Consistent with its function as a chloride channel regulated entirely from the cytoplasmic side of the plasma membrane, the cystic fibrosis transmembrane conductance regulator (CFTR) glycoprotein exposes little of its mass on the exterior surface of cells. The first and fourth extracytoplasmic loops (ELs) contain ~15 and 30 residues, respectively; the other four ELs are extremely short. To examine the influence of missense mutants in ELs detected in patients with cystic fibrosis, we have expressed them in mammalian (baby hamster kidney (BHK21)) cells and assessed their biosynthetic processing and chloride channel activity. In contrast to previous findings that 18 of 30 disease-associated missense mutations in cytoplasmic loops caused retention of the nascent polypeptides in the endoplasmic reticulum, all the EL mutants studied matured and were transported to the cell surface. This pronounced asymmetry is consistent with the notion that endoplasmic reticulum quality control of nascent CFTR is exerted primarily on the cytoplasmic side of the membrane. Although this set of EL mutations has little effect on CFTR maturation, most of them seriously compromise its chloride channel activity. Substitutions at six different positions in EL1 and single positions in EL2 and EL4 all destabilized the open state, some of them severely, indicating that the ELs contribute to the stability of the CFTR ion pore.

Of the 1480 amino acids in human cystic fibrosis transmembrane conductance regulator (CFTR), only ~59 are predicted to be exposed at the exterior surface of the cell membrane (1). These few residues are distributed among six extracytoplasmic loops that join successive pairs of membrane-spanning sequences (TMs). Most of these putative loops are extremely short; all except the first (EL1) and the fourth (EL4) are five residues or less in length (1). EL1 and EL4 are only 15 and 31 residues in length, respectively, with two N-linked oligosaccharide chains attached to the latter. This relative lack of exposure to the cell exterior is not unexpected because the CFTR ion channel is not regulated from this side of the membrane but from the cytoplasmic side where most of the mass of the protein resides. In addition to the large nucleotide binding domains and R-domain even the cytoplasmic loops joining the TMs with lengths of ~60 residues are much longer than the ELs. Hence little attention has been paid to these short external sequences in studies of the structure-function relationships of CFTR. However, one relatively common missense mutation in EL1, R117H, was shown earlier to reduce chloride conductance (2). Subsequently several other disease-associated single residue substitutions in the ELs have been reported (CF Genetic Analysis Consortium). To determine what influence they may have on the biosynthetic processing and function of the molecule that might lead to the disease phenotype, we have reconstructed these mutants in an expression plasmid and established them in stable cell lines. In contrast to 18 of 30 disease-associated missense mutations that were found to prevent maturation (3–5), none of the 13 EL mutations examined in this study had that effect. Instead, they had strong effects on the stability of the CFTR Cl− channel.

MATERIALS AND METHODS

Cell Culture and Stable Expression of CFTR—The BHK cells expressing wild-type CFTR have been described in our earlier publications (6, 7). The mutated CFTR sequences described below in the pNUT expression vector (8) and the Bluescript plasmid (Stratagene). CF-associated point mutations were reconstructed in the Bluescript cloning vector containing the CFTR cDNA using the Quick Exchange kit from Stratagene with the oligonucleotide primers listed in Table I. To allow efficient stable transfection, the mutated fragments were transferred to pNUT-CFTR, utilizing Xmal and DraIII for mutations in EL1 and EL2 or the two endogenous DraIII restriction sites of CFTR for mutations in EL4 and EL5. The correct sequence of the inserted fragments was confirmed by sequencing.

Metabolic Labeling with [35S]Methionine—After a 30-min starvation of methionine, cells were labeled metabolically with [35S]methionine for 30 min as described in Loo et al. (8). For the following chase, the [35S]methionine-containing medium was replaced by complete medium containing 1% fetal bovine serum and 1 mM methionine.

Surface Labeling of Cells—Cells were grown to confluency in 10-cm plates. Plates were placed on ice for 30 min and then washed twice with 10 ml of ice-cold PBS containing 0.1 mM CaCl2 and 1 mM MgCl2. All subsequent steps were performed at 4 °C. Surface proteins were labeled by incubation for 30 min in 1 ml of PBS, pH 8.0, containing 1 mg/ml sulfo-NHS-SM-biotin (Pierce). Plates were washed four times with PBS containing 1% bovine serum albumin and four times with PBS. Cells were solubilized in 1 ml of Nonidet P-40 lysis buffer as described below for immunoprecipitation. After centrifugation the supernatant was transferred to fresh centrifuge tubes containing 50 μl of prewashed streptavidin-agarose beads (Pierce) and incubated overnight with gen-
In the enlarged ELs are depicted as shaded circles. Each mutation is designated as the original amino acid residue and the first letter nated as the original amino acid residue. SDS-polycrylamide gel electrophoresis (6% acrylamide) and transfer to nitrocellulose, Western blots were probed with M3A7 (19).

**Cell Lysis and Immunoprecipitation**—Cells were lysed in Nonidet P-40 lysis buffer (50 mM Tris, pH 7.4, 150 mM NaCl, 20 mM Na3MoO4, and 0.09% Nonidet P-40 plus a mixture of protease inhibitors (EDTA (3.5 µg/ml), benzamidine (100 µg/ml), aprotinin (5 µg/ml), leupeptin (10 µg/ml), and Pefabloc (50 µg/ml)). After centrifugation at 4 °C at 15,000 × g for 15 min, the supernatant was incubated overnight with the monoclonal antibody M3A7 followed by a 4-h incubation with Protein G-agarose (Life Technologies, Inc.). After four washings with radiomimune precipitation buffer, attached complexes were dissolved in electrophoresis sample buffer.

**SDS-Polyacrylamide Gel Electrophoresis and Immunoblotting**—To electrophoresis sample buffer. After SDS-polyacrylamide gel electrophoresis (6% acrylamide), proteins were precipitated with biotin. After cell lysis, biotinylated cell surface proteins were covalently labeled with biotin. After cell lysis, biotinylated cell surface proteins were covalently labeled with biotin. After cell lysis, biotinylated cell surface proteins were covalently labeled with biotin.

**Mutation Primer**

![Oligonucleotide primers used to generate mutations](https://example.com/mutation_primers.png)

**Table I**

| Mutation | Primer |
|----------|--------|
| S108F    | GGAAGAATCATAGCCTTCTATGACCGGATACGACAT |
| Y109C    | AGAATCATACCCCTCTTCTGACCGGATACGACAT |
| D110H    | ATCAGATCCTTCTTCTTCTGACCGGATACGACAT |
| P111A    | TATGcAGATCCTTCTTCTTCTGACCGGATACGACAT |
| P111L    | TATGcAGATCCTTCTTCTTCTGACCGGATACGACAT |
| P111M    | TATGcAGATCCTTCTTCTTCTGACCGGATACGACAT |
| P111R    | TATGcAGATCCTTCTTCTTCTGACCGGATACGACAT |
| R117H    | GATAcAAGGAGGAGACCTTCTATCGCGATTATA |
| R117L    | GATAcAAGGAGGAGACCTTCTATCGCGATTATA |
| E116K    | CCGGcATAACCGGAGACCTTCTATCGCGATTATA |
| R117C    | GATAcAAGGAGGAGACCTTCTATCGCGATTATA |
| T908N    | TATGcAGATCCTTCTTCTTCTGACCGGATACGACAT |
| P1013L   | GTCGcAGATCCTTCTTCTTCTGACCGGATACGACAT |

**Expression of Disease-associated EL Variants**—Fig. 1A sketches the positions of the EL substitutions. Although most are in EL1, three other loops are represented also. One muta-

**RESULTS**

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**Expression of Disease-ass
FIG. 2. Biosynthesis and stability of EL variants as assessed in pulse-chase experiments. Cells were labeled metabolically with 100 μCi of [35S]methionine for 20 min. After this pulse, the [35S]methionine-containing medium was replaced by complete medium supplemented with 1 mM methionine and chased for the times indicated above each film image. 35S radioactivity in the same dried gels was quantified by electronic autoradiography using a Packard Instrument Co. Instant Imager and plotted relative to the amount in the immature band after the pulse.
cloned with loading buffer containing 1 μCi of ³⁶Cl⁻ for 1 h at room temperature. The cells were washed three times with chloride-free efflux buffer. From time 0 the efflux buffer contained 10 μM forskolin, 1 mM isobutylmethylxanthine, and 100 μM dibutyryl cyclic AMP. The efflux of ³⁶Cl⁻ was determined with a Topcount scintillation counter (Packard Instrument Co.). Each point is the average of three independent samples. A, squares, wild type; circles, S108F; triangles, Y109C; diamonds, D110H; crosses, wild type without stimulation. B, squares, P111A; circles, P111L; triangles, R117H; circles, R117C; diamonds, R117P. D, squares, E217G; circles, T908N; triangles, P1013L.

Extracytoplasmic Loop Mutations Destabilize CFTR Ion Pore

Fig. 3. ³⁶Cl⁻ efflux form cells expressing wild-type and CF-associated mutated CFTR variants. Cells were incubated with loading buffer containing 1 μCi of ³⁶Cl⁻ for 1 h at room temperature. The cells were washed three times with chloride-free efflux buffer. From time 0 the efflux buffer contained 10 μM forskolin, 1 mM isobutylmethylxanthine, and 100 μM dibutyryl cyclic AMP. The efflux of ³⁶Cl⁻ was determined with a Topcount scintillation counter (Packard Instrument Co.). Each point is the average of three independent samples. A, squares, wild type; circles, S108F; triangles, Y109C; diamonds, D110H; crosses, wild type without stimulation. B, squares, P111A; circles, P111L; triangles, R117H; circles, R117C; diamonds, R117P. D, squares, E217G; circles, T908N; triangles, P1013L.

Single Channel Properties of EL—Fig. 4 contains representative recordings of single channels in planar lipid bilayers with which membrane vesicles isolated from cells expressing each of the variants and the wild type were fused. Amplitude histograms accompany each tracing. Most of the salient features of the wild-type CFTR channel are illustrated in the first tracing shown. At this temperature of 21 °C with 300 mM Cl⁻ on both sides of the bilayer, the principal mode of the wild-type channel exhibits two well defined conductance levels of 10.1 and 11.5 pS similar to those described by Gunderson and Kopito (11).

The behavior of the most N-terminal mutant in EL1, S108F, indicates that substitution of the small hydroxyl amino acid with the larger aromatic phenylalanine results in a channel with no stable open state. Channel openings are detected but these are extremely brief. No peak value for current through the open channel can be discerned in the all-points histogram. Simply put, this mutant channel attempts frequent opening, but the open state cannot be maintained suggesting that this residue or the region of EL1 it occupies is crucial to the stability of the open-state structure. If a parameter I equal to the mean current through a single channel at −75 mV is used to represent the total charge transported by the channel per unit of time, one can employ a ratio of that value for the mutant to that of the wild type to obtain a relative measure of the charge transport ability of the mutant compared with the wild type. The value of the parameter I is derived from the area under the channel openings divided by the time interval. As indicated in

³⁶Cl⁻, and its efflux followed after stimulation to increase cAMP levels. The rates of efflux at times after stimulation are plotted in Fig. 3. Although appearing to be generally reduced compared with the wild type, there were substantial rates of efflux from cells expressing all of these variants. Thus it was feasible to undertake studies of the single channel properties of each as described below. As far as the comparison of the rates of ³⁶Cl⁻ efflux goes, it has to be kept in mind that the amount of CFTR protein in each clonal cell line is somewhat variable. However, some significant changes are apparent. For example, E217G in EL2 reduces the efflux rate greatly. On the other hand, P1013L in EL5 exhibits rates as high as wild type.

To gain some initial information on how these mutations influence the chloride channel activity of CFTR, cells were loaded with tracer...
Table II, the $I_{S108F}/I_{WT}$ is $\sim 11\%$. The substitution of the aromatic tyrosine in the adjacent position by the small thiol residue (Y109C) also results in a very unstable open state, but the tracing is different from that of S108F. There is a burstlike behavior but within the burst there are rapid closings. This channel is capable of gating but there is large fluctuation in the open-state structure. The mean current carried at $-75$ mV is $\sim 15\%$ of the wild type (Table II). Replacing the aspartate residue in the next position by histidine (D110H) resulted in a much more normal looking channel with a major mean conductance of about 8.5 pS. Although a minor peak for the channel open state is detectable on the all-points histogram, the duration of the openings is much less than those of the wild type. Hence like the mutants at the previous two residues, instability of the open state is the most pronounced feature of this channel.

Two different mutations found in patients at the next position were analyzed at the single channel level. P111L appears very much like wild type with a mean conductance of 10.3 pS. The $P_o$ was 0.45 with a mean open time of 500 ms and closed time of 600 ms. There is no indication that this variant has any difficulty in maintaining its open-state structure at this temperature (21 °C). However, a marked difference in its behavior is revealed at higher temperature (35 °C; Fig. 5) at which its $P_o$ is reduced to about half that of the wild type. Substitution of the proline with the smaller aliphatic alanine residue (P111A) produced a channel with much more rapid kinetics and a reduced conductance of 9.2 pS even at 21 °C (Fig. 4).

The mutation five residues further in the C-terminal direction resulted in a charge reversal (E116K). This mutant displays properties quite similar to S108F; channel openings occur but cannot be maintained. No defined peak is apparent for openings in the all-points histogram.

The R117H mutant was reported previously to exhibit a small reduction in both current amplitude and open time (2). Our observations confirm a conductance decrease of 1.5 pS in both of the two conductances observed in the wild type. Otherwise the kinetic behavior at this temperature was not very different from wild type. In fact we found this substitution at Arg-117 to have far less effect than the other three disease-associated replacements at this position. Both R117C and R117L had very unstable open states like S108F and E116K with the cysteine substitution able to maintain openings.

![Fig. 4. Single channel kinetics of different CF-associated CFTR variants. Phosphorylated CFTR single channels were incorporated into lipid bilayers by fusion of the microsomes with a preformed planar bilayer. Representative current traces were obtained at 21 °C and amplitude histograms are shown for each. Time scales are indicated by the horizontal bars.](http://www.jbc.org/doi)
slightly longer than the leucine substitution. R117P also displayed only transient openings. Thus the more frequent R117H mutation seems to compromise open-channel structure less than the other three substitutions at this position. This may be because of the structural similarity of the arginine and histidine residues not shared by the other three substituting residues. Overall the set of EL1 mutations examined points to an involvement of this loop in the formation of a stable pore structure.

Strikingly, the single missense mutation (E217G) in the short EL2 also results in channels with only transient rather than stable openings, perhaps implying that this loop is involved also in stabilizing open pore structure.

The T908N mutation in EL4, the second of the two larger extracytoplasmic loops of CFTR, has a somewhat similar effect on the single channel behavior as those in EL1 that cause a very unstable open state. Cells expressing this variant in the large glycosylated loop at the beginning of the second half of the molecule display channels with a noisy open state and a mean conductance of 9.2 pS. This behavior is distinct from the EL1 and EL2 variants in that the openings are not as extremely transient. As seen in the T908N trace, there are in fact relatively long openings with several brief closings within to generate burstlike behavior. An intraburst mean open time of ~90 ms and a mean burst duration of ~200 ms can be derived. The brief closings appeared as intraburst closings with a time constant of ~15 ms and intraburst time constant of ~800 ms. The overall open probability is 0.14. The mean conductance is just a little less than the major wild-type conductance. This mutant was studied also at the higher temperature of 35 °C (Fig. 5) at which its difference from the wild type was more apparent in the current tracing.

The final disease-associated mutant analyzed, P1013L, in the fifth exterior loop exhibited robust wild-type-like behavior, and consistent with its 36Cl efflux ability, it has a $P_o$ of 0.5, higher than the wild type. However, because the gating of some of the other less severely impaired mutants became more obvious at a higher temperature, this variant was assessed also at 35 °C (Fig. 5). The conductance remained unaltered but the $P_o$ was reduced to approximately half of that of the wild type. Thus although replacement of this hydroxyl amino acid does not destabilize the channel to the extent of several of the other mutations, it does have some impact.

**DISCUSSION**

Although only a relatively small proportion of the large number of mutant versions of CFTR detected in CF patients have been expressed in heterologous systems, the analysis of those that have has been informative in several ways (for reviews see Refs. 10, 14, and 16). Of greatest impact was the finding that the ΔF508 mutation that is present on at least one allele in 90% of patients caused defective biosynthetic maturation (12). A considerable number of missense mutations has a similar consequence (13). Other single residue substitutions alter specific properties of the CFTR ion channel (14). For example a nucleotide binding domain mutation, G551D, precludes virtually all
activity and R-domain mutations have a variety of effects (15). Substitutions in membrane-spanning sequences may alter conduction, selectivity, occupancy, or gating of the pore (16). Missense mutations changing residues in the cytoplasmic loops separating the transmembrane helices have relatively minor effects on channel gating and regulation, but the majority of them prevent normal processing and maturation of the polypeptide, as does ΔF508 (13). Of missense mutations identified in codons for residues in extracytoplasmic loops, only R117H, which occurs relatively frequently in patients, has been studied in any detail (2). It was found to mature when heterologously expressed but the whole-cell current it generated was much reduced compared with wild type. Single channel conductance was diminished only a small amount but open probability was reduced because of altered gating. Our observations are generally in agreement with those, although the replacement of the large positively charged arginine residue by histidine had much less effect on gating than the other substitutions at this position. Each of those three drastically altered gating. This effect was most extreme with the hydrophobic leucine residue at this location precisely at the junction of EL1 and TM2. In this case, only extremely brief openings were detected. These were only slightly longer when either a cysteine or a proline was in this position.

The charge-reversal mutation, E116K, at the immediately preceding position had a remarkably similar effect to that of the most perturbing substitutions of Arg-117. Hence these two contiguous oppositely charged amino acids seem essential for maintenance of the open state. Although prolines often are considered crucial structure-determining residues, replacement of Pro-111 had less impact than some of the other changes. The P111L variant in contrast to all the other EL1 mutants differed from wild type only at elevated temperatures. The substitutions at residues 110, 109, and 108 were similar to Glu-116 and Glu-117 changes in causing a very unstable open state. The E217G mutant in EL2 had a similar effect. Hence the overwhelming consequence of disease-associated mutations in EL1 and EL2 is destabilization of the CFTR channel open state.

The T908N mutation in EL4, which is novel in that it results in the introduction of an additional consensus site for N-glycosylation that is used (17), also alters channel gating. Thus although the P1013L change in EL5 did not seem to compromise channel activity except at higher temperatures, all of the others analyzed seriously detracted from the ability of CFTR to sustain a stable open pore. This suggests that these short loops that link the extracellular ends of the TMs that are believed to form the pore may be crucially involved in maintaining their precise orientation or relationship to each other. The restraint on the TMs by these short loops, in contrast to the freedom that the much longer cytoplasmic loops may allow, conjures up an image somewhat different from that provided by the low resolution three-dimensional structural image of P-glycoprotein (18). In that case, the funnel-like formation suggested was narrow on the cytoplasmic side and wide on the exterior face of the membrane. However, because there are as yet not even low resolution images of CFTR, extrapolation of the effects of mutagenesis on function to structural interpretations may be misleading.

Nevertheless, analysis of this set of disease-associated mutations in the extracytoplasmic loops has provided interesting results, some of which might not have been expected. The ELs are the only parts of the protein in which none of the mutations studied had strong effects on biosynthetic processing, suggesting that recognition of mutant CFTR by endoplasmic reticulum quality control occurs primarily on the cytoplasmic rather than the luminal face of the endoplasmic reticulum membrane. Second, none of the mutations prevent channel opening, but most of them preclude formation of a stable open-state structure implying that the ELs may play an essential role in this function.

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REFERENCES
1. Riordan, J. R., Rommens, J. M., Kerem, B., Alon, N., Rozmahel, R., Grzelczak, Z., Zielenski, J., Lok, S., Plavsic, N., Chou, J. L., et al. (1989) Science 245, 1066–1073
2. Sheppard, D. N., Rich, D. P., Ostedgaard, L. S., Gregory, R. J., Smith, A. E., and Welsh, M. J. (1993) Nature 362, 160–164
3. Seibert, F. S., Jia, Y., Mathews, C. J., Hanrahan, J. W., Riordan, J. R., Loo, T. W., and Clarke, D. M. (1997) Biochemistry 36, 11966–11974
4. Seibert, F. S., Linsell, P., Loo, T. W., Hanrahan, J. W., Clarke, D. M., and Riordan, J. R. (1996) J. Biol. Chem. 271, 15139–15143
5. Seibert, F. S., Linsell, P., Loo, T. W., Hanrahan, J. W., Riordan, J. R., and Clarke, D. M. (1996) J. Biol. Chem. 271, 27493–27499
6. Chang, X.-B., Tabcharani, J. A., Hou, Y.-X., Jensen, T. J., Kartner, N., Alon, N., Hanrahan, J. W., and Riordan, J. R. (1993) J. Biol. Chem. 268, 11304–11311
7. Seibert, F. S., Tabcharani, J. A., Chang, X.-B., Dushanta, A. M., Mathews, C., Hanrahan, J. W., and Riordan, J. R. (1995) J. Biol. Chem. 270, 2158–2162
8. Loo, M. A., Jensen, T. J., Cui, L., Hou, Y.-X., Chang, X.-B., and Riordan, J. R. (1998) EMBO J. 17, 6879–6887
9. Aleksandrov, A. A., and Riordan, J. R. (1998) FEBS Lett. 431, 97–101
10. Kopito, R. R. (1999) Physiol. Rev. 79, S167–S173
11. Gunderson, K. L., and Kopito, R. R. (1995) Cell 82, 231–239
12. Cheng, S. H., Gregory, R. J., Marshall, J., Paul, S., Souza, D. W., White, G. A., O’Riordan, C. R., and Smith, A. E. (1996) J. Biol. Chem. 271, 27393–27397
13. Seibert, F. S., Loo, T. W., Clarke, D. M., and Riordan, J. R. (1996) J. Bioenerg. Biomembr. 29, 429–442
14. Sheppard, D. N., and Welsh, M. J. (1999) Physiol. Rev. 79, S23–S45
15. Pasyk, E. A., Morin, X. K., Zeman, P., Garami, E., Galley, K., Huan, L. J., Wang, Y., and Bear, C. E. (1998) J. Biol. Chem. 273, 31759–31764
16. Dawson, D. C., Smith, S. S., and Mansoura, M. K. (1999) Physiol. Rev. 79, S47–S75
17. Hammerle, M., Aleksandrov, A. A., Chang, X.-B., and Riordan, J. R. (2001) Glycoconjug. J., in press
18. Rosenberg, M. F., Callaghan, R., Ford, R. C., and Higgins, C. F. (1997) J. Biol. Chem. 272, 10685–10694
19. Kartner, N., Augustinins, O., Jensen, T. J., Naismith, A. L., and Riordan, J. R. (1992) Nat. Genet. 1, 321–327
Disease-associated Mutations in the Extracytoplasmic Loops of Cystic Fibrosis Transmembrane Conductance Regulator Do Not Impede Biosynthetic Processing but Impair Chloride Channel Stability
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