F-Prime and R-Prime Factors

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INTRODUCTION

Our review of F-prime factors in 1987 (64) was the first comprehensive treatment of this area since 1972 (85). While the use of prime factors grew considerably during the 1970s and early 1980s, the development of cloning procedures for individual genes has to a large extent superseded the role that prime factors played. Nevertheless, an understanding of the biology of prime factors is an essential component of identifying the role that *Escherichia coli* has played in the characterization of genetic exchange mechanisms in prokaryotes and in providing a basis for modern molecular genetics. In addition, prime factors continue, in many instances, to be the most convenient replicons for low-copy-number dominance and complementation studies.

EARLY HISTORY AND DEFINITION OF PRIMES

Discovery of F-Prime Factors

Geneticists of the 1950s barely questioned the dogma that genetic recombination could not take place between segments of DNA from two nonhomologous chromosomes. Hence, results obtained in the late 1950s and early 1960s which indicated that the F plasmid of *E. coli* could undergo various interactions with the bacterial chromosome were difficult to interpret (1, 56, 69, 70, 111).

Genetic evidence soon showed that a fragment of the *E. coli* chromosome could become incorporated into the continuity of the F plasmid genome and be replicated as part of that genome and that this hybrid could exist autonomously in the bacterial cell and express bacterial genes carried on the chromosome fragment. Such hybrid plasmids were given the name F-prime (F′), and this nomenclature has been retained in the use of the term R-prime to include those hybrids derived from plasmids carrying antibiotic resistance determinants (R plasmids) which carry fragments of bacterial chromosome. We also use here the term prime to designate F-, ColV-, and R-prime factors. Of special significance concerning these hybrid plasmids is that the events that produced them were among the earliest demonstrated occurrences of genetic recombination between different sources of genetic material. The discoveries of the integration of F into the bacterial chromosome (chapter 127), the production of λ*gal* transducing phage particles (chapter 131), and the formation of F-prime factors were important in demonstrating to geneticists that recombination of DNA followed much broader rules than those established by research on classical eukaryotic organisms.

The first F-prime factors detected were the result of unexpected behavior of the F plasmid. It was found by Richter (111) that a particular Hfr strain which had lost the F factor was converted to the same type of Hfr donor when reinfected with F. Subsequently, Jacob and Adelberg (69) isolated a derivative of the F plasmid which carried bacterial chromosomal genes for the metabolism of lactose. When this F plasmid was transferred to a *lac*$^-$ strain of *E. coli*, in addition to conferring chromosome donor ability, it also conferred the ability to ferment lactose. Selection for such hybrid plasmids was achieved by using a *lac*$^-$ recipient and an Hfr donor which transferred *lac* as a very late gene and by looking for abnormally early recovery of *lac*$^+$.

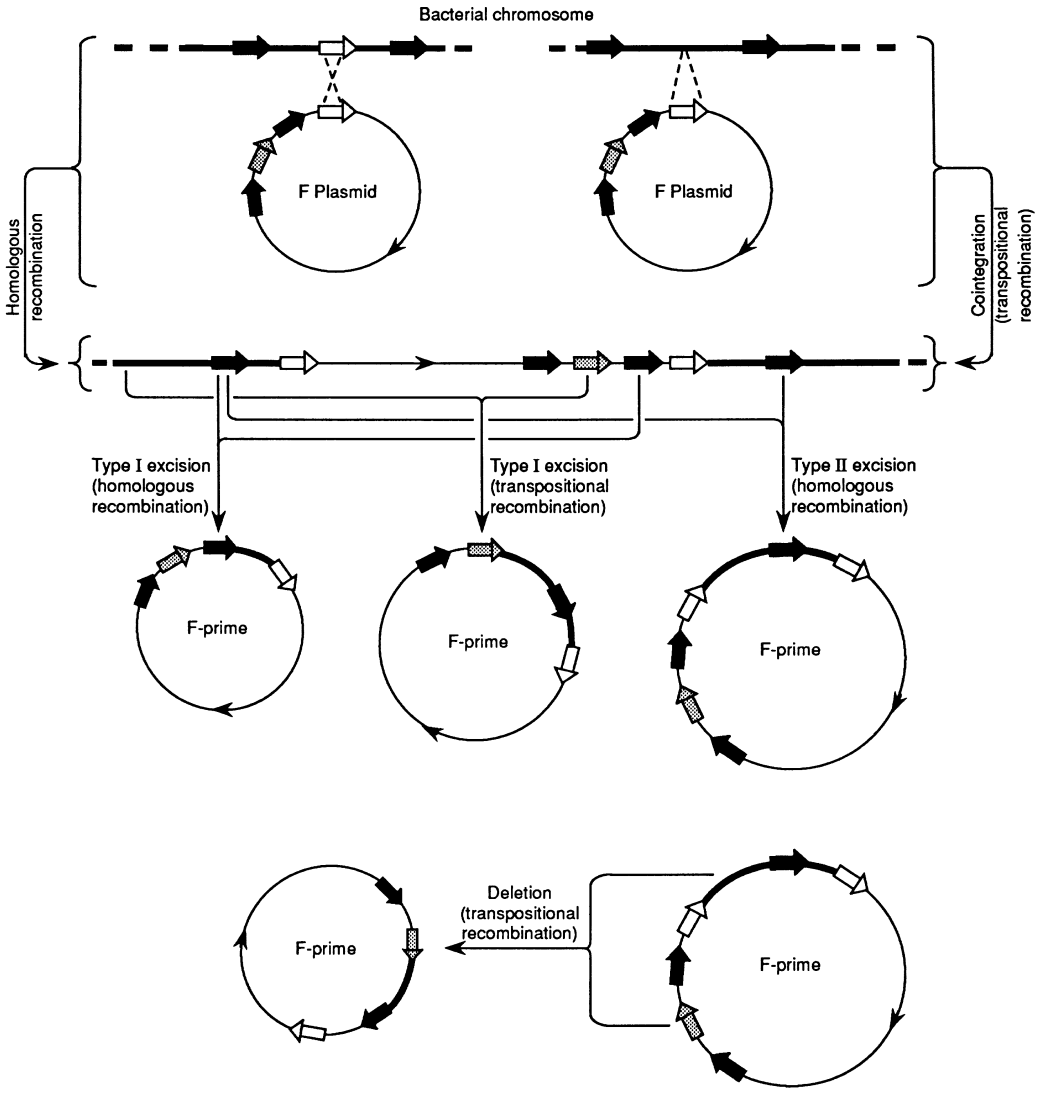

FIGURE 1 Representations of typical F integration and F-prime excision and deletion events as mentioned in the text. The top horizontal line represents the E. Coli chromosome on which are situated several IS elements such as IS2 (open arrows) and IS3 (filled arrows). Tn1000 ($\gamma\delta$) is represented by the hatched arrows. The middle horizontal line represents a typical Hfr chromosome, from which F-primes can be formed. (Adapted from Fig. 8 of reference 30.)

Primary and Secondary Prime Strains

Different types of prime strains can be distinguished. Primary F′ (or R′) strains result from deletion from the chromosome of the genes carried by the prime, so that the genes carried by the prime exist in the haploid state. Secondary F-prime strains are formed when a prime is transferred to a strain which has a complete haploid chromosome. Thus, secondary F-prime strains are diploid for the chromosomal region that is carried by the prime.

Type I and Type II Primes

In addition to F-prime and R-prime plasmids, two other types of prime plasmids can be distinguished. Type I primes carry genes from either the proximal or the distal chromosomal region of the Hfr insertion site, but not from both. Those primes carrying early Hfr genes are called type IA; those primes carrying only late Hfr genes are called type IB. Type II primes carry both proximal and distal regions of the parental Hfr chromosome (11). The topology of formation of these various types is shown for the case of F in Fig. 1.

It can be seen that type I primes arise from a crossover between a chromosomal site and an adjacent site in the integrated sex factor, whereas type II primes result from a crossover between chromosome sites on either side of the integrated sex factor. Such a mechanism would predict deletion of part of the sex factor. For the type I prime plasmids, this mechanism has been demonstrated by Sharp et al. (121) (see below). If the crossover event which produces the prime factor is reciprocal, the continuity of the bacterial chromosome is restored and a primary prime strain is formed. As has been pointed out (85), some primes initially identified as type I by genetic criteria may be type II when further identified. In addition to simple prime types, multiple recombination events, including deletions and fusions, can give rise to a variety of more complicated F-prime and R-prime structures (13, 65, 77, 85, 89, 104, 105, 108, 109, 132) (see below).

ISOLATION OF NEW PRIMES

The isolation of primes is generally achieved by one of the following procedures.

Early Selection of Late-Situated Markers in Hfr × F⁻ Crosses

Isolation of primes by early selection of late-situated markers in Hfr × F⁻ crosses is limited to those regions of the chromosome fairly close to the known Hfr sites, since the selection procedure involves interruption of conjugation after only part of the chromosome has been transferred (69, 70). However, the great variety of Hfr points of origin available (85; chapters 127 and 128) or constructible (6, 16, 17, 49, 78, 81, 131) greatly facilitates the selection of prime factors from virtually any region of the *E. coli* chromosome.

Selection of Early Markers in Hfr × F⁻ Crosses

Fiil (37) showed that it is possible to isolate type IA F-prime factors from crosses of Hfr strains with *rec*A$^+$ recipients, provided that multiple donor and recipient marker selection was such that only a small number of haploid recombinants were formed due to the multiple crossovers necessary.

Hfr × F⁻ *recA*⁻ Crosses

In Hfr × F⁻ *recA*⁻ crosses, normal haploid recombinants cannot be formed, thus allowing the detection of transferred preformed prime factors (43, 44, 84). This method of isolation can result in all types (IA, IB, and II) of primes. Not all regions of the chromosomes are equally amenable to the isolation of primes. Different Hfr derivatives (chapter 127) differ widely in their propensity to generate primes and in the spectrum of F-prime types that they generate (13, 85, 86, 107). Perhaps some regions of the bacterial chromosome are either lethal or inhibitory in the diploid configuration, minimizing or preventing prime formation for these regions (75, 84). In addition, the recombination events required for prime formation are much more likely in certain regions of the chromosome than in others, reflecting the distribution of specific chromosomal sequences (see below).

Use of Double Male Strains

By crossing two different Hfr strains, Clark isolated a strain which inherited F from each parent to form a double male strain (18, 36; see chapter 127). It was found that when this strain is mated with an F^- recipient, F-prime factor formation can be as high as one in every 300 donor parent cells (19). The segment of the chromosome carried appears to correspond to the segment located between the two points of origin (F insertion sites) in the double male strain, and in this case it carried over 30% of the chromosome in a diploid configuration. This method of isolating prime factors has also been used by other investigators (74, 138; A. R. Kaney, Ph.D. thesis, University of Illinois, Urbana, 1966; C. W. Vermeulen, Ph.D. thesis, University of Illinois, Urbana, 1966).

Generalized Transduction

Pittard and Adelberg reported in 1963 the surprising finding that when the generalized transducing phage P1 was grown on an F-prime strain, the resulting lysate was able to transduce either the entire F-prime factor (F14) or smaller deletion derivatives of it (reviewed in reference 53). The mechanisms of these processes are still unclear. Nevertheless, transduction has been used to advantage in isolating primes of various sizes for genetic analysis (53, 90, 101). It has also been found that P1 transduction of an integrated R factor can give rise to R-prime factor selection in the recipient cells (99). The potential for isolation of primes by this approach has been largely unexplored.

STRUCTURES OF PRIMES AND MODES OF FORMATION

The molecular structure of F is described in detail in chapter 126. Specific sequences of DNA carried by F are critical for prime formation of this plasmid. These are the IS*3* (formerly αβ) sequence, which occurs in two copies at coordinates 100/0 to 1.3 and 15.0 to 16.3, respectively, and the IS*2* (εζ) sequence, which has one copy in F at 17.6 to 18.9 and five copies in the *E. coli* K-12 chromosome (24; chapter 111). The insertion of F into the *E. coli* K-12 chromosome is often a result of genetic interaction between identical sequences on F and the bacterial chromosome, including IS*2*, IS*3*, and γδ (=Tn*1000*, located at coordinates 4.2 to 9.9 on F) (27, 29, 45) (Fig. 1). In a number of primes, for example, F13, which is formed by a type II excision event, all of the F plasmid DNA is present, with IS*2* flanking the genes of the plasmid and the bacterial chromosome (67). In other primes, for example, F42 and F152–1, both type I prime factors, at one junction of the plasmid and chromosomal DNA there is an IS*3* sequence, and the other junction occurred at the endpoint of the γδ sequence within F (24, 26). The transfer of *E. coli* F-prime factors to *Salmonella typhimurium* (official designation, *Salmonella enterica* serovar Typhimurium) has facilitated the characterization of a number of chromosomal insertion sequence (IS) elements (118).

F-prime plasmids of both type I and type II have been analyzed by electron microscope heteroduplex procedures (24, 29, 30, 47, 67, 68, 101–104, 121) to identify the locations of IS*2*, IS*3*, and γδ sequences; these locations act as recombinational hot spots which are active in type I F-prime factor formation. Hadley and Deonier (48) studied a type of F-prime which has been isolated repeatedly by various workers (4, 11) and which carries a segment of the *E. coli* chromosome which includes the genes *lac*, *proC*, and *purE*. They used various Hfr strains in which F is integrated at the chromosomal element IS*3* (αβ). The type II excision process was found to be more frequent than the type I process for this region of the chromosome. The endpoints for all of the primes studied tended to cluster at a few sites. This analysis has been extended by Umeda and Ohtsubo (130), who have correlated the positions of chromosomal IS elements with the positions of F insertion (to form Hfrs) and excision (to form F-primes).

The significance of the repeated formation of primes carrying the same region of the *E. coli* chromosome has been pointed out by Hadley and Deonier (47) in that selected regions of the chromosome

are “cloned” in vivo and mobilized by IS-mediated recombination as a block of genes to new sites, with obvious implications for bacterial evolution (113; see chapter 116). Guyer et al. (44) and Hadley and Deonier (48) examined a novel class of F-prime factors isolated from matings between an Hfr donor and a *recA* recipient with selection for proximal Hfr markers. Such F-primes sometimes lack the *tra* operon of F and are conjugationally defective. By using restriction endonuclease and hybridization analyses, Hadley and Deonier (48) showed that most of the plasmids that they studied were formed by site-specific processes involving specific bacterial and F loci, in particular the origin of transfer (*oriT*) region of F (66). Two such bacterial loci were located, one each at 3.3 and 11.7 min on the *E. coli* map, and a third locus is near the IS*2* element, between *lac* and *proC* at about 8.3 min. The significance of IS*5* in the formation of type II plasmids for the *lac-proC-purE* region has been demonstrated by Timmons et al. (128); excision of prime plasmids for this region was shown to result from recombination between pairs of IS*5* elements. In addition to IS × IS recombination, crossovers between rRNA genes have been shown to give rise to the formation of type II primes (9).

SIZE, REPLICATION, AND STABILITY OF PRIMES

The amount of chromosome carried by F-prime factors may vary from less than 1 min of chromosome (i.e., 1%) to more than 30% of the *E. coli* genome (85). There tends to be some selective advantage for shorter primes since larger plasmids generally retard bacterial cell doubling times (123).

The number of copies of an F-prime factor per *E. coli* cell has been estimated to be one to two (40, 97, 125), and in at least one case, the replication of an F-prime (F′-*lac*) was found to occur at a discrete time in the cell cycle (39). F-prime derivatives have been used in the genetic analysis of the replication of F (50) and of the *E. coli* chromosome (82).

Attempts have been made to construct strains carrying two independently replicating F-prime factors, both for the analysis of incompatibility functions (33) and for complementation. Reports that the use of a *dnaB* mutation allowed stable comaintenance of two F-primes (7, 8) have not been independently confirmed (71). One special case of a chromosomal mutation which allowed comaintenance of two F-primes was reported (114), and the normal Hfr–F-prime incompatibility can be bypassed in cases in which the F-prime factor carries the bacterial origin of replication (55, 91, 134).

Two kinds of instability are associated with primes. First, the sex factor can be excised from the prime in a process which is the reverse of the parental Hfr formation. This process can involve recombination between IS (or γδ) elements and can be independent of the host *recA* function (10, 28, 83).

The second type of instability is the creation of internal deletions of part of the DNA derived from the bacterial chromosome. Such internal deletions have been observed to arise spontaneously (5, 13, 31, 54, 85, 98, 103, 117) or after selection (2), and these deleted derivatives are often useful for mapping or complementation. In some cases, the involvement of IS (or γδ) or *oriT* sequences has been implicated in producing internal deletions (31, 45, 83). However, not all IS sequences appear to take part (129). If sufficient chromosomal DNA remains on both sides of such a deletion, the original size prime factor can be reconstructed by recombination, and this is useful for picking up mutant chromosomal alleles (42, 103).

F-PRIME FACTORS IN OTHER SPECIES

F-prime plasmids of *S. typhimurium* were first isolated by Sanderson and Hall (115) by using Hfr donors of *S. typhimurium* and methods similar to those developed with *E. coli* (116). Various interspecific matings have also been used to isolate and use prime factors (9, 12, 15, 17, 38, 41, 75, 95, 96, 135, 137).

For many years, it was believed that F plasmids had a host range restricted to members of the family *Enterobacteriaceae* (87). For example, Datta and Hedges (23) found that selected F-primes could not be transferred to a range of *Pseudomonas, Rhizobium,* or *Agrobacterium* strains. However, one recipient originally identified as *Rhizobium lupini* 6.2, but subsequently more correctly identified as *Pseudomonas*

fluorescens, was shown to be capable of accepting a range of F-prime plasmids which could complement many but not all auxotrophic markers (92, 93). Leary et al. (79) have shown the conjugal transfer of F-*lac* from *Erwinia chrysanthemi* to *Pseudomonas syringae* pv. glycinea, with integration of the F-*lac* into the chromosome of *P. syringae* pv. glycinea.

R-PRIME AND ColV-PRIME FACTORS AND DEVELOPMENTS IN SYSTEMS OF INTERACTION WITH A BROAD RANGE OF HOSTS

The First R-Prime Factors

Soon after the discovery of R factors (or R plasmids, plasmids with drug resistance determinants), it was discovered that they could mobilize bacterial chromosomes for conjugational transfer (20, 51, 52, 126). In the case of the plasmid R1, there was evidence of a fixed origin of transfer characteristic of the Hfr state of the F plasmid. Integration of the R plasmids could be achieved by the technique of integrative suppression (100). Nishimura et al. (99) were able to integrate the R plasmid R100 into the chromosome of *E. coli* K-12 by this technique. By P1 transduction of the region of integration, an R-prime plasmid which carried the plasmid genes and most of the *lac* operon of *E. coli* was isolated. Kahn and Clement (73) showed that an integrated ColV plasmid can also give rise to primes. The identification of IncP1 plasmids has attracted the interest of a number of workers for the construction of R-primes. IncP1 plasmids were initially identified in strains of organisms associated with infections in burns (88), and their wide host range was demonstrated by Olsen and Shipley (106). These plasmids have been used extensively to establish chromosome-mobilizing systems in a variety of gram-negative bacteria (60, 62, 110), including *E. coli*.

Use of Bacteriophage Mu

Denarie et al. (25) constructed an IncP1 plasmid carrying Mu, RP4::Mu, which can promote chromosome transfer effectively in *E. coli* (RP4 alone is very ineffective in this respect). By using *recA* strains as recipients, RP4::Mu primes were identified. This system was further developed by the construction of an RP4::mini-Mu derivative which overcame problems encountered in prime construction by Mu, including the need to use a recipient both lysogenic and resistant for Mu. The mini-Mu derivatives have deletions which remove all viral functions lethal to the host but still induce Mu-mediated chromosomal changes (35). By intergeneric matings between *E. coli* and each of *S. typhimurium*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, primes which carried chromosomal fragments of all three genera were isolated (133). In general, the use of Mu to produce transpositions has permitted a notable degree of flexibility in the construction of primes (14).

R68 Derivatives

Starting with the IncP1 plasmid R68, which is very similar to the more widely studied RP1, RP4, and RK2, Stanisich and Holloway (124) showed that this plasmid could mobilize chromosome in some strains of *Pseudomonas aeruginosa*. A successful search was made for a derivative of R68 which could mobilize chromosome in the genetically most studied strain of *P. aeruginosa*, PAO (46, 58, 61), resulting in the isolation and characterization of R68.45. This plasmid can mobilize chromosome in most gram-negative bacteria (62). It can also form prime factors in a variety of gram-negative bacteria (59, 62), including *E. coli* (63). R68.45 possesses two copies in tandem of a 2.1-kb insertion sequence which occurs in one copy in R68. This sequence has been termed IS*21* and can move from R68.45 (but not R68) to other plasmids at high frequency and low specificity in *recA*$^-$ backgrounds. The sequence was identified as a characteristic pattern of restriction endonuclease sites and has been found only in certain IncP1 plasmids, not in any bacterial DNA (32, 80, 112, 136). Additional interesting aspects of the behavior of IS*21* in the fusion of

plasmids and other replicons are reviewed by Reimmann and Haas (110).

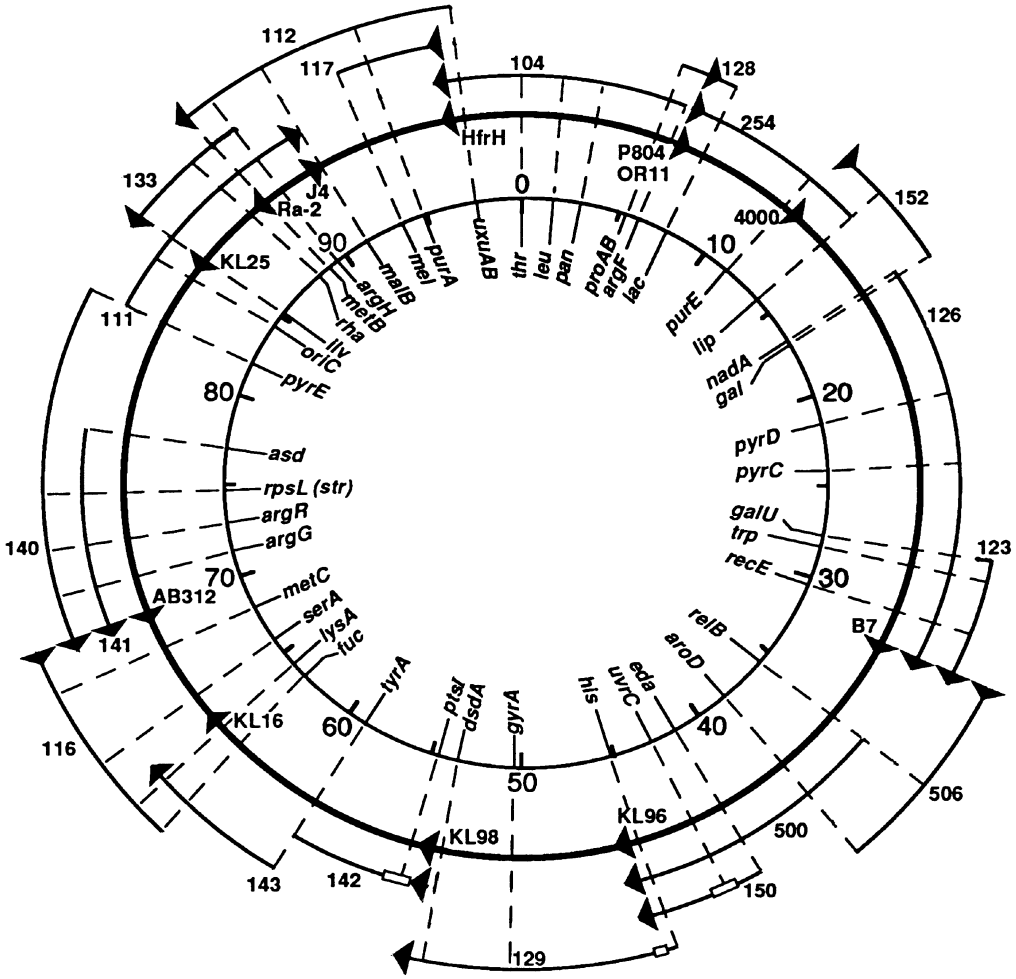

FIGURE 2 Genetic map locations of commonly used F-prime factors. These and certain other individual F-primes, or the entire set shown, are available from the E. *Coli* Genetic Stock Center, c/o Mary Berlyn, Dept. of Biology, Osborn Laboratory, Yale University, New Haven, CT 06510.

R68.45 is not unique; other plasmids (enhanced chromosome mobilization [ECM] plasmids) with similar properties and molecular structure (tandem IS*21*) have been isolated, and one has been isolated from nature (63). Prime plasmids derived from R68.45 and similar ECM plasmids possess two copies of IS*21*, one each at the junction of the plasmid and the bacterial chromosome (80, 94, 139). A promoter has been identified at the left-hand end of IS*21* which reads outward. Thus, in the tandem structure found in R68.45, readthrough proceeds from the right-hand copy into the left-hand copy, possibly explaining the high transpositional activity of the tandem configuration of IS*21* (119). An R-prime plasmid was used for the construction of a physical and genetic map of a 125-kb segment of the *P. aeruginosa* PAO chromosome (139). One of the advantages of prime plasmids generated from IncP1 ECM plasmids is that they retain the wide bacterial host range of the parent plasmid. By this in vivo cloning procedure, bacterial genes can be

readily transferred to other genera in which their expression can be studied or used for the construction of bacterial hybrids with novel characteristics. RP4-prime plasmids containing fragments of *E. coli* chromosome have been constructed in vitro and have been shown to promote polarized transfer of chromosome (3, 72).

PRIMES FOR GENERAL USE IN *E. COLI* AND *S. TYPHIMURIUM*

A Basic Set of F-Prime Factors from *E. coli* K-12

The F-prime factors depicted in Fig. 2 cover most of the *E. coli* chromosome and have been used by numerous investigators. Their isolation and that of many more F-primes can be traced in reference 85 (note that the former *E. coli* map coordinates were used in reference 85). Lists of F-prime factors isolated for particular regions of the *E. coli* chromosome with references were provided in our earlier review of prime plasmids (64).

The Importance of Primes for Complementation Studies

One of the most important practical roles for prime factors continues to be in tests for genetic mapping and complementation (21, 34, 42, 49, 57, 76, 123), particularly when the genes involved in a pathway are clustered in a region of the chromosome but are not contiguous. Examples include the genetic analysis of flagellar mutants in *E. coli* (76, 122) and ribosomal proteins (120, 127) and utilization of aromatic substrates in *P. aeruginosa* (139). Purified F-prime DNA is also a useful source for cloning particular genes (22).

SUMMARY

Prime plasmids have been an essential component in understanding the function of plasmids in promoting chromosomal transfer and in the recombination between plasmid and chromosomal replicons. The dearth of new references since the first version of this chapter (64) clearly demonstrates that while prime factors are of historical importance, the advances of bacterial genetics have provided newer and better ways for most aspects of genetic analysis which were once the domain of the primes.

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