A Nail Patella Syndrome-causing human Lmx1b variant disrupts mouse serotonin neuron development

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Impaired signaling of the monoamine neurotransmitter serotonin (5-HT) is linked to a series of neuropsychiatric disorders including anxiety, autism, depression, attention deficit hyperactivity disorder (ADHD), and schizophrenia. Research suggests that altered expression of genes encoding 5-HT synthesis (*Tph2*) and reuptake (*Slc6a4, Sert*) can lead to altered 5-HT signaling, behavioral pathogenesis, and neuropsychiatric disorders. These 5-HT pathway genes, among many others required for 5-HT synthesis, transmission, and metabolism, are co-activated by an upstream gene regulatory network (5HTGRN). Studies over the past 15 years identified several transcription factors within this network, including Insm1, Gata2, Gata3, Pet1, and Lmx1b. The 5HTGRN is required for the induction of 5-HT pathway genes and therefore serotonergic neurotransmission. Given their direct regulation of the 5-HT pathway, the 5HTGRN is an intriguing source of potential psychiatric disease causing variation. Our first clue may come from an autosomal dominant human disease called Nail Patella Syndrome (NPS), largely caused by mutations in *LMX1B*. NPS is most commonly diagnosed by absent or misshapen nails, malformed patella, elbow dysplasia, and the presence of iliac horns on the pelvis. Notably, although small in number, there are studies that show ADHD, major depressive disorder, and decreased mechanosensitivity are associated with NPS. However, there have been very few investigations into the mental well-being of these patients. Given the well-described role of Lmx1b in the 5HTGRN, a compelling hypothesis is that NPS mutations adversely impact the development of human brain serotonin neurons. To test this hypothesis, we generated CRISPR/Cas9 edited humanized mutant mice carrying an NPS N246K missense variant to determine if mouse 5-HT neuron development is altered. We found that the N246K knock-in leads to a stable mutant Lmx1b protein and a loss of 5-HT identity during embryonic stages of development. These were accompanied by significant changes in hindbrain morphology. To determine the 5-HT intrinsic effect of N246K, we generated mice carrying the N246K allele and a 5-HT specific conditionally targeted Lmx1b allele. We again found a loss of 5-HT identity that was additionally accompanied by severe changes in axon morphology in the adult. Together, these results suggest that naturally occurring variants in the 5HTGRN can severely impact 5HT development.