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Head and neck squamous cell carcinomas (HNSCC) are a genetically heterogeneous group of cancers with a poor survival rate. Lui and colleagues evaluated the mutation frequency of mitogenic pathways in HNSCCs and found that 30.5% of tumors harbored PI3K pathway mutations. Patient-derived tumor grafts with hotspot and noncanonical PIK3CA mutations were highly sensitive to PI3K inhibitors. Pickering and colleagues performed integrated genomic analyses of oral squamous cell carcinomas (OSCC), a particularly lethal, poorly characterized HNSCC subtype. The Notch pathway was deregulated in 66% of OSCCs, and inactivation of NOTCH1 was shown to drive OSCC growth. Common inactivating mutations of FAT1 and CASP8 were also identified. Together, these findings provide insight into the etiology of HNSCC and identify potential therapeutic targets. For details, please see the article by Lui and colleagues on page 761 and the article by Pickering and colleagues on page 770.