frontiers in
NEUROSCIENCE

GENERAL COMMENTARY
published: 08 October 2010
doi: 10.3389/fnins.2010.00177

Murine warriors or worriers: the saga of *Comt1*, B2 SINE elements, and the future of translational genetics

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Catechol-O-methyltransferase (COMT) is an extremely well characterized enzyme that degrades catecholamines. A common coding polymorphism (rs4680; Val158Met) in the human *COMT* gene has been associated with a diverse array of phenotypes including personality, cognition, pain sensitivity, and risk for psychiatric disorders (Tunbridge et al., 2006; Sheldrick et al., 2008; Wray etal., 2008; Andersen and Skorpen, 2009). The Val allele has been associated with an advantage in stress resiliency (warrior strategy), while the Met allele has been associated with increased anxiety and cognitive performance (worrier strategy; Goldman et al., 2005; Stein et al., 2006).

Three independent groups have just reported the presence of a common polymorphism in *Comt1*, which is the mouse homologue of *COMT* (Kember et al., 2010; Li et al., 2010; Segall et al., 2010). This polymorphism (*Comt1*^{B2i1}; MGI:4819952) was shown to influence *Comt1* mRNA abundance, protein levels, enzymatic activity, and behavioral phenotypes. Using a combination of extant and novel data from panels of inbred strains, recombinant inbred strains, and outbred heterogeneous stocks, they showed associations between the presence of a B2 SINE element and numerous complex traits including pain sensitivity, novel object exploration, anxiety-like behavior, general activity, response to haloperidol and chlordiazepoxide, and dopamine D1 and D2 receptor binding.

All three studies share two common jumping-off points: the observation of a robust *cis*-eQTL for *Comt1* and prior knowledge of its function. These factors focused their attention on a region that was not highly polymorphic among the inbred mice they were studying, and might otherwise have been ignored. The eQTL data were initially confusing because probesets that targeted the 3′ UTR showed that one group of strains had lower expression, while probesets that targeted more 5′ exons showed expression differences in the opposite direction. All three groups traced these expression differences to the insertion of a B2 SINE element in the 3′ UTR. Insertion of a B2 SINE element produces a truncated mRNA that lacks the most distal 3′ region. Thus, the distal 3′ region was much more abundant in strains lacking the insertion. Probes targeting the more 5′ exons provided an assay for overall mRNA abundance, which was increased by insertion of a B2 SINE element, and thus showed a change in the opposite direction. Studies using RNA sequencing may one day provide a more holistic picture of gene expression traits that may help to more rapidly unravel similar situations. Li et al. (2010) explored this possibility, but alignment was difficult because the reference genome (based on C57BL/6J) contained a B2 SINE element.

Gene expression differences that are the result of SINE element insertions are likely to be a recurrent theme in the study of complex traits. Current estimates suggest that about a million B1 and B2 SINE elements are present in the mouse genome and the story is similar in other species; the SINE element Alu makes up an estimated 10% of the human genome. Furthermore, approximately 5% of mouse genes have been estimated to have SINE element insertions in the 3′ region (Lee et al., 2008), suggesting that we have probably not heard the last of their impact on complex traits.

Because the role of COMT in the metabolizing catecholamines was first described more than 50 years ago by Nobel Laureate Julius Axelrod (Axelrod, 1957), it could be argued that these papers do not provide any novel or fundamental insight into the genetic control of behavior; the same could be said of earlier studies of the Val/Met *COMT* polymorphism in humans. This is not entirely fair: it is by experimental manipulation, either man-made or naturally occurring, that we come to understand function of genes, and the present studies exemplify this. Moreover, these three studies undoubtedly provide convincing proof-of-concept (*as if it was needed*) of the enormous and largely untapped potential of mouse models to identify genes that influence medically important phenotypes. We have previously used a similar approach to identify a copy number variant (CNV) that alters gene expression and behavior among inbred and outbred mice (Williams 4th et al., 2009). It is overwhelmingly likely that numerous additional alleles in genes of both known and unknown function still await discovery. Resources like panels of inbred strains, panels of recombinant inbred strains, the collaborative cross, and outbred populations such as the HS-stock will continue to be valuable for these endeavors (Flint, 2010). Their use in combination with gene expression, exhaustive SNP genotyping and CNV discovery will continue to move our field forward.

A subject that can elicit a spirited debate among geneticists of all stripes is the extent to which polymorphisms in the same genes will influence related traits across species. These three papers provide an example of a situation in which polymorphisms in a gene influence similar traits in both mice and humans; however, the picture is not completely simple. For example, the Val158 allele (higher function) and transgenic overexpression of the Val158 allele in mice have been associated with reduced pain sensitivity. Similarly, strains with higher *Comt1* expression due to the presence of a B2 SINE insertion were reported to be less sensitive to nociceptive stimuli. However, findings regarding anxiety phenotypes are more complex and less consistent. While the human Met allele (lower function; Enoch et al., 2003; Domschke et al., 2004) as well as knockout of *Comt1* (Gogos

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et al., 1998) have been linked to increased anxiety, strains without the SINE element insertion (lower function) showed inconsistent anxiety-like traits: reduced locomotion, increased rearing in the open field, more novel object exploration, and reduced time in the light compartment in the light/dark test. In summary, changes in *Comt1* expression altered many different behaviors in mice but the directionality of these differences was only somewhat similar to what has been observed in humans.

A final word about thresholds for statistical significance is in order. Had commonly accepted standards for genome-wide significance been applied in these three papers, only the eQTLs would have been deemed statistically significant. However, there is abundant prior evidence from genetic and non-genetic sources, from mice and humans, that *Comt1* has the potential to influence behavioral traits. Thus, all three groups incorporated their own prior knowledge of this gene in interpreting the results of their statistical tests. Similarly, the literature regarding the Val158Met allele in *COMT* uses the candidate gene approach, where the threshold for significance does not correct for all possible genotype–phenotype tests across the genome and is thus many orders of magnitude below that required for significance in an unbiased GWAS design. All three of these groups essentially performed tests under the *a priori* hypothesis that the eQTL for *Comt1* would alter behavior. As such, they don't require corrections for genome-wide testing. Clearly the most exciting discoveries will be those that identify genes that have not previously been implicated in their respective phenotypes. These breakthroughs will continue to require more stringent thresholds for significance and will therefore require larger and more powerful samples.

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Received: 21 September 2010; accepted: 21 September 2010; published online: 08 October 2010.
*Citation: Palmer AA and Dulawa SC (2010) Murine warriors or worriers: the saga of Comt1, B2 SINE elements, and the future of translational genetics. Front. Neurosci. **4**:177. doi: 10.3389/fnins.2010.00177*
This article was submitted to Frontiers in Neurogenomics, a specialty of Frontiers in Neuroscience.