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Distinct Genetic Risk Based on Association of *MET* in Families With Co-occurring Autism and Gastrointestinal Conditions

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What's Known on This Subject

Gastrointestinal conditions are common among individuals with autism, but it is not known if co-occurring gastrointestinal conditions represent a unique autism subgroup. Some speculate that gastrointestinal dysfunction impacts brain development or that altered nervous system development affects gastrointestinal function.

What This Study Adds

The MET receptor tyrosine kinase participates in brain development and gastrointestinal repair. A MET gene variant was associated with co-occurring gastrointestinal conditions suggesting that disrupted MET signaling may contribute to both medical conditions in this subgroup.

ABSTRACT

OBJECTIVE. In addition to the core behavioral symptoms of autism spectrum disorder, many patients present with complex medical conditions including gastrointestinal dysfunction. A functional variant in the promoter of the gene encoding the MET receptor tyrosine kinase is associated with autism spectrum disorder, and MET protein expression is decreased in the temporal cortex of subjects with autism spectrum disorder. MET is a pleiotropic receptor that functions in both brain development and gastrointestinal repair. On the basis of these functions, we hypothesized that association of the autism spectrum disorder–associated *MET* promoter variant may be enriched in a subset of individuals with co-occurring autism spectrum disorder and gastrointestinal conditions.

PATIENTS AND METHODS. Subjects were 918 individuals from 214 Autism Genetics Resource Exchange families with a complete medical history including gastrointestinal condition report. Genotypes at the autism spectrum disorder–associated *MET* promoter variant rs1858830 were determined. Family-based association test and χ^2 analyses were used to determine the association of *MET* rs1858830 alleles with autism spectrum disorder and the presence of gastrointestinal conditions.

RESULTS. In the entire 214-family sample, the *MET* rs1858830 *C* allele was associated with both autism spectrum disorder and gastrointestinal conditions. Stratification by the presence of gastrointestinal conditions revealed that the *MET* *C* allele was associated with both autism spectrum disorder and gastrointestinal conditions in 118 families containing at least 1 child with co-occurring autism spectrum disorder and gastrointestinal conditions. In contrast, there was no association of the *MET* polymorphism with autism spectrum disorder in the 96 families lacking a child with co-occurring autism spectrum disorder and gastrointestinal conditions. χ^2 analyses of *MET* rs1858830 genotypes indicated over-representation of the *C* allele in individuals with co-occurring autism spectrum disorder and gastrointestinal conditions compared with non-autism spectrum disorder siblings, parents, and unrelated controls.

CONCLUSION. These results suggest that disrupted MET signaling may contribute to increased risk for autism spectrum disorder that includes familial gastrointestinal dysfunction. *Pediatrics* 2009;123:1018–1024

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Key Words

autism, genetics, gastrointestinal system, hepatocyte growth factor, HGF

Abbreviations

ASD—autism spectrum disorder
AGRE—Autism Genetic Resource Exchange
FBAT—family-based association test
TDT—transmission disequilibrium test

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AUTISM SPECTRUM DISORDER (ASD) is a complex, behaviorally defined developmental disorder characterized by social deficits, language impairments, and repetitive behaviors with restricted interests. Beyond this triad of core diagnostic criteria, many individuals with ASD also exhibit gastrointestinal or immunologic dysfunction, seizures, and nonspecific neurologic symptoms.^{1–6}

Gastrointestinal symptoms are frequently reported by parents of individuals with ASD. Reported gastrointestinal conditions include chronic diarrhea, constipation, abdominal discomfort, gastroesophageal reflux, and food intolerance.^{1,7} High rates of gastrointestinal conditions in individuals with ASD have been reported in several studies.^{1,3,8} The

conclusive validity of these reports has been questioned on a methodologic basis,⁹ and at least 1 retrospective review of medical charts failed to reveal evidence for an increased incidence of gastrointestinal conditions in individuals with ASD compared with controls.¹⁰ However, a recent well-controlled prospective study provides evidence for an increased prevalence of disrupted gastrointestinal function in individuals with ASD.² Valicenti-McDermott et al² used a structured interview and reported a significantly increased prevalence of gastrointestinal conditions in children with ASD compared with matched controls that included both typically developing children and those with non-ASD developmental disorders.

The etiology of ASD is currently unknown, but genetic vulnerability and gene-environment interactions contribute to ASD risk.^{11–13} We recently described robust genetic association with ASD of a functional variant in the 5' promoter of the gene encoding the MET receptor tyrosine kinase.¹⁴ The *MET* promoter variant, rs1858830, is a common G-to-C single nucleotide polymorphism; the C allele is inherited by individuals with ASD more often than predicted by chance and is more common in individuals with ASD than in a sample of the general population.¹⁴ The C allele is functional, causing a reduction in gene transcription and transcription factor binding.¹⁴ The relative risk of an ASD diagnosis for individuals of C/C genotype is 2.27 compared with individuals of G/G genotype.¹⁴ We followed-up the genetic study by demonstrating a significant decrease in both *MET* transcript and MET protein in the postmortem temporal cortex of individuals with ASD compared with age- and gender-matched controls.¹⁵ Given the studies demonstrating key roles for MET signaling in neural development^{16–19} and function,^{20–22} the genetic and expression data suggest that decreased MET signaling may contribute to altered brain development that underlies disrupted behavioral and cognitive functions in ASD.

As a pleiotropic receptor tyrosine kinase, MET also participates in immune function^{23–25} and gastrointestinal repair.^{26–28} If MET is altered in the immune and gastrointestinal systems of individuals with ASD, as it is in the postmortem brain of individuals with ASD, then 1 prediction is that disrupted MET signaling may contribute to both behavioral and gastrointestinal conditions. As a first step in testing this hypothesis, we performed an exploratory study by examining association of the *MET* promoter variant rs1858830 C allele in a family sample stratified by the presence or absence of co-occurring gastrointestinal conditions. We hypothesized that ASD association of the functional *MET* promoter variant rs1858830 may be enriched in a subset of patients with both ASD and gastrointestinal dysfunction.

PATIENTS AND METHODS

Patients

All subjects were collected by the Autism Genetics Resource Exchange (AGRE) consortium. On February 1, 2008, 2 data sets were downloaded from the AGRE Web site (www.agre.org): (1) the pedigree file, which con-

tains information on family structure and autism diagnosis; and (2) the medical history files, which contain the results of the parent-reported gastrointestinal conditions questionnaire. Presence of gastrointestinal conditions was defined in the downloaded AGRE data file as evidence of any of the following in the medical history: chronic constipation, chronic diarrhea, irritable bowel syndrome, gastroesophageal reflux, and peptic ulcer disease. A single data file containing the pedigree information and the results of the gastrointestinal conditions questionnaire was constructed by cross-referencing each individual by a unique identifier. The AGRE collection included 5166 individuals from 950 families; results of the gastrointestinal conditions questionnaire were available for 1301 individuals from 299 families.

Exclusion Criteria

DNA samples were available for 232 (78%) of the 299 families with complete gastrointestinal status results. Eighteen families were excluded from analyses because of AGRE-indicated flags of nonidiopathic autism, including a known chromosomal abnormality, prenatal/perinatal insult, premature birth (<35 weeks), or significant dysmorphism. The remaining 214 families included 152 families that were genotyped for the original report of *MET* association with autism¹⁴ and an additional 62 families for whom genotype was not yet available.

Genotyping and Quality Control

Genotyping of *MET* rs1858830 was performed as described in the supplemental Methods, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018. All 384 well plates were seeded with 8 to 17 no-DNA control wells and 8 to 15 repeats of 3 control samples; each plate contained 32 to 60 wells (8%–15%) with quality control samples. All no-DNA wells were required to lack a genotype call and all control DNA samples were required to generate the same genotype before release for analysis. Any experimental sample not assigned a genotype with >95% confidence by Sequence Detection Systems Software (version 2.3; Applied Biosystems; Foster City, CA) was genotyped by direct sequencing. The overall no-call rate was <2%.

Analyses

All analyses included only the 214 families with both gastrointestinal condition phenotype and *MET* rs1858830 variant genotypes. Both ASD diagnosis and gastrointestinal condition phenotypes were binary (“present” or “absent”). Transmission disequilibrium of the *MET* promoter variant rs1858830 was determined using the Family-Based Association Test (FBAT) version 1.7.2 (www.biostat.harvard.edu/~fbat). All FBAT analyses were performed with an additive model and the “-e” option to account for association in the presence of linkage and to use the empirical variance. Random selection of a single individual with ASD and a single non-ASD sibling was performed blind to genotype. Random selection was achieved by generation of a random number for each individual in the pedigree and selection

TABLE 1 Description of Sample

Gastrointestinal Conditions?	Individuals With ASD	Parents	Non-ASD Siblings	Total
Yes	163	103	9	275
No	233	323	87	643
Unknown	32	22	20	74
Total	428	448	116	992

of 1 individual with ASD and 1 non-ASD full sibling with the lowest random number. Transmission disequilibrium test (TDT) analysis of ASD-parent trios was performed with Haploview 3.32 (www.broad.mit.edu/mpg/haploview). All allele, genotype, and phenotype data are categorical and were analyzed by using χ^2 , and a P value of $<.05$ was considered significant. Allelic χ^2 results are presented; genotypic χ^2 results are similar.

RESULTS

Sample

The sample consisted of 992 individuals from 214 families. Gastrointestinal conditions were present in 275 (28%), absent in 643 (65%), and unknown in 74 (7%) individuals. Table 1 shows the distribution of gastrointestinal conditions in the 428 children with ASD, 116 unaffected siblings, and 448 parents. The distributions of specific gastrointestinal conditions are listed in Table 6, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018.

Gastrointestinal Conditions in ASD Family Sample

Among the 918 individuals with known gastrointestinal status, the incidence of gastrointestinal conditions was 41% in individuals with ASD, 24% in parents, and 9% in unaffected siblings ($\chi^2 = 49.855$; $P = 1.5 \times 10^{-12}$). These data indicate that gastrointestinal conditions are more prevalent in individuals with ASD than in their immediate family members.

Association of MET With ASD and Gastrointestinal Conditions

We previously reported association of the *MET* promoter variant rs1858830 allele *C* with ASD diagnosis in 2 large, family-based samples that included 357 AGRE families.¹⁴ FBAT analysis revealed that the *MET C* allele was transmitted from parent to child with ASD more often than predicted by chance. In the 214 AGRE families with

gastrointestinal history data, the *MET* promoter variant rs1858830 allele *C* was associated with ASD diagnosis ($P = .014$) (Table 2). The *MET* promoter variant rs1858830 allele *C* also was associated with the presence of gastrointestinal conditions in the entire 214-family, 992-individual sample (FBAT: transmissions observed = 107; transmissions expected = 93; $P = .036$). Because 95% of the individuals positive for gastrointestinal conditions in this sample also had ASD, this signal suggested transmission of the *MET C* allele to individuals with co-occurring ASD and gastrointestinal conditions.

Stratification of ASD Families According to Presence of Gastrointestinal Conditions

The observation that the *MET C* allele was associated with ASD diagnosis and with gastrointestinal conditions in the offspring led us to hypothesize that transmission of the rs1858830 *C* allele might be enriched in families with co-occurring ASD and gastrointestinal conditions. Stratification indicated that 118 of the 214 families included at least 1 child with co-occurring ASD and gastrointestinal conditions and that 96 families did not have an offspring with co-occurring ASD and gastrointestinal conditions. Application of the FBAT to examine allelic transmission in the 118 families in which at least 1 child had co-occurring ASD and gastrointestinal conditions revealed that the *MET* rs1858830 allele *C* was associated with both ASD ($P = .009$; Table 2) and gastrointestinal conditions (FBAT: transmissions observed = 105; transmissions expected = 91; $P = .042$). In contrast, there was no association of the rs1858830 allele *C* with ASD in the 96 families lacking an offspring with co-occurring ASD and gastrointestinal conditions ($P = .373$; Table 2).

Random Selection of a Single Individual With Co-occurring ASD and Gastrointestinal Conditions From Each Family

To further characterize the association of the *MET* rs1858830 *C* allele with ASD in the context of gastrointestinal conditions, we randomly selected from each of the 118 families a single individual with co-occurring ASD and gastrointestinal conditions and a single non-ASD sibling. For comparison, we also randomly selected a single offspring with ASD and a single non-ASD sibling from each of the 96 families in which no individual had co-occurring ASD and gastrointestinal conditions. Tables 7 through 11 (which are published as supporting infor-

TABLE 2 FBAT Analyses of *MET* rs1858830 Association With ASD in the Entire Sample and the Sample Stratified According to the Presence of an Individual With Co-occurring ASD and Gastrointestinal Conditions

Sample	Families	Allele	Inf Fams ^a	T_{OBS}^b	T_{EXP}^c	z	P
ASD with gastrointestinal condition ^d	118	C	50	121	103	2.626	.009
ASD without gastrointestinal condition	96	C	49	107	100	0.891	.373
Combined	214	C	99	228	203	2.447	.014

^a Inf Fams indicates number of informative families.

^b T_{OBS} indicates transmissions observed; equivalent to the "S" statistic in FBAT.

^c T_{EXP} indicates transmissions expected; equivalent to "E(S)" statistic in FBAT.

^d Families in which at least 1 individual had co-occurring ASD and gastrointestinal conditions.

TABLE 3 χ^2 Analyses of *MET* rs1858830 in Individuals With Co-occurring ASD and Gastrointestinal Conditions Compared to Non-ASD Siblings, Parents, Unrelated Individuals With ASD but No Gastrointestinal Conditions, and Unrelated Controls

	<i>n</i>	<i>MET</i> Genotype			<i>MET</i> Allele		χ^2	<i>P</i>
		C/C	C/G	G/G	C	G		
Co-occurring ASD and gastrointestinal condition	115	0.348	0.522	0.130	0.609	0.391	Reference	
Parents	221	0.262	0.516	0.222	0.520	0.480	4.770	.029
Non-ASD siblings	40	0.200	0.550	0.250	0.475	0.525	4.339	.037
ASD without gastrointestinal condition	94	0.333	0.440	0.226	0.554	0.446	1.216	.270
Unrelated controls	189	0.217	0.524	0.259	0.479	0.521	9.676	.002

mation at www.pediatrics.org/content/123/3/3/1018) list the specific gastrointestinal conditions in these samples. TDT analysis of allelic transmission from parent to child with co-occurring ASD and gastrointestinal conditions indicated a significant association of the *MET* rs1858830 C allele ($P = .0002$; Table 12, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018). In contrast, the *MET* rs1858830 C allele was not associated with ASD in the families without co-occurring gastrointestinal conditions ($P = .6662$; Table 12). In the combined sample, the C allele was associated with ASD ($P = .0105$; Table 12).

χ^2 Analysis of *MET* Association With Gastrointestinal Conditions in ASD Families

With a single randomly selected ASD and non-ASD offspring from each family, we were able to perform χ^2 analyses to examine allelic distribution. In the 118 families with an offspring with co-occurring ASD and gastrointestinal conditions, the *MET* C allele was significantly more frequent in individuals with co-occurring ASD and gastrointestinal conditions compared with their non-ASD siblings ($P = .037$), their parents ($P = .029$), and the previously published allele frequencies of unrelated controls¹⁴ ($P = .002$) (Table 3; Fig 1, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018). Although frequency of the *MET* C allele was lower in non-ASD siblings compared with parents (Table 3; Fig 1) in families with co-occurring ASD and gastrointestinal conditions, this difference did not reach statistical significance (χ^2 , $P = .455$). The frequency of the *MET* C allele for individuals with ASD from the 96 families without co-occurring gastrointestinal conditions was not significantly different from indi-

viduals with co-occurring ASD and gastrointestinal conditions ($P = .270$) (Table 3; Fig 1).

Stratification to Account for Potential Reporting Bias

A potential limitation of parent-reported gastrointestinal conditions is the possibility of a reporting bias for children with ASD. We, therefore, performed 2 additional stratifications of our 214-family sample. First, we identified 68 families for which a gastrointestinal status report was available for both parents, at least 1 offspring with ASD, and at least 1 non-ASD sibling. A description of the sample is provided in Tables 13 and 14 (which are published as supporting information at www.pediatrics.org/content/123/3/3/1018). TDT analysis revealed association with ASD of the *MET* C allele in 41 families including an individual with co-occurring ASD and gastrointestinal conditions ($P = .0191$), but no association in 27 families without an individual with co-occurring ASD and gastrointestinal conditions ($P = >0.9999$) (Table 15, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018). χ^2 analysis indicated that the *MET* C allele was significantly more frequent in individuals with co-occurring ASD and gastrointestinal conditions than in their non-ASD siblings ($P = .019$) and previously published allele frequencies of unrelated controls¹⁴ ($P = .006$) (Table 4; Fig 2, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018). Despite a trend toward lower frequency of the *MET* C allele in non-ASD siblings compared with parents (Table 4; Fig 2) in families with co-occurring gastrointestinal conditions, this difference was not significant (χ^2 , $P = .410$). There was no significant difference in allele frequency between the 41 individuals with co-occurring ASD and gastrointestinal

TABLE 4 χ^2 Analyses of *MET* rs1858830 in 68 Families With Complete Gastrointestinal Status Report Comparing Individuals With Co-occurring ASD and Gastrointestinal Conditions to Parents, Non-ASD Siblings, Unrelated Individuals With ASD but No Gastrointestinal Conditions, and Unrelated Controls

	<i>n</i>	<i>MET</i> Genotype			<i>MET</i> Allele		χ^2	<i>P</i>
		C/C	C/G	G/G	C	G		
Co-occurring ASD and gastrointestinal condition	41	0.415	0.463	0.122	0.646	0.354	Reference	
Parents	79	0.213	0.532	0.215	0.519	0.481	3.558	.059
Non-ASD siblings	40	0.175	0.575	0.250	0.463	0.538	5.543	.019
ASD without gastrointestinal condition	27	0.370	0.444	0.185	0.593	0.407	0.401	.526
Unrelated controls	189	0.217	0.524	0.259	0.479	0.521	7.565	.006

TABLE 5 χ^2 Analyses of *MET* rs1858830 in 64 Families With Discordant Gastrointestinal Condition Report Among Individuals With ASD Comparing Individuals With Co-occurring ASD and Gastrointestinal Conditions to Siblings With ASD but No Gastrointestinal Conditions, Parents, Non-ASD Siblings, and Unrelated Controls

	n	<i>MET</i> Genotype			<i>MET</i> Allele		χ^2	P
		C/C	C/G	G/G	C	G		
Co-occurring ASD and gastrointestinal condition	60	0.400	0.467	0.133	0.633	0.367	Reference	
ASD without gastrointestinal condition siblings	63	0.222	0.619	0.159	0.532	0.468	2.606	.106
Parents	118	0.246	0.576	0.178	0.534	0.466	3.204	.073
Non-ASD siblings	22	0.136	0.545	0.318	0.409	0.591	6.617	.010
Unrelated controls	189	0.217	0.524	0.259	0.479	0.521	8.706	.003

conditions and the 27 individuals with ASD lacking gastrointestinal conditions ($P = .526$) (Table 4; Fig 2).

In the second stratification, we identified 64 families that included at least 1 child with co-occurring ASD and gastrointestinal conditions and at least 1 child with ASD without gastrointestinal conditions. In these 64 families with discordant gastrointestinal status report among multiple children with ASD, parent report of gastrointestinal conditions was selective among siblings with ASD and thus less likely to be biased. The sample is described in Tables 16 and 17 (which are published as supporting information at www.pediatrics.org/content/123/3/3/1018). TDT analyses involving the same parents indicated significant association of the *MET* C allele with ASD in transmissions to children with co-occurring gastrointestinal conditions ($P = .0111$) but no association with ASD in transmissions to children without co-occurring gastrointestinal conditions ($P = .7995$) (Table 18, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018). χ^2 analysis revealed that the *MET* C allele was significantly more frequent in individuals with co-occurring ASD and gastrointestinal conditions compared with non-ASD siblings ($P = .010$) and previously published allele frequencies of unrelated controls¹⁴ ($P = .003$) (Table 5; Fig 3, which is published as supporting information at www.pediatrics.org/content/123/3/3/1018). The decreased frequency of the *MET* C allele in non-ASD siblings (Table 5; Fig 3) was not significantly different from either parents (χ^2 , $P = .128$) or siblings with ASD lacking gastrointestinal conditions (χ^2 , $P = .161$). Similarly to the unstratified sample, there was no significant difference in allele frequencies of individuals with co-occurring ASD and gastrointestinal conditions compared with siblings with ASD lacking gastrointestinal conditions ($P = .106$; Table 5; Fig 3).

DISCUSSION

The results of this study suggest that association of the functional *MET* promoter variant rs1858830 allele C is enriched in a subset of ASD patients with co-occurring gastrointestinal conditions. Parent-to-child transmission of the *MET* rs1858830 C allele was associated individually with ASD and with gastrointestinal conditions in the entire sample. Moreover, our family stratification approach revealed association of *MET* with ASD in families in which at least 1 individual had co-occurring ASD and

gastrointestinal conditions, but not in the remaining families. The significance of this association was further supported in our random selection of a single child from each family with co-occurring ASD and gastrointestinal conditions. Because the C allele disrupts transcription of the *MET* gene, the biological translation of these genetic findings is consistent with a hypothesis that reduced *MET* signaling may contribute to a syndrome that includes ASD with co-occurring gastrointestinal conditions.

We raise several issues of caution regarding the interpretation of the findings from this exploratory study. First, the presence of gastrointestinal conditions was determined by retrospective analysis of medical charts. Therefore, there may be a reporting bias concerning the presence of gastrointestinal conditions, particularly when comparing individuals with ASD to parents or unaffected siblings. However, it also should be noted that, because parents were blind to genetic information at the time of gastrointestinal condition report, the genetic associations reported here are not influenced by a reporting bias. Second, sample sizes are relatively small. After stratification of families by presence of an individual with co-occurring ASD and gastrointestinal conditions, the number of families in both strata was <120. Genetic association studies are more reliable when using hundreds of families, and thus the data reported here should be considered exploratory. Third, the genotypic frequencies at the rs1858830 locus do not differ significantly between individuals with co-occurring ASD and gastrointestinal conditions and individuals with ASD but no gastrointestinal conditions. Thus, although parent-to-child transmissions and allele frequencies indicate association of the *MET* C allele, genotype at the rs1858830 locus alone does not explain completely the presence of co-occurring gastrointestinal conditions in individuals with ASD. Finally, the gastrointestinal condition diagnosis is sometimes vague in the medical charts as the term "multiple" is entered for several individuals. Despite our data replicating significant association of the *MET* C allele in 68 families with complete gastrointestinal status reports and in 64 families with discordant gastrointestinal condition reports among individuals with ASD, replication using a larger number of families and careful prospective diagnosis of specific gastrointestinal conditions will be needed to establish firmly an association between

the *MET* gene and a subset of individuals with co-occurring ASD and gastrointestinal conditions.

Two possibilities are of interest to pursue with future studies, even in the context of these cautionary issues. First, reduced *MET* signaling may define a subset of individuals with ASD and co-occurring gastrointestinal conditions. Second, the genetic distinctions discerned from analyzing families based on co-occurring ASD and gastrointestinal conditions versus ASD alone indicate that there may be a fundamental difference in specific heritable risk etiologies between family types.⁶ Thus, it may be parsimonious to subdivide ASD cases and families by the associated phenotypes, including the presence or absence of gastrointestinal conditions, when analyzing genetic association. The rationale for such stratification is particularly relevant when considering a pleiotropic signaling system such as the *MET* receptor tyrosine kinase pathway. The *MET* receptor, along with its hepatocyte growth factor ligand, contributes to brain development and neural plasticity and to gastrointestinal function. Hypomorphic *MET* signaling in the cerebral cortex results in abnormal interneuron migration from the ganglionic eminence and reduced interneurons in the frontal and parietal regions of cortex as well as the hippocampus.^{18,19,29} In the cerebellum, hypomorphic *MET* signaling causes decreased proliferation of granule cells and a reduction in the size of the cerebellum.¹⁶ In mature neurons, *MET* signaling augments N-methyl-D-aspartate currents and long-term potentiation,³⁰ contributes to glutamatergic synapse formation,²² and enhances clustering of postsynaptic proteins.²¹ In the gastrointestinal system, *MET* signaling modulates intestinal epithelial cell proliferation, and thus acts as a critical factor in intestinal wound healing. For example, activation of *MET* signaling via application of exogenous hepatocyte growth factor has been shown to reduce the effects of experimentally induced colitis, inflammatory bowel disease, and diarrhea.^{26,27,28,31,32} Subgroups of individuals with ASD are reported to have a variety of co-occurring medical and mental health conditions. The current data set is consistent with the hypothesis that the genetic risk that underlies disruption of a single cell signaling system, the *MET* signaling system, can lead to independently generated brain-based and systemic dysfunctions that ultimately interact to influence long-term pathophysiological processes.

CONCLUSIONS

The results of this exploratory, retrospective study indicate genetic association of a functional variant of the *MET* gene in ASD patients in families with affected individuals who are reported to have co-occurring gastrointestinal conditions. Future prospective studies should replicate this genetic association, and further determine if there are correlations among *MET* promoter variant genotype, *MET* protein expression in the gastrointestinal system, and specific gastrointestinal conditions in individuals with ASD.

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NO MUGS, BUT WHAT ABOUT THOSE FEES?

“New pharmaceutical industry guidelines should stop most drug companies from distributing a wide range of trinkets and office supplies designed to keep their brand names before doctors as a subliminal inducement to prescribe high-priced drugs. The new code, which kicked in on New Year’s Day, bars the free distribution of everything from pens to coffee mugs and staplers by some 40 drug companies that have agreed to the restrictions. That may seem like small potatoes, but in the aggregate the promotional products probably cost about \$1 billion a year, as Natasha Singer reported in *The Times*. The updated rules are the industry’s latest attempt to restore public confidence that doctors are prescribing medicines in the patient’s interest. The code still has too many loopholes. Although it prohibits company sales representatives from providing restaurant meals to health care professionals, it allows the sales teams to continue providing modest meals in professional offices while pitching their products. It allows companies to continue paying for so-called ‘continuing medical education’ for physicians while correctly leaving the selection of content, speakers and study materials to conference organizers. There appear to be no loopholes in bans against providing free tickets to the theater, sporting events or resort junkets.”

Editorial. *New York Times*. January 4, 2009

Noted by JFL, MD

**Distinct Genetic Risk Based on Association of MET in Families With
Co-occurring Autism and Gastrointestinal Conditions**

Daniel B. Campbell, Timothy M. Buie, Harland Winter, Margaret Bauman, James S. Sutcliffe, James M. Perrin and Pat Levitt

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