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The consequences proteins mutations: The association of these mutations on protein quality and their relationship to diseases

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Abstract

Genetic variations can cause protein modifications, Whether at the level of folding, constancy, abundant quantities, localization, molecular Interplay, and biological activities. So, these Characteristics are not substitutable: a distinguishable protein may be defective, while reduced amount does not lead fasted degeneration. this recent review assesses how variations -link with molecular changes related with cellular protein quality-control (PQC) pathways to detect consequences of protein mutations. It considers transcript surveillance, molecular chaperones, the ubiquitin–proteasome

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systems (UPSs), e ndoplasmic-reticulum-associated degeneration (ERAD), autophagy–lysosome pathways, mis localization, and protein aggregation. Examples for elected diseases evolving CFTR-associated cystic fibrosis, mutant TP53 in cancer and activity-altering PTEN and GCK mutants clarify special routes from sequence variation to disease phenotype. Evidences from large-scale variant assessments and the studies concerned with diseases beside experimental restrictions. The review projects an evidence-based interpretive framework in which protein abundances, stability, folding, localization, and biological activities are evaluated as correlated but special measurements. This review is targeting the improvement the mechanical interpretations of variants that associated with diseases and lead the selection of complementary experimental assays; it is not viewed as a supported predictive model.

Keywords: mutant proteins; protein quality control; proteostasis; protein stability; protein abundance; protein mis localization; ubiquitin–proteasome system; autophagy; genetic variants.

Introduction

Genome sequencing has greatly expanded the identification of protein-coding variants, but determining their functional consequences remains at challenge. A sequence changes may reduce protein disturbance, alteration the intracellular or molecular interactions, or defect the activity despite the continued presence of the proteins. The correlation between genotypes and phenotypes cannot always be inferred from variant class or predicted structure alone [1].

Cells preserve Protein homeostasis (proteostasis) by correlated regulation of protein synthesis, formation, maturation, Protein sorting, convention, and degradation. Chaperones and quality-control pathways make a response to qualities such as insecure hydrophobic area, abnormal configurations, false assembling, and unfit positioning. They do not by a direct rout detecting whether a protein is caused the diseases or not. so, a functionally imperfect proteins may skip efficiently from the removing while the other variants rapidly degraded [2]. universal researches show the multifaceted nature of variant effects. [1] revealed the reducing stability for roughly 60% of pathogenic missense mutations in their data, while [3] detected the Mispositioning in round about one-sixth of the pathogenic variants estimated. These results reinforced the integrated view, while their analyzing systems and cellular models should be observed when projecting to individual proteins and disease tissues.

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The recent review corelate the five dimensions for protein mutations destiny—profusion, stability in structure, rotations, cellular localization, and biological activity/interactions Its focal excuse is that these dimensions must be recognized experimentally before a molecular mechanism is assigned.

1- From the variations in Genetics to Protein-Level conclusions

Missense mutations may change the topical structures, catalytic residues, ligand binding, folding, or protein–protein interfacing. Nonsense and frameshift mutations can introduce the early termination (ending) codons, presumably exciting nonsense-mediated mRNA decay (NMD) and reduce the transcripts available for translations.
NMD rest on copy construction and region of the termination-codon; it is not general, and copies that escape monitoring may produce truncated polypeptides with changed stability, localization, or activity [4].

Variation category singly, hence it does not predict protein fate. A switching in an Interred structural region may weaken the proteins folding and reducing abundance, while a change in an active site or interaction interface may damage the functions without clearly altering the overall constancy. The consequences depend on protein/ domains architecture, cellular type, expression plane, and ready quality-control machinery [1].

Three commonly registed measurements require clear separation. Protein abundance is the amount detected at a sited time; structural or conformational stability reveal resistance to uncoiling or structural disruption under specific conditions; and half-life is a kinetic measures of protein evanescence
Steady-state plenty reverberate the balancing between production and removal. It cannot singly recognize transcription, translation, or degradation as the cause of an alteration. Increased synthesis may repay for faster turnover, while reduced synthesis may lowering the abundance without changing half-life [5][6].

Localization and biological activities add more dimensions. the proteins may be ready and structurally perfect but they can not to reach the compartment, membranes, substrates, or partner required for its function. the contrary, a correctly localized protein may remain without any activities because a catalytic or binding site has been damaged. In a large-scale microscopy study, mis localization was defined across a substantial subset of pathogenic variants, supporting its inclusions in variant explanation [3].

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2. Cellular Protein Quality Control

PQC is an interconnected network which help conformation, prevents unsuitable aggregation, monitors maturation, and directs selected materials toward degeneration. Molecular chaperones can assist proteins gain or recover functional conformations. But when recovery fails, materials may be retained, ubiquitinated, or routed to proteasomal or lysosomal degradation. The relative contribution of each pathway depends on the protein, its location, the nature of the defect, and cellular state [2][7].

2.1. Ubiquitin–proteasome system

The ubiquitin–proteasome system (UPS) controls the turnover of many intracellular proteins. Ubiquitin is attached through E1 activating, E2 conjugating, and E3 ligase enzymes; E3 ligases contribute to substrate selection. Misfolding can expose degrons or hydrophobic regions that are recognized by chaperones and quality-control factors. However, the presence of a potential degradation signal does not guarantee removal: recognition depends on accessibility, substrate context, and the availability of the relevant machinery. Ubiquitination can also regulate processes other than proteasomal degradation [8][9].

2.2. ER-associated degradation and autophagy–lysosome pathways

Secreted and membrane proteins undergo folding and maturation in the endoplasmic reticulum (ER). Proteins that defeat Endoplasmic Reticulum quality-control requirements may be directed to Endoplasmic Reticulum linked degeneration (ERAD), which includes realization, retro-translocation, ubiquitination, and proteasomal degradation. The unfolded protein response helps restore ER homeostasis, while ER-phagy delivers portions of the ER to lysosomes. Autophagy–lysosome pathways also contribute to the handling of selected protein assemblies and aggregates that are not efficiently processed by the proteasome [10][11][12][13].

2.3. Accumulation, and confined proteostasis strength

Aggregations can reduce the soluble functional protein reservoir, segregate interactivity partners, defect the organelles, and raise order on chaperones and degeneration systems. Soluble oligomers, amorphous aggregations, and larger inclusions are not equivalent in structure, reversibility, toxicity, or rescue. Visible inclusions do not identify the toxic species or prove that aggregations-initiated disease.

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Further, restricted PQC capacity should not be used as a universal explanation for protein perseverance: a dysfunctional protein may remain abundant because its defect does not expose a degradation signal [7][17]

3. Functional Consequences of Mutant Protein Persistence

A protein detected at near-normal abundance may still have substantial functional impairment. Variants can affect catalytic residues, ligand binding, DNA binding, protein–protein interfaces, or allosteric communication without causing extensive global destabilization. Thus, abundance and activity should be measured independently, and the assay must reflect the protein's relevant biological role [6][18].

Loss of function (LOF) describes reduced or absent normal activity and may result from protein loss, mislocalization, defective assembly, or a specific functional-site defect. Gain of function (GOF) describes a new or dysregulated activity that contributes to disease. A dominant-negative effect occurs when a mutant protein interferes with the wild-type protein or a required molecular complex. These mechanisms are distinct and may overlap in particular contexts; they should not be assigned from protein abundance alone [16].

Mutant TP53 illustrates this distinction. Some missense variants lose tumor-suppressor activity and may interfere with wild-type p53 or acquire additional pro-tumorigenic functions. Certain mutant p53 proteins accumulate in tumor cells, but accumulation alone does not establish GOF; altered stability, degradation, stress responses, and mutation-specific activities must be distinguished. Functional evidence and appropriate genetic controls are required to demonstrate a gain-of-function mechanism [17][16].

Mislocalization may be a primary targeting defect or a secondary consequence of altered folding, membrane insertion, or stability. Similarly, aggregation may change the accessibility of degradation signals and affect other proteins through sequestration or co-aggregation. These effects are protein- and context-dependent, so causal claims require more than imaging or steady-state abundance measurements.

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4. Disease Examples: Distinct Routes from Variant to Phenotype

4.1. CFTR and cystic fibrosis

The CFTR p.Phe508del (F508del) variant disrupts folding and processing. The mutant protein is inefficiently folded, retained by ER quality control, and directed toward ERAD, reducing delivery of functional chloride channels to the apical membrane. Disease-relevant dysfunction therefore involves both defective trafficking and impaired channel activity [19][20].

CFTR modulators demonstrate why the molecular defect matters therapeutically. Correctors such as elexacaftor and tezacaftor improve processing and trafficking of responsive variants, whereas ivacaftor potentiates channel activity at the cell surface. Correcting delivery and enhancing channel function are different interventions, and response depends on the variant [21][22].

4.2. TP53 in cancer

Cancer-associated TP53 missense variants may impair normal p53 activity, exert dominant-negative effects, or acquire mutation-dependent oncogenic activities. Increased mutant p53 abundance is not sufficient evidence of GOF. Studies implicating HSP90-mediated effects on MDM2 and CHIP illustrate how altered turnover can contribute to mutant p53 stabilization, but the biological consequence still requires functional demonstration [17][16].

4.3. PTEN and glucokinase

PTEN regulates PI3K–AKT signaling, while glucokinase (GCK) contributes to glucose sensing and phosphorylation. Studies combining abundance and activity measurements show that variant-associated functional impairment may not be proportional to protein quantity. An activity–abundance discrepancy indicates an abundance-independent defect, but does not by itself prove a particular allosteric or structural mechanism; biochemical and interaction studies are needed for mechanistic resolution [6][23][18].

Disease/protein	Representative defect	Interpretive lesson
CFTR F508del	Folding defect, ER retention, reduced membrane delivery and channel function	Protein processing, localization and activity must be considered together.

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Mutant TP53	Loss of normal activity; selected variants may show dominant-negative or gain-of-function effects	Accumulation alone does not establish oncogenic gain of function.
PTEN / GCK variants	Activity changes may not parallel abundance changes	Protein quantity alone can underestimate functional impairment.

5. An Evidence-Based Framework for Experimental Interpretation

No single assay establishes the complete fate of a mutant protein. The first step is to define the observed phenotype, then select complementary measurements that distinguish competing explanations. Reduced abundance should initially be reported as reduced abundance—not accelerated degradation—until transcript, synthesis, and turnover evidence supports that conclusion. Preserved abundance with reduced activity requires a protein-appropriate functional assay. Abnormal localization requires assessment of targeting, retention, trafficking, and total abundance.

Question	Useful approaches	What the result does not establish alone
How much protein is present?	Western blot, quantitative immunoassay, targeted proteomics	Synthesis rate, half-life, folding or activity.
Is transcript abundance altered?	RT-qPCR, RNA sequencing	Protein synthesis or degradation rate.
Where is the protein located?	Immunofluorescence, confocal imaging, cell fractionation	Whether mislocalization is primary or causal.
Is the protein functional?	Enzyme kinetics, ligand/channel assays, reporter or pathway readouts	All functions of a multifunctional protein.
Is turnover altered?	Pulse–chase or cycloheximide-chase with controls; pathway perturbation	A specific degradation pathway without supporting evidence.
Does it aggregate or interact abnormally?	Soluble/insoluble fractionation, co-immunoprecipitation, binding assays	Aggregate toxicity or causal interaction by itself.

Several limitations must be considered. Overexpression may saturate chaperones, alter stoichiometry, or promote non-physiological aggregation. Fluorescent tags can affect trafficking; antibodies may differ in specificity or epitope accessibility; and

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proteasome, lysosome, or translation inhibitors can produce indirect effects. Static autophagy markers do not establish autophagic flux, and increased ubiquitination does not prove efficient proteasomal degradation. Where possible, comparisons should use matched expression levels, endogenous or disease-relevant models, and rescue experiments. Conclusions should remain proportionate to the measurements obtained [5][3][7].

6. Therapeutic priority and Research Implications

Therapeutic program should coordinate with predominant, molecular imperfections. controlling or pharmacological chaperones may enhance the folding potentiators or activity-restoring agents may enhance excess functions; selective inhibition or degeneration may be considered for toxic function of proteins. wide modifications of the UPS, autophagy, or chaperone systems are challenging because these pathways adjust the normal cellular proteins and biological activities. A mutant protein found alone is not a enough for therapeutic biomarker [2][24].

Most Important researches concerns including validating high-throughput variant detections in endogenous, disease-detected systems; measuring plenty, folding, localization, and activity in the same variants; and using time-determined observations to reveal protein persistence from rapid rotations regulated by synthesis. furthermore, the work should identify which soluble or aggregated species relate to dysfunction. Computational structure and protein-language-model predictions can prioritize tests, but it cannot change direct cellular and functional index.

Conclusion:

Mutant proteins destiny appears from correlations between variant-specific molecular consequences and cellular quality-control systems. Genetic alterations may alter folding, abundance, turnover, localization, interactions, or activity, and several effects may coexist. Protein invention does not exhibit functional unity, while decrease the quantity does not detect degradation as the single cause. Integrating complementary measurements supply a more reliable basis for interpreting disease-associated variants and selecting mechanism-matched therapeutic strategies. The framework presented here is an interpretive guide, not a validated predictive model.

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