HERV-K in Cancer: The Phoenix of the Human Genome?

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What is HERV-K?

Viruses have infected humans for millions of years, ever since the divergence from chimpanzees. Some viral infections are short-term, such as influenza, while others cause longer, more serious infections. A prime example of the latter is human immunodeficiency virus (HIV). This kind of virus is known as a retrovirus; these viruses enter cells and insert their genes into human DNA. The natural processes in which our cells create proteins from genes occurs in these viruses too, producing copies of the virus which can infect more cells. If retroviruses infect germ cells and do not produce a sufficient viral infection, the virus may be passed on through generations (Weiss, 2006). Retroviruses in which this occurs are called endogenous retroviruses, specifically HERVs in humans.

Many families of HERV exist, with HERV-K being the most active. HERV-K consists of genes required to create new viruses, flanked by long repeat sequences known as LTRs. However, most of the 127 different HERV-K insertions have been broken down so that only the LTRs remain (Pačes *et al*, 2002). As such, HERVs were long thought to be unimportant in disease, though work since suggests otherwise.

HERV-K and Cancer

As the most active family, HERV-K has been theorised to play a role in many diseases (Hohn *et al*, 2013). In particular, HERV-K has been associated with several cancers, with multiple mechanisms linking the viruses to the disease. One such mechanism suggests that individual HERV-K insertions can aid the progression of cancer through their LTRs; these sequences can cause other genes that are nearby to produce more of their respective proteins (Cohen *et al*, 2009). If these genes, and therefore the proteins, are known to cause cancer, the presence of LTRs may also cause cancer. As such, LTRs may be described as "promoters" for cancer-related genes (termed proto-oncogenes).

Figure 1: A flowchart briefly showing how HERV-K insertions were found

Aim and Methods

The aim of the project was to see whether HERV-K insertions were associated with a risk in hepatocellular carcinoma (HCC), the most common form of liver cancer. To do this, I needed to search my 24 sample genomes for HERV-K insertions and compare their frequency compared to a general population using values derived from Wildschutte *et al* (2016). However, HERV-K is not the only insertional element, so many steps were required, as shown in the flowchart (figure 1). Firstly, all insertions were found; these were searched for the LTR of the youngest HERV-K (113) since this is the youngest and most intact LTR and is similar to all other HERV-K LTRs. The results were then studied to differentiate between HERV-K and another element that contains part of the LTR, called SVAs.

Results

When comparing the total number of each HERV-K insertion found in the genome samples, it was clear that the majority were far less common in HCC than in a general population. As seen in figure 2, all but one of the 36 HERV-K insertions were decreased in the cancer, 18 of which were significantly so ($p < 0.05$).

Discussion

The results obtained from this project oppose findings made by other studies which suggest that HERV-K may contribute to cancer. In fact, a study similar to this just last year announced results that contradict my own (Ma *et al*, 2016).

However, my results can be explained using one of the theories suggested to cause cancer; if HERV-K LTRs can act as promoters for proto-oncogenes, what says that they cannot also act as promoters for genes that prevent cancer?

If so, it would show the protective nature in a general population with increased amounts of HERV-K, although in this scenario it would require tumour-suppressor genes to be identified near insertions to see which in particular would work this way.

Either way, HERV-K insertions, previously thought to be broken pieces of junk DNA, may in fact rise from its ashes much like a phoenix, protecting us from cancer.

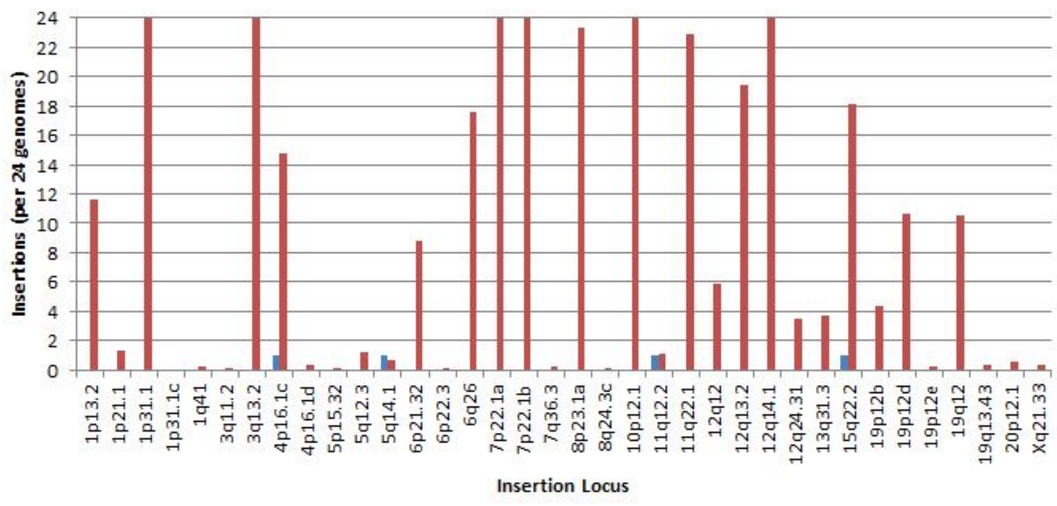

Figure 2: The frequency of each HERV-K insertion observed in HCC patients (blue) and derived from a reference population (red)

References

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Figures 1 and 2 are author's own work; phoenix icon taken from an open source website.