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Using next-generation sequencing, Crompton, Stewart, and colleagues found that Ewing sarcoma tumors were relatively genetically stable, but exhibited recurrent loss of stromal antigen 2 (STAG2) expression, which was associated with metastatic progression. In addition, relapsed tumors displayed an increased mutation rate compared with tumors at diagnosis. Using whole-genome sequencing, Tirode, Surdez, and colleagues also detected few somatic alterations in Ewing sarcoma and identified STAG2 as the most frequently mutated gene. STAG2 mutations were mutually exclusive with CDKN2A deletion, but often coexisted with TP53 mutations, were associated with poor outcome, and expanded at tumor relapse. Together, these findings provide insight into the genomic landscape of Ewing sarcoma and suggest potential therapeutic targets. For details, please see the article by Crompton, Stewart, and colleagues on page 1326 and the article by Tirode, Surdez, and colleagues on page 1342.