Haploinsufficency in human diseases:A mini-review

Abstract

Human disease studies have identified several hundred haploinsufficient genes affecting a range of phenotypes and cause of several diseases. Haploinsufficency (HI) results due to single functional copy of a gene. In this mini-review we review the topic of HI with reference tocauses,study models and detection methods.Further, we highlight the genetic, clinical, and pathological implications of the mechanism. Finally, the potential clinical applications are discussed. The study of HI therefore assumes significance since its spectrum extends to the realm of biophysics, gene expression, chromosome biology, quantitative traits, and evolutionary biology.

Key words: Haploinsufficency,Dosage effects, heterozygous mutations, Loss of functions, Fitness consequences.

1. Introduction

Haploinsufficency (HI) is defined as insufficient function to maintain a wild-type phenotype in the presence of one wild-type allele and one mutant allele(Adam F Johnson et al., 2019). (HI) can arise through mutations that lead to loss of function, or partial or complete loss of expression of one allele. Occasionally haploinsufficency can be additive or unlinked. Such genetic interactions are interesting to biologists for as they provide evidences two gene products physically interact or cooperate in a network. In case of sex-linked linked to mutation of one gene copy may help identify pathways that are limiting for cellular function. Whereas, in the case of autosomal dominance the HI interfere with wild-type function from mutations that do not interfere with function of the remaining wild-type allele(Fuller et al., 2019). Heterozygosity may be deleterious in diploid organisms because it may disrupt a proper balance between various components within a complex or network. Many critical cellular processes must be exquisitely sensitive to the dosage of their effectors.

Historical studies of dosage preceding HI-The link between gene deletions and disease was not recognized until advancements in human karyotyping made reliable analysis possible (Lejeune et al., 1963). Most mutant alleles are recessive, meaning a single normal allele (haplosufficient, HS) maintains the typical phenotype.The dominance of wild-type alleles has been debated for nearly a century. Fisher (1928) suggested that modifier genes evolved to counteract mutant effects, while Wright (1934) argued that recessiveness arises from biochemical properties, as enzyme activity plateaus beyond a certain concentration. Later studies favored Wright's simpler model (Kondrashov&Koonin, 2004). Kacser& Burns (1981) suggested metabolic control analysis, showing that a 50% enzyme reduction often has minimal impact, especially in long metabolic pathways. Additional evidences using*S. cerevisiae*genome-wide knockout library (Deutschbauer*et al*.,2005) found that ~3% of yeast genes exhibit HI.Notably, essential and nonessential HI strains show similar fitness, and only 98 of 1102 essential genes are HI suggesting a complex link between gene essentiality and HI.

All branches of life, from bacteria to humans, carry HI which they accumulate throughout development and life term. As a result their genome may contain amplifications and deletions,

inactivated genes, or gains and loss of whole chromosomes. At the allelic level they include spectrum of mutations involve gene inactivation-point mutations, single nucleotide insertions and deletions(https://www.nature.com/scitable/). The mutational event depends on the cellular process affected and location in the genome. For example, sub-chromosomal rearrangements are particularly likely to occur in repetitive areas of the genome, whereas whole chromosomal gains and losses are only likely to occur during cell division. Finally, HI can occur due to errors in mitosis or meiosis can result from perturbation to the mitotic machinery, or the chromosome surveillance mechanisms. (Rendy Hosea et al., 2024). Whole genome duplication (WGD)-throughout eukaryotic evolution, genomes undergoes increase in ploidy (Anthony Levasseur and Pierre Pontarotti 2011 14).Model organisms such as *Saccharomyces cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster* have been instrumental in the cellular and biological studies of HI.

2.Genetic and cellular causes

A phenotype may manifest when the reduced function at two separate loci present in combination (termed unlinked non-complementation) exhibits the additive nature of HI. According to several researchers, mechanistic and evolutionary forces drive HI. An example is the imbalance due to Arid1b protein. HI produces abnormal gamma-aminobutyric acid (GABA) neurotransmission Moffat *et al*. (2019). The gene has been linked to autism spectrum disorder (ASD) and intellectual disability (ID) (Santen *et al*., 2012; Santen *et al*., 2014).Altered epigenetic modifications are associated with HI. The *ARID1B* gene encodes 1B (ARID1B), an AT-rich-interactive-domain-containing protein that is a subunit of the chromatin remodeling complex, BRG1/BRM-associated factor (BAF), which regulates expression via nucleosome remodeling (Singhal *et al*., 2010; Alver *et al*., 2017). An example of cellular manifestation is the survival motor neuron gene (*SMN2*). *SMN2* is a paralogue of the survival motor neuron 1 (*SMN1*) gene present in humans, but not other primates (Levasseur and Pontarotti 2020). *SMN1* mutations cause spinal muscular atrophy disease associated with progressive loss of motor neurons. Because of a noncoding point mutation, the *SMN2* mRNA splicing pattern typically lacks exon 7 and produces a truncated protein unable to complement the lack of SMN protein in patients.

Major theories aimed to explain the mechanisms of HI include the dosage balance hypothesis and the insufficient amounts hypothesis (Johnson *et al*., 2019; Morrill and Amon, 2019). The latter attributes HI to a stoichiometric imbalance of members of a protein complex, whereas the former claims that the reduced quantity of protein that is produced is insufficient for keeping its normal function. Explanation by several researchers on the insufficient amounts hypothesis suggests that transcriptional regulators work close to a threshold level, thus making the system extremely dosage sensitive (Veitia, 2002).The hypothesis is based on transcription factor (TF) cooperativity and positive feedback. Figure 2 is a pictorial depiction of the mechanisms. Using a systems-biology perspective, Roman Zug's (2022) explain cell fate decisions as bi-stable switches, requiring both positive feedback and cooperativity. The author proposes that HI of transcriptional regulators, as well as associated (developmental disorders (DDs), result from disruption of bi-stability (i.e., disruption of positive feedback or cooperativity) in the gene regulatory network (GRN) underlying the cell fate decision in several cells involved in hematopoiesis (Palii *et al*., 2019), neurogenesis (Faure *et al*., 2020), gonad development (Stévant*et al*., 2019), and other cells.

Several TFs (in their activation domains) and cofactors possess substantial intrinsically disordered regions (IDRs), which serve as the source of cooperativity (Liu *et al*., 2006; Dyson and Wright, 2016). Few examples include the PAX6 and SOX2 during eye development (Kamachi*et al*., 2001 30), PAX3 and SOX10 during neural crest development (Bondurand*et al*., 2000), and FLI1 and GATA2 during hematopoiesis (Shi *et al*., 2014), and several others are crucial to cell fate determination (and whose HI results in DDs). The positive feedback loops between master TFs and their super enhancers (SEs) become particularly sensitive to changes in TF/cofactor concentration owing to the high level of cooperativity found at (SEs), through several binding sites of TF and transcriptional regulators (Hnisz*et al*. (2017). When cells shift towards one fate, the dose sensitivity becomes evident. Furthermore, decline in TF levels causes de-activation. Finally,coo-operativity may be mediated by a number of indirect processes, such as cofactors, or by direct TF–TF interactions (Spitz and Furlong, 2012; Reiter *et al*., 2017).

3. **Models to study haploinsufficency (cellular and animal)**

3.1. Cellular advances in modeling human diseases using patient-cultured cells—fibroblasts, HeLa cells, and pluripotent stem cells (iPSCs)—have revolutionized biomedical research, paving the way for human disease research. These methods have been complemented with gene editing methods such as clustered regularly interspaced short palindromic repeats (CRISPR). Several researchers have successfully demonstrated the use of these methods to study human mutations) in wide spectrum of neuropsychiatric diseases. The preceding paragraphs enlist a representative list.

a. human embryonic stem cells (hESCs). Arel-Gallily*et al*., 2022 using human embryonic stem cells (hESCs) and the CRISPR method, established a heterozygous genome-wide loss-of-function (HI) library. The study highlights over 600 essential (HI) genes enriched in several pathways, with the WNT and TGF-b pathways being the major affected. In another example, Niggle *et al*., 2023 report that in the heterogeneous nuclear ribonucleoprotein (*HNRNPC)* gene (HI) affects alternative splicing of intellectual disability using induced pluripotent stem cells (iPSCs) due defective mRNA processing. With several advances and modifications in the methods, several neuropsychiatric diseases are now amenable to iPSC and several researchers have used them to study cellular and molecular mechanisms of disease.

b. Patient cultured cells (fibroblast) Schuster *et al*., 2022, report the generation of dermal fibroblasts from a patient with Dravet syndrome carrying a deletion on chromosome 2 encompassing *SCN1A* and flanking genes. Dravet syndrome is an early-onset, devastating epilepsy syndrome caused by heterozygous mutations in *SCN1A*. In another example, James *et al*., 2024 demonstrates altered mitochondrial function in fibroblast cell lines of carriers of SMA, an childhood-onset neuromuscular disease. Major findings include depolarized mitochondrial membrane potential, increased levels of reactive oxygen species, and reduced citrate synthase activity.

c. HeLa cell lines. Salviati *et al*., 2012 report HI of genes involved in CoQ10 biosynthesis. (*COQ4)-The* coenzyme Q4 gene encodes a protein that organizes the multi-enzyme complex for the synthesis of coenzyme Q10 (CoQ10). HeLa cells demonstrated reduction of CoQ10. Neuromuscular symptoms include mental retardation, encephalomyopathy and dysmorphic features. In another example Alghusen*et al*., 2023 report O-GlcNAcmisregulation in the

mitochondrial integrated stress response by regulating ATF4 in Alzheimer's disease (AD). Several neuropsychiatric diseases are now cultured *in cellulo* to gain insights into the cellular and molecular mechanisms of diseases.

d. Yeast. Yeasts have been instrumental in gaining insights into the molecular basis of many human disorders, particularly those resulting from impaired cellular metabolism owing to the conservation of several cellular and metabolic proteins. Ficociello *et al*., 2018 used yeasts as a model system to study the molecular basis of Hailey-Hailey disease (HHD), a skin disorder caused by HI of the gene ATPase secretory pathway Ca2+ transporting 1 *(ATP2C1) gene.* The study report defects in *PMR1* yeast ortholog of the gene with similarities with HHD-derived keratinocytes. Another example is of Parkinson's disease (PD) in which Fanning *et al*., 2019 demonstrate α-synuclein (αS) pathologically impacting the brain, a highly lipid-rich organ. Lipidomic investigations in human αS-expressing yeast show alterations in αS or lipid/fatty acid homeostasis.

3.2. Laboratory methods

At the clinical laboratory level, HI detection methods rely on CNV and exome sequencing. Variations in the number of copies of specific DNA segments can be detected using fluorescent in situ hybridization (FISH), comparative genomic hybridization (CGH), and high-resolution array-based tests based on array comparative genomic hybridization (or aCGH), SNP array technologies, and high-resolution microarrays. Exome sequencing identifies genetic variations in the protein-coding regions (exomes) of DNA. The method relies on the size advantage of the human exome and cost-effectiveness. A few examples of CNV and sequencing are listed below.

a. CNV (copy number variation array): Xi *et al*. 2024 report 1q22 microdeletion of 936.3 Kb in ASH1-like histone lysine methyltransferase gene using CNVs array in developmental delay and intellectual disability (DD/ID) in patients. The microdeletion involves 24 genes, including the *ASH1L* (also known as KMT2H and encoding a histone lysine methyltransferase) gene. The protein has a role in transcription and in excision repair of chemical induced mutations. In another example Houwer*et al*., 2024 report two novel variants in the GRN (progranulin) gene in frontotemporal lobar degeneration (FTLD). The pathogenicity of variants was supported by typical neuropathological features and reduced PGRN levels.

b. Exome sequencing: Wu and Li. 2022 report a total of 488 (33.5%) pathogenic variations among 1,457 global developmental/intellectual disabilities (GDD/ID) children cohorts, including cases of monogenic mutations and chromosomal microdeletions or micro-duplications. Rat hippocampal neurons overexpressing the variant showed an increase in NMDAR-induced currents; additionally, immunocytochemistry revealed reduced localization between the GluN2C subunit and 14-3-3 proteins during membrane trafficking. In the ionotropic receptor N-methyl-D-aspartate receptor (NMDA) type subunit-2C (GluN2C) gene (*GRIN2C*), Rubino *et al*., 2025 report a rare damaging variant in familial late-onset AD. The study enabled genetic discernment of late-onset of disease.

3.3. Animal models. Several animal models have been used to study HI; these include mice, Drosophila, zebrafish, and *Caenorhabditis elegans.* The preceding paragraph only lists a few examples to describe the range and applications.

a. Mice: Longakit*et al*., 2022 demonstrate Loss of Neurofibromatosis type 1(NF1) gene accelerated uveal and intra-dermal melanoma tumorigenesis. NF1 encodes the multifunctional tumor suppressor protein neurofibromin which regulates MAPK signaling. Transgenic mice demonstrate accelerated melanoma formation and/or growth in melanocytes and Schwann cells of peripheral nerves. RNA-seq analysis reveals cAMP signaling and myogenesis. In another example, Kaijie Ma *et al*., 2024, demonstrate autism-like social deficits in Ash1l HI mouse in the absent, small, or homeotic-like 1 a histone methyltransferase (*ASH1L*) gene. Mice displayed social deficits, increased self-grooming, and cognitive impairments. The neurons demonstrated the excitability of pneurons in the prefrontal cortex (PFC) with enhanced glutamatergic synaptic transmission, and diminished GABAergic synaptic inhibition.

b. *Drosophila*: Matsuoka *et al*., 2024 report HI of syntaxin-binding protein 1 (*STXBP1*) gene in encephalopathy with α-synucleinopathies. The protein plays an important role in synaptic vesicle docking and fusion. Pathology in *Drosophila melanogaster* overexpression analysis demonstrates partial loss-of-function mechanisms leading to reduction in brain size. Also exacerbation of eye, degeneration, locomotor dysfunction, and dopaminergic neurodegeneration with a significant increase in detergent-insoluble α-Syn levels. In another example Huang *et al*., 2024, report loss-of-function in retinoblastoma-binding protein *(5RBBP5)* results in a syndromic

neurodevelopmental disorder associated with microcephaly. RBBP5 encodes a core member of the protein complex that methylate's the histone-3 lysine-4. Epigenetic dysregulation has been associated with the disease. Variants affect evolutionarily conserved amino acids located at the interface between RBBP5 and the nucleosome.

c. Fish: Wu*et al*.,52 report impaired development of neural-crest cell-derived organs and (ID) caused by the mediator complex subunit 13Lp (*MED13L*) gene HI in zebrafish. Knockout of med13b ortholog showed early defective migration of cranial neural crest cells (NCCs) contributing to cartilage deformities. Abnormal distribution of developing neurons in different brain regions was observed. Finally, transcriptome analysis revealed differential expression of components of Wnt and FGF signaling pathways. In another example Sadler *et al*., 2020, report rare and *de novo* coding variants in chromo domain genes in Chiari I malformation (CM1), characterized by displacement of the cerebellum, a pediatric neurological condition. Genetic screening demonstrated significant enrichment of rare and *de novo* non-synonymous variants in the chromo domain. Finally, HI in zebrafish demonstrated macrocephaly and posterior hindbrain displacement reminiscent of CM1.

d. *Caenorhabditis elegans*: Robert *et al*., 2023 report HI in SIN3 Transcription Regulator Family Member A (*SIN3*) gene as the underlying cause of Witteveen-Kolk syndrome and related (ID) and autism syndromes. SIN-3 regulates the germline transcriptional program in *C. elegans* and gene expression through multiple interactions, such as histone deacetylases. In another example lazar *et al*., 2015, 55 report HI mutations in the human progranulin gene resulting in causing frontotemporal lobar degeneration with TAR DNA-binding protein-43 (TDP-43) inclusions. The progranulin cleavage products and granulins, exacerbate TDP-43 toxicity. *C. elegans* model demonstrated complete loss of the progranulin gene; however, it did not worsen TDP-43 toxicity, whereas the progranulin heterozygosity did.

4. Haploinsufficency in human diseases

The spectrum of human diseases affected by HI includes organs and organ systems and affects diverse cellular and metabolic pathways. In the following paragraphs, representative examples are discussed to highlight the aforementioned spectrum. For a detailed and updated list, the

reader is referred to OMIM and PubMed. Table-1 is a brief list of human diseases associated with haploinsufficency.

A novel condition with cytopenia and susceptibility to hematological malignancies is defined by the ETS-related gene (*ERG*) gene HI. The transcription factor ERG is essential for stem cell activity and hematopoiesis. ERG localizes to promoters or enhancers of genes that control hematopoiesis. Variants of the gene exhibit loss-of-function (LOF) traits, which interfere with nuclear localization, DNA binding, and/or transcriptional transactivation. In mouse model fetal liver cells are unable to induce myeloid differentiation as well as cytokine-independent proliferation. Zerella*et al*.,2024. Another example is the Mitochondrial Dynamin-Like GTPase (*OPA1*) gene. Mutations in the gene induce adult-onset and progressive auditory neuropathy in mice. OPA1, which codes for a major GTPase associated with mitochondrial dynamin. Ultrastructural examination reveals selective loss of sensory inner hair cells and degeneration of the axons and myelin sheaths. Also ahigher level of Opa1 mRNA expression supports HI as a disease mechanism. Affortit*et al*., 20.HI in the complement dysregulation is a key component in the pathogenesis of age-related macular degeneration (AMD) and early-onset macular drusen (EOMD). iPSCs of variants with loss of complement factor (CFH) and factor H-like protein 1 (FHL-1) display reduced mRNA expression and protein expression. Under inflammatory or oxidative stress conditions, CFH and FHL-1 expression paralleled that of controls, Lim RR 2024. In the genes expressed in kidney heterozygosity, inverted formin-2 (INF2) gene mutations cause focal segmental glomerulosclerosis (FSGS) with or without Charcot-Marie-Tooth disease. Knockout mice are susceptible to glomerular disease, in contrast to INF2 knockout mice after response to puromycin amino nucleoside (PAN)-induced kidney injury. Cellular measurements showed that mutation confers a gain-of-function effect. RNA expression analysis showed altered adhesion and mitochondria-related pathways. Podocytes in mice and human kidney organoids recapitulate adhesion and mitochondrial phenotypes. In skeletal disorders Subramanian *et al*., 2024 report pathogenic variants in the desmoplakin (*DSP*) gene encoding DSP, leading to heterogeneous skin, adnexa and heart-related phenotypes. DSP is a desmosomal component expressed in skin and heart, essential for desmosome stability and intermediate filament connection. Keratinocytes showed fragile cell-cell connections and perinuclear retracted intermediate filaments. EGFR upregulation was observed, implicating the use of EGFR

inhibitors as a therapeutic alternative. Epidermal growth factor receptor (EGFR) is a transmembrane protein expressed in the basal epidermal layer involved in proliferation and differentiation processes (Daniela *et al*., 2024).

Several genes confer HI in diabetes, such as the heterozygous mutations in the genes encoding transcriptional regulators, hepatocyte nuclear factor (HNF)-1alpha and HNF-4alpha, which cause maturity-onset diabetes of the young (MODY). MODY is a result of defective pancreatic islet cell functions. HNF-1alpha functions through genetic network that is activated during differentiation, allowing cells to maintain critical specialized functions. At the core lies a cross-regulatory feedback circuit between HNF-1alpha and HNF-4alpha. The loss of either gene allele s can increase the feedback circuit resulting in decreased expression of all four alleles selectively in beta-cells (Ferrer *et al*., 2002). Of the several genes expressed in the liver, the FERM Domain Containing Kindlin2 (*FERMT2*) gene codes for the Kindlin-2 protein. HI protects against fatty liver and glucose intolerance without affecting energy metabolism in mice by targeting. Kindlin-2 binds and stabilizes Foxo1 by inhibiting its ubiquitination and degradation through the Skp2 E3 ligase. Kindlin-2 overexpression in the liver exacerbates lipid metabolism disorder in hepatocytes through Foxo1 phosphorylation (Huanqing*et al*., 2022). Several genes are implicated in human intellectual disability and other associated diseases. AT-hook DNA binding motif containing 1 (*AHDC1*) HI causes Xia-Gibbs syndrome (XGS), a rare syndromic disorder characterized by developmental delay with intellectual disability, muscular hypotonic, brain anomalies, and nonspecific dysmorphic features. The interstitial deletion (1p36.11p35.3) encompasses the coding region of the *AHDC1* gene (Bertrand *et al.*, 2024). In the gastrointestinal (GI) Lynch syndrome (LS), the tract is susceptible to carcinogenesis. According to Knudson's two-hit hypothesis, tumors of (LS) patients exhibit high levels of microsatellite instability (MSI), which is caused by failure of DNA mismatch repair (MMR). Colon of knock-out mice indicate variable MLH1 levels are leading to tissue-specific MSI in advanced stages of neoplasia. Shrestha *et al*., 2021.

HI in several genes and networks involved in several human disorders, such as asthma, diabetes, cancer, and several other disorders, has been reported by several investigators. In the foregoing paragraph we describe a few representative genes and associated pathways. The reader is referred to PubMed for a detailed literature review. Few genes belonging to this category are

listed in Table-2. Transcription factor 3 (*TCF3*) is a transcription factor contributing to early lymphocyte differentiation. Germline mono-allelic dominant negative and bi-allelic loss-of-function (LOF) null *TCF3* mutations cause a fully penetrant severe immunodeficiency with reduced transcription or translation resulting in reduced wild-type TCF3 protein expression. and in B-cell defects. Murine TCF3 HI resulted in a reduction of circulating B cells RNA sequencing analysis implies gene-dosage effect (Boast *et al.*, 2023). Yan Li *et al.*, 2021 report HI in the Hedgehog interacting protein (*HHIP*) gene. HHIP protein represses airway remodeling and metabolic reprogramming in chronic obstructive pulmonary disease (COPD)-derived airway smooth muscle cells.

Several genes are implicated in cancer, which include oncogenes, tumor suppressor genes, and genes coding for several cellular pathways. AaRS-interacting multifunctional protein 3 (*AIMP3),* previously known as p18, a tumor suppressor gene, is shown to up-regulate p53 in response to DNA damage. *AIMP3* HI disrupts oncogene p53-induced activation and genomic stability. Growth factor- or Raps-dependent induction of p53 was blocked by loss of *AIMP3*. Heterozygous cells were susceptible to cell transformation induced by oncogenes Ras or Myc alone and displayed cell division and chromosomal structure abnormalities (Bum-Joon Park *et al.*, 2006). Another example is the serine-/arginine-rich splicing factor 2 gene (*SRSF2*). Recurrent mutations in the gene are common in neoplastic diseases. The gene plays pivotal roles in pre-mRNA processing and gene transcription and regulates bi-directional transcription of DNA replication and repair genes. HI induces DNA damage without halting the cell cycle. In mice, deletion or homozygous mutation both cause extensive DNA damage. Frost, Erin L. 2024**.**Numerous tumor suppressor genes (TSGs), including *p27Kip1*, *p53*, *DMP1*, *NF1*, and *PTEN,* have been found to exhibit HI, resulting in the cell's incapacity to carry out regular cellular tasks, aiding the growth of tumors. *AML1, EGR1, TGFβR1/2,* and *SMAD4* are among the recently identified TSGs in which (HI) is demonstrated. Both human samples and gene knockout mice models have validated these results. Multiple (HI) TSGs may collaborate in 5q-, 7q-, and 8q- disorders, according to recent research (Inoue and Fry 2017). Network analyses of genes in cancer are also reported. In ovarian cancer (OV) HI network (KEGG) pathways indicate autophagy and compensatory proteolysis pathways as significant (Delaney *et al.*, 2017).

Glycogen synthase kinase 3 (*GSK-3*) gene, which encodes a serine-threonine kinase with two isoforms (α-and β), is implicated in type 2 diabetes mellitus (T2D). Animal models of HI suggest an isoform-specific role of GSK-3 in high-fat diet (HFD)-induced obesity and glucose intolerance. Tamoxifen-inducible global GSK-3α/β gain implicates the dose-response effect of GSK-3 isoforms in heterozygote mice. Post-HFD, GSK-3α heterozygous and controls displayed a comparable phenotype; however they were significantly protected against glucose intolerance (Gupte *et al.*,2024). Another gene is the regulatory factor X 6 (*RFX6), indicated in* pancreatic endocrine development and differentiation. RFX6 HI predisposes to diabetes through impaired beta cell function. Heterozygous RFX6+/- SC-islets exhibited HI associated with reduced beta cell maturation. Allelic series suggest defective pancreatic beta cells, mirroring the phenotype observed in Mitchell-Riley syndrome (Ibrahim *et al.*, 2024).

HI affects several genes in the cardiac system. An example is the TGF-beta-activated kinase 1/MAP3K7 binding protein 2 gene (MAP3K7)causing congenital heart defects (CHDs). The role of HI of this gene is further supported by its conserved expression in the developing zebrafish heart and dosage sensitivity (Thienpont*et al*., 2010). Mutations in the lamin A/C (*LMNA*) gene which encodes nuclear membrane protein cause dilated cardiomyopathy (DCM) and apoptosis-triggered cardiac conduction system disease. HI caused early-onset programmed cell death of atrioventricular (AV) nodal myocytes and progressive electrophysiological disease. Conduction system investigations indicate (AV) nodal myocytes had abnormally shaped nuclei and active apoptosis. Telemetric and *in vivo* electrophysiological studies showed arrhythmias and impaired contractility (Wolf *et al*., 2008).

Finally, HI is demonstrated in several human multi-organ disorders; an example is reported by (Del Viso *et al*., 2025), where HI of *SF3B2* is associated with anomalies such as skeletal extra craniofacial, cardiac, renal, and abnormalities of the central nervous system (CNS). *De novo* or inherited variants have been associated with either or both inter- and interfamilial variability. In summary, HI affects several genes involved in several organs, organ, and multi-organ systems, reflecting their abrogating roles in the spectrum of cellular pathways and cellular mechanisms (functions, DNA replication, and recombination) and surveillance (DNA repair). Also, they affect metabolic and cardiac, blood, renal, and skeletal disorders.

5. Applications of HI and conclusion

The findings on model organisms have clarified few aspects regarding the molecular basis of HI. In the budding yeast, Saccharomyces cerevisiae, dosage-sensitive genes are believed to be either that interact widely with protein partners. In flowering plants, interaction networks(mathematical) or part of an essential metabolic pathway crucial elements shaping HI(Navarro-Quiles *et al.*,2024).Hence the phenomenon of HI extends to other eukaryotes. Hence, it can be used to test several gene produts and hypothesis.

From a human genetics perspective recent advancements in high-throughput sequencing and computational biology have enabled an exhaustive genome-wide study of HI loci in the human genome.Theobservation of dosage and balance hypothesis which explains why mutations affecting HI genes are often associated with dominantly inherited conditions, from congenital malformations to neoplasias.This will enable genetic-testing in the clinical setup(prenatal).Large-scale sequencing efforts to identify human genes that are intolerant to or under strong selection against heterozygous loss-of-function are sparking tremendous interest in HI and its role in disease etiology (Kaplanis *et al.*, 2020; Karczewski *et al.*, 2020). With increased recognition of age-related health problems globally, the role of insufficient DNA methylation and its effects on healthy aging is another area of intense research (Liu *et al.*, 2011). In the area of basic research, such as the pluripotent reprogramming factors, iPSC quality and efficiency studies the role of HI in pluripotent cells and affect developmental potential and their cell derivatives given significance (Benchetrit*et al.*, 2019; Sebban and Buganim 2015). A complete knockout of a single key pluripotency gene may drastically affect embryonic stem cell function and epigenetic reprogramming. Additionally, methylation can complicate the program. Defective telomerase activity is a key cause of various diseases due to telomerase RNA component (*TERC*) (Calado and Young 2009b). HI cause telomere shortening and is implicated in several diseases.

In summary ,high-throughput genomic data, computational modeling, and comparative analyses from different biological systems converge into an integrated understanding of the molecular and evolutionary basis for HI in humans. Such integration signifies that gene dosage, molecular interactions, and selective pressures are intimately interconnected, and thus provide vital insights into the pathogenesis of dosage-sensitive diseases and into the design of appropriate therapeutic strategies.The study of HI has important implications for human biomedical research. The author acknowledges that several areas of relevance to human biology, genetics have not been included in the review.

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Figures and tables

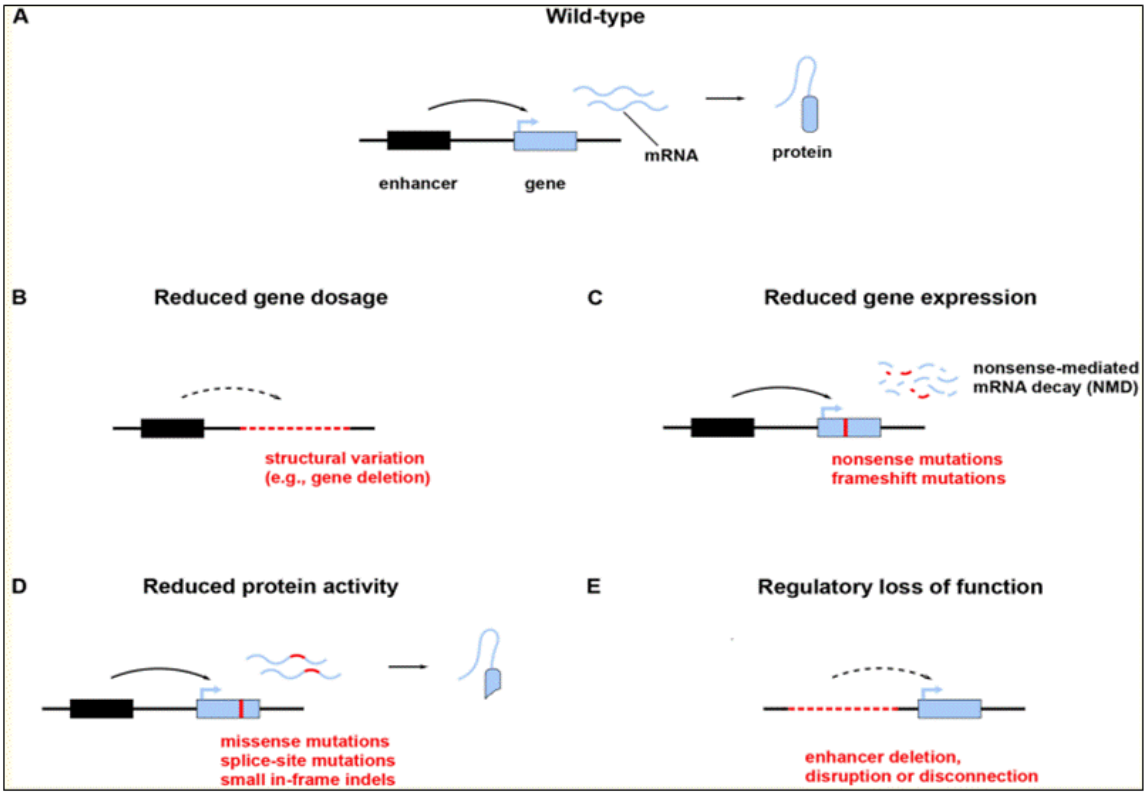

Figure-1 . Possible genetic and cellular consequenes of Haploinsufficieny(HI).Adapted from Roman Zug 2022.

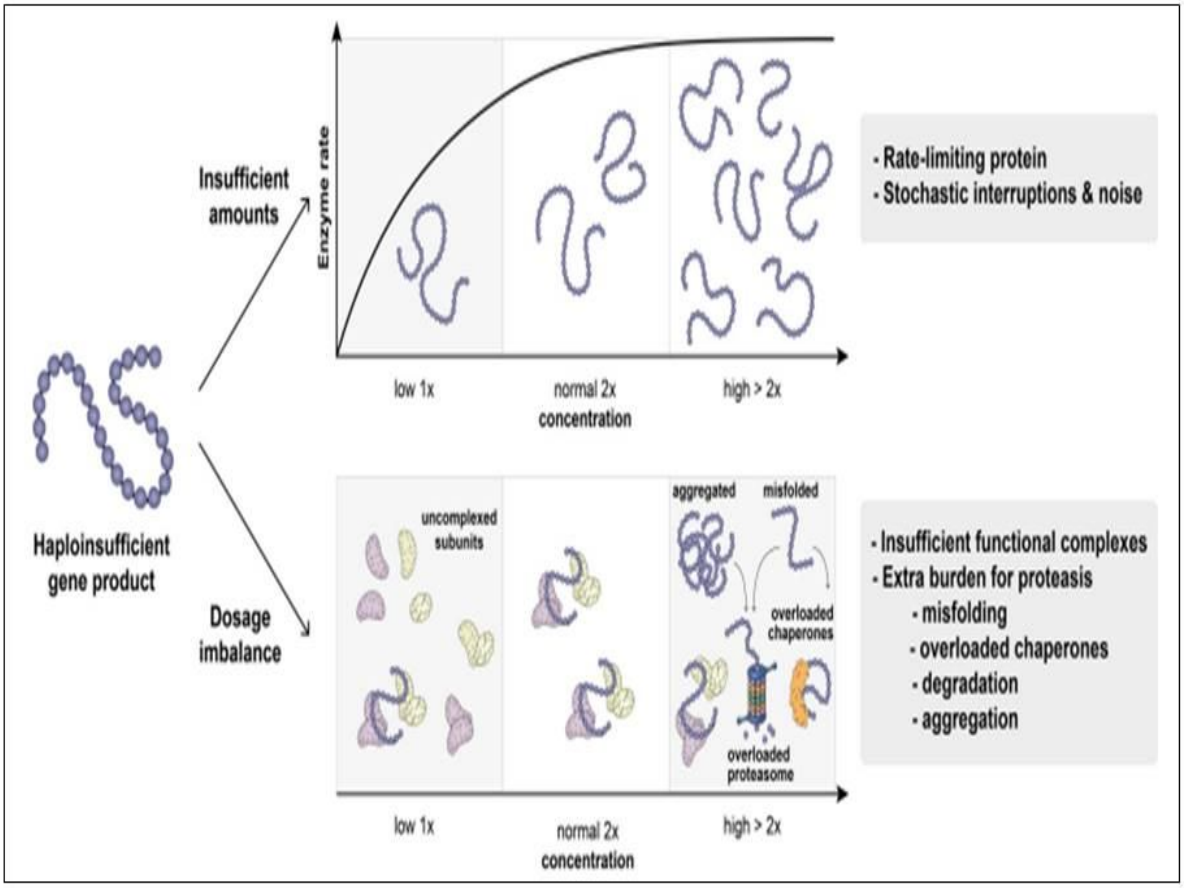

Figure-2. Molecular consequences due to gene dosage alterations.Adapted from M. Felicia BasilicataID, Claudia Isabelle Keller ValsecchiI 2021.

Table1.Brief list of human diseases associated with Haploinsufficency.

Sl. no	Disease	Gene involved	Organ involved/Major anomalies	Associated pathology	Reference
1	Xia-Gibbs Syndrome	AT-hook DNA binding motif containing 1AHDC1)	Intellectual disability, muscular hypotonia, brain anomalies.	Foot deformity, skin and connective tissue abnormalities.	Bertrand M *et al*., 2024
2	Nedlaad disorder	cell cycle associated protein 1(CAPRIN1)	Dysmorphic facial and digital, hand anomalies feature. Respiratory difficulties. Central nervous system.	Delay in walking, language delay, anomalies mainly of the corpus callosum. Mild hearing loss.	Pavinato L *et al*., 2024
3	Von recklinghausen disease	NF1 (Neuro fibromin gene)	Skin Lesions and afé-au-la spots on skin. Lisch Nodules on Iris.	Fibromatous tumors on skin.Benign and malignant tumor of skin.	William *et al* 2009
4	Autoimmune lymhoproliferative disease	cytotoxic T-lymphocyte associated protein 4(CTLA4)	Abnormal lymphocytic infiltration of non lymphoid organs include brain,lung and gastrointestinal tract.	Inflamatory lung lesions. Lymphocytic enteropathy.Seizures and Headache.	Lopez nevado*et al*., 2021
5	Leri-weill dyschondrosteosis	SHOX (homeobox SHOX)	Skeletal dysplasia of bone and cartilage,medulung wrist deformity includes proximal carpal bones.	Tibiofibular disproportion. Problems on limbs.	Ross *et al*., 2005
6	Niemann-pick disea	NPC intracellular cholesterol	Neurological abnormalities include ataxia, seizures. Loss	Amentia. Extension of spine and legs. Retinal degeneration.	Vance 2006

	se	transporter 1(NPC1)	of speech and myoclonic jerks.	Myoclonus or Bulbar involvement. Hepatosplenomegaly.	
7	Darier-white disease	ATPase sarcoplasmic/ endoplasmic reticulum Ca2+ transporting 2ATP2A2	Crusted plaques, painfullerosions,warty papules and plaques in seborrheic areas and distinctive nail abnormalities.	Bullous lesions.Multiple bone cysts resulting in non-traumatic fractures of the long bones.	Castori*et al*., 2009
8	Mowat-wilson syndrome	zinc finger E-box binding homeobox 2(ZEB2)	Impaired intellectual development. Delayed motor development.	Microcephaly. Mental retardation. Epilepsy.	Mowat *et al*., 2003
9	Charcot-marie-tooth dise ase, neuronal, type 2d	glycyl-tRNA synthetase 1(GARS1)	Muscle weakness.Distal sensory Impairment. Induced hand cramps.	Severe muscle weakness and atrophy of the hands and mild to moderate weakness of the feet. Scoliosis.	Yalcouye, A *et al*., 2019
10	William-beuren syndrome	membrane associated guanylate kinase, WW and PDZ domain containing 2(MAGI2)	Dental anomalies and peripheral pulmonary artery stenosis.	Abnormal scarring, wrinkles, soft skin, difference in skin elasticity.	Kozel BA *et al*., 2014

Table-2.Human clinical syndromes associated with haploinsufficency

Sl.no	Gene involved	Associated condition/brief description	Reference
1	transcription factor 3(TCF3	Immunodeficiency/B-cell Defects and reduced serum immunoglobulin	Boast B *et al*., 2023
2	Hedgehog interacting protein (HHIP)	Chronic obstructive pulmonary disease (COPD) Inhibited aerobic glycolysis and repressed cell proliferation.	Li Y*et al*., 2021
3	The serine-/arginine-rich splicing factor 2 (SRSF2)	Squamous cell carcinoma. DNA damage with cell cycle alterations. clonal expansion.	Frost, Erin L *et al*., 2024
4	The arginine methyltransferase (PRMT5)	Inflammatory bowel disease and colorectal cancer. reduced mucosal defense	Hernandez JE *et al*., 2023.
5	Filamin C (FLNC)	Cardiomyopathies,myofibrillar myopathy,cardiac arrhythmias.	Job A J Verdonschot*et al*., 2020
6	Paired like homeodomain 1(Pitx1)	Clubfoot, muscle hypoplasia	David M Alvarado *et al*., 2010.
7	OTU deubiquitinase with linear linkage specificity (OTULIN)	Fasciitis and skin necrosis, auto-inflammation	Rob J W Arts *et al*., 2023
8	Melanocortin 4 receptor (Mc4r)	Monogenic severe obesity, hyperphagia, hyperinsulinemia, and hyperglycemia.	Navneet Matharu *et al*., 2019
9	Protein associated with LIN7 1, MAGUK p55 family member (PALS1)	Defects in renal functions, proteinuria and cyst formation.	Thomas Weide *et al*., 2017
10	Nuclear receptor	Nonalcoholic fatty liver disease (NAFLD), insulin resistance.Non-alcoholic	Yueqi Zhang *et al*., 2024.

	coactivator 5 (NCOA5)	Steatohepatitis.	