Much recent progress has been made in understanding restless legs syndrome (RLS), focusing mainly on genetic predisposition and dysregulation of iron metabolism and the dopaminergic system. We provide in this review an update of the most recent scientific advances on the pathophysiology of primary RLS. Genome-wide association studies identified six genetic variants including MEIS1 and BTBD9 with potential relationships with iron. Brain iron level is low in RLS and neuropathological studies have shown significant decreases in dopamine D2 receptors in the putamen that correlated with RLS severity, and increased tyrosine hydroxylase in the substantia nigra. An overly activated dopaminergic system was reported in both animal and cell models of iron insufficiency thus suggesting that in at least a subgroup of RLS patients altered iron metabolism plays a role in the disorder. Also, dysregulation of iron uptake and storage within brain microvessels was recently reported and might play a role in a subgroup of RLS patients. RLS is a genetically heterogeneous complex trait with high prevalence but large phenotype variability. Current theories of RLS pathophysiology emphasize brain iron deficiency with abnormal dopaminergic consequences, together with a strong underlying genetic background.