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Recurrent cystitis episodes are caused by "ordinary" uropathogenic *Escherichia coli* strains

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Introduction

Recurrent cystitis (i.e. more than 2 episodes over a 6-month period) is a public health concern as it impacts significantly the patients' quality of life. Both **sporadic cystitis (SC)** and **recurrent cystitis (RC)** are mainly caused by Uropathogenic *Escherichia coli* (UPEC). However, specific determinants associated with "recurrent" UPEC remain poorly characterized.

→ **Objective: to describe genomic and phenotypic traits associated with recurrence and to explore within host genomic adaptation of sequential UPEC isolates.**

Method

September 2015 – January 2017 : prospective collection of UPEC isolates

RCI : Recurrent cystitis isolate
iRCI = initial RCI
rRCI = relapse RCI
SCI = Sporadic cystitis isolate

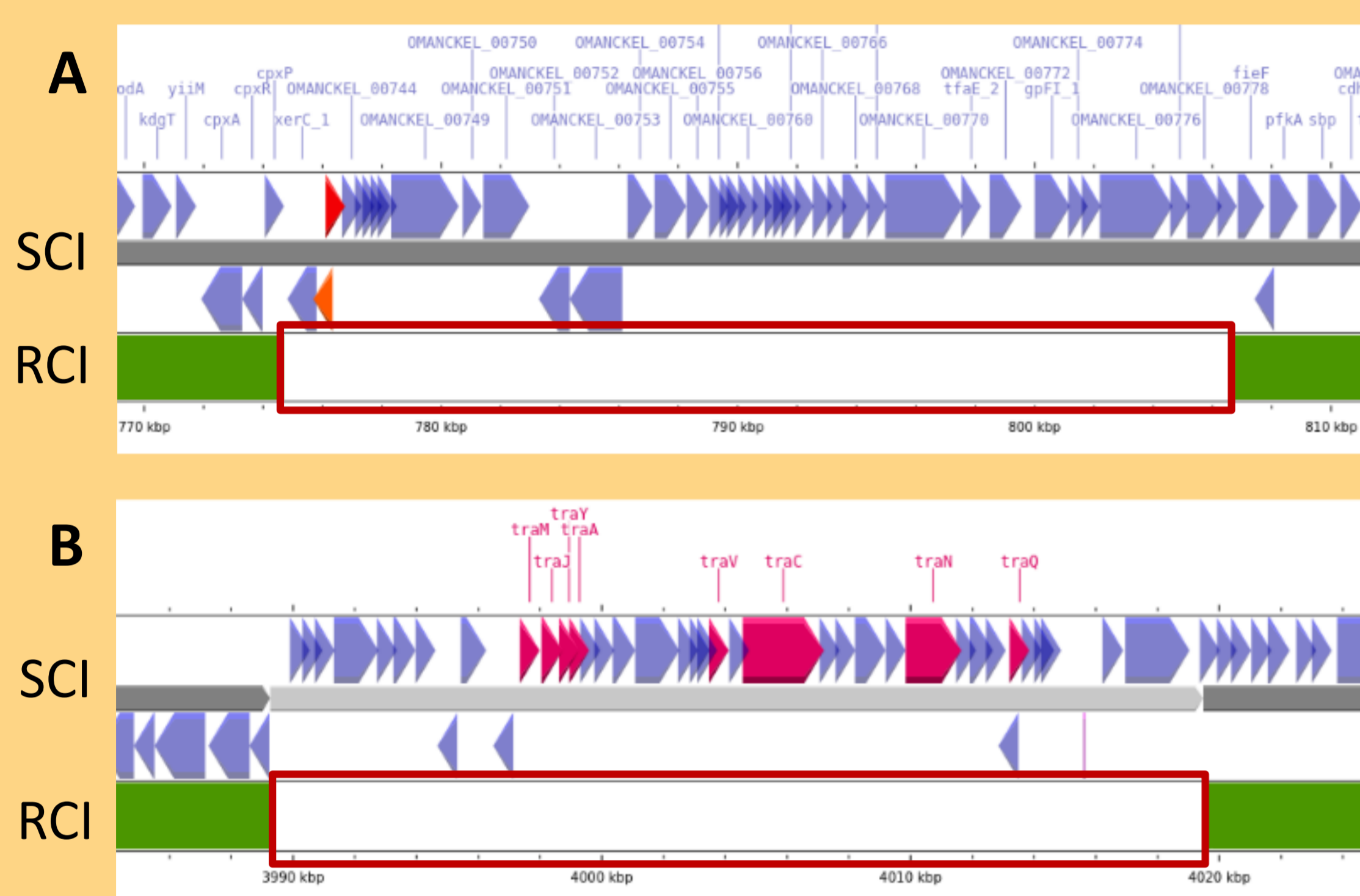
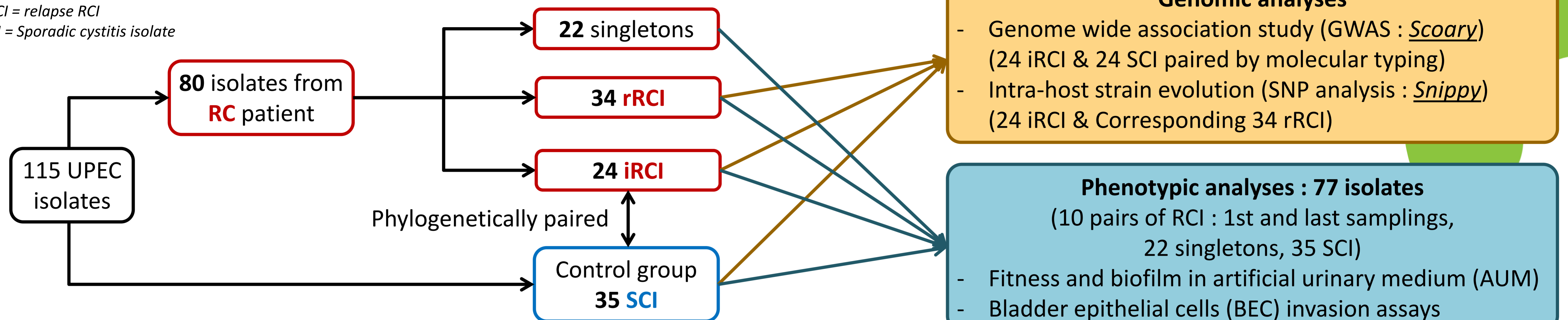


Figure 1 : Missing mobile genetic element (MGE) when iRCI are compared to genetically paired SCI. (A) Prophage loss (with gene S2 in orange and S3 in red); (B) Plasmid loss

Genomic comparative analysis (RCIs vs SCIs)

- **RCI** genomes were significantly smaller than that of **SCI**
 - ▶ 5,01Mb vs 5,11Mb ; $p < 0,05$
- Difference might be explained by MGE lower prevalence in **RCI** group than in **SCI** (Figure 1 A & B)
- GWAS : 3 phage associated genes significantly more prevalent in the **SCI** group ($p < 0.01$)
 - ▶ S1 : Putative bacteriophage tail protein GP41 (InterPro : IPR019289)
 - ▶ S2 : Unknown DNA binding protein
 - ▶ S3 : Regulatory phage protein Cox (InterPro : IPR019679)

→ **MGE loss = adaptation of UPEC to urinary tract ?**

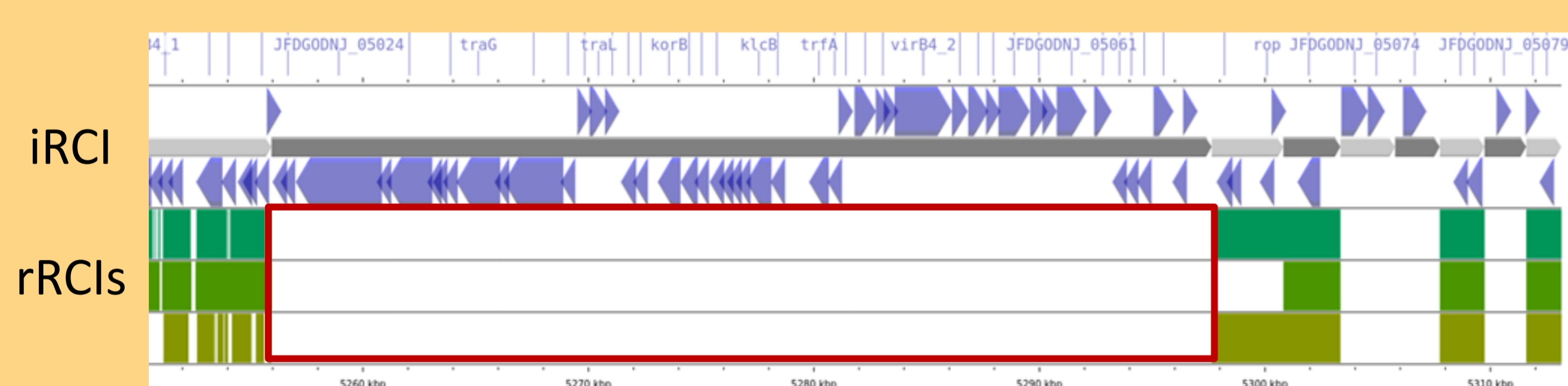


Figure 2 : Example of plasmid (pRHB15-C18) loss within the series of RCIs of one patient

Within-host evolution

- **Plasmid loss across relapse series** for 3 patients
- **SNPs accumulation over time** in **RCI**, mainly in genes coding :
 - ABC transporters
 - Proteins involved in various metabolic pathways

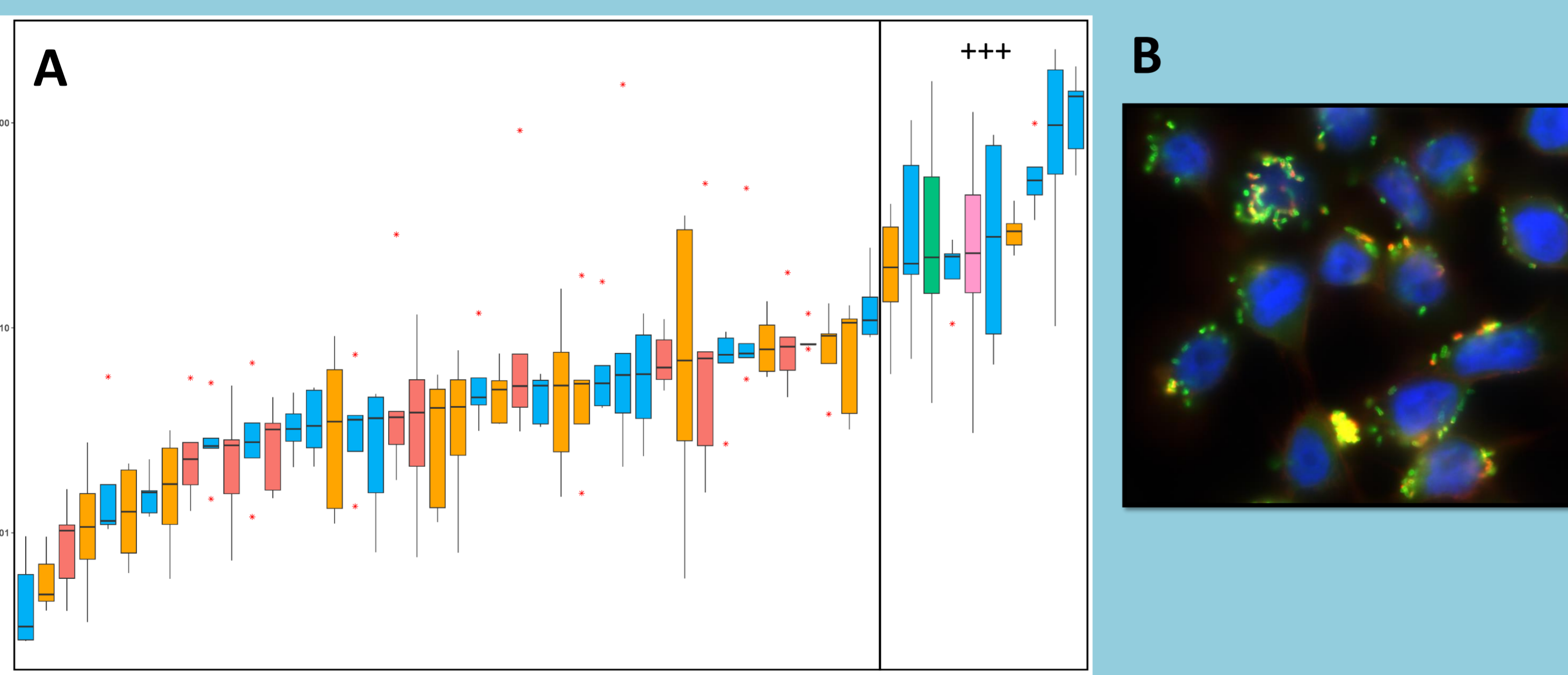


Figure 3 : Bladder epithelial cells (BEC) invasion results. (A) Invasion rates of RCI (in red), SCIs (in blue), *E. coli* K12 (green), UT189 (pink) and singletons (orange). (B) Evidence for presence of intracellular UPEC (green fluorescence) in BEC during our invasions experiments. Extracellular UPEC were also observed (red and yellow fluorescence). Nuclear DNA of BEC is colored in blue.

Phenotypic analyses

- No significant differences between **RCIs** and **SCIs** :
 - In fitness & biofilm formation in AUM
 - In BEC invasion capacity
 - Great intra-group diversity observed for fitness, biofilm formation and BEC invasion
 - Very few isolates able to strongly invade BEC ; none of these were **RCIs**
 - Phenotype of **iRCIs** not modified by genetic adaptation observed over time
- **RCIs do not seem to exhibit specific phenotypic traits**

Conclusion

Recurrent UPEC strains do not seem to exhibit specific genomic nor phenotypic traits. Nonetheless **RCIs** seem to adapt to the host through SNPs accumulation and MGE loss. The mechanisms driving recurrence are probably complex and may involve multiple combinations of several parameters including gene expression as well as bacterial and host factors.

