exhibit reduced HGF levels [25,89] suggesting reduced HGF-Met signaling, and possible alterations to HGF mediated developmental processes. HGF has been reported to facilitate forebrain GABAergic interneuron migration [89,90]. Several studies have found decreased numbers of GABAergic interneurons in the brains of Plaur−/− mice [25,28,91,92]. Fewer GABA positive cells were found in the cingulate and parietal cortex of Plaur−/− mice than in WT mice [28]. In a parallel study, Gad67−/− cells were found to be decreased in the parietal cortex, as well as in the dentate gyrus and the CA1 region of the hippocampus [91]. No change in either GABA or Gad67 staining was observed in occipital cortex [28,91]. Among GABAergic interneurons, PV expressing cells seem to be preferentially affected in Plaur−/− mice. Decreases in PV−/− interneurons have been noted in the frontal areas, including the anterior cingulate [28], and orbital frontal cortex (OFC) [92], and parietal cortex, in particular in somatosensory areas [25,28,91], as well as in the striatum (Bissonnette et al., 2010). In the hippocampus, however, the PV−/− population is unaffected, and there is a reduction in somatostatin+ (SST+) cells in the dentate gyrus and CA1[91]. In the cases of the somatosensory and orbital frontal cortical regions and the striatum, over expression of HGF in astrocytes restored the numbers of PV−/− interneurons [25,92], suggesting that the decrease in HGF levels seen in Plaur−/− mice is responsible for the observed interneuron deficits.

Behavioral Consequences of Altered HGF-Met Signaling

While cellular and physiological changes in mice with altered HGF-Met signaling are informative, they would not make for convincing animal models without accompanying behavioral alterations reflective of ASD symptoms. While not all of the mouse lines which have been examined have been extensively characterized, several show behavioral phenotypes which suggest that altered HGF signaling could contribute to autistic-like behavior.

Plaur−/− mice show a number of behavioral alterations when compared to WT littermates. Among these, Plaur−/− mice have been shown to display increased anxiety-like behaviors in the light-dark avoidance test and the elevated plus maze [25,28]. In addition to increased anxiety, Plaur−/− mice have impaired cognitive flexibility as measured by reversal learning a process which has been shown to be dependent on the OFC [92-94]. Plaur−/− and WT animals both learn the rules similarly, but once the rules are reversed, the Plaur−/− mice require more trials to master the task [92]. The Plaur−/− mice exhibit abnormal electroencephalogram (EEG) activity and have spontaneous seizures, as well as an increased sensitivity to chemically induced seizures [28]. HGF supplementation rescues the seizures and anxiety behaviors seen in Plaur−/− mice [25]. Our recent findings indicate impaired social interactions and attentional processing in Plaur−/− mice (unpublished observations) and current studies are focused on assessing communication responses in the WT and Plaur−/− groups.

Met+/−/Dlx5−/− mice show no alterations in locomotor activity in the open field or in tests of anxiety-like behavior such as light-dark avoidance or the elevated plus maze [19]. Met+/−/Dlx5−/− mice were also tested in the Morris water maze, which can be used to test both spatial learning (mediated by the hippocampus) and procedural learning (mediated by the striatum) [95,96]. In the water maze, Met+/−/Dlx5−/− mice performed similarly to controls during a probe test, as well as during a reversal probe test where the hidden platform was moved to the opposite quadrant from where it was during training. Both tests are used to measure hippocampal-dependent spatial learning [95,97]. However, in a cued platform task, which is dependent on striatal function [95,97], Met+/−/Dlx5−/− mice were slower to reach the platform than control mice. This suggests that despite abnormalities in the population of interneurons in both the hippocampus and striatum of Met+/−/Dlx5−/− mice, hippocampal function remains relatively normal, while striatal function, mainly habit learning, is disrupted.

Reversal learning was also affected in Met+/−/Dlx5−/− mice [19], similarly to Plaur−/− mice. Met+/−/Dlx5−/− mice performed similarly to controls in learning the initial discrimination task, but required significantly longer to reach criterion during the reversal portion [19]. That the mice acquire the initial discrimination normally suggests that they have no problem learning the task or discriminating between the cues, while their deficit in the reversal portion of the task suggests a lack of behavioral flexibility or a problem inhibiting the previously rewarded response. A similar loss of behavioral flexibility may be involved in the restricted or repetitive behavior which is frequently observed in autistic children [98].

Conclusions

Mice with altered HGF-Met signaling show alterations in the interneuron populations of the frontal cortex, striatum, and hippocampus. While spatial learning (dependent on the hippocampus) appears normal in Met+/−/Dlx5−/− and Plaur−/− mice, Met+/−/Dlx5−/− mice show deficits in procedural learning, and both strains are impaired on a reversal learning task. In Plaur−/− mice, restoration of normal HGF levels via genetic intervention restores both interneuron numbers and normal behavior. Repetitive behaviors are frequently observed in ASD [98], and have been associated with diminished inhibitory control of prior responses [99], which depends on frontal-striatal circuits [100,101].
Inhibition of previously-rewarded responses is a critical component of reversal learning, and this may be inhibited in Metflox/DlxCre mice and Plaur−/− mice [19,92]. It would therefore appear as though the loss of GABAergic (and in particular PV+) interneurons in the frontal cortex and striatum could contribute to the behavioral alterations observed in Plaur−/− mice, and possibly in Metflox/DlxCre mice as well. For example, the OFC has been shown to be required for normal reversal learning [93], and both Plaur−/− and Metflox/DlxCre mice show both reduced numbers of PV− interneurons in the OFC and impaired reversal learning. Furthermore, supplementation of HGF levels in Plaur−/− mice restores both PV cell number and reversal learning to normal [92]. While other causes cannot be ruled out, it would appear that the changes in interneuron numbers in the striatum and frontal cortex could lead to the behavioral changes seen in Plaur−/− and Metflox/DlxCre mice by altering cortical and striatal signaling. While cortico-striatal signaling has been shown to be altered in Metflox/EnxlCre mice [82]. Further studies are needed to elucidate the effects of loss of Met signaling in excitatory neurons on behavior.

References
1. Nalini L, Weidner KM, Vigna E, Gaudino G, Bardelli A, et al. (1991) Scatter factor and hepatocyte growth factor are indistinguishable ligands for the MET receptor. EMBO J 10: 2867-2878.
2. Trusolino L, Comoglio PM (2002) Scatter-factor and semaphorin receptors: cell signaling for invasive growth. Nat Rev Cancer 2: 289-300.
3. Lee SL, Dickson RB, Lin CY (2000) Activation of hepatocyte growth factor and urokinase/plasminogen activator by metatripeptide, an epithelial membrane serine protease. J Biol Chem 275: 36720-36725.
4. Shimomura T, Miyazawa K, Komiyama Y, Hirakoa H, Naka D, et al. (1995) Activation of hepatocyte growth factor by two homologous proteases, blood-coagulation factor XIIa and hepatocyte growth factor activator. Eur J Biochem 229: 257-261.
5. Mars WM, Zarnegar R, Michalopoulos GK (1993) Activation of hepatocyte growth factor by the plasminogen activators uPA and tPA. Am J Pathol 143: 949-958.
6. Nalini L, Tamagnone L, Vigna E, Sachs M, Hartmann G, et al. (1992) Extracellular proteolytic cleavage by urokinase is required for activation of hepatocyte growth factor/scatter factor. EMBO J 11: 4825-4833.
7. Ellis V, Behrendt N, Dana K (1991) Plasminogen activation by receptor-bound urokinase. A kinetic study with both cell-associated and isolated receptor. J Biol Chem 266: 12752-12758.
8. Ponzetto C, Bardelli A, Zhen Z, Maina F, dalla Zonca P, et al. (1994) A multifunctional docking site mediates signaling and transformation by the hepatocyte growth factor/scatter factor receptor family. Cell 77: 261-271.
9. Defrances MC, Wolf HK, Michalopoulos GK, Zarnegar R (1992) The presence of hepatocyte growth factor in the developing rat. Development 116: 387-395.
10. Hamanoue M, Takekoto N, Matsumoto K, Nakamura T, Nakajima K, et al. (1996) Neurotrophic effect of hepatocyte growth factor on central nervous system neurons in vitro. J Neurosci Res 43: 754-764.
11. Maina F, Hilton MC, Ponzetto C, Davies AM, Klein R (1997) Met receptor signaling is required for sensory nerve development and HGF promotes axonal growth and survival of sensory neurons. Genes Dev 11: 3341-3350.
12. Maina F, Klein R (1999) Hepatocyte growth factor, a versatile signal for developing neurons. Nat Neurosci 2: 213-217.
13. Seeds NW, Basham ME, Hafke SP (1999) Neuronal migration is retarded in mice lacking the tissue plasminogen activator gene. Proc Natl Acad Sci U S A 96: 14118-14123.
14. Caton A, Hacker A, Naeem A, Livet J, Maina F, et al. (2000) The branchial arches and HGF are growth-promoting and chemonaesthetic for cranial motor axons. Development 127: 1751-1766.
15. Powell EM, Mars WM, Levitt P (2001) Hepatocyte growth factor/scatter factor is a motogen for interneurons migrating from the ventral to dorsal telencephalon. Neuron 30: 79-89.
16. Powell EM, Mühlfriedel S, Bolz J, Levitt P (2003) Differential regulation of thalamic and cortical axonal growth by hepatocyte growth factor/scatter factor. Dev Neurosci 25: 197-206.
17. Gutierrez H, Dolcet X, Tolcos M, Davies A (2004) HGF regulates the development of cortical pyramidal dendrites. Development 131: 3717-3726.
18. Niihara M, Takagi N, Takagi K, Funakoshi H, Nakamura T, et al. (2006) Effects of hepatocyte growth factor on phosphorylation of extracellular signal-regulated kinase and hippocampal cell death in rats with transient forebrain ischaemia. Eur J Pharmacol 535: 114-124.
19. Martins GJ, Shahrokh M, Powell EM (2011) Genetic disruption of Met signaling impairs GABAergic striatal development and cognition. Neuroscience 176: 199-209.
20. Jung W, Castren E, Odenthal M, Vande Woeye GF, Ishii T, et al. (1994) Expression and functional interaction of hepatocyte growth factor-scatter factor and its receptor c-met in mammalian brain. J Cell Biol 126: 485-494.
21. Honda S, Kagoshima M, Hanaka A, Tohyama M, Matsumoto K, et al. (1995) Localization and functional coupling of HGF and c-Met/HGF receptor in rat brain: implication as neurotrophic factor. Brain Res Mol Brain Res 32: 197-210.
22. Achim CL, Katyal S, Wiley CA, Shiratori M, Wang G, et al. (1997) Expression of HGF and c-Met in the developing and adult brain. Brain Res Dev Brain Res 102: 299-303.
23. Martins GJ, Plachez C, Powell EM (2007) Loss of embryonic MET signaling alters profiles of hippocampal interneurons. Dev Neurosci 29: 143-158.
24. Judson MC, Bergman MV, Campbell DB, Eagleson KL, Levitt P (2009) Dynamic gene and protein expression patterns of the autism-associated met receptor tyrosine kinase in the developing mouse forebrain. J Comp Neurol 513: 511-531.
25. Bae MH, Bissonette GB, Mars WM, Michalopoulos GK, Achim CL, et al. (2010) Hepatocyte growth factor (HGF) modulates GABAergic inhibition and seizure susceptibility. Exp Neurol 221: 129-135.
26. Yamada T, Yoshimura Y, Tsuboi Y, Shimomura T (1997) Astroglial expression of hepatocyte growth factor and hepatocyte growth factor activator in human brain tissues. Brain Res 762: 251-256.
27. Judson MC, Amaral DG, Levitt P (2011) Conserved subcortical and divergent cortical expression of proteins encoded by orthologs of the autism risk gene MET. Cereb Cortex 21: 1613-1626.
28. Powell EM, Campbell DB, Stanwood GD, Davis C, Noebels JL, et al. (2003) Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction. J Neurosci 23: 623-631.
29. Iyer A, Kniecik TE, Park M, Daar I, Blair D, et al. (1990) Structure, tissue-specific expression, andtransforming activity of the mouse met protooncogene. Cell Growth Differ 1: 87-95.
30. Honda S, Kagoshima M, Hanaka A, Tohyama M, Matsumoto K, Nakamura T (1995) Localization and functional coupling of HGF and c-Met/HGF receptor in rat brain: implication as neurotrophic factor. Brain Res Mol Brain Res 32: 197-210.
31. Achim CL, Katyal S, Wiley CA, Shiratori M, Wang G, Oshika E, Petersen BE, Li JM, Michalopoulos GK (1997) Expression of HGF and c-Met in the developing and adult brain. Brain Res Dev Brain Res 102: 299-303.
32. Bauman M, Kemper TL (1985) Histoanatomic observations of the brain in early childhood and adult brain. Brain Res 225: 197-210.
33. Shimomura T, Miyazawa K, Komiyama Y, Hirakoa H, Naka D, et al. (1995) Localization and functional coupling of HGF and c-Met/HGF receptor in rat brain: implication as neurotrophic factor. Brain Res Mol Brain Res 32: 197-210.
34. Honda S, Kagoshima M, Hanaka A, Tohyama M, Matsumoto K, Nakamura T (1995) Localization and functional coupling of HGF and c-Met/HGF receptor in rat brain: implication as neurotrophic factor. Brain Res Mol Brain Res 32: 197-210.
35. Achim CL, Katyal S, Wiley CA, Shiratori M, Wang G, Oshika E, Petersen BE, Li JM, Michalopoulos GK (1997) Expression of HGF and c-Met in the developing and adult brain. Brain Res Dev Brain Res 102: 299-303.
36. Bauman M, Kemper TL (1985) Histoanatomic observations of the brain in early childhood and adult brain. Neuroimage 16: 1038-1051.
37. Carper RA, Moses P, Tigue ZD, Courchesne E (2002) Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage 16: 1038-1051.
38. Tsatsanis KD, Rourke BP, Klin A, Volkmar FR, Cicchetti D, et al. (2003) Reduced
thalamic volume in high-functioning individuals with autism. Biol Psychiatry 53: 121-129.

37. Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, et al. (2004) The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci 24: 6392-6401.

38. Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. Trends Neurosci 31: 137-145.

39. Folstein S, Rutter M (1977) Infantile autism: a genetic study of 21 twin pairs. J Child Psychol Psychiatry 18: 297-321.

40. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, et al. (1995) Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Stud 25: 63-77.

41. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN (1999) Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol 14: 388-394.

42. Folstein SE, Rosen-Shedelley B (2001) Genetics of autism: complex aetiology for a heterogeneous disorder. Nat Rev Genet 2: 943-955.

43. Connors SL, Crowell DE, Eberhart CG, Copeland NJ, Newshacher CJ, et al. (2005) beta2-adrenergic receptor activation and genetic polymorphisms in autism: data from dizygotic twins. J Child Neurol 20: 876-884.

44. Abrahams BS, Geschwind DH (2008) Advances in autism genetics: on the threshold of a new neurobiology. Nat Rev Genet 9: 341-355.

45. Croen LA, Connors SL, Matevia M, Qian Y, Newshacher C, et al. (2011) Prenatal exposure to β2-adrenergic receptor agonists and risk of autism spectrum disorders. J Neurodev Disord 3: 307-315.

46. Veltman MW, Craig EE, Bolton PF (2005) Autism spectrum disorders in Prader-Willi and Angelman syndromes: a systematic review. Psychiatr Genet 15: 243-254.

47. Hogart A, Wu D, LaSalle JM, Schanen NC (2010) The comorbidity of autism with the genomic disorders of chromosome 15q11.2-13. Neurobiol Dis 38: 181-191.

48. Brown WT, Jenkins EC, Friedman E, Brooks J, Wisniewski K, et al. (1982) Autism is associated with the fragile-X syndrome. J Autism Dev Disord 12: 303-308.

49. Bailey DB Jr, Mesibov GB, Hatton DD, Clark RD, Roberts JE, et al. (1998) Autistic behavior in young boys with fragile X syndrome. J Autism Dev Disord 28: 499-508.

50. Mount RH, Charnam T, Hastings RP, Reilly S, Cass H (2003) Features of autism in Rett syndrome and severe mental retardation. J Autism Dev Disord 33: 435-442.

51. Lewis WW, Sahin M, Scherrer B, Peters JM, Suarez RO, et al. (2012) Impaired language pathways in tuberous sclerosis complex patients with autism spectrum disorders. Cereb Cortex.

52. IMGSAC (1998) A Full Genome Screen for Autism with Evidence for Linkage to a Region on Chromosome 7q. International Molecular Genetic Study of Autism Consortium. Hum Mol Genet 7: 571-578.

53. Petit E, Héraud J, Martinez J, Perrot A, Barthélémy C, et al. (1995) Association study with two markers of a human homeogene in infantile autism. J Med Genet 32: 269-274.

54. Ingram JL, Stoddell CJ, Hyman SL, Figlewicz DA, Weitkamp LR, et al. (2000) Discovery of allelic variants of HOXA1 and HOXB1: genetic susceptibility to autism spectrum disorders. Cereb Cortex.

55. Lewis WW, Sahin M, Scherrer B, Peters JM, Suarez RO, et al. (2012) Impaired language pathways in tuberous sclerosis complex patients with autism spectrum disorders. Cereb Cortex.

56. IMGSAC (1998) A Full Genome Screen for Autism with Evidence for Linkage to a Region on Chromosome 7q. International Molecular Genetic Study of Autism Consortium. Hum Mol Genet 7: 571-578.

57. Petit E, Héraud J, Martinez J, Perrot A, Barthélémy C, et al. (1995) Association study with two markers of a human homeogene in infantile autism. J Med Genet 32: 269-274.

58. Persico AM, Bourgeron T (2006) Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. Trends Neurosci 29: 349-358.

59. Persico AM, Bourgeron T (2006) Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. Trends Neurosci 29: 349-358.

60. Fukuyama R, Ichijoh Y, Minoshima S, Kitamura N, Shimizu N (1991) Regional localization of the hepatocyte growth factor (HGF) gene to human chromosome 7 band q21.1. Genomics 11: 410-415.

61. Campbell DB, Sutcliffe JS, Ebet PJB, Millern R, Bravaccio C, et al. (2006) A genetic variant that disrupts MET transcription is associated with autism. Proc Natl Acad Sci U S A 103: 16834-16839.

62. Campbell DB, Li C, Sutcliffe JS, Persico AM, Levitt P (2008) Genetic evidence implicating multiple genes in the MET receptor tyrosine kinase pathway in autism spectrum disorder. Autism Res 1: 159-168.

63. Campbell DB, Buie TM, Winter H, Bauman M, Sutcliffe JS, et al. (2009) Distinct genetic risk based on association of MET in families with co-occurring autism and gastrointestinal conditions. Pediatrics 123: 1018-1024.

64. Sousa I, Clark TG, Toma C, Kobayashi K, Choma M, et al. (2009) MET and autism susceptibility: family and case-control studies. Eur J Hum Genet 17: 749-758.

65. Thanseem I, Nakamura K, Miyachi T, Toyota T, Yamada S, et al. (2010) Further evidence for the role of MET in autism susceptibility. Neurosci Res 68: 137-141.

66. Zhou X, Xu Y, Wang J, Zhou H, Liu X, et al. (2011) Replication of the association of a MET variant with autism in a Chinese Han population. PLoS One 6: e27428.

67. Borglum AD, Byskov A, Reagon P, Rodland AL, Trippe P, et al. (1992) Assignment of the urokinase-type plasminogen activator receptor gene (PLAUR) to chromosome 19q13.1-13.2. Am J Hum Genet 50: 492-497.

68. Campbell DB, D’Oronzo R, Garbett K, Ebet PJB, Mimics K, et al. (2007) Disruption of cerebral cortex MET signaling in autism spectrum disorder. Ann Neurol 62: 243-250.

69. Campbell DB, Warren D, Sutcliffe JS, Lee EB, Levitt P (2010) Association of MET with social and communication phenotypes in individuals with autism spectrum disorder. Am J Med Genet B Neuropsychiatr Genet 153B: 438-446.

70. Lin MT, Huang KH, Huang CL, Huang YJ, Tsai GE, et al. (2012) MET and AKT genetic influence on facial emotion perception. PLoS One 7: e36143.

71. Campbell DB, D’Oronzo R, Garbett K, Ebet PJB, Mimics K, Levitt P, Persico AM (2007a) Disruption of cerebral cortex MET signaling in autism spectrum disorder. Ann Neurol 62:243-250.

72. Sousa I, Clark TG, Toma C, Kobayashi K, Choma M, et al. (2009) MET and autism susceptibility: family and case-control studies. Eur J Hum Genet 17: 749-758.

73. Uehara Y, Minowa O, Mori C, Shiota K, Kuno J, et al. (1995) Placental defect in autism susceptibility: family and case-control studies. Eur J Hum Genet 17: 518-524.

74. Schmidt C, Bladt F, Goedecke S, Brinkmann V, Vzichiesche W, et al. (1995) Scatter factor/hepatocyte growth factor is essential for liver development. Nature 373: 702-705.

75. Uehara Y, Minowa O, Mori C, Shiota K, Kuno J, et al. (1995) Placental defect and embryonic lethality in mice lacking hepatocyte growth factor/scatter factor. Nature 373: 702-705.

76. Judson MC, Bergman MV, Campbell DB, Eagleson KL, Levitt P (2009) Dynamic gene and protein expression patterns of the autism-associated met receptor tyrosine kinase in the developing mouse forebrain. J Comp Neurol 513: 511-531.

77. Marin O, Rubenstein JL (2003) Cell migration in the forebrain. Annu Rev Neurosci 26: 441-483.

78. Gorski JA, Talley T, Qiu M, Puelles L, Rubenstein JL, et al. (2002) Cortical excitatory neurons and glia, but not GABAergic neurons, are produced in the Emx1-expressing lineage. J Neurosci 22: 6309-6314.

79. Spruston N (2008) Pyramidal neurons: dendritic structure and synaptic integration. Nat Rev Neurosci 9: 206-221.

80. Judson MC, Eagleson KL, Wang L, Levitt P (2010) Evidence of cell-
nonautonomous changes in dendrite and dendritic spine morphology in the met-signaling-deficient mouse forebrain. J Comp Neurol 518: 4463-4478.
81. Kasai H, Matsuzaki M, Noguchi J, Yasumatsu N, Nakahara H (2003) Structure-stability-function relationships of dendritic spines. Trends Neurosci 26: 360-368.
82. Qiu S, Anderson CT, Levitt P, Shepherd GM (2011) Circuit-specific intracortical hyperconnectivity in mice with deletion of the autism-associated Met receptor tyrosine kinase. J Neurosci 31: 5855-5864.
83. Courchesne E, Pierce K (2005) Why the frontal cortex in autism might be talking only to itself. local over-connectivity but long-distance disconnection. Curr Opin Neurobiol 15: 225-230.
84. Langen M, Leemans A, Johnston P, Ecker C, Daly E, et al. (2012) Fronto-striatal circuitry and inhibitory control in autism: findings from diffusion tensor imaging tractography. Cortex 48: 183-193.
85. Turner KC, Frost L, Linsenbardt D, McIlroy JR, Müller RA (2006) Atypically diffuse functional connectivity between caudate nuclei and cerebral cortex in autism. Behav Brain Funct 2: 34.
86. Di Martino A, Kelly C, Grzadzinski R, Zuo XN, Mennes M, et al. (2011) Aberrant striatal functional connectivity in children with autism. Biol Psychiatry 69: 847-856.
87. Bladt F, Riethmacher D, Isenmann S, Aguzzi A, Birchmeier C (1995) Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. Nature 376: 768-771.
88. Dewerchin M, Nuffelen AV, Wallays G, Bouché A, Moons L, et al. (1996) Generation and characterization of urokinase receptor-deficient mice. J Clin Invest 97: 870-878.
89. Powell EM, Mars WM, Levitt P (2001) Hepatocyte growth factor/scatter factor is a motogen for interneurons migrating from the ventral to dorsal telencephalon. Neuron 30: 79-89.
90. Levitt P, Eagleson KL, Powell EM (2004) Regulation of neocortical interneuron development and the implications for neurodevelopmental disorders. Trends Neurosci 27: 400-406.
91. Eagleson KL, Bonnin A, Levitt P (2005) Region- and age-specific deficits in gamma-aminobutyric acidergic neuron development in the telencephalon of the uPAR(-/-) mouse. J Comp Neurol 488: 449-466.
92. Bissonette GB, Bae MH, Suresh T, Jaffe DE, Powell EM (2010) Astrocyte-mediated hepatocyte growth factor/scatter factor supplementation restores GABAergic interneurons and corrects reversal learning deficits in mice. J Neurosci 30: 2918-2923.
93. Bissonette GB, Martins GJ, Franz TM, Harper ES, Schoenbaum G, et al. (2008) Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. J Neurosci 28: 11124-11130.
94. Bissonette GB, Powell EM (2012) Reversal learning and attentional set-shifting in mice. Neuropharmacology 62: 1168-1174.
95. Devan BD, Goad EH, PETRI HL (1996) Dissociation of hippocampal and striatal contributions to spatial navigation in the water maze. Neurobiol Learn Mem 66: 305-323.
96. Packard MG, Teather LA (1997) Double dissociation of hippocampal and dorsal-striatal memory systems by posttraining intracerebral injections of 2-amino-5-phosphonopentanoic acid. Behav Neurosci 111: 543-551.
97. Vorhees CV, Williams MT (2006) Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc 1:848-858.
98. Turner M (1999) Annotation: Repetitive behaviour in autism: a review of psychological research. J Child Psychol Psychiatry 40:839-849.
99. Mosconi MW, Kay M, D’Cruz AM, Seidenfeld A, Guter S, et al. (2009) Impaired inhibitory control is associated with higher-order repetitive behaviors in autism spectrum disorders. Psychol Med 39: 1559-1566.
100. Kelly AM, Hester R, Murphy K, Javitt DC, Foxe JJ, et al. (2004) Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI. Eur J Neurosci 19: 3105-3112.
101. Rubia K, Smith AB, Taylor E, Brammer M (2007) Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. Hum Brain Mapp 28: 1163-1177.

This article was originally published in a special issue, Animal Models in Autism handled by Editor(s), Dr. Craig M. Powell, The University of Texas Southwestern Medical Center Dallas, USA.