

## **SAMHD1 is mutated recurrently in chronic lymphocytic leukemia and is involved in response to DNA damage**

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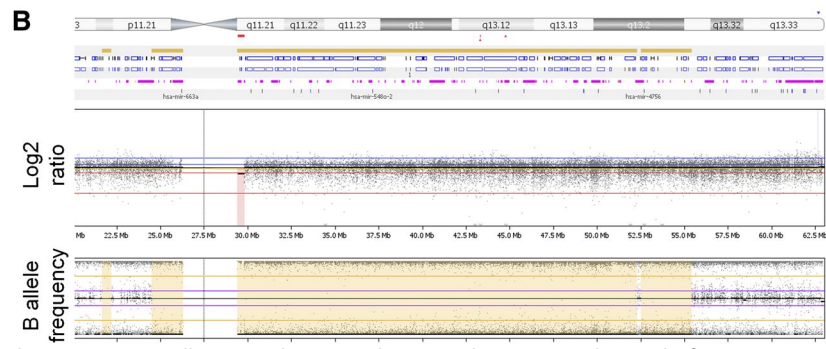
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Clinically, CLL displays extreme heterogeneity, with patients surviving for many years, with asymptomatic disease and no need for therapy, while others have rapidly progressive disease despite aggressive treatment. This clinical heterogeneity is underpinned by considerable biological diversity, which contributes to disease pathogenesis driven by a variety of molecular and cellular mechanisms. It is now clear that much of this clinical heterogeneity originates from variability at the genetic level, exemplified by the presence of recurrently somatically-acquired genetic lesions, many of which have been functionally-linked to disease pathophysiology. These genetic lesions include established copy number changes, including deletions of 17p13.1 involving *TP53* and deletions of 11q22.3 involving *ATM*, which are both of independent prognostic significance. Recent data from whole genome and exome sequencing have confirmed the heterogeneous nature of CLL, and identified a number of novel gene mutations, which can be used to predict disease progression and survival. Whilst our understanding of the genetic basis of CLL is expanding, there remains new genes to be identified, that will expand our understanding of the disease by delineating biological pathways that may represent therapeutic targets.

One such study recently emerged from Oxford University, from Dr Ruth Clifford and colleagues. They identified recurrent mutations in the deoxynucleoside triphosphate triphosphohydrolase and nuclease, *SAMHD1*. Now, the story starts not with CLL, but with the congenital autoimmune condition, Aicardi-Goutieres syndrome (AGS), an autosomal recessive disorder where *SAMHD1* mutations have been identified. When the authors reviewed a cohort of AGS patients with germ-line *SAMHD1* mutations, they made a startling observation, one patient developed CLL at the age of only 24, which is very young for a diagnosis of CLL. Indeed, only 0.2% of CLL patients are diagnosed at this age. When they

looked at the patients CLL cells, they showed that the mutation had been duplicated (Figure 1), suggesting that the CLL process had selected for cells with further dysfunction of *SAMHD1*.



Part of Figure 1 showing a somatically acquired copy number neutral LOH event. This results from a somatic recombination event that duplicates a mutation but retains normal copy number

This led the authors to hypothesize that *SAMHD1* might be a target for cancer-associated genetic lesions in CLL, so they set about try to prove it. In 100 CLL patients, they identified 5 with somatically-acquired *SAMHD1* mutations, four of which has evidence that these mutations had been further targeted by duplication events. Importantly, these mutations were in the vast majority of tumour cells, suggesting that they occurred early in the pathogenesis of the disease, and could be possible ‘initiating lesions’. The authors also provide preliminary data suggesting that the presence of a *SAMHD1* mutation was associated with poor response to therapy and MRD-positivity in the context of two UK clinical trials. Further studies will be required to establish their precise clinical value, but it is certainly an exciting observation. Supporting the notion that *SAMHD1* mutations are clinically relevant, the authors showed a four-fold enrichment of mutations in patients who were relapsed or refractory to first-line therapy.

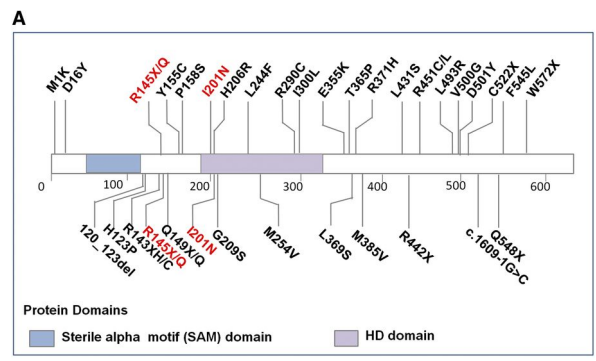


Figure 2 shown the distribution of *SAMHD1* mutations across the protein structure.

Mutations in *SAMHD1* were associated with reduced mRNA and protein expression. Interestingly, they showed heterogeneous *SAMHD1* mRNA and protein levels in non-mutated cases, suggesting that other mechanisms of regulation may be at play in CLL.

*SAMHD1* plays an important role in regulating the cellular dNTP pool, and it has been suggested that an imbalance in this pool may induce genomic damage and compromise appropriate DNA damage repair. Therefore the authors hypothesized that *SAMHD1* mutation may impact of DNA damage response. Using transfected cell lines, the authors show that a *SAMHD1* mutation protects the cells from chemical induced death. Furthermore, they show that *SAMHD1* is recruited to sites of DNA damage in response to DNA double stranded breaks.

This is a really elegant series of experiments that expand our understanding of the CLL genome, and show how genomic defect might contribute to the disease. Clinically, the implication might be that *SAMHD1* mutations could contribute to chemo-resistance. After all, the gene is functionally linked to DNA damage response, mutations were enriched in relapse patients (without enrichment of other high-risk features), and mutated patients seemed to exhibit poor response to first-line therapy. Alternatively, mutations may drive an aggressive phenotype, but larger studies will be required to prove this.

This study represents an important step towards a full catalogue of the genetic defects that occur in CLL, and this is a worthy and important pursuit. Clifford and colleagues contribute an important new observation to an international effort, and provide fascinating biological insights too. They show recurrent mutations in *SAMHD1*, that result in reduced protein expression and have a putative role in DNA damage response and clinical outcome. Of course, as the authors state, research remains to be conducted that will ultimately define the clinical utility and biological importance of this lesion in the context of disease diagnosis, natural history, transformation, prognostication and therapeutic response.

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