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Commentary

Of mice and men, periodic limb movements and iron: how the human genome informs the mouse genome

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The gene, *BTBD9*, was recently linked to restless legs syndrome, periodic limb movements and iron status in humans. In a homologous region in mouse, an area containing *btbd9* was also identified as being related to iron homeostasis. This finding is important as iron status in brain has been implicated in restless legs syndrome.

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A single nucleotide polymorphism in the gene *BTBD9* was recently found to be associated with restless legs syndrome (RLS; Winkelmann *et al.* 2007) and, more specifically, periodic limb movements (PLMs) during sleep, a common feature of RLS (Stefansson *et al.* 2007). The biological explanation for this association is not immediately apparent; however, one hypothesis is that iron-related mechanisms may be involved. Iron deficiency is associated with RLS (Allen & Earley 2007), and although its exact role is unclear, there is evidence that iron deficiency affects nigrostriatal dopamine functioning, which is also altered in RLS (Beard & Connor 2003). In this context, it is very interesting that the PLM-related *BTBD9* variant was also related to serum ferritin, an indicator of iron status, in the study by Stefansson *et al.* (2007). This finding is particularly striking to us and brings our own research to mind. We too have observed associations between a marker in a homologous genomic region and iron regulation in mice.

For several years, we have been studying RLS in clinical settings as well as iron–dopamine interactions and genetic influences of iron in mice. Our work with mouse models has centered on iron in the ventral midbrain, especially the substantia nigra, normally an iron-rich region in which we have observed iron deficits in early-onset RLS patients (Earley *et al.* 2006). Recently, we identified several quantitative trait loci (QTL) related to iron in the ventral midbrain in recombinant inbred mice (Jones *et al.* 2003). Indeed, one of the suggestive QTL we identified is located in the region of *Btbd9* on mouse chromosome 17, homologous to the *BTBD9* region on human chromosome 6 (Jones *et al.* 2003). This QTL is also related to iron in the nucleus accumbens and caudate–putamen as well as copper and zinc in the prefrontal cortex, and thus may be involved in general trace metal regulation (Jones *et al.* 2006). The highest peak of this QTL, at 42.82 Mb, is slightly distal to *Btbd9*, which is positioned at approximately 30 Mb on chromosome 17; however, a second peak appears in this region at approximately 30 Mb, directly over *Btbd9*. Thus, two QTL in this region may influence the divalent metals. This requires further investigation. Although the LOD score of the second peak (over *Btbd9*) is not as strong, the coincidental link of a *BTBD9* variant to iron status by Stefansson *et al.* suggests that we revisit the possible role of polymorphisms in this gene in brain iron regulation.

It is also worth noting that the *BTBD9* variant of interest lies in an intron and is not in a known coding region, thus the affected gene may be *BTBD9* or a nearby gene (Stefansson *et al.* 2007). Considering this point, we also noticed that the striatal expression of *Glo1*, a close neighbor of *Btbd9*, shows heritable variation and is significantly correlated with ventral midbrain iron in female mice ($r = 0.62$, $P < 0.02$), according to the public gene expression database at http://genenetwork.org.

Restless legs syndrome is a complex syndrome often with unclear etiological origins, but altered iron homeostasis appears to play a role in at least some cases. There is no known function for *BTBD9* in iron homeostasis, and thus, it is yet to be determined whether or not the *BTBD9* variant acts through iron-related mechanisms. Also, we note that Winkelmann *et al.* (2007) omitted iron-deficient cases and did not measure iron status in their subjects. Thus, it is not known if serum ferritin and/or brain iron, which have a range of normal variation, were covariates in their analysis. Nevertheless, based on the findings of Stefansson *et al.* and our preliminary findings in mice, perhaps further investigation of the candidate gene(s) and biochemical pathways can shed light on how iron is involved in RLS and PLMs.

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