The PCBP1 gene encoding poly(rC) binding protein I is recurrently mutated in Burkitt lymphoma

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The genetic hallmark of Burkitt lymphoma is the translocation t(8;14)(q24;q32), or one of its light chain variants, resulting in IG-MYC juxtaposition. However, these translocations alone are insufficient to drive lymphomagenesis, which requires additional genetic changes for malignant transformation. Recent studies of Burkitt lymphoma using next generation sequencing approaches have identified various recurrently mutated genes including ID3, TCF3, CCND3, and TP53. Here, by using similar approaches, we show that PCBP1 is a recurrently mutated gene in Burkitt lymphoma. By whole-genome sequencing, we identified somatic mutations in PCBP1 in 3/17 (18%) Burkitt lymphomas. We confirmed the recurrence of PCBP1 mutations by Sanger sequencing in an independent validation cohort, finding mutations in 3/28 (11%) Burkitt lymphomas and in 6/16 (38%) Burkitt lymphoma cell lines. PCBP1 is an intron-less gene encoding the 356 amino acid poly(rC) binding protein 1, which contains three K-Homology (KH) domains and two nuclear localization signals. The mutations predominantly (10/12, 83%) affect the KH III domain, either by complete domain loss or amino acid changes. Thus, these changes are predicted to alter the various functions of PCBP1, including nuclear trafficking and pre-mRNA splicing. Remarkably, all six primary Burkitt lymphomas with a PCBP1 mutation expressed MUM1/IRF4, which is otherwise detected in around 20-40% of Burkitt lymphomas. We conclude that PCBP1 mutations are recurrent in Burkitt lymphomas and might contribute, in cooperation with other mutations, to its pathogenesis.

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