Unfoldomics of Human Genetic Diseases: Illustrative Examples of Ordered and Intrinsically Disordered Members of the Human Diseasome

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Abstract: Intrinsically disordered proteins (IDPs) constitute a recently recognized realm of atypical biologically active proteins that lack stable structure under physiological conditions, but are commonly involved in such crucial cellular processes as regulation, recognition, signaling and control. IDPs are very common among proteins associated with various diseases. Recently, we performed a systematic bioinformatics analysis of the human diseasome, a network that linked the human disease phenome (which includes all the human genetic diseases) with the human disease genome (which contains all the disease-related genes) (Goh, K. I., Cusick, M. E., Valle, D., Childs, B., Vidal, M., and Barabasi, A. L. (2007). The human disease network. Proc. Natl. Acad. Sci. U.S.A. 104, 8685-90). The analysis of this diseasome revealed that IDPs are abundant in proteins linked to human genetic diseases, and that different genetic disease classes varied dramatically in the IDP content (Midic U., Oldfield C.J., Dunker A.K., Obradovic Z., Uversky V.N. (2009) Protein disorder in the human diseasome: Unfoldomics of human genetic diseases. *BMC Genomics.* In press). Furthermore, many of the genetic disease-related proteins were shown to contain at least one molecular recognition feature, which is a relatively short loosely structured protein region within a mostly disordered segment with the feature gaining structure upon binding to a partner. Finally, alternative splicing was shown to be abundant among the diseasome genes. Based on these observations the human-genetic-disease-associated unfoldome was created. This minireview describes several illustrative examples of ordered and intrinsically disordered members of the human diseasome.

Keywords: Intrinsic disorder; diseasome; unfoldome; genetic disease.

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INTRODUCTION

Many biologically active proteins, known as intrinsically disordered proteins (IDPs) among other names are unstructured or incompletely structured under physiological conditions. Intrinsic disorder (ID) can be manifested either at the regional level or at the whole protein level [1-9]. The non-foldability of IDPs and IDRs is encoded in their amino acid sequences, which are noticeably different from the sequences of structured globular proteins and domains [2, 3, 8, 10]. Therefore, in addition to the well-known "protein folding code" stating that all the information necessary for a given protein to fold is encoded in its amino acid sequence [11], we have proposed that there exists a "protein non-folding code", according to which the propensity of a protein to stay intrinsically disordered is likewise encoded in its amino acid sequence [2, 3, 12, 13].

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IDPs are highly abundant in nature, and eukaryotic proteomes are significantly more enriched in IDPs in comparison with bacterial and archaeal proteomes [14, 15]. This increased utilization of IDPs in higher organisms was attributed to the greater need for signaling and coordination among the various organelles in the more complex eukaryotic domain [3, 16]. IDPs carry out numerous biological functions, which usually complement those of ordered proteins and protein regions: while structured proteins are mainly involved in molecular recognition leading to catalysis or transport, disordered proteins and regions are typically involved in signaling, recognition, regulation, and control by a diversity of mechanisms [17-19]. IDPs often serve as scaffolds for organizing the components of multi-step pathways [20]. Furthermore, IDPs are key players in various protein-protein interaction networks, where they typically function as hubs; i.e., highly promiscuous proteins interacting with many different partners [6]. Even some highly structured hubs (such as 14-3-3 [9] and calmodulin [21]), utilize ID, as their partner protein binding regions are intrinsically disordered [7]. Overall, these observations support two previously

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proposed mechanisms by which ID is utilized in protein-protein interactions: namely, one disordered region binding to many partners and many disordered regions binding to one partner [7, 22].

Not surprisingly, numerous IDPs were shown to be associated with cancer [16], cardiovascular disease [23], amyloidoses [24], neurodegenerative diseases [25], diabetes and other human diseases [26], an observation that was used to introduce the "disorder in disorders" or D^2 concept [26]. Recently we showed also that IDPs are abundant in the human diseasome [27], a framework that systematically linked the human disease phenome (which includes all the human genetic diseases) with the human disease genome (which contains all the disease-related genes) [28]. This framework was constructed from the analysis of two networks, a network of genetic diseases, the "human disease network", where two diseases are directly linked if there is a gene that is directly related to both of them, and a network of disease genes, the "disease gene network", where two genes are directly linked if there is a disease to which they are both directly related [28]. Our analysis revealed that there were noticeable differences in the abundance of ID in human disease-related as compared to disease unrelated proteins [27]. Furthermore, various disease classes were significantly different with respect to the IDP content. Also certain genetic diseases were shown to have significantly greater fraction of genes involved in alternative splicing, which is related to the current studies because previous work indicates a high association between ID and protein regions that are coded by alternatively spliced RNA [29].

Recently, the correlation between the amount of ID in a given protein and its function was found based on the analysis of the functional annotations over the entire Swiss-Prot database from a structured-versus-disordered viewpoint. The first step in this approach was to find keywords associated with 20 or more proteins in SwissProt. For each keyword-associated set, one thousand length-matching and number-matching sets of random proteins were drawn from Swiss-Prot. Order-disorder predictions were carried out for the keyword-associated sets and for the matching random sets. If a function described by a given keyword were carried out by a long region of disordered protein, one would expect the keyword-associated set to have a greater amount of predicted disorder compared to the matching random sets. The keyword-associated set would be expected to have less prediction of disorder compared to the random sets if the keyword-associated function were carried out by structured protein. Given the predictions for the function-associated and matching random sets, it is possible to calculate the p-values, where a p-value > 0.95 suggests a disorder-associated function, a p-value < 0.05 suggests an order-associated function, and intermediate p-values are ambiguous [17-19]. Such an analysis revealed that out of 710 keywords each being assigned to at least 20 proteins, 310 had p-values < 0.05, suggesting order-associated functions, 238 had p-values > 0.95, suggesting disorder-associated functions, and the remainder, 170, gave intermediate p-values, yielding ambiguity in the likely function-structure associations [17-19].

We showed previously that the proteins from several disease classes (e.g., Metabolic, Gastrointestinal, Nutritional, Renal, and Respiratory diseases) showed very low disorder content including few proteins suggested to be wholly ordered [27]. These low levels of ID in corresponding proteins were correlated well with their functionality, as in many cases the key proteins were enzymes. This observation confirmed earlier finding that catalytic proteins (enzymes) are more ordered than proteins from other functional classes. In several genetic pathologies, specific membrane proteins, receptors, transporters, structural proteins, proteins involved in catalysis, metabolism and biosynthesis are affected. These functional classes were associated with mostly ordered proteins using a described above bioinformatics approach for finding the relationship between disorder and function in the Swiss-Prot database [17-19].

On the other hand, our data clearly showed that several disease classes had median disorder content higher or comparable with the human gene set with the human gene set (Skeletal, Bone, Dermatological, Cancer, Developmental, Multi-class disease), and/or several classes had a higher or comparable fraction of highly disordered genes (Skeletal, Bone, Dermatological, Cancer, Developmental, Multi-class disease, Psychiatric). Unfortunately, structural information on proteins associated with various genetic diseases is sparse. Therefore, in analyses below we used an established earlier correlation between various protein functions and ID [17-19]. The strongest correlation with ID possessed proteins with regulatory functions involved in such biological processes as described by the following functional keywords: differentiation, transcription, transcription regulation, spermatogenesis, DNA condensation, cell cycle, mRNA processing, mRNA splicing, mitosis, apoptosis, protein transport, meiosis, cell division, Ubl conjugation pathway, Wnt signaling pathway, chromosome partition, neurogenesis, ribosome biogenesis, chondrogenesis, and growth regulation [17-19]. The major ID-associated functional keywords covered a wide spectrum of protein activities including ribonucleoprotein, ribosomal protein, developmental protein, chromatin regulator, hormone, growth factor, GTPase activation, cytokine, GAP protein, repressor, cyclin, activator protein phosphatase inhibitor.

Many of these processes and functions are performed by proteins associated with various human genetic diseases. Based on this correlation between ID and protein function, a given protein was assigned either to the ordered protein family or to the IDR class, assuming that if this protein possesses ID-associated function then it likely contains at least one long IDR. A brief overview of ID-enriched classes of human genetic diseases is presented below. In addition, several examples of disease-related genes encoding for important well-characterized IDPs are discussed. These include disordered proteins, mutations in which were associated with particular diseases, α-synuclein (one of the major players in the Parkinson's diseases pathogenesis), p53 (a key cancer-associated protein), huntingtin (a protein involved in the Huntington's disease pathogenesis), BRCA1 (a breast and/or ovarian cancer-associated protein) and EWS-FLI1 fusion protein (a protein associated with the Ewing's sarcoma family of tumors).

The goal of this study is to validate the found earlier correlations and to represent genetic diseases with high and low

IDP contents. Several illustrative examples of these diseases and their corresponding genes/proteins are considered below.

GENETIC DISEASES WITH LOW LEVELS OF IDPS

Metabolic Diseases

Metabolic diseases are diseases that are associated with various metabolic dysfunctions that cause the loss of the homeostasis control. More than half of the metabolic diseases contain "*XYZ deficiency*" in their names, where "XYZ" corresponds to a name of a specific enzyme. A very brief list of these deficient enzymes includes 2-methyl-3-hydroxybutyryl-CoA dehydrogenase, 3-b-hydroxysteroid dehydrogenase, acyl-CoA dehydrogenase, adenylosuccinase, α-methylacyl-CoA racemase, aromatase, aromatic L-amino acid decarboxylase, β-ureidopropionase, biotinidase, carnitine-acylcarnitine translocase, chitotriosidase, cortisone reductase, creatine phosphokinase, dihydropteridine reductase, dimethylglycine dehydrogenase, dopamine β-hydroxylase, enolase-β, fructose-bisphosphatase, fumarase, galactokinase, glucosidase I, hepatic lipase, HMG-CoA synthase-2, S-adenosylhomocysteine hydrolase, inosine triphosphatase, lactate dehydrogenase-B, methylmalonate semialdehyde dehydrogenase, multiple sulfatase, N-acetylglutamate synthase, placental steroid sulfatase, pyruvate dehydrogenase, ribose 5-phosphate isomerase, sepiapterin reductase, succinic semialdehyde dehydrogenase, and transaldolase.

Several metabolic diseases are associated with increased *sensitivity* or *intolerance* to various substances, including alcohol, debrisoquine, fluorouracil toxicity, sucrose, codeine, warfarin, and fructose. These intolerances and sensitivities are due to the deficiency in the specific enzymes processing these substances in the organism. Another example of the metabolic disease is *citrullinemia*, a disease caused by a defect of urea metabolism resulting from an inherited deficiency of argininosuccinate synthetase 1 (ASS1) thereby leading to a markedly low level of citrulline. Fig. (**1A**) shows that this protein is predicted to be mostly ordered. In hereditary *maple syrup urine disease*, which is characterized by a specific maple-syrup-like odor of urine, a deficiency in branched-chain keto acid decarboxylase that leads to the accumulation of high concentrations of leucine, isoleucine, and valine and the immediate products of their metabolism in the plasma and urine. *Niemann-Pick disease* is a hereditary sphingolipidosis due to an acid sphingomyelinase deficiency resulting in the abnormal accumulation of sphingomyelin. *Schindler disease* is an inherited glycoprotein storage disease associated with a deficiency of α-N-acetylgalactosaminidase. Schindler disease is one of the numerous lysosomal storage diseases. Lysosomes contain specific enzymes responsible for the utilization of various oligosaccharides. Misfunction of these enzymes leads to the accumulation of the specific oligosaccharides in the lysosome. *Tyrosinemia* is a metabolic disease, in which the deficiency of the enzyme *p*-hydroxyphenylpyruvic acid oxidase leads to the abnormally high blood levels of tyrosine and sometimes methionine.

Gastrointestinal Diseases

Gastrointestinal diseases are all diseases that pertain to the gastrointestinal tract. A few illustrative examples of these diseases are outlined below. *Congenital chloride diarrhea* is a recessively inherited intestinal disorder affecting electrolyte transportation, being characterized by massive loss of chloride in stool. This disease is associated with a number of mutations in the human *SLC26A3* gene, also known as down-regulated in adenoma (hDRA). hDRA is a membrane protein that is expressed in the apical membrane and that mediates bidirectional Cl^--Cl^- and Cl^--HCO_3^- exchange [30]. Disorder prediction for this protein, also known as solute carrier family 26 member 3, SCL26A3, is shown in Fig. (**1B**), which clearly shows that this protein is mostly ordered, possessing only a few short predicted disordered regions. *Cholelithiasis* is characterized by the presence or formation of gallstones and is associated with mutation in another membrane transporter, ABCB4 (MDR3), which is a lipid translocator, that moves phosphatidylcholine from the inner to the outer leaflet of the canalicular membrane [31]. *Chylomicron retention disease* belongs to the group of lipid absorption disorders linked to deficiencies in B apolipoprotein (apoB) biosynthesis and secretion. The causative gene encodes the SARA2 protein, a member of a Sar1-adenosine diphosphate-ribosylation factor family of small guanosine triphosphatases, which governs the intracellular trafficking of proteins into protein-coated vesicles [32]. Some forms of *cirrhosis*, a chronic, degenerative disease in which normal liver cells are damaged and are then replaced by scar tissue, might be associated with mutations in genes encoding internal epithelial keratins, e.g., keratin 8 and 18. Keratins constitute a family of highly homologous and chemically stable structural proteins that constitute the intermediate filaments in epithelia. Some other gastrointestinal diseases are associated with the *deficiency* of specific enzymes, e.g., *enterokinase deficiency*.

Nutritional Diseases

Nutritional diseases are various pathologies that are related (directly or indirectly) to nutrition. *Anorexia nervosa* is a pathology characterized by fear of weight gain and self-starvation. It is associated with the A allele of a -1438 G/A polymorphism in the HTR2A gene encoding for the type 2A serotonin receptor, which is a membrane protein and a member of the G-protein coupled receptor (GPCR) super-family. Fig. (**1C**) shows that the central domain of HTR2A (residues 60-420) is predicted to by mostly ordered, whereas N- and C-terminal domains (first and last 60 residues) are predicted to be disordered. *Inherited leanness* is associated with Ala67Thr polymorphism in agouti-related protein, which is an antagonist of the melanocortin-3 and melanocortin-4 receptor. The 87-132 amino acid C-terminal domain of hAGRP was shown to possess five disulfide bridges and a well-defined three-dimensional structure that displayed full biological activity as compared to the full-length protein [33]. *Obesity* is an abnormal accumulation of body fat, usually >20% of an ideal body weight, which is linked to polymorphism in a number of genes, including *leptin* (*LEP*), *leptin receptor* (*LEPR*), *adiponectin* (*ADIPOQ*), *proopiomelanocortin* (*POMC*), *peroxisome proliferative-activated receptor α* (*PPARα*), *peroxisome proliferative-activated receptor γ* (*PPARγ*), *retinoid X receptor γ* (*RXRγ*), *ghrelin* (*GHRL*), and *insulin-induced gene 2* (*INSIG2*) [34]. Leptin is a highly ordered protein, a member of the four-helical cyto-

kine family [35]. *Scurvy* is a condition caused by the lack of vitamin C (ascorbic acid) in the diet. It is characterized by swollen bleeding gums, the opening of previously healed wounds, deformity of the legs, multiple fractures, osteoporosis, growth retardation and haemorrhagic tendencies. The development and manifestations of scurvy is related to the tissue storage of ascorbic acid and depend on factors influencing the rate at which it is used in or released from the tissues. Genetically, the failure to biosynthesize ascorbic acid was traced to the lack of L-gulono-gamma-lactone oxidase, which catalyzes the terminal step in the biosynthesis of AscA.

Renal Diseases

Renal diseases are a set of pathological conditions affecting kidneys. *Alport syndrome* is a hereditary disease of the kidneys that primarily affects men, causing blood in the urine, hearing loss and eye problems. This disease is caused by mutations in the *COL4A3*, *COL4A4*, and *COL4A5* genes, which code for proteins related to the collagen biosynthesis. *Cryptorchidism* is a developmental defect marked by the failure of the testes to descend into the scrotum. The peptide hormone insulin-like peptide 3 (INSL3) is essential for testicular descent, and this hormone acts in a complex with the INSL3 receptor, which is a leucine-rich repeat-containing G protein-coupled receptor 8 (LGR8). LGR8 is a membrane protein that possesses a large extracellular ectodomain containing 10 leucine-rich repeats, within which lies the primary hormone binding site [36]. Each leucine-rich repeat-containing unit consists of a β-strand and an antiparallel linear extended structure connected by short loops [37]. These units are arranged so that the β-strands of consecutive leucine-rich repeats lie parallel to each other to form an arced solenoid-like structure with a concave β-sheet lining the inside surface [37]. *Cystic fibrosis* is an inherited disease that affects the lungs, digestive system, sweat glands, and male fertility. It originates from the mutation in cystic fibrosis transmembrane conductance regulator, CFTR, which is a highly ordered multidomain, integral membrane protein containing two transmembrane domains, two nucleotide-binding domains (NBD1 and NBD2), and a regulatory region (R domain) [38]. Fig. (**1D**) shows that this protein is predicted to by mostly ordered, possessing a disordered central domain (residues 620-820). *Cystinosis*, a hereditary disease affecting the renal tubules, is caused by abnormal transport of the amino acid cystine from lysosomes of all tissues, resulting in a massive intra-lysosomal cystine accumulation. This abnormal transport is due to the mutations in the gene CTNS which codes for cystinosin, the lysosomal cystine transporter. Similarly, inactivating mutations in another transporter, thiazide-sensitive sodium-chloride co-transporter (NCCT), are associated with the development of *Gitelman syndrome,* a rare congenital defect in the renal tubule of kidneys, causing the kidneys to pass sodium, magnesium, chloride, and potassium into the urine, rather than allowing them to be reabsorbed into the bloodstream. *Nephrolithiasis* is a kidney stone disease, the primary form of which is associated with the mutation in a number of genes, including *sAC* (coding for a bicarbonate sensor), *VDR* (encoding for a vitamin D receptor), *CaSR* (producing a membrane protein that is sensitive to extracellular calcium ions) and others [39]. *Polycystic kidney disease* is an incurable genetic disorder characterized by the formation of fluid-filled cysts in the kidneys. Mutation in the *PKD1* or *PKD2* gene accounts for 95% of the polycystic kidney disease [40]. *PKD1* and *PKD2* encode a large 11-transmembrane spanning receptor (TRP polycystin 1, TRPP1) and transient receptor potential channel (TRP polycystin 2, TRPP2), respectively [41].

Respiratory Diseases

One of the forms discussed above, *cystic fibrosis,* also affects the lungs and therefore can also be classified as a respiratory disease. *Pulmonary alveolar proteinosis* is characterized by the progressive impairment of the gas exchange in lungs due to the accumulation of phospholipids. One of the genes involved in the pulmonary alveolar proteinosis development is *SFTPC*, which codes for the pulmonary surfactant protein C (SP-C). SP-C was originally identified as a highly hydrophobic protein of ~3.5-kDa purified from broncho-alveolar lavage fluid from a patient with pulmonary alveolar proteinosis [42]. Another respiratory disease, *SP-C deficiency*, is associated with low levels of this important protein. Fig. (**1E**) shows that >50% of residues in this protein are predicted to be disordered. Finally, some respiratory diseases are associated with the deficiency of specific enzymes, e.g., *alpha-1-antichymotrypsin deficiency.*

GENETIC DISEASES WITH HIGH LEVELS OF IDPS

Skeletal Diseases

The majority of skeletal diseases involve developmental pathologies characterized by various abnormalities associated mainly with mutations in regulatory proteins, including various transcription factors and scaffold proteins. Previous bioinformatics studies established a new paradigm according to which signaling and regulatory proteins are highly enriched in functionally crucial IDRs. Therefore, the finding that proteins with skeletal disease-associated mutations are highly disordered is in agreement with these earlier observations. A few illustrative examples of skeletal diseases are considered below.

Acheiropodia is an autosomal recessive developmental disease characterized by bilateral congenital amputations of the upper and lower extremities and absence of the hands and feet, with no other systemic manifestations reported. Acheiropodia is associated with the deletion of the portion of the *C7orf2* gene, which is the human orthologue of the *Lmbr1* gene [43], the product of which is involved in the Sonic hedgehog pathway regulation [44]. Abnormal regulation of the indian hedgehog signal transduction pathway via mutations in *EVC* gene is associated with the development of the human chondroectodermal dysplasia *Ellis-van Creveld syndrome* [45]. Fig. (**1F**) shows that EVC protein is predicted to be mostly disordered. In *Achondroplasia*, which is the major cause of dwarfism, a mutation in the fibroblast growth factor receptor gene 3 (*FGFR3*), the product of which has a negative regulatory effect on bone growth, produces the receptor which is constitutively active, and this leads to severely shortened bones. *Acromesomelic dysplasia*, an extremely rare, inherited, progressive skeletal disorder that results in a particular form of short stature (short-limb dwarfism), is caused by mutation in cartilage-derived

morphogenetic protein-1 (CDMP-1). Cdmp1 is a member of the large TGF-β superfamily of signaling molecules, which are secreted as biologically active dimers [46]. A homozygous missense mutation in the prodomain of CDMP-1 was recently associated with *Brachydactyly* type C (BDC), a diseases characterized by shortening of the middle phalanges of the index, middle, and little finger with hyperphalangy, usually of the index and middle finger [47].

Campomelic dysplasia is a congenital skeletal malformation syndrome often connected to XY sex reversal [48]. The development of abnormal curvature of the long bones, particularly from lower extremities, is associated with the mutation in the SOX9 protein [49], which belongs to a large class of transcription factors related to SRY, the testis-determining factor, through their HMG domains that bind and bend DNA in a sequence-specific manner. Importantly, several groups have recently shown transcription factors to be highly enriched in IDRs, which play a number of crucial roles in these proteins including the binding to various partners [50-53].

Mutations in a transcription factor Cbfa1/Runx2 associated with the osteoblast differentiation result in the developmental defect known as *Cleidocranial dysplasia*. Mutations in the transforming growth factor β-1 (TGFβ-1), which controls cell proliferation, are associated with another skeletal pathology, *Camurati-Engelmann disease*, which is primarily characterized by increased bone density, particularly affecting the long bones of the arms and legs. *Currarino syndrome*, which is a severe autosomal dominant disease caused by mutation in *HLXB9* gene, involves partial sacral agenesis, presacral mass, and anorectal malformations [54]. The HLXB9 protein functions as a transcription factor regulating gene expression in both developing and adult tissues, although little is known about target genes or protein partners. Structurally, HLXB9 contains a homeodomain, a highly conserved region of 82 amino acids, and a polyalanine region consisting of 16 alanines [55]. Mutations in another transcription factor, p63, are associated with one of the five forms of congenital malformation split hand-foot malformation (SHFM, or *Ectrodactyly*) [56]. These malformations are characterized by a medial cleft of hands and feet, and missing central fingers. *Hypodontia* (or *Oligodontia*, the congenital absence of teeth) is associated with a mutation in transcription factor PAX9. Malfunction of the transcription repressor Gli3 originating from the mutation in the corresponding gene affect development of the limbs, head, and face resulting in such skeletal pathologies as *Greig cephalopolysyndactyly syndrome* and *Polydactyly*. *Orofacial clefts* are the birth defects where mouth or roof of mouth does not form properly. In the Van der Woude syndrome, the orofacial cleft is caused by the mutations in the *IRF6* gene [57], which encode the interferon regulatory factor 6, a member of the IRF family of transcription factors.

Two forms of congenital dwarfism, *Chondrodysplasia* and *Hypochondroplasia*, as well as such skeletal developmental pathologies as *Thanatophoric dysplasia* (a severe inhered disease characterized by extremely short limbs and folds of extra skin on the arms and legs), and *Craniosynostosis* (a defect in which one or more of the flexible and fibrous joints between the skull bones closes too soon, which stops the normal capacity of the skull to expand in early childhood) are due to the genetic defects in the fibroblast growth factor receptor 3 gene (*FGFR3*) [58]. This involvement of a *FGFR3* gene in a number of skeletal diseases is definitely due to the hub-like functionality of its product. In fact, *FGFR3* belongs to a family of four genes (*FGFR1–4*) encoding receptors with tyrosine kinase activity. These genes encode for structurally related proteins that exhibit an extracellular domain (ECD) composed of three immunoglobin-like domains, an acid box, a single transmembrane domain and a split tyrosine kinase (TK) domain. These proteins are involved in multiple protein-protein interactions. In particular, binding of 1 of the 22 fibroblast growth factor (FGF) ligands in the presence of cell-surface heparan sulfate proteoglycans acting as coreceptors, induces receptor dimerization and *trans*-autophosphorylation of key tyrosine residues in the cytoplasmic domain. Phosphorylated residues serve as docking sites for the adaptor proteins and effectors that propagate FGFR signals via different signalling pathways resulting in the regulation of many cellular processes including proliferation, differentiation, migration and survival [59, 60]. Mutations in another member of the *FGFR* gene family, *FGFR2*, are associated with another congenital disease, *Jackson-Weiss syndrome*, which is characterized by the foot abnormalities and the premature fusion of certain bones of the skull.

Craniofrontonasal dysplasia, an X-linked malformation syndrome, is caused by mutations in *EFNB-1* gene encoding ephrin-B1 and is manifested by abnormalities of the head and face (craniofacial area), hands and feet, and certain skeletal bones. Ephrin-B1 is a transmembrane bidirectional signaling protein that sends a forward signal through the activation of its cognate receptor tyrosine kinase, residing on another cell, whereas a reverse signal is transduced into the ephrinB-expressing cell via tyrosine phosphorylation of its conserved C-terminal cytoplasmic domain [61]. Mutations in the *SLC26A2* gene are associated with *Diastrophic dysplasia*. Because the protein encoded by the *SLC26A2* gene is essential for the regulation of normal development of cartilage and for its conversion to bone, diastrophic dysplasia is characterized by short stature, very short arms and legs and joint problems that restrict mobility.

Frontometaphyseal dysplasia is an X-linked trait characterized by a skeletal dysplasia comprising hyperostosis of the skull and modeling anomalies of the tubular bones. It is associated with mutations in filamin-A [62], a cytoskeletal protein that is involved in the dynamic remodeling of the actin filaments and is known to bind numerous cellular components other than F-actin, including membrane receptors, enzymes, channels, signaling intermediates, and transcription factors, thereby modulating the functional activities of these various binding partners [63]. *Laron dwarfism* is characterized by the insensitivity to growth hormone, caused by mutations in the growth hormone receptor, which mediates the general pleiotropic and specific somatic responses to its ligand, growth hormone [64].

Several autosomal dominant mutations in the *GJA1* gene encoding connexin-43 result in the appearance of the *Oculodentodigital dysplasia*, characterized by developmental defects in the craniofacial bones around the eyes and nose, loss

of enamel resulting in early destruction of the teeth, and lack of soft tissue separation of two or three digits. Connexin-43 is the most abundant protein of the 21-member connexin family. Connexins are gap junction proteins; i.e., they are involved in the regulation of the communication between cells within the vast majority of human tissues through clustered arrays of intercellular channels called gap junctions [65]. Mutation in *CUL4B*, which encodes a scaffold protein that organizes a cullin-RING ubiquitin ligase (E3) complex involved in ubiquitination, causes X-linked *Smith-Fineman-Myers syndrome* [66], characterized by microcephaly and dolicocephaly with a narrow face, short stature, a chest deformity, mental deficiency, and other dysmorphic features.

Syndactyly, a congenital abnormality characterized by two or more fused fingers or toes, is caused by mutations in the *Sfrp* gene encoding the secreted frizzled-related protein 2 (Sfrp2), which is a member of the family of the WNT signaling pathway inhibitors [67]. *Synpolydactyly (SPD)* is a rare limb deformity showing a distinctive combination of *syndactyly* (see above) and *polydactyly* (characterized by the presence of more than the normal number of fingers or toes). Three genetically distinct SPD malformations are now known and have been designated as SPD1, SPD2 and SPD3. The phenotype of SPD1 is associated with the expansion mutations in the polyalanine repeat of the HOXD13 transcription factor [68]. *Weyers acrodental* dysostosis is an autosomal dominant skeletal dysplasia characterized by short limbs, short ribs, postaxial polydactyly and dysplastic nails and teeth that is caused by the mutations in the collapsin response mediator protein 1 (CRMP1), which is one of the CRMP family members that mediates signal transduction of axon guidance molecules [69].

Bone Diseases

Similar to skeletal diseases, many bone diseases are associated with some developmental defects originating from the mutations in genes encoding regulatory proteins. Some of these diseases are associated with mutations in structural and matrix proteins.

Achondrogenesis-hypochondrogenesis is an inherited pathology of bone growth characterized by a short body and limbs and a lack of bone formation in the spine and pelvis and associated with the mutations in the *COL2A1* gene encoding a type II collagen, which is crucial for the normal development of bones and other connective tissues. Results of disorder prediction for the COL2A1 collagen are shown in Fig. (**1G**), which illustrates that the central 1200 residues of this protein are highly disordered. Importantly, this protein is predicted to possess an α-helical molecular recognition feature (α-MoRF), a disordered fragment that folds upon interaction with binding partner [70]. Furthermore, this protein has an alternatively spliced region which is located inside the disordered domain. Mutations in another collagen gene, *COL2A2*, have been implicated in causing the autosomal dominant form of *Weissenbacher-Zweymuller syndrome* as well as non-ocular *Stickler syndrome* and the autosomal recessive syndrome *otospondylomegaepiphyseal dysplasia* (*OSMED*). Another group of genetic diseases known as *Osteogenesis imperfecta* where bones are formed improperly, making them fragile and prone to break, are associated with mutations in the collagen genes *COL1A1* and/or *COL1A2*.

Amelogenesis imperfecta is a group of developmental conditions characterized by the impaired teeth development due to the mutations in the *AMELX*, *ENAM*, *MMP20*, and *KLK-4* genes encoding proteins that are essential for normal tooth development. Amelogenin, the major extracellular enamel matrix protein, which plays critical roles in controlling enamel mineralization, was shown to be intrinsically disordered by several experimental techniques [71]. *Dentin dysplasia* is characterized by presence of normal enamel but atypical dentin with abnormal pulpal morphology, whereas *Dentinogenesis imperfecta* is manifested by a translucent or opalescent color of the teeth, easy fracturing of the enamel, wearing of occlusal surfaces, and staining of exposed dentin. Both of these diseases are associated with mutations in the *DSPP* gene encoding a highly soluble dentin sialophosphoprotein (DSPP) [72], which belongs to the family of non-collagenous matrix proteins termed the SIBLING family, where SIBLING stands for Small Integrin-Binding LIgand, N-linked Glycoprotein. DSPP is processed into only two proteins: a glycoprotein dentin sialoprotein (DSP) and a highly acidic protein dentin phosphoprotein (DPP).

Progressive osseous heteroplasia is characterized by the abnormal development of bone in areas of the body where bone is not normally present and is due to the mutations in the *GNAS1* gene. The product of this gene is the guanine nucleotide binding protein alpha stimulating activity polypeptide 1, which activates cyclic AMP (cAMP)-dependent pathways [73]. *Familial expansile osteolysis* is an active resorption or dissolution of bone tissue, associated with the mutations in the TNFRSF11A gene that encodes a member of the tumor necrosis factor-receptor-associated group of scaffold proteins that link receptors of the IL-1R/Toll and TNF receptor family to signalling cascades, leading to the activation of NF-kappaB and mitogen-activated protein kinases [74].

Loss of function mutations in the *LEMD3* gene, encoding an inner nuclear membrane protein that influences Smad signaling, were implicated as a cause of *Osteopoikilosis*, *Buschke-Ollendorff syndrome*, and *Melorheostosis*. *Paget's disease of bone* is a common condition that is characterized by focal increases in bone turnover, leading to bone deformity, pathological fractures, and various other complications. This disease is associated with mutations in four genes, all of which are involved in the RANK-NF-kappaB signaling pathway. For example, mutations in SQSTM1, which encodes an important scaffold protein in this pathway, have been found to be a common cause of classical Paget's disease of bone [75]. *Rickets* (also know as *rachitis*) is a deficiency disease resulting from a lack of vitamin D or calcium and from insufficient exposure to sunlight, characterized by defective bone growth and occurring mainly in children. The vitamin D-resistant form of this disease is associated with the mutation in the *VDR* gene, which encodes the vitamin D receptor and which resides in the cell nucleus. This receptor is needed for a diverse set of rapid responses to vitamin D, some examples of which include the rapid intestinal absorption of Ca^{2+} (transcaltachia), secretion of insulin by pancreatic β-cells, opening of voltage-gated Ca^{2+} and Cl^- channels

in osteoblasts, and the rapid migration of endothelial cells [76].

Dermatological Diseases

Many of the dermatological diseases are associated with mutations in various structural cytoskeletal proteins, including keratins, and in transport proteins (pumps). In several dermatological diseases, crucial regulatory proteins and cytokines are also affected.

Acrokeratosis verruciformis is an autosomal dominant form of genodermatosis characterized by multiple plane wart-like lesions typically observed on the hands and feet. Mutations in the *ATP2A2* gene were shown to be associated with this disease and with *Darier's disease*, another genetic dermatologic disease that also involves mucous membranes [77]. In humans, multiple isoforms of sarco(endo)plasmic reticulum (SER) Ca^{2+} ATPase (SERCAla,b, SERCA2a-c, SECA3a-f) are generated by developmental or tissue-specific alternative splicing from 3 genes (*ATP2A1-3*). SERCA proteins represent a highly conserved family of Ca^{2+} pumps that actively transport Ca^{2+} from the cytosol to the SER against a large concentration gradient [78]. Fig. (**1H**) shows that although a member of this family, ATP2A2, is predicted to be mostly ordered, it has several disordered regions, likely located outside the membrane. It also has an alternatively spliced region at its C-terminus, which comprises a region of predicted disorder, a short ordered region, and a disordered tail. Mutations in another pump, a calcium and manganese pump SPCA1 (secretory pathway calcium/manganese-ATPase) encoded by the *ATP2C1* gene are responsible for the onset of the *Hailey-Hailey disease*.

Albinism is a complex genetic disease, which is a result of the melanin pigment deficiency in the skin, hair, and eye [oculocutaneous albinism (OCA)], or primarily in the eye [ocular albinism (OA)]. Albinism is associated with mutations in six genes, including the tyrosinase gene (*TYR*), the *OCA2* gene, the tyrosinase-related protein 1 gene (*TYRP1*), the Hermansky-Pudlak syndrome (*HPS*) gene, the Chediak-Higashi syndrome (*CHS*) gene, and the X-linked ocular albinism gene [79]. Tyrosinase is a glycosylated transmembrane copper-containing enzyme that is responsible for conversion of tyrosine to dopaquinone, which is the rate-limiting step in the melanin pathway [80]. The enzyme contains 529 amino acids, including an 18-amino acid signal peptide, two putative copper-binding sites, and a hydrophobic transmembrane region at the C-terminal end [81]. Tyrosinases are activated *in vivo* by limited proteolytic cleavage [82]. All these proteins are predicted to have long regions of intrinsic disorder [19].

Birt-Hogg-Dube syndrome is characterized by multiple noncancerous tumors of the hair follicles, particularly on the face, neck, and upper chest associated with the mutations in the *FLCN* gene encoding a tumor suppressor folliculin. Similarly, mutations in the cylindromatosis (*CYLD*) gene (encoding another tumor suppressor) are associated with a genetic syndrome *Familial cylindromatosis*, in which numerous benign tumors of skin adnexa (such as the sweat glands) develop, principally on the head and neck.

Cyclic ichthyosis with epidermolytic hyperkeratosis (also known as *Epidermolytic hyperkeratosis*) is associated with mutations in the 2B domain of keratin K1 and with the mutations in keratin K1 [83]. Mutations in this keratin are also associated with the *Epidermal nevus epidermolytic hyperkeratotic type* pathogenesis, which is characterized by growth or mark on the skin, such as a mole or birthmark [84]. Keratins are cytoskeleton proteins that are produced by a large family of the intermediate filament genes. Keratin-associated disorders are rather abundant, being caused by pathogenic keratin mutations in a total of 19 genes [85]. Some of these diseases are considered below. Mutations in K5 or K14 cause *Epidermolysis bullosa simplex*, in which the basal cells are fragile and may fracture if the epidermis is subjected to even quite mild physical trauma such as rubbing or scratching. *Epidermolytic palmoplantar keratoderma* is due to the mutations in Keratin 9. Mutations in stress response keratins K6, K16, and K17 are associated with *Pachyonychia congenita*, characterized by grossly thickened nails. K17 mutations have been found in a dominantly inherited condition characterized by cysts of sebaceous ducts and hair shaft, *Steatocystoma multiplex*. *Meesmann epithelial corneal dystrophy* originates from the mutated keratins K3 and K12. Mutations in keratin K2e have been associated with another form of epidermal blistering and superficial skin thickening known as *Ichthyosis bullosa of Siemens*. *White sponge naevus* affects buccal mucosa and other orogenital epithelia, producing plaques of loosened white epithelium and is associated with the dominant mutations in keratins K4 and K13. Mutations in hair keratins are associated with *Monilethrix* and *Ectodermal dysplasia of hair and nail type*, whereas mutations in hair follicle-specific epithelial keratins are responsible for *Pseudofolliculitis barbae* [86].

Dyskeratosis congenita is characterized by multiple features including mucocutaneous abnormalities, bone marrow failure and an increased predisposition to cancer. X-linked recessive dyskeratosis congenita bears mutations in *DKC1*, the gene encoding dyskerin, a component of H/ACA small nucleolar ribonucleoprotein particles; autosomal dominant form of the disease has heterozygous mutations in either *TERC* or *TERT* genes, encoding the RNA and enzymatic components of telomerase, respectively [87]. *Griscelli syndrome*, being defined by the characteristic hypopigmentation, is caused by the knock out of the RAB27 gene that encodes Rab27A protein, a member of the Ras-associated binding (Rab) proteins and Rab-associated proteins that are key regulators of vesicle transport essential for the delivery of proteins to specific intracellular locations. *Kindler syndrome* (characterized by the propensity to blister with minor trauma) is associated with mutations in the *KIND1* gene encoding kindlin-1, a protein that regulates interactions between actin and the extracellular matrix [88].

Netherton syndrome, a form of ichthyosis (a genetic dermatological diseases caused by an abnormality in skin growth that results in drying and scaling), is associated with the mutations in the *SPINK5* gene encoding serine peptidase inhibitor Kazal type 5, a protein containing two classical Kazal-type and 13 non-Kazal-type domains, which may be crucial for epidermal cell growth and differentiation [89]. *Piebaldism* is characterized by the congenital absence of melanocytes in affected areas of the skin and hair, due to

mutations of the *KIT* proto-oncogene. The *KIT* gene encodes the cell-surface receptor transmembrane tyrosine kinase for the steel factor, an embryonic growth factor, mutations in which affects differentiation and migration of melanoblasts [90]. *Psoriasis* is characterized by inflamed lesions covered with silvery-white scabs of dead skin. The following cytokines are directly involved in psoriasis: TNF, IL-1, IL-2, IL-6, IL-7, IL-8, IL-15, IL-18, IL-19, IL-20, IL-23 whereas IL-4, IL-10, IL-12 as well as IL-11, IL-17 and IFN-gamma are rather indirectly engaged [91]. *Psoriatic arthritis* is an inflammatory arthritis associated with psoriasis. Similar to psoriasis, it is associated with mutations in genes encoding cytokines, e.g., TNF-alpha and IL-12/23 [92].

Pyogenic sterile arthritism, pyoderma gangrenosum and acne syndrome are members of the family of autoinflammatory diseases, which are caused by primary dysfunction of the innate immune system. This syndrome is due to the mutations in the *PSTPIP1* gene encoding proline/serine/threonine phosphatase-interacting protein 1, a cytoskeletal protein co-localizing with actin filaments that can be dephosphorylated by proline, glutamate, serine, threonine (PEST)-type tyrosine phosphatase (PTP-PEST). Co-localization with actin filaments likewise guide the PTP-PEST towards dephosphorylation of Wiscott–Aldrich syndrome protein (WASP) [93].

Restrictive dermopathy is a rare form of the laminopathy that is lethal for the newborn in the neonatal period. It is caused by dominant mutations of the *LMNA* (primary laminopathy) or recessive mutations of the *ZMPSTE24* (*FACE1*) (secondary laminopathy) genes. The LMNA gene encodes lamin A/C, which belongs to type V intermediate filaments and constitutes the nuclear lamina and nuclear matrix, where a variety of nuclear activities occur [94]. *Xeroderma pigmentosum* is a rare DNA repair disease characterized by extreme sensitivity to sunlight and severe predisposition to UV-induced skin cancer. Seven genes, ranging from *XPA* to *XPG*, are defective in xeroderma pigmentosum [95]. Structural analysis of the DNA-repair protein XPA, which is a crucial component of the nucleotide excision repair pathway, revealed that a significant part of this protein is highly disordered [96].

Cancer

Abundance of intrinsic disorder in various cancer-related proteins was a subject of the thorough bioinformatics study, which revealed that ~80% of human cancer-associated proteins possess long IDRs [16]. An illustrative example of highly disordered cancer-related proteins is breast cancer 1 early onset protein, BRCA1. Women with the *BRCA1* mutations are susceptible to the development of a breast cancer before age 35–40 and of an ovarian cancer with a probability rate of, respectively, 45%–60% and 20%–40% [97]. BRCA1 participates in many different cellular pathways, including transcription, apoptosis and DNA repair, through direct or indirect interaction with a variety of partners [98]. It has multiple alternatively spliced isoforms. One of the most studied BRCA1 isoform has 1863 amino acids and comprises a long highly disordered central region flanked by ordered domains at the two termini. At the N-terminus is a RING finger domain of 103 residues. This domain is reported to form a heterodimer with BARD1 (BRCA1 associated RING domain 1) and to bind to the ubiquitin carboxy-terminal hydrolase BAP1. At the C-terminus are two tandem copies of the BRCA1 C-terminal domain (BRCT) with 218 total residues for the two domains. These two domains are reported to bind with transcriptional activators and repressors like CtlP. The structural characterization by various spectroscopic techniques revealed that the 1500 amino acid long central region of BRCA1 is completely disordered [99]. However this disordered central region contains molecular recognition domains for both DNA and several protein binding partners, including tumor suppressors such as p53, retinoblastoma protein (RB) and BRCA2; oncogenes like c-Myc and JunB; DNA damage repair proteins such as Rad50 and Rad51; and the Fanconi anemia protein (FANCA) [99]. Importantly, BRCA1 was shown to have at least 24 alternatively spliced isoforms [100]. Alternative splicing was shown to affect mostly central IDR of BRCA1 modulating its functionality by removing different functional domains [29]. In agreement with these impressive experimental data, Fig. (**1I**) clearly shows that BRCA1 is predicted to be highly disordered, possesses several α-MoRFs and multiple regions of alternative splicing.

Developmental Diseases

Developmental diseases occur at various stages of the child development, often retarding the development. Many of these diseases are associated with malfunction of regulatory proteins and transcription factors and therefore are expected to be enriched in IDPs.

Angelman syndrome is characterized by a severe mental retardation, absence of speech, microcephaly, facial dysmorphism, seizures, neonatal hypotonia, ataxic movements, and a characteristic happy and excitable demeanor. It is due to the failure to inherit a normal active maternal copy of the ubiquitin protein ligase E3A (UBE3A) either via deletion of the 15q11-13 region of the maternal chromosome 15 or via the uniparental paternal disomy, defects in imprinting and single point mutations in the *UBE3A* gene [101]. Trisomy 15 (extra copy of chromosome 15) is one of the causes of *Holoprosencephaly*, a pathology characherized by failure of the forebrain to grow as two separate hemispheres in the first few weeks of fetal life. Mutations in another gene located on chromosome 15, *NIPBL*, are linked to the *Cornelia de Lange syndrome*, which is a multiple malformation disease characterized by dysmorphic facial features, mental retardation, growth delay and limb reduction defects [102]. *NIPBL* encodes one of the developmental regulators, delangin, which regulates sister chromatid cohesion [103]. Fig. (**1J**) clearly shows that nipped-B homolog from drosophila (NIPBL) has several long disordered regions, an α-MoRF and an alternatively spliced region at its C-terminus, which comprises a region of predicted disorder, an ordered region, and a disordered tail. *Cleft lip/palate ectodermal dysplasia syndrome* is caused by the mutations in the p63 protein, an ectoderm-specific p53-related transcription factor [56]. *Focal cortical dysplasia* caused by the mutations in cyclin-dependent kinase 5 is the most common malformation of cortical development characterized by cortical mislamination, dysplastic neurons and, in a subgroup of cases, balloon cells [104]. *Growth retardation with deafness and mental retardation*

due to IGF1 deficiency is due to the mutations in the insulin-like growth factor I, which plays a crucial role in fetoplacental growth throughout gestation and also affects the growth of individual fetal tissues and influences the uptake and utilization of nutrients by the fetal and placental tissues [105]. *Left-right axis malformations* are associated with mutations in *ACVR2B*, the gene for human activin receptor type IIB, a member of the TGFb family of cell-signaling molecules [106].

Leprechaunism is a rare, usually fatal, autosomal recessive disease caused by mutations in the insulin receptor gene and characterized by intra-uterine and postnatal growth restriction, lipo-atrophy, characteristic facial features, acanthosis nigricans, abnormal glucose homeostasis and severe insulin resistance. *McKusick-Kaufman syndrome* is characterized by developmental anomalies, including vaginal atresia with hydrometrocolpos, polydactyly, and congenital heart defects. It is associated with the mutations in the *MKKS* gene that encodes a centrosome-shuttling protein with weak but significant similarity to group II chaperonins [107]. *Mowat-Wilson syndrome* caused by the mutations in the transcriptional repressor *ZFHX1B* gene on the chromosome 2q22–q23 [108]. *Noonan syndrome* is characterized by facial anomalies, postnatal growth retardation, webbing of the neck, pectus excavatum/carinatum, pulmonic stenosis and undescended testicles in boys. This syndrome is caused by the mutations in the PTPN11 gene on chromosome 12, resulting in a gain of function of the non-receptor protein tyrosine phosphatase SHP-2 protein [109].

Persistent Müllerian duct syndrome is characterized by the presence of a uterus and sometimes other müllerian duct derivatives in a male. It is associated with the mutations in the *AMH* gene that encodes a member of the transforming growth factor-β (TGF-β) superfamily, anti-Müllerian hormone (AMH), produced by Sertoli cells of the fetal testis from 7 weeks gestation. The AMH gene product is responsible for the regression of Müllerian ducts in male fetuses, the first step of male sex differentiation of the genital tract [110]. *Roberts syndrome* is characterized by pre and postnatal growth retardation, severe shortening of limbs with radial defects, oligodactyly and characteristic facial features. Mutations in the *ESCO2* gene, encoding an acetyltransferase that is required for the establishment of sister chromatid cohesion during S phase, are associated with this syndrome. Esco2 was shown to interact with several component proteins of the CoREST complex, including a transcription corepressor CoREST, histone demethlyase LSD1, HDAC1, HDAC2, BRAF35, and PHF21A [111]. *Saethre-Chotzen syndrome* is characterized by premature closure of one or more of the sutures between the bones of the skull and is associated with mutations in the Twist transcription factor [112]. *Seckel syndrome* is an autosomal recessive disease presenting with microcephalic dwarfism, mental retardation and facial and skeletal abnormalities. It is associated with mutations in the *PCTN* gene, which encodes a centrosomal protein pericentrin [113].

Sotos syndrome is an overgrowth condition characterized by excessive growth during childhood, macrocephaly, distinctive facial gestalt and various degrees of learning difficulty. Mutations and deletions of the *NSD1* gene coding for a histone methyltransferase implicated in transcriptional regulation are responsible for more than 75% of cases [114]. Mutations in the *NSD1* gene are also associated with the *Weaver syndrome.*

Treacher Collins mandibulofacial dysostosis is an autosomal dominant disease of craniofacial development resulting from loss-of-function mutations in the gene *TCOF1* that encodes the nucleolar phosphoprotein, treacle, which plays a key role in pre-ribosomal processing and ribosomal biogenesis [115]. *Trichorhinophalangeal syndrome* is characterized by alopecia, facial dysmorphism and bone deformities. It is associated with deletions and nonsense mutations of the *TRPS1* gene encoding a presumptive GATA DNA-binding domain [116].

Multi-Class Diseases

This dataset includes diseases that were assigned to class "Multiple" by the authors of the original study [28]. Unfortunately, for diseases in "multiple" class, the multiple classes that they belong to were not listed. As it will be seen from several illustrative examples below, diseases from this class are manifested by syptoms that could be simultaneously assigned to two or more disease classes, but they are still mostly caused by mutations in a single gene. This class is one of the mostly populated datasets in our study (see Table 1 in [27]). It includes 155 diseases. Because of the space limitations, we cannot cover all these diseases and therefore provide below only a few illustrative examples that were were randomly chosen from the published list of multi-class diseases [28]. Detailed analysis of this very intersting class of proteins is in progress and its results will be published elsewhere.

Aarskog-Scott syndrome (also know as *Faciogenital dysplasia*) is an X-linked malady characterized by craniofacial, skeletal, and urogenital malformations and short stature. This syndrome is associated with mutations in the FGD1 gene that encode a guanine nucleotide exchange factor (GEF). GEF specifically activates the Rho GTPase Cdc42 via its RhoGEF domain. The Cdc42 pathway is involved in skeletal formation and multiple aspects of neuronal development [117]. Fig. (**1K**) represents the results of disorder prediction and shows that FGD1 protein has several long diordered regions. *ABCD syndrome* is an autosomal recessive syndrome manifested by albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness. It is induced by the mutations in the endothelin B receptor (*EDNRB*) gene encoding endothelin B receptor, a member of the G protein-coupled receptors whose activation results in elevation of intracellular-free calcium [118]. Mutations in the *EDNRB* gene (together with the mutations in the endothelin-3 and *SOX10* genes) are also associated with another multi-class disease, *Waardenburg syndrome*, which is characterized by sensorineural deafness in association with pigmentary anomalies and defects of neural-crest-derived tissues [119]. *Acrocallosal syndrome* is a rare congenital disease characterized by absence or only partial formation of the corpus callosum accompanied by skull and facial malformations, and some degree of finger or toe malformations. Individuals may display motor and mental retardation. This malady is associated with the mutations in the nuclear receptor DAX1 [120].

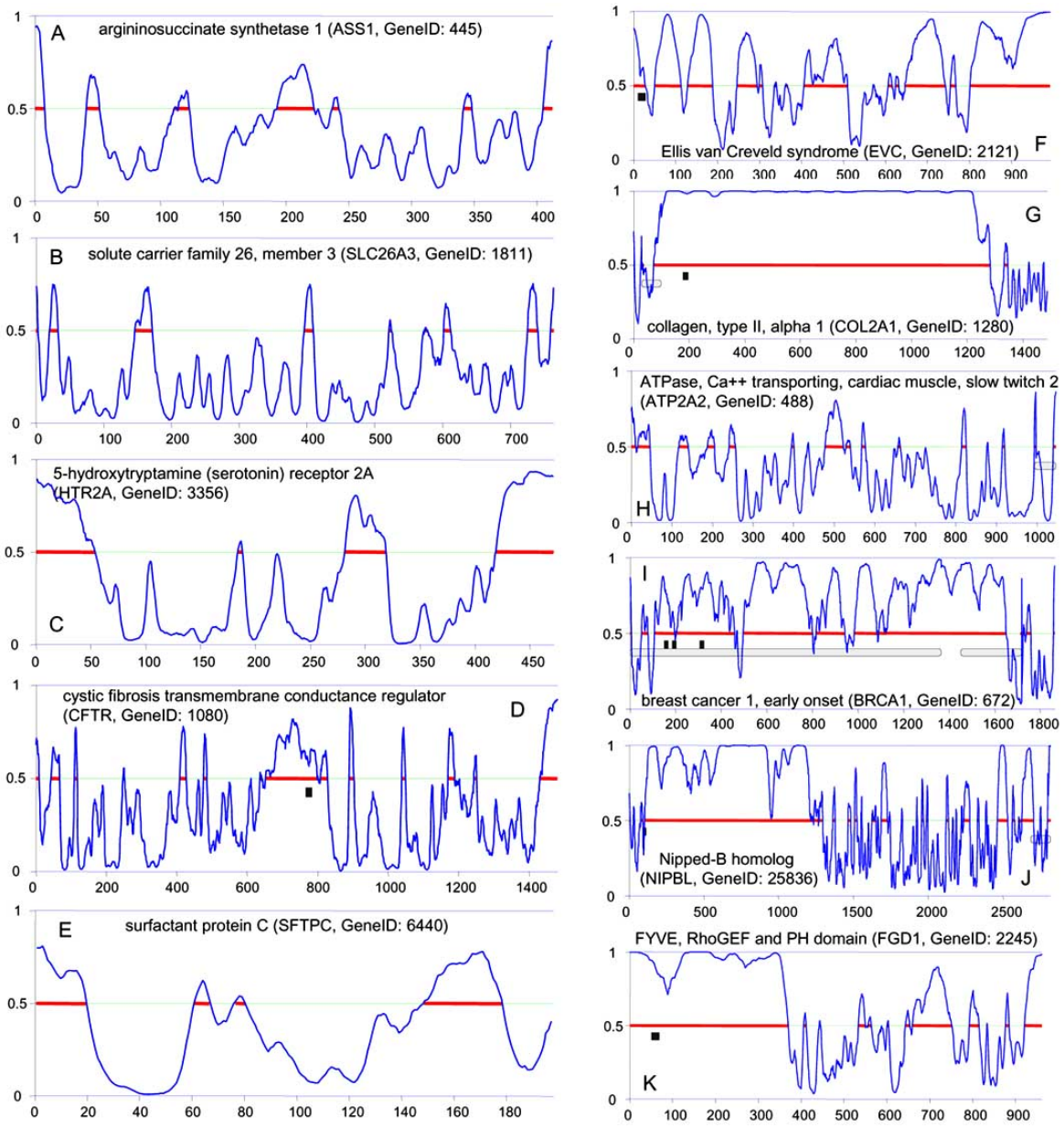

Figure 1. Results of intrinsic disorder predictions for representative genes from five classes of diseases with low levels of IDPs: metabolic diseases (ASS1), gastrointestinal diseases (SLC26A3), nutritional diseases (HTR2A), renal diseases (CFTR), respiratory diseases (SFTPC), as well as for representative genes from six classes of diseases with high levels of IDPs: skeletal diseases (EVC), bone diseases (COL2A1), dermatological diseases (ATP2A2), cancer (BRCA1), developmental diseases (NIPBL), multi-class diseases (FGD1). The horizontal line in the middle of a plot represents the threshold (0.5) used to map the real-valued prediction values into binary classification; the line is red and wider at positions classified as disordered. The positions of predicted molecular recognition features (MoRFs) are marked with black rectangles. The alternative-splicing (AS) regions are shown as light-gray oval rectangles.

Alagille syndrome affects the liver, heart, and other systems of the body and is caused by mutations in the *JAG1* gene encoding a ligand for the Notch receptor and therefore playing a crucial role in a critical signaling pathway during development [121].

Bardet-Biedl syndrome, being manifested by mental retardation, pigmentary retinopathy, polydactyly, obesity, and hypogenitalism, is associated with mutations in one or several of the 12 *BBS* genes, products of which, BBS proteins, are involved in crucial pathways such as the non-canonical Wnt and Sonic Hedgehog pathways [122]. *Bart-Pumphrey syndrome* is characterized by sensorineural hearing loss, palmoplantar keratoderma, knuckle pads, and leukonychia. It is caused by mutations in the *GJB2* gene encoding the gap junction protein connexin-26 [123]. *Carney complex* is characterized by myxomas, spotty pigmentation of the skin and mucous membranes, and endocrine overactivity, which are caused by the mutations in the *PRKAR1-α* gene that acts as a tumor-suppressor gene [124]. *Chediak-Higashi syndrome* is

characterized by hypopigmentation, recurrent infections, mild coagulation defects and varying neurologic problems. This malady is associated with mutations in the *CHS1/LYST* gene, which encodes the CHS1/LYST protein involved in vesicle fusion and/or fission [125]. *Cockayne syndrome* is characterized by dwarfism, precociously senile appearance, pigmentary degeneration of the retina, optic atrophy, deafness, sensitivity to sunlight, and mental retardation. It is caused by the mutations in the *ERCC6* and *ERCC8* genes encoding proteins involved in repairing damaged DNA by the transcription-coupled repair mechanism, particularly the DNA in active genes [126]. *Combined oxidative phosphorylation deficiency* is caused by the mutations in the *EFG1* gene than encodes mitochondrial elongation factor G1 [127].

Duane-radial ray syndrome (also know as Okihiro syndrome) affects the eyes and causes abnormalities of bones in the arms and hands. It is associated with the mutations in the *SALL4* gene, which is a member of the SALL family genes encoding transcription factors [128]. *Fraser syndrome* is characterized by cryptophthalmos, cutaneous syndactyly, malformations of the larynx and genitourinary tract, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal anomalies. Mutations in the extracellular matrix proteins Fras1 and Frem are associated with this syndrome [129]. *Hand-foot-uterus syndrome* is characterized by abnormalities of the hand, foot, urinary tract, and reproductive tract. It is associated with the mutations in the *HOXA13* gene encoding the transcription factor HOXA13, which is crucial for the normal development of the placental vascular labyrinth [130]. *Immunodeficiency-centromeric instability-facial anomalies syndrome* is characterized by immunodeficiency, mild facial dysmorphism, growth retardation, failure to thrive, psychomotor retardation, and by the characteristic rearrangements in the vicinity of the centromeres. This syndrome always involves limited hypomethylation of DNA and arises from mutations in one of the DNA methyltransferase genes (*DNMT3B*) [131]. *Keutel syndrome* (characterized by diffuse cartilage calcification, characteristic physiognomy, brachytelephalangism, peripheral pulmonary stenosis, hearing loss, and borderline to mild mental retardation) is caused by the mutations in the matrix Gla protein gene (*MGP*) encoding an extracellular matrix protein MGP that acts as a calcification inhibitor by repressing bone morphogenetic protein 2. Loss-of-function mutations of MGP result in abnormal calcification of the soft tissues [132]. *Limb-mammary syndrome* is characterized by split-hand-split-foot malformation (ectrodactyly) and aplasia or hypoplasia of the mammary gland and nipple. Similar to *ADULT syndrome* (manifested by ectrodactyly, syndactyly, fingernail and toenail dysplasia, hypoplastic breasts and nipples, intense freckling, lacrimal duct atresia, frontal alopecia, primary hypodontia, and loss of permanent teeth), *LADD syndrome* (that has aplasia or hypoplasia of the puncta with obstruction of the nasal lacrimal ducts, cup shaped pinnae with mixed hearing deficit, small and peg shaped lateral maxillary incisors, and mild enamel dysplasia), *EED syndrome* (characterised by the triad of ectrodactyly, ectodermal dysplasia, and facial clefting) and several other multy-class diseases, limb-mammary syndrome are due to the mutations in the p63 transcription factor [133].

McCune-Albright syndrome is defined by the clinical triad of polyostotic fibrous dysplasia, café-au-lait pigmented skin lesions and endocrinopathy. It is determined by the activation mutations in the *GNAS1* gene encoding the alpha subunit of the G protein [134]. Cells that carry the activating mutation are distributed in a mosaic pattern. *Nijmegen breakage syndrome* is characterized by microcephaly, growth retardation, immunodeficiency, chromosome instability, radiation sensitivity, and a strong predisposition to lymphoid malignancy. It is caused by the mutations in the *NBS1* gene encoding a protein nibrin, which forms a protein complex with Mre11 and Rad50, both involved in DNA repair [135]. *Otopalatodigital syndrome* is characterized by craniofacial, skeletal, visceral, brain, auditory and palatal defects. This syndrome is caused by gain of function mutations in the *FLNA* gene, which encodes filamin A, an actin-binding protein that regulates reorganization of the actin cytoskeleton by interacting with integrins, transmembrane receptor complexes, and second messengers [136]. *Pallister-Hall syndrome* is a disease that affects the development of many parts of the body. It is one of the multitude of diseases associated with mutations in the hedgehog signaling network that plays a key role in embryonic patterning. This syndrome is due to the mutations in the *GLI3* gene encoding a zinc finger transcription factor that is expressed early in development[137]. *Rabson-Mendenhall syndrome* is characterized by severe insulin resistance, extreme hyperinsulinemia, postprandial hyperglycemia, growth retardation, dysmorphisms and medullary sponge kidney due to the mutations in the insulin receptor gene [138]. *Simpson-Golabi-Behmel syndrome* (characterized by macroglossia, macrosomia, and renal and skeletal abnormalities as well as an increased risk of embryonal cancers) is due to the deletions or point mutations involving the glypican-3 (*GPC3*) gene that encodes an extracellular proteoglycan, glypican-3 playing an important role in growth control in embryonic mesodermal tissues in which it is selectively expressed [139]. *Townes-Brocks syndrome* is defined by imperforate anus, hand anomalies, and ear malformations with sensorineural hearing loss. It is associated with the mutations in the *SALL1* gene encoding a zinc finger transcription factor [140]. *Ulnar-mammary syndrome* is characterized by hypoplasia or aplasia of upper limbs on the ulnar side, mammary glands and nipples, and of apocrine glands in both sexes. It is linked to the mutations in the *TBX3* gene, a member of the T-box gene family that encodes a large family of transcription factors with more than 20 members [141]. *Yemenite deaf-blind hypopigmentation syndrome* is characterized by severe early hearing loss, microcornea and colobomata, and cutaneous pigmentation abnormalities. It is associated with mutations in the *SOX10* gene that encodes SOX10 protein, a member of the family of transcription factors that are characterized by a DNA-binding domain similar to the HMG domain of the sex determining factor SRY and are therefore able to bind and bend DNA [142].

SUMMARY COMMENTS

Sporadic mutations, known as "experiments of nature" can lead to altered phenotypes. Studying nature's experiments has long been a source to gain a deeper understanding of the relationships between genotype and phenotype. Here

we are using this approach to compare the roles of structured proteins with the roles of intrinsically disordered proteins. Our previous work suggests that structured proteins primarily function as enzymes, as binders of small ligands, or as transport proteins, while intrinsically disordered proteins and regions most often function in molecular recognition, regulation, and signaling [2, 3, 5-9, 13, 16-22, 50, 143]. Here we have studied more than 40 mutations associated with structured proteins and more than 90 mutations associated with proteins rich in intrinsic disorder. In those cases for which the studies have reached the molecular level, there is a consistency with the concepts that mutations in structured proteins are affecting catalysis or transport, while mutations in disordered regions are affecting signaling processes.

An interesting case is provided by the p63 protein, mutations of which were found to be associated with a diverse set of genetic diseases. This protein is a member of the homologous p53, p63, and p73 group. While p53 is established as a key tumor suppressor, p73 appears to be especially important in neurogenesis, sensory pathways and homeostatic control, while p63 is a critical player in the development of stratified epithelial tissues such as epidermis, breast and prostate [144]. Thus, many mutations in p53 are associated with the loss of its tumor-suppressor function and thus with the development cancer, while mutations in p63, on the other hand, are more often associated with various developmental disorders as discussed above.

Of course, enzyme catalysis often contributes to signaling and disordered regions are often used to regulate enzyme catalysis. Thus, it is no surprise that there is no clear separation between the types of genetic diseases associated with mutations in structured proteins as compared to mutations in disordered regions. Further analysis of the changes in the molecular biology that arise from mutations in structured as compared to disordered regions of proteins will be an important source of better understanding of the molecular mechanisms that underlie the pathogenesis of human genetic diseases.

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LIST OF ABBREVIATIONS

ID = Intrinsic disorder

IDP = Intrinsically disordered protein

IDR = Intrinsically disordered region

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