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# DIVERSITY OF $\beta$ -RETROVIRUSES CAUSING RESPIRATORY CANCERS IN SMALL RUMINANTS

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## CONTEXT AND OBJECTIVES

- **Oncogenic  $\beta$ -retroviruses** are responsible for respiratory cancers in small ruminants. While **JSRV** (Jaagsiekte Sheep RetroVirus) induces **lung cancers** in sheep, **ENTV** (Enzootic Nasal Tumor Virus) induces **nasal tumors** in sheep for ENTV-1 and goats for ENTV-2. The **envelop glycoprotein (Env)**, more specifically the intracytoplasmic tail of the transmembrane region, carries the transforming capacity and is referred as the **main oncogenic determinant**.
- Multiples copies of highly related  **$\beta$ -endogenous retroviruses ( $\beta$ -ERVs)** resulting from ancestral infections of germinal cells during evolution are **present in the small ruminant genomes**.
- JSRV and ENTV are endemic in many countries. As we observe in France, the **clinical expression varies** in terms of severity and morbidity/mortality rates in flocks, from isolated/**sporadic** cases to cancer **outbreaks**.

## OBJECTIVES

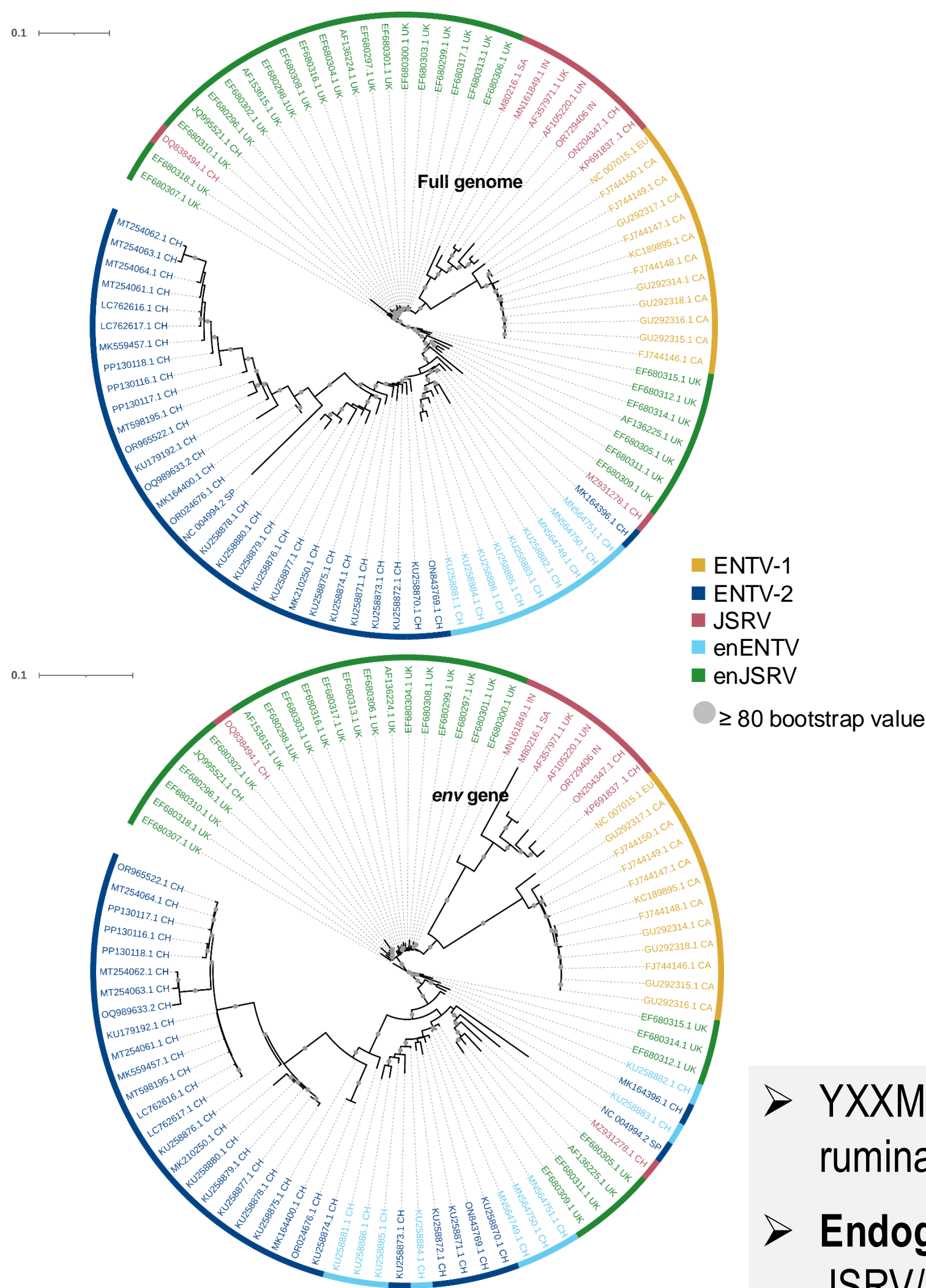
**What is the diversity of  $\beta$ -retroviruses circulating in France and how does their diversity relate to the clinical expression?**

We focused on the genetic characterization of the oncogenic  $\beta$ -retroviruses (30 JSRV, 3 ENTV-1 and 21 ENTV-2) from various regions of France (31 flocks), and on their sequence analysis to identify specific strains associated with increased clinical expression in some flocks.

## METHODS AND RESULTS

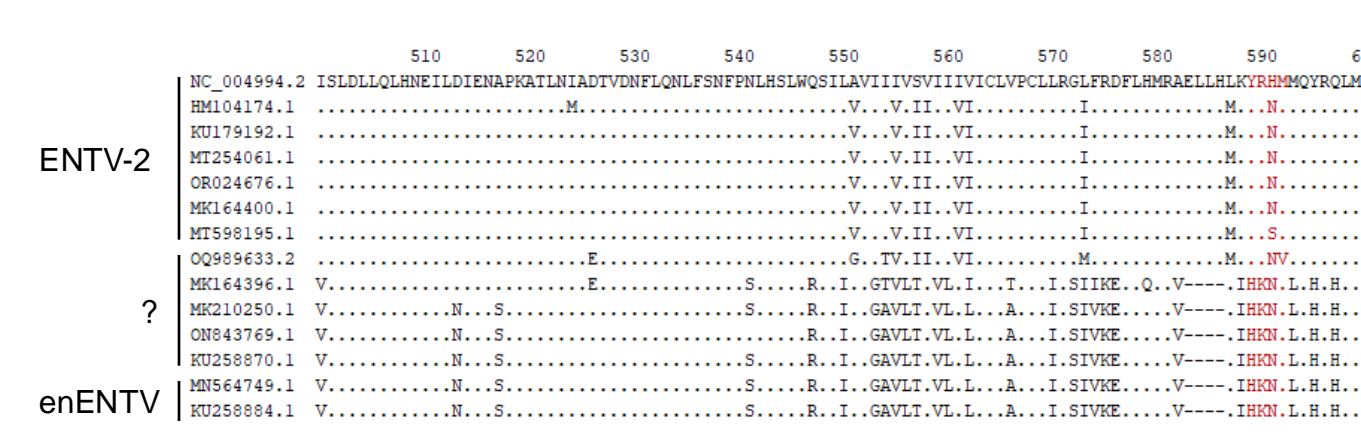
### ① ENDOGENOUS / EXOGENOUS CHALLENGE IN PUBLIC DATABASES

Phylogenetic reconstructions based on JSRV, ENTV-1, ENTV-2 and small ruminant ERV (available in public databases)

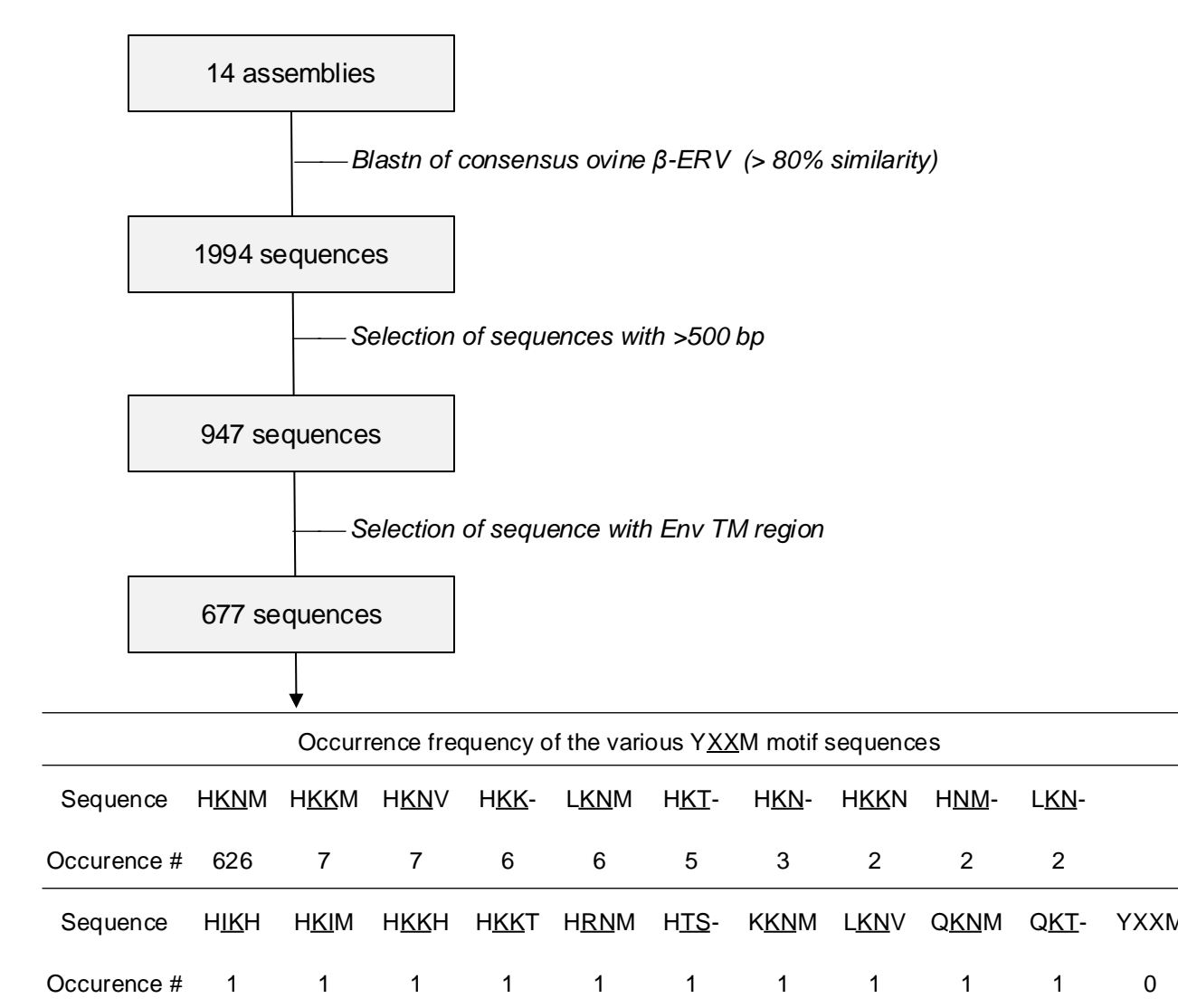


- YXXM motif in the Env protein is absent of all related  $\beta$ -ERV sequences found in small ruminant genome assemblies. It constitutes a **signature of exogenous JSRV/ENTV**.
- **Endogenous/exogenous status dilemma** : sequences described as exogenous JSRV/ENTV clustering with ERV and/or lacking the exogenous YXXM signature.

AA alignment of Env oncogenic region



Detection of YXXM motif of ERV copies in 14 ovine/caprines genome assemblies

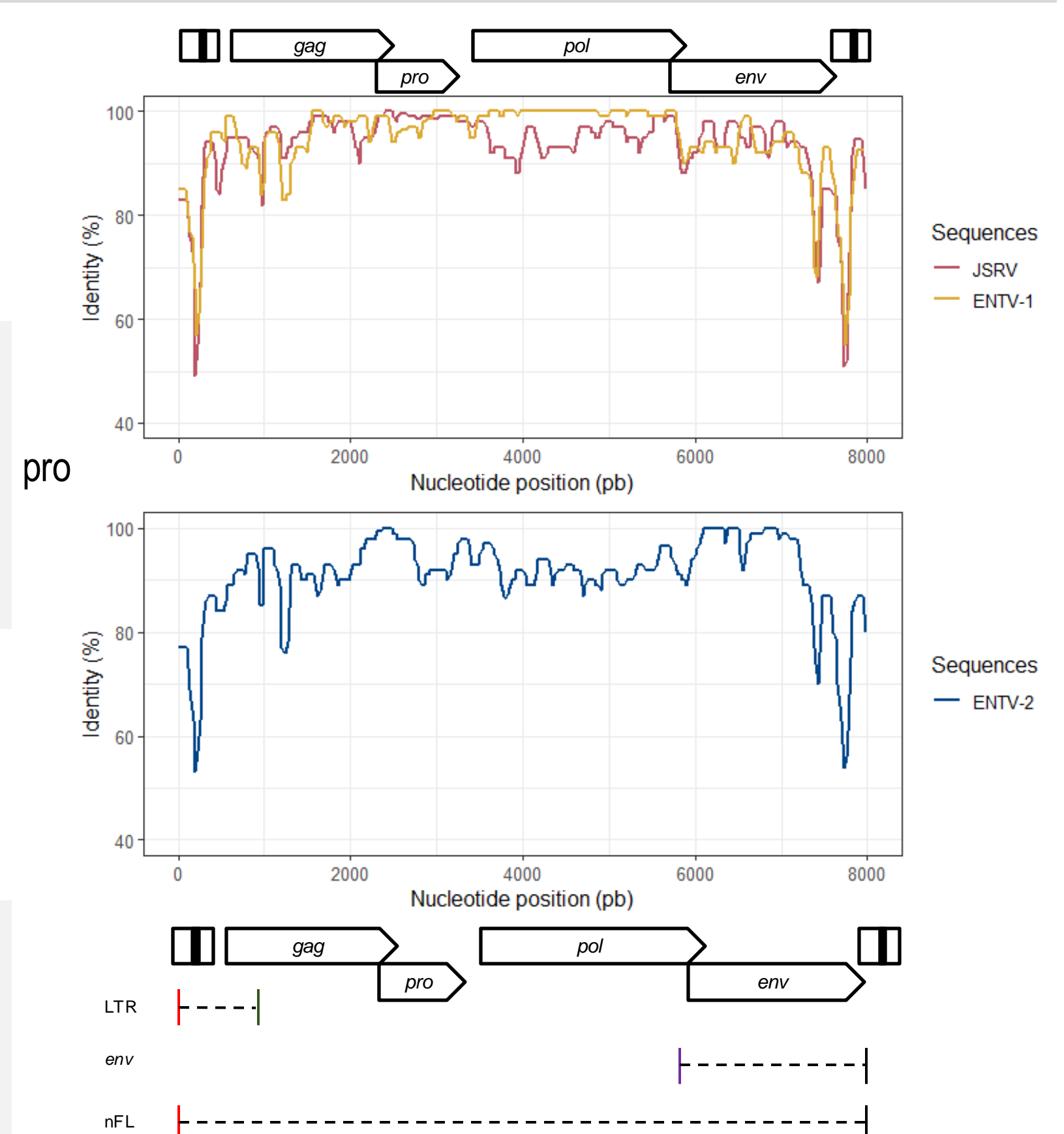


### ② LIMITED DISCRIMINATING REGIONS BETWEEN EXOGENOUS AND ENDOGENOUS $\beta$ -RETROVIRUS

- Compared to ERVs, only short and localized regions are **specific of the exogenous  $\beta$ -retroviruses** located in the terminal part of *env*, the U3 region of both LTRs and *gag*.

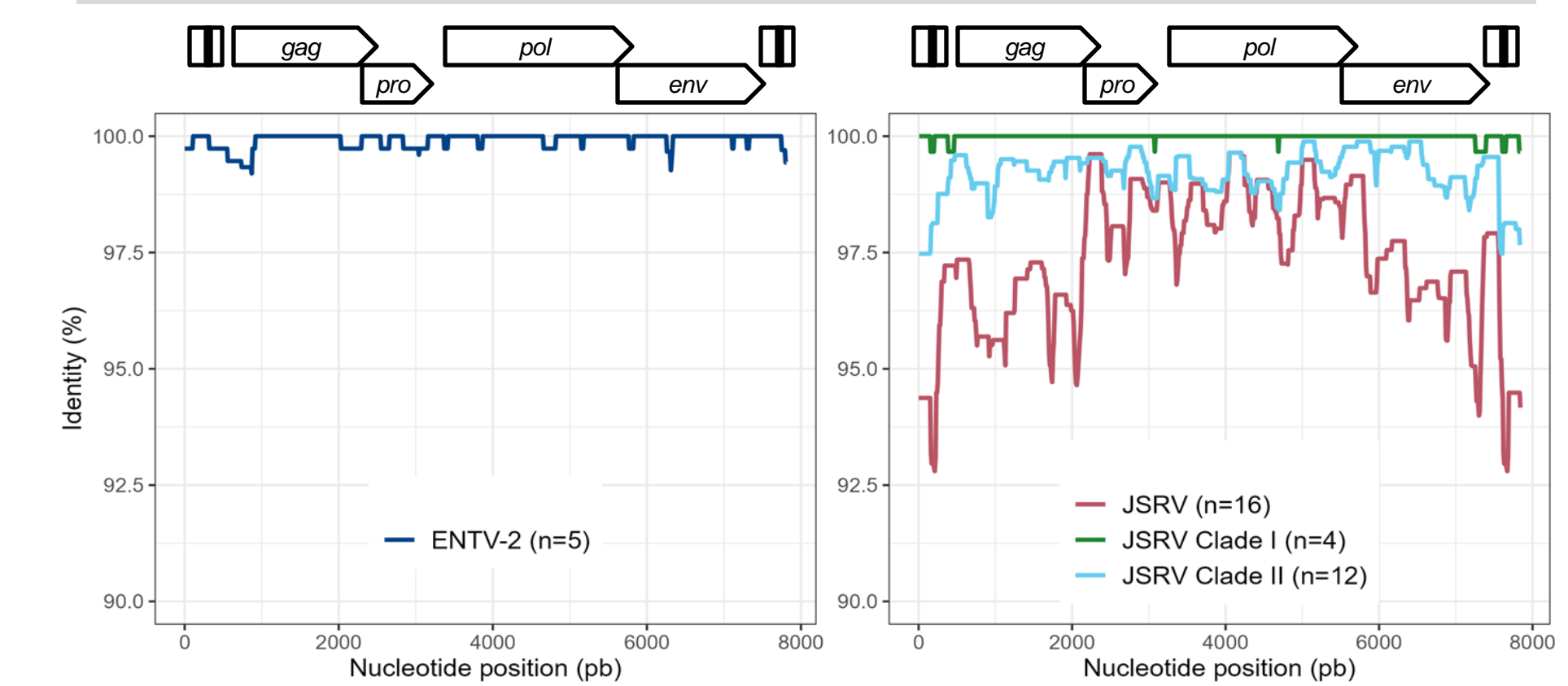
- We have developed a **highly specific strategy** to selectively amplified and sequence the **exogenous ENTVs** and JSRV genomes.

Identity plot (nt) along the  $\beta$ -retrovirus genome against a consensus sequence of related ERVs



### ④ LIMITED GENOMIC VARIABILITY OF JSRV AND ENTV

French ENTV-2 and JSRV variability along the genome

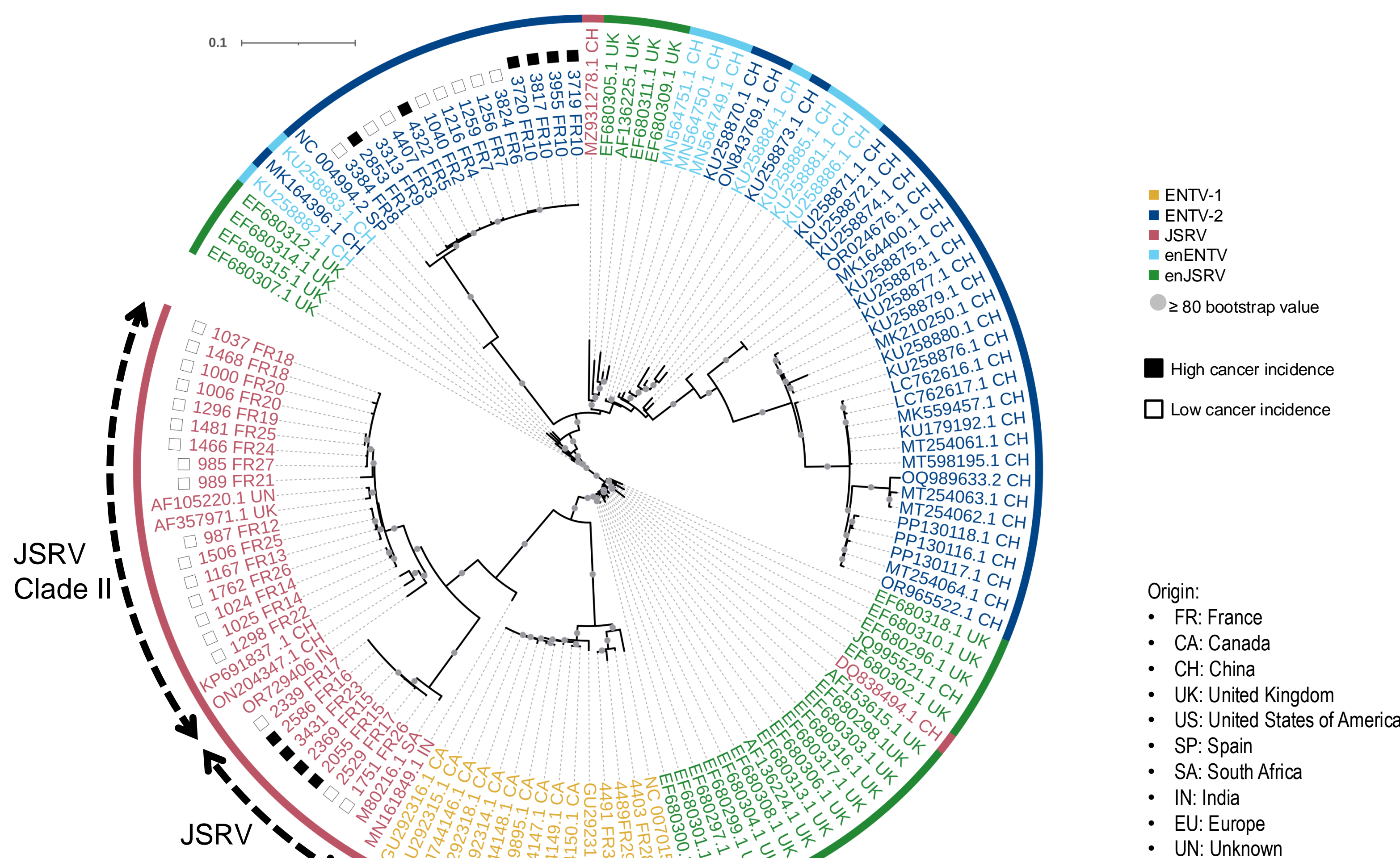


- Lower variability of ENTV-2 compared to JSRV.
- **Low intra clade variability** for JSRV.
- Peak of variability for JSRV in *env* oncogenic region, end of *gag* and LTR.

Virus	n flocks	LTR	% (± sd) divergence					
			<i>gag</i>	<i>pro</i>	<i>pol</i>	<i>env</i>	NFL	
ENTV-1	2	nt	0.27	0.33	0.78	0.49	0.38	0.46
		aa	NA	0.16	0.33	0.49	0.16	NA
ENTV-2	5	nt	0.32 (± 0.16)	0.31 (± 0.19)	0.33 (± 0.20)	0.20 (± 0.04)	0.33 (± 0.08)	0.29 (± 0.08)
		aa	NA	0.39 (± 0.30)	0.52 (± 0.49)	0.19 (± 0.11)	0.13 (± 0.10)	NA
JSRV	16	nt	5.36 (± 4.58)	4.25 (± 3.94)	2.55 (± 1.89)	2.11 (± 1.44)	4.08 (± 3.80)	3.56 (± 3.02)
		aa	NA	1.09 (± 0.92)	0.94 (± 0.70)	1.06 (± 0.55)	1.22 (± 1.14)	NA

### ③ DIVERSITY OF $\beta$ -RETROVIRUSES CIRCULATING IN FRANCE

Phylogenetic reconstruction based on French JSRVs and ENTVs in the *env* coding region (ML Tree with a 10000 ultrabootstrap replicates)



Based on their sequences in *env* regions, we report :

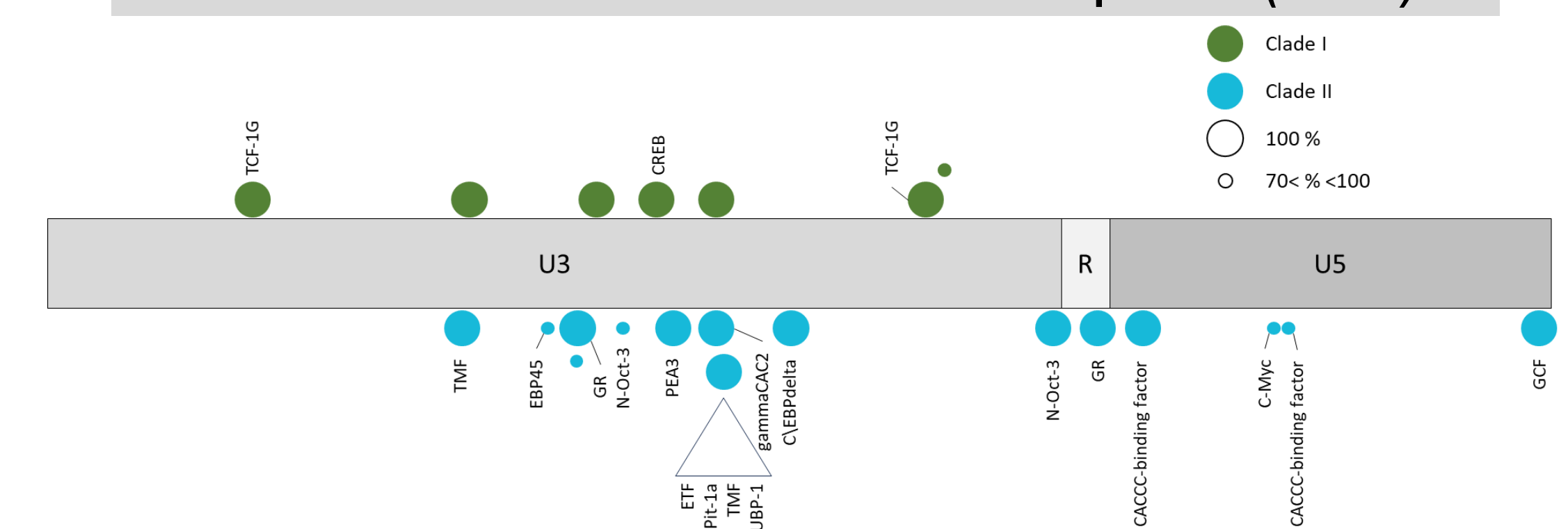
- the relative **stability** of JSRVs and ENTVs, sampled from geographically distinct French areas with ~95% of nt similarity.
- the circulation of **two genetically distinct groups of JSRV**, with clade I strains being often associated to **more severe clinical expression** (in terms of morbidity/mortality rates).

## CONCLUSIONS & PERSPECTIVES

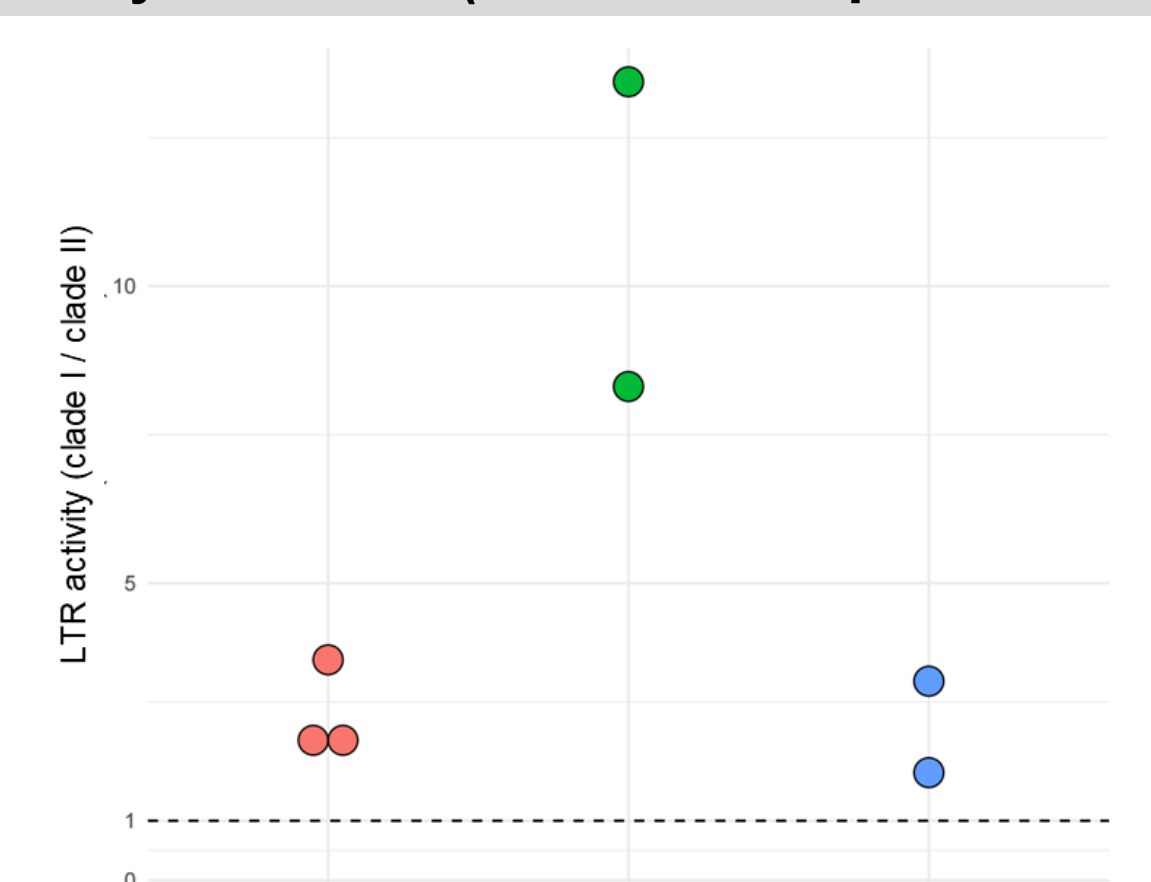
- ☑ **First report** on French strains of oncogenic  $\beta$ -retroviruses responsible for cancers in sheep and goats.
- ☑ In France, **low sequence diversity** of ENTV while **JSRV strains are more diverse**.
- ☑ JSRV clade I is **associated with higher incidence of cancer** in flocks.
- ☑ Perspectives : test of the impact of the genetic signatures on the **oncogenic properties of JSRV**.

### ⑤ POLYMORPHISM IN JSRV LTR IS ASSOCIATED WITH DIFFERENTIAL PROMOTER STRENGTH

Prediction of differential transcription factor binding sites between JSRV clade I and clade II LTR consensus sequences (*tfscan*)



JSRV LTR promoter strength in epithelial pulmonary cell lines (luciferase expression assay)



- ☑ Identification of **distinct transcription factor binding-sites** between strains isolated from **outbreaks (LTR I)** and **sporadic (LTR II)** events.
- ☑ **Higher promoter activity** for JSRV LTR I (outbreaks) in all pulmonary epithelial cell lines.
- ☑ Link with higher replication and/or oncogenic Env expression in JSRV clade I strains?