Forward genetics and brain iron relation to restless legs syndrome

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Evaluating a forward genetics model of restless legs syndrome (RLS): A murine strain with iron-deficient diet ventral midbrain but not peripheral iron loss produces an RLS-like behavior pattern made worse with iron deficiency and less with dopamine treatment.

Brain iron deficiency (BID) is the best-documented biological abnormality in RLS and has been reported in 20 of 22 studies. It occurs without peripheral iron deficiency. Moreover, in studies evaluating regional iron it is almost always found in the substantia nigra. An evaluation of 22 recombinant BXD strains found one (BXD40 females) that showed this pattern with dietary iron deficiency (ID), i.e. VMB iron decrease with minimal hemoglobin changes. This animal was also found to have milder versions of this pattern on a normal diet. On the normal diet they showed an RLS-like behavior of increased activity in the last 2 hours of the active period that was not shown by any other strain evaluated. Increasing severity of RLS occurs with earlier onset of RLS symptoms when resting during the afternoon and evening, sometimes into the morning. It was hypothesized that the ID diet making the VMB iron lower without disrupting peripheral iron would produce both earlier onset and larger magnitude increased activity with less resting time in the last part of the active period and that dopaminergic treatment would decrease this end of the active-period activity and increase resting time. Both of these RLS-like behavioral changes occurred for BXD40f evaluated (7 on iron-deficient diet and 6 on normal diet).

The BXD40f provide an example of a genetic animal model developed to match the iron biology of RLS that also displays RLS-like behavioral patterns. The BXD40f thus provide one reasonable animal model of RLS. This provides further support that brain iron deficiency without peripheral iron deficiency suffices to produce RLS symptoms.