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Cell clones containing BCOR frameshift mutations in the first coding exons of the gene retain BCOR protein expression

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Human BCOR (BCL6 co-repressor) is a key component of the non-canonical PRC1.1 (ncPRC1.1) and plays an important role in regulation of development, stem cell differentiation and hematopoiesis. Germinal *BCOR* loss of function mutations result in male lethality and lead to oculofaciocardiodental (OFCD) syndrome (OMIM 300166) in females. Somatic *BCOR* mutations that disrupt ncPRC1.1 are recurrent in hematologic neoplasms. Importantly, *BCOR* loss of function variants and truncating mutations that result in functional loss of the C-terminus of BCOR, which is essential for the complete assembly of ncPRC1.1, are related to resistance to BCR-ABL tyrosine kinase inhibitor therapy in acute myeloid leukemia (AML). *In silico* analysis indicate that certain regions of the canonical *BCOR* transcript are insensitive to non-sense mediated mRNA decay (NMD) upon mutation. Hence, loss of function mutations in NMD-insensitive regions of *BCOR* are predicted to yield a N-terminally truncated but functional BCOR protein. To experimentally test this hypothesis, we investigated the effects of 16 CRISPR-Cas9-induced frameshift mutations in either exon 2 (first coding exon) or exon 4 of the *BCOR* gene in the classic Hodgkin lymphoma (cHL) cell line L428 and the Burkitt lymphoma cell lines NAMALWA and CA46. We showed that whereas mutations in exon 2 failed to produce a functional knockout of *BCOR*, mutations in exon 4 resulted in a complete loss of the BCOR protein. Our results demonstrate that mutations in exon 2 of *BCOR*, representing the N-terminal region of the BCOR protein, are not subject to NMD. This insight may have important implications for anticipating AML patients' response to BCR-ABL inhibitor therapy.

Keywords: BCOR; ncPRC1.1; classic Hodgkin lymphoma; NMD; truncation
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