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Koala Retrovirus (KoRV) and its Variants

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Abstract. The recent, independent identification by several research groups of koala retrovirus (KoRV) variants was the focus of one of the break-out sessions at the *Koala Conservation Workshop: The koala and its retroviruses: implications for sustainability and survival* held at San Diego Zoo, April 17–18, 2013. The goals of this session were to discuss the differences and similarities between variants identified, to determine approaches to their nomenclature, the prevalence of these variants in wild and captive koalas, the relative pathogenicity of the variants, and the significance of the variants in managing koala populations.

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The nucleotide sequence of a koala retrovirus thought to be associated with lymphoma was first reported by Hanger in 2000 (Hanger *et al*., 2000) and named KoRV. More recently, separate research groups in Australia, Japan, and the United States have independently identified a number of KoRV variants (Miyazawa *et al*., 2011; Xu *et al*., 2013; Shojima *et al*., 2013; Shimode *et al*., 2014; own unpublished observations). At the time of this meeting in April, 2013 the only sequence analysis that had been publicly presented on KoRV variants was by the Miyazawa group at the 21st International Workshop on Retroviral Pathogenesis in Italy, September 2009. They showed that a variant, isolated from a captive koala at the Kobe Municipal Oji Zoo (KMOZ) was characterized by a significant sequence modification in the *env* gene, within the receptor binding domain (RBD), specifically in the variable region A (VRA) motif that is known to be involved in defining host cell receptor specificity. They referred to this variant as KoRV-B with the original Hanger strain designated KoRV-A and published the isolation of these viruses in the following year (Miyazawa *et al*., 2011). Recognition by other groups of variants with differing sequence stretches in this same region of the RBD VRA has led to the adoption of the Miyazawa labeling convention. Discussions during this break-out session at the 2013 San Diego meeting didn't reach consensus on KoRV nomenclature nor on a number of other issues raised, primarily because none of the sequences had at that stage been published and so direct comparative analyses could not be made. However, subsequent publications have helped to clarify the situation and the discussion below is intended to summarize the current state-of-play.

KoRV variant nomenclature

The natural extension of the above naming convention has resulted in the publication so far of five KoRV variants with the original sequenced virus being designated KoRV-A and the remaining four being named KoRV-B, KoRV-C, KoRV-D, and KoRV-J (summarized in Denner & Young, 2013). The original Miyazawa KoRV-B had to be re-named KoRV-J as an isolate from the Los Angeles Zoo (LAZ) was given the KoRV-B designation in the first published sequence analysis of a KoRV variant (Xu *et al*., 2013). Ironically, subsequent sequence comparisons indicate that the LAZ KoRV-B VRA sequence is strikingly similar to KoRV-J placing these two viruses in the same phylogenetic grouping (Shimode *et al*., 2014). Furthermore, both of these viruses were shown to utilize the same receptor, the thiamin transport protein 1 (THTR1) for cell entry, a different receptor to that used by KoRV-A, the sodium-dependent phosphate transporter, Pit1 (Shojima *et al*., 2013; Xu *et al*., 2013). Full genome sequencing of these isolates has identified additional sequence variation from the prototype KoRV-A with both KoRV-B and KoRV-J showing additional, but distinct tandem repeats in the U3 region of the LTR (Shimode *et al*., 2014). Interestingly, the KoRV-J LTR was shown to display a significantly higher promoter activity than the KoRV-A LTR in selected cell populations hinting at a possible role in up-regulating the expression of host cell genes adjacent to proviral insertions (Shimode *et al*., 2014). Given the striking similarities between KoRV-B and KoRV-J it would be appropriate for both to be referred to as KoRV-B but each with a strain designation to separately identify them