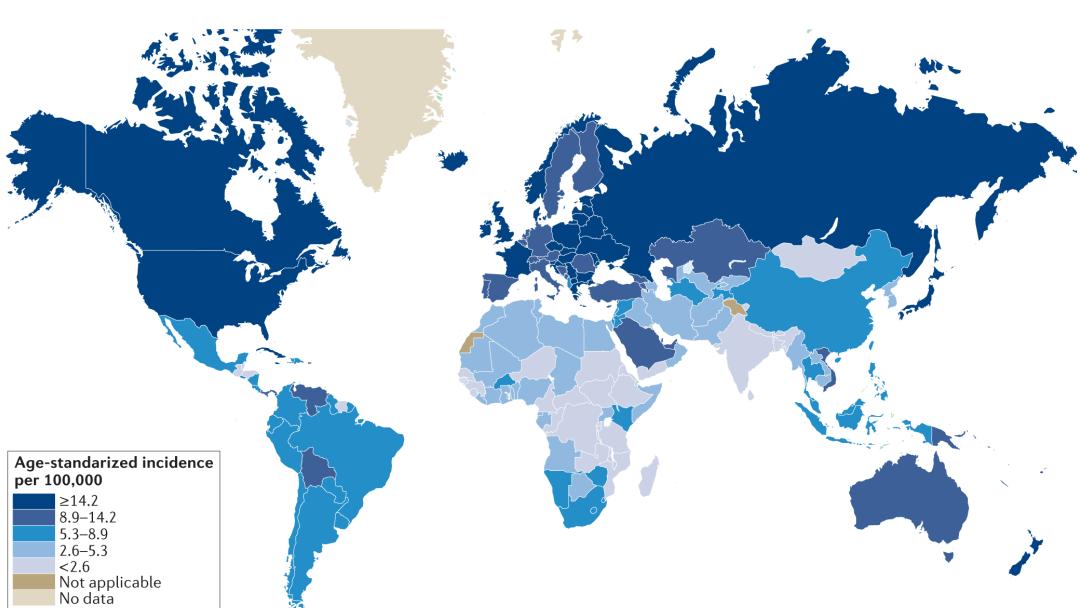


Chromatin modifiers in endometrial cancer

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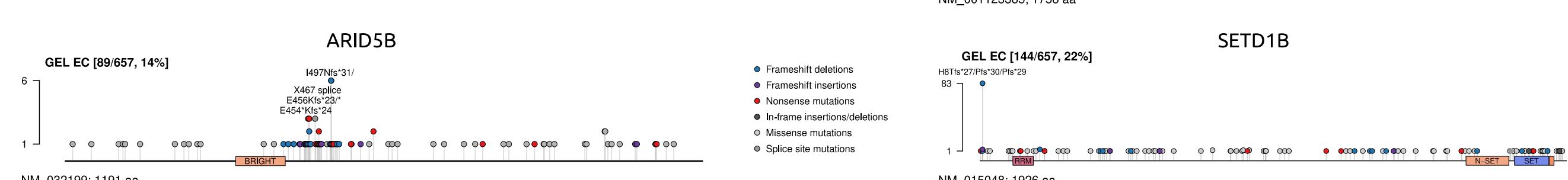
Endometrial cancer - most frequent gynecological



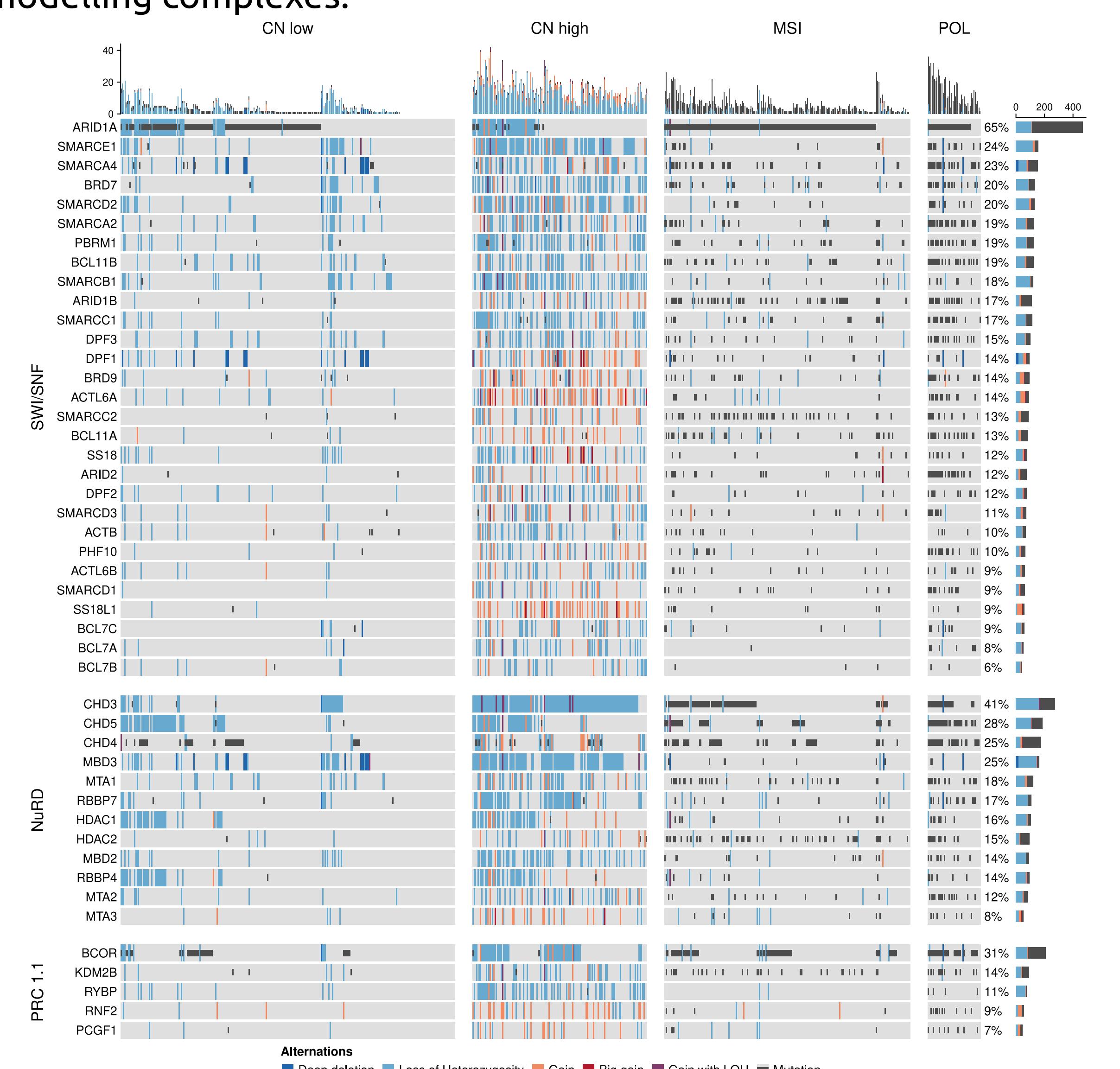
Endometrial cancer (EC) - cancer of the lining of the uterus, is the most common gynecological cancer in the UK and US. In 2020, there were **417,000 new diagnoses**. EC is the 6th leading cause of cancer-related deaths among women in the US and 8th in Europe.

Chromatin modifiers are frequently altered in EC

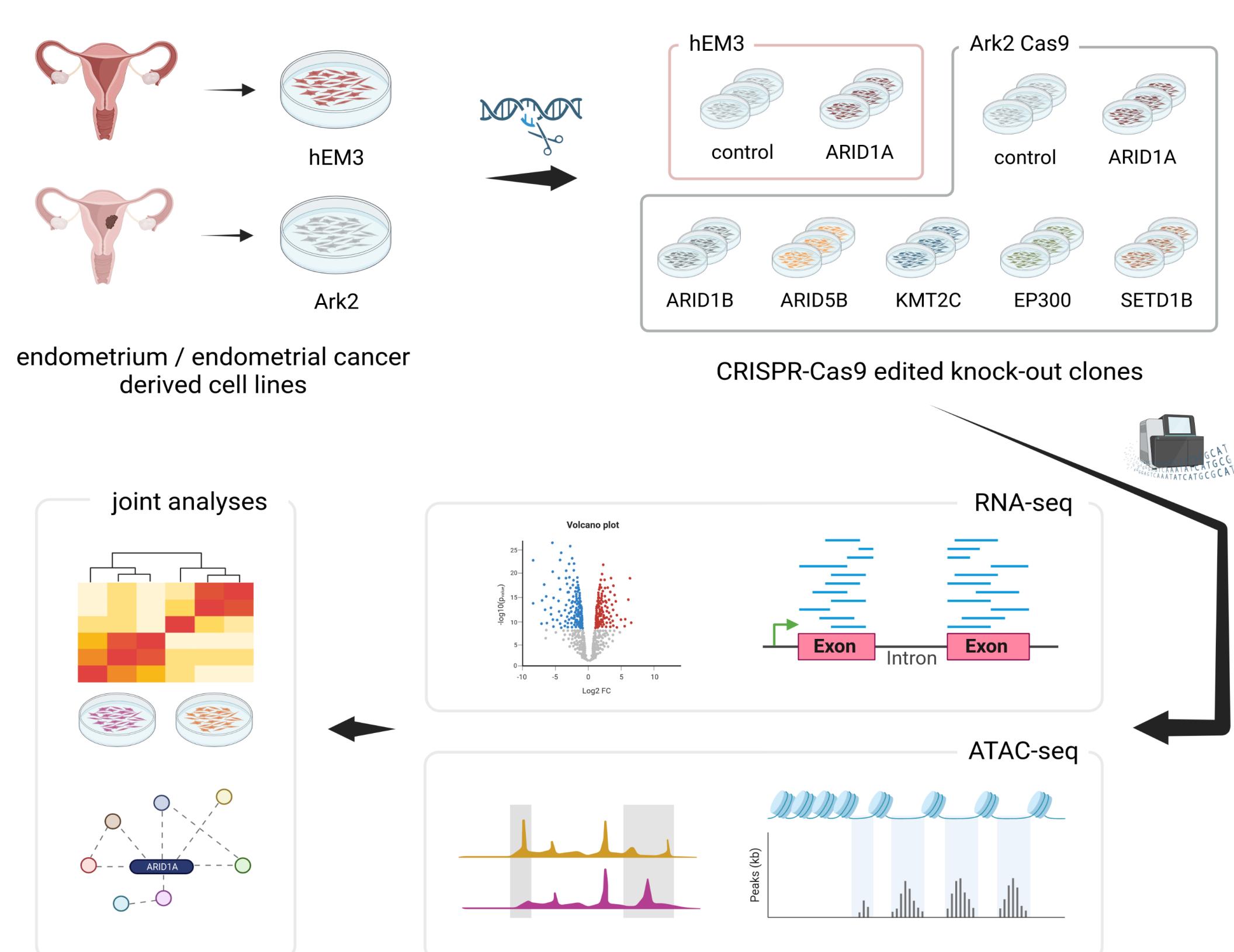
Mutations are often found in chromatin modifiers. **ARID1A** is characterized by truncating mutations. **BCOR N1459S** hotspot mutation is near unique to EC. Frameshifts are also frequent in other chromatin modifiers such as **ARID5B** or **SETD1B**.



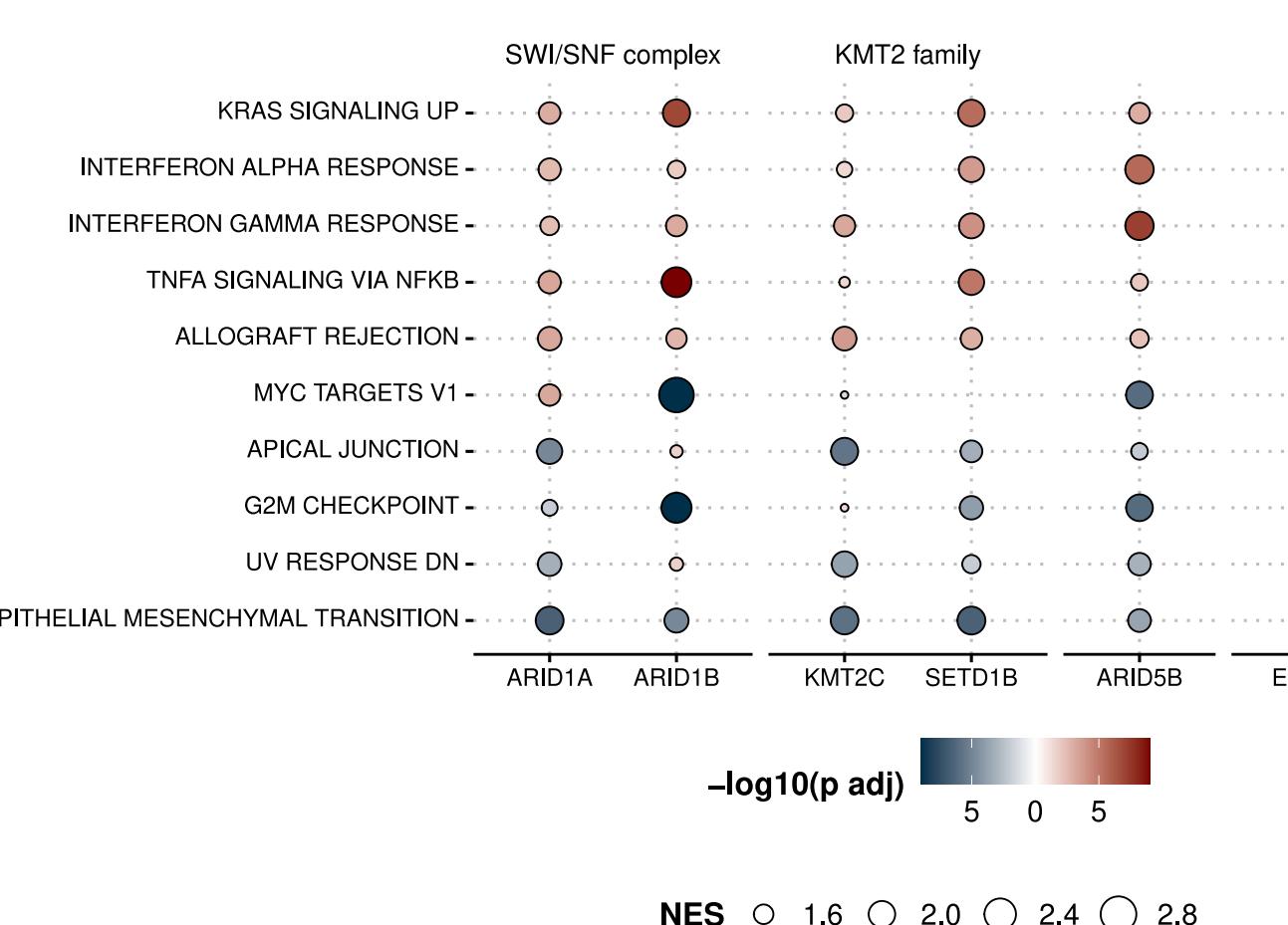
Alterations in chromatin modifiers differ with respect to EC molecular subtype. Modifications are found in various members of chromatin remodelling complexes.



Methods overview



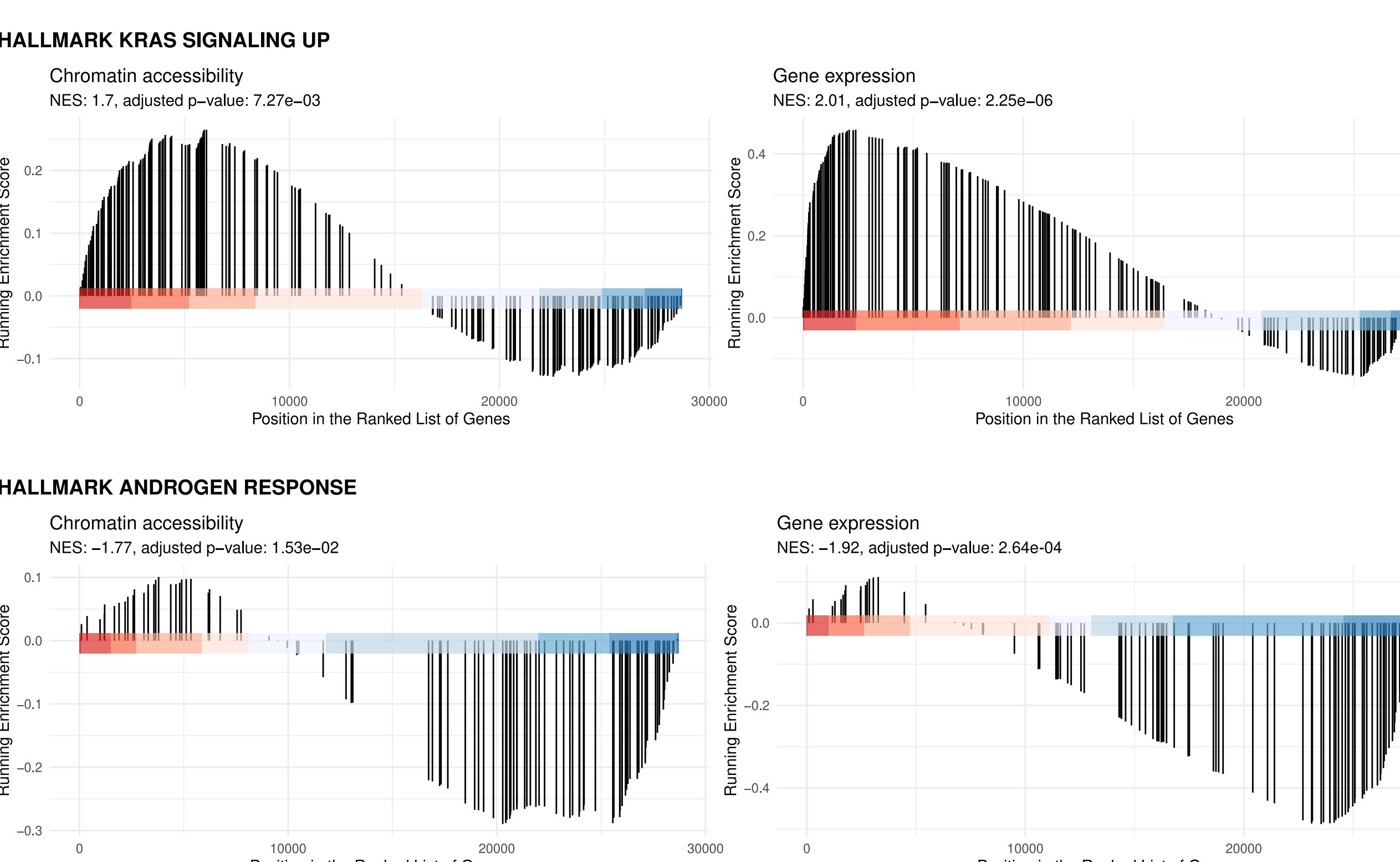
Loss of chromatin modifiers changes chromatin organization and transcriptome profiles



Loss of chromatin modifiers up-regulates **KRAS signaling pathway** and interferon responses.

EMT is down-regulated at the gene set level, however several genes such as **SPOCK1** or **IGFBP2** are up-regulated.

Dysregulation of pathways is driven by the altered chromatin accessibility. Up-regulation of **KRAS signaling** in Ark2 Cas9 *SETD1B* knock-out and down-regulation of **Androgen response** in Ark2 Cas9 *KMT2C* knock-out shown below.



Loss of chromatin modifiers results in changes in transcription factors motifs accessibility

