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NEWS AND COMMENTARY

Confirmation of *MET* gene association with autism

When linkage signal for autism *MET* candidate gene

Daniel B Campbell

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A decade after the first genome-wide linkage studies from the International Molecular Genetic Study of Autism Consortium (IMGSAC) found evidence for an autism susceptibility locus on chromosome 7q, recent advances are beginning to focus on the functional variants that may account for this linkage signal. Sousa *et al* report association of a potential functional variant of the *MET* gene with autism in two patient samples.[1] These results increase to five the cohorts in which variants of the *MET* gene are reported to be associated with autism, suggesting that the MET receptor tyrosine kinase and the molecular cascade through which it signals contribute to autism risk.

The Sousa *et al* manuscript[1] is a continuation of the ongoing efforts by the IMGSAC to identify autism risk genes. The IMGSAC was the first to publish a genome-wide linkage screen for autism, and the first to identify a linkage peak on the chromosome 7q region including the *MET* gene.[2] In the decade since that first report, subsequent linkage screens and the results of large-scale meta-analyses support the contribution of genetic variants on chromosome 7q to autism risk. The IMGSAC and others systematically tested association of genes under the linkage peak, but the identity of the genetic variant(s) accounting for the linkage signal remained elusive. There are a number of reasons for the difficulty in identifying the chromosome 7q autism risk genes, including genetic and phenotypic heterogeneity—not all cases of autism are impacted by the same genetic variation and the same genetic variation may not always result in autism. Further compounding difficulties in identifying the autism risk genes on chromosome 7q is the broad linkage peak that includes over 200 mapped genes,[1] and evidence that there may be multiple overlapping linkage signals that contribute to the peak.[3] Consistent with the existence of multiple genes contributing to overlapping linkage signals, evidence of genetic association with autism have been reported for genes located in three different regions of the broad peak: at chromosome 7q21 (*RELN*, *SERPINE1*), chromosome 7q31 (*MET*) and chromosome 7q35–36 (*CNTNAP2*, *EN2*). Each of these chromosome 7q genes, and possibly others, may contribute to autism risk.

As detailed by Sousa *et al*,[1] the evidence in support of a contribution of the *MET* gene to autism risk continues to mount (Figure 1). The MET receptor tyrosine kinase participates not only in development of the cerebral cortex and cerebellum, both of which may be altered in autism, but also contributes to gastrointestinal and immune function, disruptions of which co-occur in some individuals with autism. The expression of *MET* transcript and MET receptor tyrosine kinase protein was shown to be reduced in postmortem brains of individuals with autism compared to age- and gender-matched controls.[4] A number of genetic mechanisms may contribute to the decreased expression of MET in autism. Significant association of the *MET* promoter rs1858830 C allele was first reported in a 204 family Italian cohort and replicated in a 539 family US cohort.[5] Association of the same genetic allele was reported recently in a third cohort of 101 US families.[6] Importantly, this autism-associated *MET* promoter allele is functional in cell-based assays, reducing the binding of the transcription factor SP1 and transcription from the *MET* promoter.[5] The results of Sousa *et al* failed to replicate genetic association of the rs1858830 C allele, but identified association of another allele with a similar potential to regulate the expression of the *MET* gene.[1] Sousa *et al* described association of the rs38845 A allele with autism risk in 335 IMGSAC families and replicated association of the same allele in an Italian case–control sample.[1] Although direct evidence to indicate function of the rs38845 A allele is not presented, Sousa *et al*[1] discuss *in silico* evidence that the A allele creates a binding site for the transcription factor IRF1, and present a hypothesis of how the A allele may contribute to decreased MET protein expression in individuals with autism. In addition to the SNP alleles that may regulate transcription, rare *de novo* copy number variation losses of the chromosomal region including the *MET* gene have also been reported.[7] A theme of monogenic diseases is that multiple mutations of the same gene may result in a similar phenotype. For example, more than 130 different mutations of the *DHCR7* gene have been identified in individuals with the monogenic disorder Smith–Lemli–Opitz syndrome. The results of Sousa *et al*[1] raise the possibility that multiple common variants, together with rare copy number variation losses, lead to the decrease in MET protein observed in the brains of individuals with autism.

As with all findings of genetic association, these are just the first steps to understanding how disruption of a candidate gene contributes to autism risk. An admitted limitation of the studies by Sousa *et al*[1] was the lack of a screen for rare variants in the *MET* gene, leaving open the possibility that the association of rs38845 may be due to linkage disequilibrium to an unidentified rare functional variant of *MET*. Further studies are also required to test the hypothesis that the

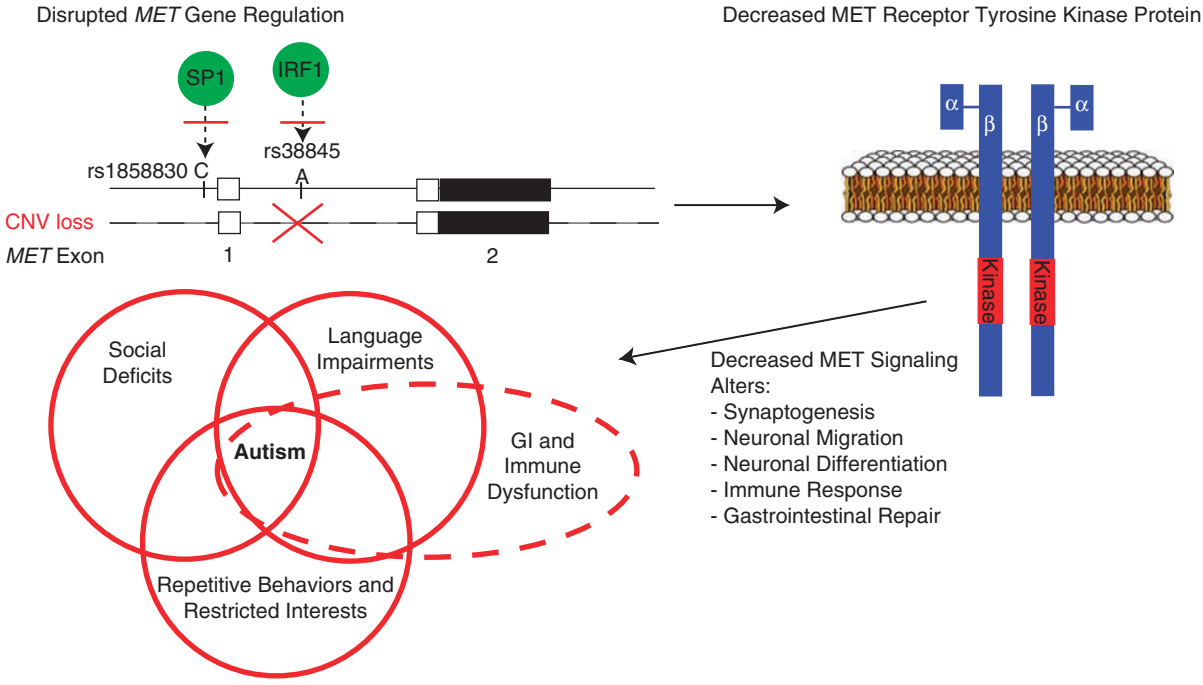

Figure 1 Multiple functional genetic variants of *MET* may contribute to the symptoms of autism. Three mechanisms of disrupting *MET* gene transcription are depicted: presence of the intron 1 rs38845 A allele may interfere with transcription by IRF1, as described by Sousa *et al*; the promoter variant rs1858830 C allele interrupts binding of the transcription factor SP1; and rare copy number variation (CNV) loss of the *MET* gene. Each of these mechanisms may contribute to the decrease of MET receptor tyrosine kinase observed in postmortem brain of individuals with autism. Decreased MET signaling results in altered synaptogenesis and may contribute to the core symptoms of autism as well as co-occurring gastrointestinal (GI) and immune dysfunction.

autism-associated rs38845 allele described by Sousa *et al*[1] is functional. It is clear that cellular signaling through the MET receptor tyrosine kinase contributes to neuronal migration and synaptogenesis, among other developmental processes that may be altered in individuals with autism. In the future, investigations of new genetically manipulated animal models of *MET* expression will close large gaps in our understanding of the biological mechanisms that lead from altered *MET* gene expression to altered brain circuit development to the behavioral phenotypes characteristic of autism. Nevertheless, it is exciting to note that just a decade after the first autism linkage screen by the IMGSAC identified a signal on chromosome 7q, we are beginning to address fundamental issues regarding the role of chromosome 7q genes in autism susceptibility and, possibly, treatment■

Dr DB Campbell is at the Department of Pharmacology and Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN 37232, USA.
Tel: +615 936 3862;
Fax: +615 936 3747;
E-mail: daniel.campbell@vanderbilt.edu

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