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EMPLOYING HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs) TO MODEL NF1-ASSOCIATED LOW GRADE GLIOMAS

Kelly Hartigan

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Neurofibromatosis type 1 (NF1) is a clinically heterogeneous cancer predisposition syndrome caused by a germline mutation in one of the two alleles of the *NF1* gene. Low grade gliomas (LGGs), particularly in the optic pathway, are common in patients with NF1 (15-20%). These tumors arise when the remaining allele is somatically inactivated in glial progenitor cells. *Nf1* genetically-engineered mouse (GEM) models have been employed to study NF1-associated LGGs; however, there are still a limited number of therapeutic targets available. This lack of clinical translation could reflect species-specific differences between rodents and humans or the use of “knockout” mutations in the mouse models, whereas patients with NF1 harbor a diverse number of germline *NF1* gene mutations. To study the importance of the germline mutation to LGG development and progression in human cells, the Gutmann Laboratory has created a collection of human induced pluripotent stem cells (hiPSCs) with NF1 patient mutations and hiPSC-derived cerebral organoids. Using this resource, we have generated mixed cerebral organoids comprised of hiPSCs homozygous for patient-specific *NF1* mutations and hiPSCs heterozygous for distinct *NF1* mutations spanning the *NF1* gene. Our preliminary results demonstrate that these mixed organoid cultures exhibit histological characteristics of NF1-LGGs. Future experiments employing this model will evaluate the differential effects of *NF1* mutations on LGG formation and growth.