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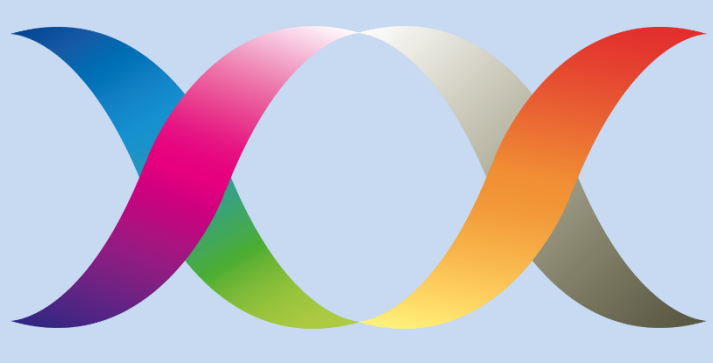
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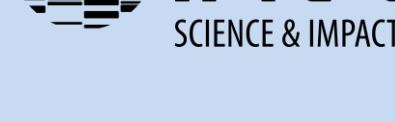
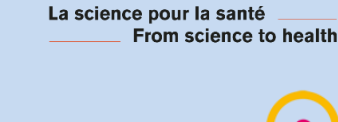
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Genome-based insights into the resistome and associated-mobilome of extended-spectrum cephalosporins resistant *Morganellaceae* spp.

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Introduction

The *Morganellaceae* family contains bacteria present in water, soil or in the intestinal tract of humans and animals. *Proteus mirabilis* and *Morganella morganii* are opportunistic pathogens responsible for various infections ranging from minor to life-threatening issues (urinary tract infections to septicemia). The apparent emergence of multidrug-resistant (MDR) *Morganellaceae* strains harbouring mobile genetic elements with extended-spectrum-β-lactamase (ESBL), AmpC cephalosporinase and/or metallo-β-lactamase (MBL) resistance genes is a serious threat to public health. Since the last decade, several MDR Integrative Conjugative or Mobilizable Elements (ICE or IME) belonging to the SXT or SGI1 families have been described to spread extended-spectrum cephalosporins (ESC) resistance in clinical *Morganellaceae* strains of diverse origins.

➤ Here, we characterized the resistome and mobilome of ESC-resistant *Morganellaceae* strains from various sources through phenotypic and genomic approaches.

Material and methods

✗ **83 *Morganellaceae* strains** based on the criteria of **ESC resistance** were isolated from humans and animals in France, Bulgaria and Taiwan between 1996 and 2017.
 ✗ After **PCR screening of major ESBL/AmpC resistance genes** and MDR mobile genetic elements, **66 *Morganellaceae* strains were whole-genome sequenced on IonProton™ platform** at the Limoges Genomic Research Facility.
 ✗ WGS analysis was performed to determine the phylogenetic diversity using bowtie2/PhyML/iTOL tree (microbial core genome alignment & SNP detection). The ResFinder and PlasmidFinder tools available at the Center for Genomic Epidemiology were used for identification of acquired resistance genes and plasmid replicon typing, respectively.

Results

✓ Phenotypic antimicrobial resistance

- ✗ Nearly all ESBL/AmpC/MBL-producing *Morganellaceae* strains showed multidrug resistance phenotype (47/52 strains resistant to > 3 antibiotic classes).
- ✗ 3 human clinical *P. mirabilis* strains isolated in Bulgaria were extensively-drug resistant showing only susceptibility to aztreonam.

Table 1. ESBL/AmpC/MBL resistance genes in *Morganellaceae* spp.

	ESBL	AmpC	MBL
<i>P. mirabilis</i>	CTX-M (21)	CMY (13)	VIM (3)
	VEB (9)		
	TEM (3)		
	SHV (3)		
<i>M. morganii</i>	CTX-M (6)	/	/
<i>P. rettgeri</i>	CTX-M (2)	/	/
<i>P. penneri</i>	/	CMY (1)	/

✓ ESBL/AmpC/MBL resistance genes (Table 1)

- ✗ The CTX-M ESBLs were predominant with a large diversity of variants: $bla_{CTX-M-15}$, $bla_{CTX-M-3}$, $bla_{CTX-M-14}$, $bla_{CTX-M-2}$, $bla_{CTX-M-24}$, $bla_{CTX-M-1}$, $bla_{CTX-M-11}$
- ✗ Six *P. mirabilis* strains harboured simultaneously up to 3 ESBL/AmpC/MBL resistance genes.

✓ Phylogeny, MDR mobile genetic elements and horizontal gene transfer

- ✗ The phylogenetic analysis revealed a great diversity among *P. mirabilis* strains except few clusters (**Fig. 1**)
- ✗ Surprisingly, Only 20 out of 66 *Morganellaceae* strains harboured conjugative elements carrying ESBL/AmpC/MBL resistance genes, mainly conjugative IncA/C plasmids or SXT-related elements.
- ✗ Moreover, 31 *Morganellaceae* strains contained a MDR SXT or SGI1 integrative elements; few strains carrying elements of both families.

Fig. 1. Maximum-likelihood tree of *P. mirabilis* strains.

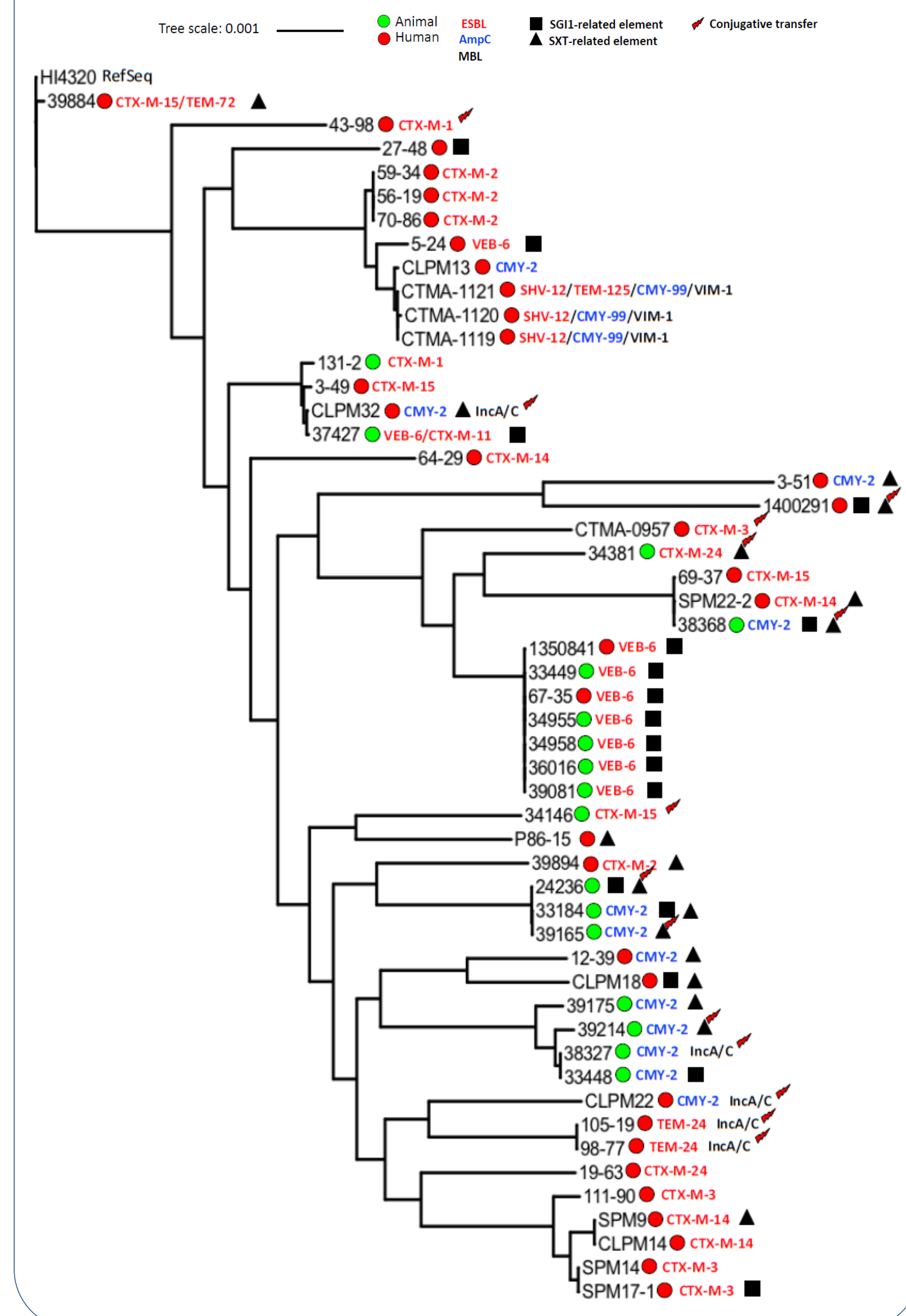
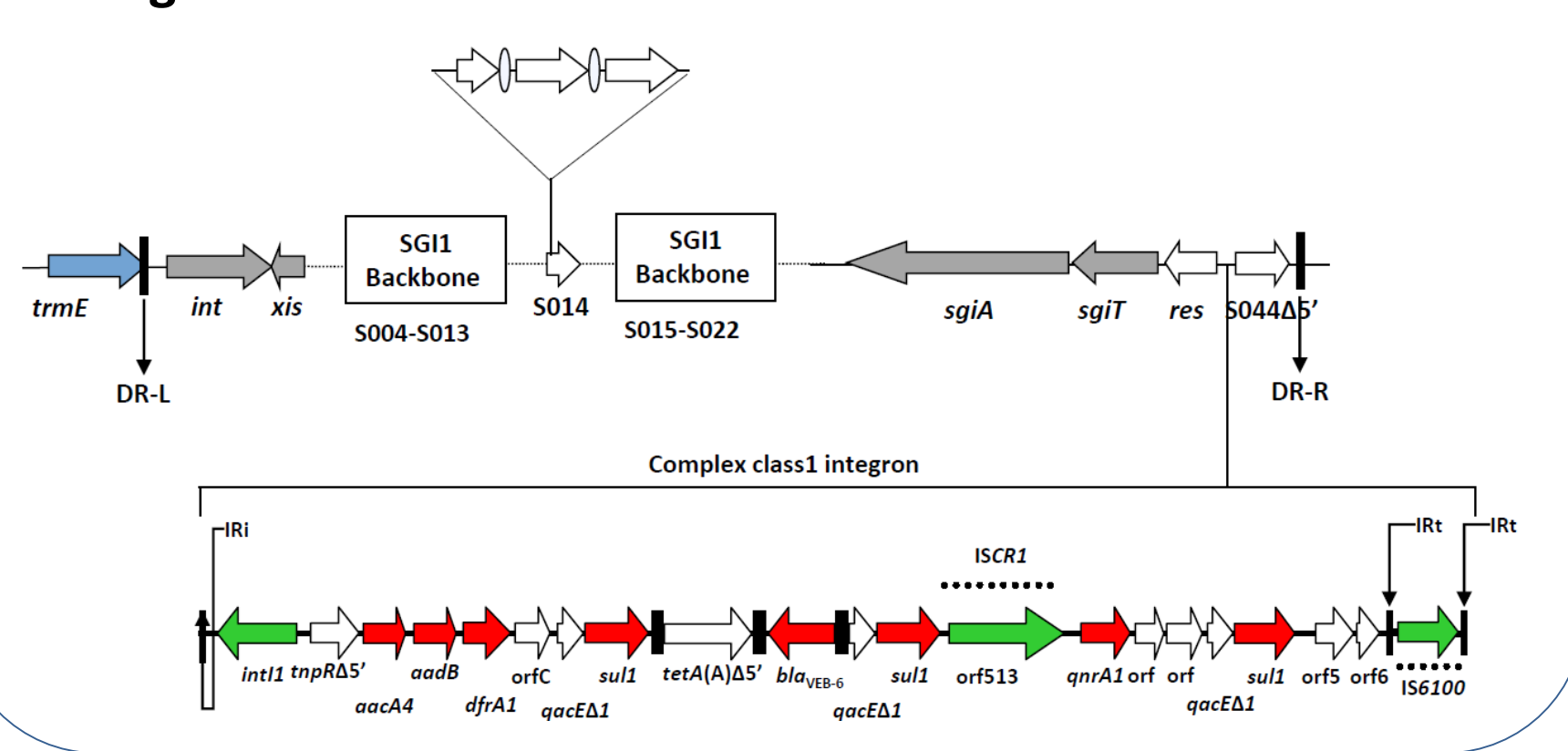
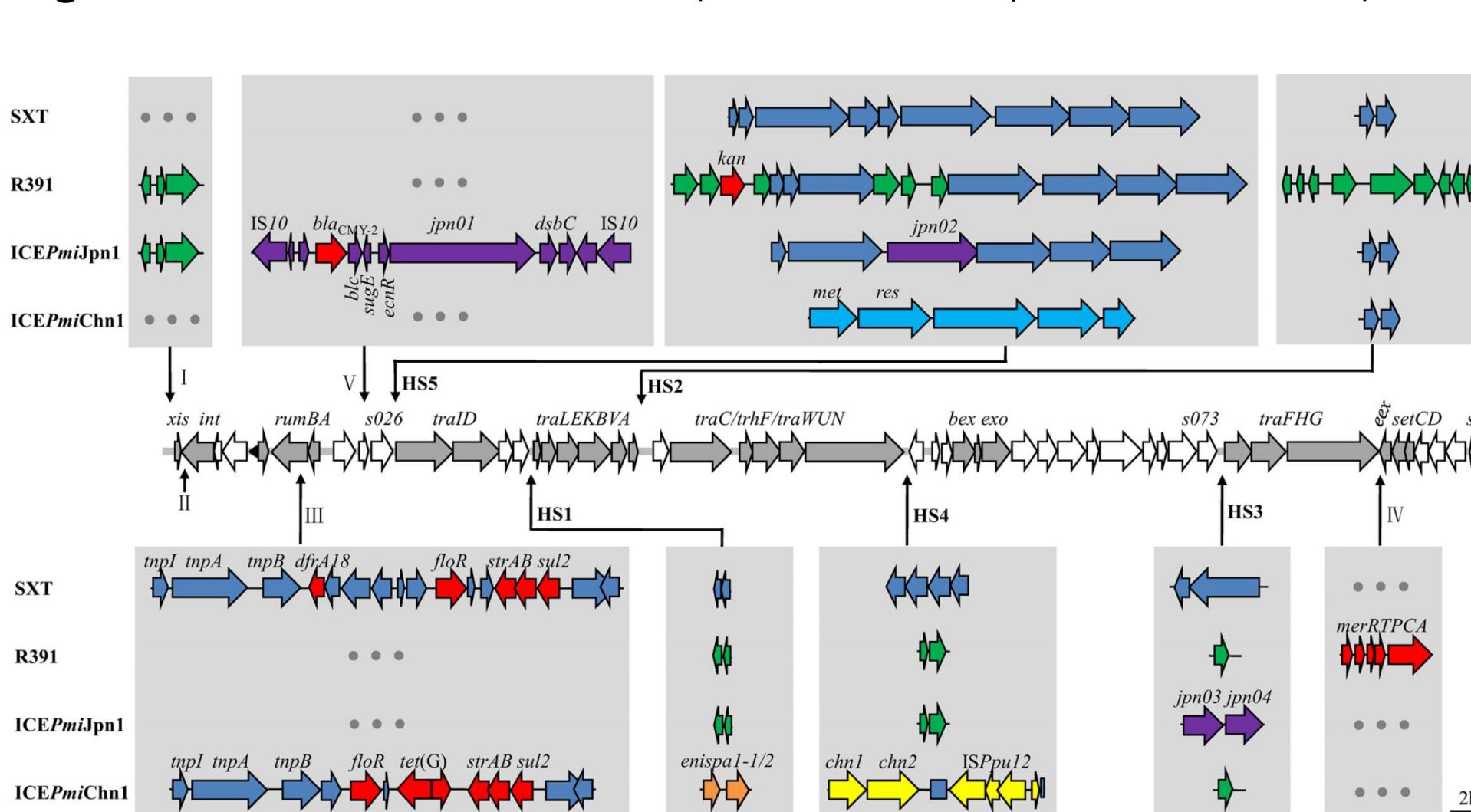


Fig. 2. Schematic view of SGI1-V.



- ✗ All ESBL resistance genes bla_{VEB-6} were carried by the MDR integrative mobilizable element SGI1-V in epidemiologically-unrelated but clustered *P. mirabilis* strains of animal and human origins (**Fig. 1 & 2**).

Fig. 3. Schematic view of SXT ICEs (SXT, R391, ICEPmiIpn1, and ICEPmiChn1).



- ✗ The cephalosporinase AmpC gene bla_{CMY-2} was carried by conjugative IncA/C plasmids or ICEs related to ICEPmiIpn1 (**Fig. 1 & 3**).

Conclusions

- ✓ In contrast to *Enterobacteriaceae* spp., ESBL/AmpC/MBL resistance genes were not mainly located on conjugative plasmids in *Morganellaceae* spp.
- ✓ **Conjugative IncA/C plasmids** and the IncA/C-related ICEs belonging to the **SXT and SGI1** families play an important role in the spread of ESBL and AmpC resistance genes in the *Morganellaceae* family.
- ✓ Further WGS analyses are ongoing to confirm the localization of ESBL/AmpC/MBL resistance genes and to fully characterize the different MDR mobile genetic elements implicated in the spread of ESC resistance.

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