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Noncoding RNAs Connect Genetic Risk Factors to the Neurodevelopmental Basis of Bipolar Disorder

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Generating patient-specific, cellular models through reprograming techniques enables novel approaches to probing the pathogenesis and discovering targets for treatment of genetically complex neuropsychiatric disorders. In the case of bipolar disorder, despite its prevalence, high heritability and debilitating nature, the molecular and cellular mechanisms underlying its pathogenesis remain largely enigmatic. Creation of induced pluripotent stem cells (iPSCs) and directly converted, induced neurons (iNs) from somatic cells from bipolar disorder patients thus opens up new possibilities to connect the emerging understanding of the genetic architecture to its neurobiological basis, for drug screening, and for diagnostics (Figure 1 top, immunostaining of Nestin in human neuronal progenitor cells (hNPCs) and MAP2 in 8-week differentiated neurons derived from iPSCs, scale bar = 50 μm; bottom, schematic of the generation of induced iNs from healthy control and bipolar disorder subjects through direct neural conversion from fibroblasts). Here, miR-34a, a member of the class of short, noncoding RNA known as microRNAs, which specifically target messenger RNAs (mRNAs) with complementary sequences resulting in their degradation or blocked translation, is shown to directly target multiple genes implicated as genetic risk factors for bipolar disorder, including ankyrin-3 (ANK3) and voltage-dependent L-type calcium channel subunit beta-3 (CACNB3). miR-34a levels were found to be increased more

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prominently in postmortem cerebellar tissue from bipolar disorder patients, as well as in bipolar disorder patient-derived iNs and iPSC-derived neuronal cultures. Using human iPSC-derived neuronal progenitor cells to investigate developmental trajectories, modulation of miR-34a expression was shown to alter neuronal differentiation, morphology and the expression of key synaptic proteins. Collectively, these data implicate miR-34a as a critical link between multiple etiological factors for bipolar disorder and its pathogenesis through the regulation of a molecular network essential for neurodevelopment and synaptogenesis. Such uses of reprogrammed human cell models, and related studies, sets the stage for future discovery of the next generation of disease-modifying therapeutics targeting molecular networks underlying bipolar disorder pathogenesis. For more information on this topic, please refer to the article by Bavamian et al. on pages 573–584.

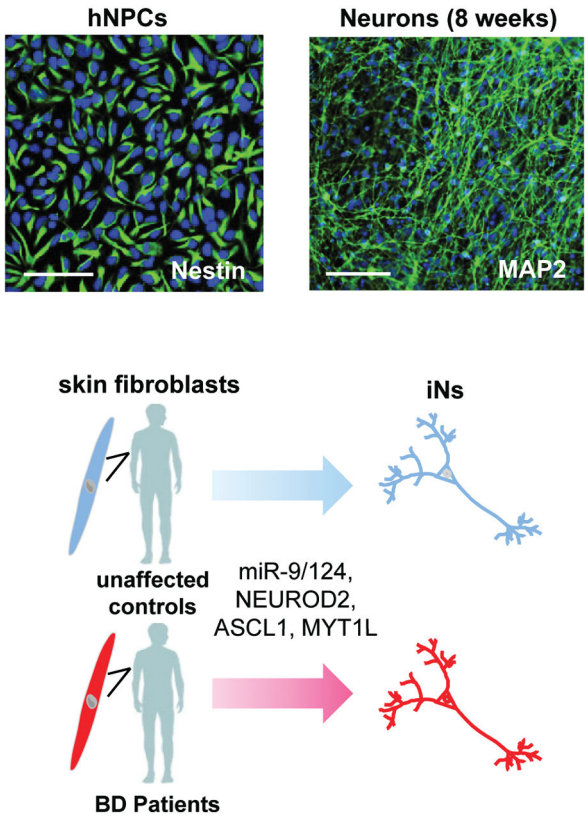

Figure 1.