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Lgl1 Controls Neural Stem Cell Lineage Progression via Intrinsic and Cell-non-autonomous Mechanisms

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The concerted production of the correct number and diversity of neurons and glia is essential for intricate neural circuit assembly. In the developing cerebral cortex, radial glia progenitors (RGPs) are responsible for producing all neocortical neurons and certain glia lineages. We recently performed a quantitative clonal analysis by exploiting the unprecedented resolution of the genetic MADM (Mosaic Analysis with Double Markers) technology and discovered a perhaps unexpected high degree of non-stochasticity and thus deterministic mode of RGP behavior. However, the cellular and molecular mechanisms controlling the precise pre-programmed RGP lineage progression through proliferation, neurogenesis and gliogenesis remain unknown. To this end we identified *Lgl1*, a regulator of cell polarity, as an important signalling hub for RGP-mediated lineage progression. By using a series of quantitative MADM-based experimental paradigms at single RGP resolution we found that *Lgl1* non-cell-autonomously controls embryonic cortical neurogenesis by RGPs. In contrast, *Lgl1* is cell-autonomously required in early postnatal progenitors for producing the correct number of cortical astrocytes. Lastly, *Lgl1* controls adult neurogenesis in the postnatal subventricular stem cell niche via intrinsic cell-autonomous signalling. Collectively, our results obtained from single cell quantitative MADM analysis define novel intrinsic cell-autonomous and non-cell-autonomous *Lgl1* functions which are essential for RGP lineage progression, cortical neuron and glia genesis and postnatal stem cell behaviour.