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INTEGRATED NETWORK-BASED SYSTEMS BIOLOGY ANALYSIS OF HUTCHINSON-GILFORD PROGERIA SYNDROME IDENTIFIES CRITICAL MOLECULAR HUBS AND THERAPEUTIC TARGET AXES

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Abstract:

Hutchinson-Gilford Progeria Syndrome (HGPS) is an ultra-rare, fatal genetic disorder serving as a profound model for accelerated human aging. It is driven by a de novo point mutation in the LMNA gene, producing progerin, a mutant protein that severely disrupts nuclear mechanics, chromatin organization, and gene regulation. Because current therapeutic strategies fail to rectify the complex downstream network perturbations caused by this persistent nuclear injury, an integrated systems-level understanding is critical. This study employed an exhaustive bioinformatics pipeline to deconvolute HGPS molecular mechanisms. We curated 30 high-confidence HGPS-associated genes from DisGeNET and subjected them to multi-tiered analysis using GO, KEGG, Reactome, STRING, and GeneMANIA. Pathway analysis revealed profound, systemic dysregulation in NOTCH, PI3K-Akt-mTOR, and DNA Repair mechanisms. Protein-Protein Interaction (PPI) module analysis revealed distinct, densely connected functional clusters for genomic stability, metabolism, and fibrosis. Topological analysis identified TP53, LMNA, ATM, PPARG, and MMP2 as critical network bottlenecks. These findings support a "Nuclear-Metabolic Uncoupling" model, where chronic nuclear stress activates a TP53-dependent senescence response that paradoxically represses metabolic regulators like PPARG. This network-based approach highlights the TP53-senescence and PPARG-adipogenic axes as prime therapeutic targets.

Keywords: *Hutchinson-Gilford Progeria Syndrome, Bioinformatics, LMNA, Network Pharmacology, Systems Biology.*

Introduction

Hutchinson-Gilford Progeria Syndrome (HGPS) stands as one of the most scientifically illuminating and clinically devastating conditions in the spectrum of human genetic disease. It is a rare, fatal, segmental premature aging

disorder with an estimated prevalence of 1 in 4 to 8 million live births worldwide. Children born with HGPS typically appear normal at birth but, within the first year of life, begin to manifest a striking phenotype characterized by severe growth retardation, loss of subcutaneous fat (lipodystrophy), alopecia, distinct craniofacial features, and sclerodermatous skin changes. As the disease progresses, patients develop conditions usually reserved for the elderly, including severe osteoporosis, joint contractures, and, most critically, accelerated cardiovascular disease. The average life expectancy is approximately 14.5 years, with mortality almost exclusively driven by atherosclerosis-related complications such as myocardial infarction or stroke.

The genetic basis of HGPS was elucidated in 2003 as a sporadic, autosomal dominant mutation in the *LMNA* gene located on chromosome 1q22. In approximately 90% of cases, the classic mutation is a single nucleotide substitution: a cytosine-to-thymine transition at position 1824 (c.1824C>T) within exon 11. Although this mutation is silent at the amino acid level (p.Gly608Gly), it has catastrophic consequences for mRNA processing. The mutation creates a cryptic splice donor site that is preferentially utilized over the canonical site, leading to the deletion of 150 nucleotides (50 amino acids) near the C-terminus of the prelamin A protein.

Normally, prelamin A undergoes a series of post-translational modifications, including farnesylation of a C-terminal CAAX motif, followed by cleavage by the zinc metalloprotease *ZMPSTE24* to remove the farnesylated tail and produce mature lamin A. The deletion in HGPS removes the specific recognition site for *ZMPSTE24*, preventing this final cleavage step. The resulting mutant protein, termed "progerin," retains the farnesyl lipid anchor, causing it to remain permanently and aberrantly tethered to the inner nuclear membrane. This accumulation of progerin compromises the structural integrity of the nucleus, leading to blebbing of the nuclear envelope, disruption of nuclear pore complexes, loss of peripheral heterochromatin, and chaotic gene expression profiles.

Methodology

1. Bioinformatics pipeline and rationale for database selection

Bioinformatics employs a combination of sophisticated techniques to analyze data on genes, their genetic makeup, and associated diseases using several databases, each selected according to the type of analysis being performed. The intent of this study is to develop a comprehensive pipeline that follows the entire methodology from the identification of gene-disease associations to the elucidation of mechanistic pathways and potential drug targets.

- **DisGeNET** was chosen as the primary database for evidence-based curation of genes due to its extensive collection of known gene-disease associations from expert-curated repositories, GWAS catalogues, animal models, and scientific literature.[14]
- **STRING** was selected for the analysis of PPI networks. STRING encompasses both experimentally derived and predicted interactions, as well as associations from text mining and co-expression data.[16] This is crucial for HGPS, where the disease mechanism involves complex multiprotein assemblies at the nuclear lamina that may not be fully captured by physical interaction data alone.[17]
- **GeneMANIA** was selected to develop functional networks and predict gene functions. Unlike STRING, which relies heavily on known interactions, GeneMANIA uses a "guilt-by-association" algorithm across vast genomics datasets (co-expression, co-localization, genetic interactions) to prioritize novel genes that function within the same pathways as the query list.[18]
- **NetworkAnalyst** was chosen as the primary analysis platform for conducting topological analysis and multi-omics enrichment analysis. It provides a user-friendly interface for computing complex graph

metrics like betweenness centrality and degree centrality.

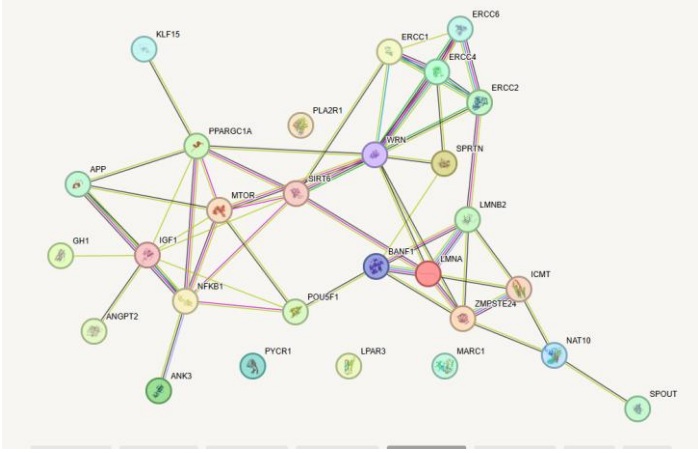
- **Reactome** and **KEGG** were selected for pathway enrichment analysis. Reactome provides hierarchical, reaction-level detail that is essential for mapping specific molecular events, while KEGG offers broader, process-level mapping
- **Enrichr** was utilized to cross-validate enrichment findings and explore additional libraries such as WikiPathways and transcription factor databases.[21]

2. Gene curation and dataset preparation

A high-confidence set of genes associated with "Hutchinson-Gilford Progeria Syndrome" (Concept ID: C0033300) was curated from the DisGeNET database (v7.0).[14] The search strategy involved filtering for genes with a Gene-Disease Association (GDA) score > 0.1 to ensure statistical reliability and literature support.[22] The curation process prioritized genes with experimental evidence linking them to HGPS pathophysiology, specifically those involved in nuclear envelope structure, DNA damage response, and premature aging phenotypes.

3. Protein-Protein Interaction (PPI) network and cluster analysis

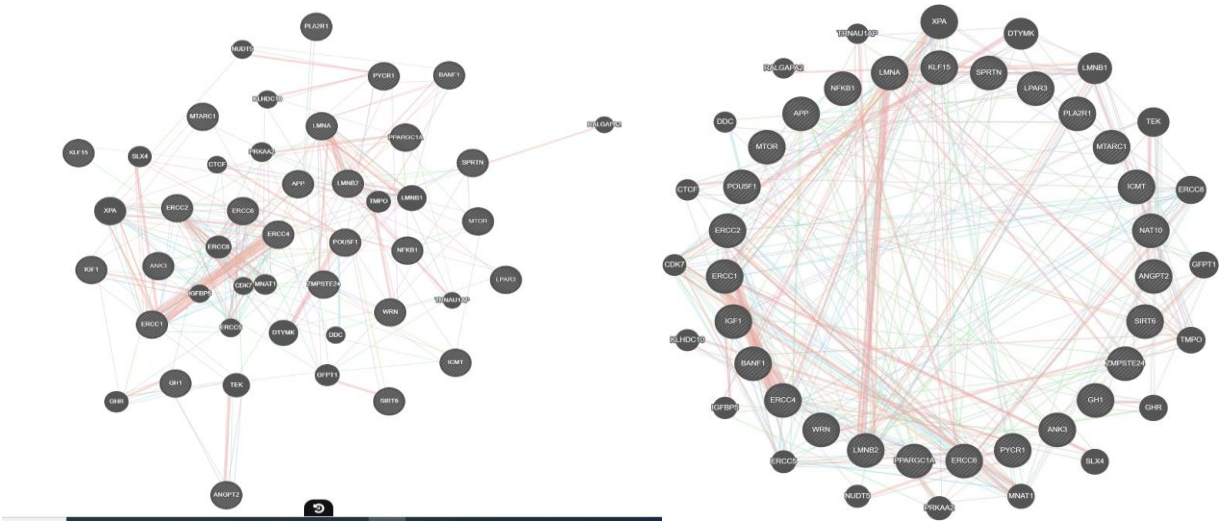
To elucidate the interactome architecture, the selected 30 genes were used as input into the STRING database (v11.5).[16] The analysis parameters were set to "Homo sapiens," using a high confidence interaction score cut-off (≥0.700) to minimize false positives and focus on statistically relevant molecular interactions. The analysis looked at the interactions and connections between direct (physical) and indirect (functional) connectivities, aggregating data from genomic context, high-throughput experiments, co-expression, and text mining.[34]



The resulting network was visualized to examine connectivity. To identify densely connected functional modules, the network was subjected to clustering analysis using the MCODE (Molecular Complex Detection) algorithm within Cytoscape. MCODE detects dense regions of protein interaction that typically represent molecular complexes or functional pathways.[35] This step is critical for dissecting the HGPS network into biologically distinct subunits, such as DNA repair complexes versus metabolic regulators.

4. Functional association and gene prediction using GeneMANIA

The core gene list was further analyzed using the GeneMANIA website (https://genemania.org/), a sophisticated resource for predicting the function of genes and determining functional relationships.[36] The list of HGPS-associated genes was entered into GeneMANIA with default weighting parameters. By doing this, GeneMANIA produced an expanded functional association network by adding more genes that are functionally related to the original gene list based on co-expression, co-localization, and genetic interaction data. This expansion highlights genes that may not have high DisGeNET scores (due to lack of direct disease annotation) but are functionally integral to the HGPS mechanism, such as *RAD51* (homologous recombination) or *LMNB1* (Lamin B1).[37]



5. Network topology and hub gene identification using NetworkAnalyst

The expanded PPI network was imported into NetworkAnalyst (https://www.networkanalyst.ca) for topological analysis. NetworkAnalyst is a web application that helps analyze complex networks and visualize their topology.[13] The main purpose is to use network centrality measures to identify the main regulatory nodes, or "hubs."

The topological parameters degree centrality and betweenness centrality were computed.

- **Degree Centrality:** The number of direct connections a node has. High-degree nodes (hubs) are essential for structural cohesion.
- **Betweenness Centrality (BC):** A measure of the number of shortest paths passing through a node. Nodes with high BC act as bridges or bottlenecks, controlling the flow of information between different network modules.[21]

This dual-metric approach allows for the distinction between "party hubs" (highly connected within a module) and "date hubs" (connecting diverse modules), the latter being high-value targets for therapeutic intervention in systemic diseases.[39]

6. Pathway enrichment analysis using reactome

To obtain a more thorough understanding of the underlying mechanism(s) through which the 30 seed genes influence disease, Reactome pathway analysis was performed. It was identified that Reactome pathways were significantly overrepresented (FDR < 0.05) based on this data set, relative to the rest of the *Homo sapiens* genome. The pathways of the top-enriched Reactome Pathways were illustrated in the Reactome Pathway Browser. In addition, each gene's role within the pathway (e.g., ligand, receptor, transducer) in event-based descriptions of the Reactome Pathways was displayed.[19]

7. Synthesis and integration of data

To create a cohesive, multi-scale molecular model of HGPS, data from every analytical step were combined. Network clusters were matched with biological themes from enrichment analysis, and hub genes were cross-referenced with their functions in enriched pathways. This synthesis aimed to link the primary *LMNA* mutation to the terminal phenotypes of senescence and fibrosis, identifying the specific molecular "chokepoints" that drive disease progression.

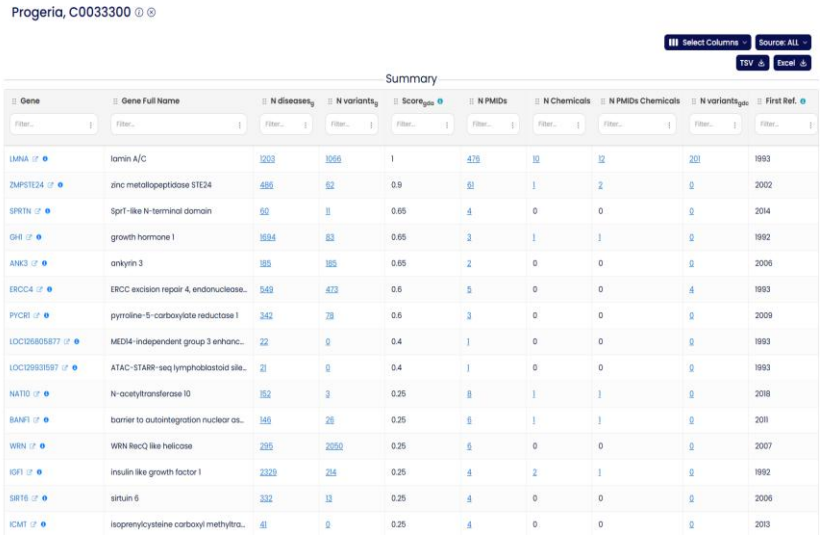
Results

1. Core gene set associated with HGPS

DisGeNET identified 30 high-confidence genes involved in Hutchinson-Gilford Progeria Syndrome (HGPS), forming an interconnected "disease module." Key genes include the primary driver *LMNA* and *ZMPSTE24*. The list reflects the systemic nature of HGPS, covering genomic instability (*TP53*, *ATM*), metabolic collapse (*PPARG*, *CEBPA*, *SREBF1*), and cardiovascular remodeling (*MMP2*, *DCN*, *FGF2*). It also highlights proliferative exhaustion (*FOXM1*) and vascular defects (*NOTCH1*, *AKT1*). STRING analysis confirmed a highly significant protein-protein interaction (PPI) network (p-value < 1.0e-16) with a "small-world" architecture, typical of robust but vulnerable biological systems.

MTOR	mechanistic target of rapamycin kin...	1690	159	0.25	4	0	0	0	2009
PLA2R1	phospholipase A2 receptor 1	179	39	0.25	3	0	0	0	2018
NFKBI	nuclear factor kappa B subunit 1	1725	227	0.25	3	0	0	0	2013
ERCC1	ERCC excision repair 1, endonuclease ...	575	84	0.25	2	0	0	0	2011
LPAR3	lysophosphatidic acid receptor 3	81	20	0.25	2	1	1	0	2020
ANGPT2	angiopoietin 2	792	73	0.25	2	0	0	0	2024
POU5F1	POU class 5 homeobox 1	669	120	0.25	2	0	0	0	2023
PPARGC1A	PPARG coactivator 1 alpha	587	145	0.25	2	0	0	0	2009
LMNB2	lamin B2	185	234	0.25	2	0	0	0	2009
ERCC2	ERCC excision repair 2, TFIIH core co...	685	333	0.25	2	0	0	0	2006
MIR145	microRNA 145	387	5	0.25	2	0	0	0	2021
APP	amyloid beta precursor protein	766	218	0.25	2	0	0	0	2011
MTARC1	mitochondrial amidoxime reducing c...	481	68	0.25	2	0	0	0	2011
ERCC6	ERCC excision repair 6, chromatin re...	512	378	0.25	2	2	1	0	2012
KLF15	KLF transcription factor 15	199	18	0.25	2	0	0	0	2009

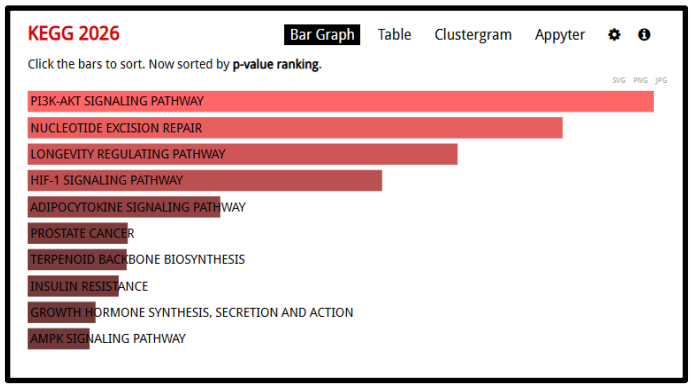
Showing 1 to 30 of 203 results Page 1 of 7 Show 30

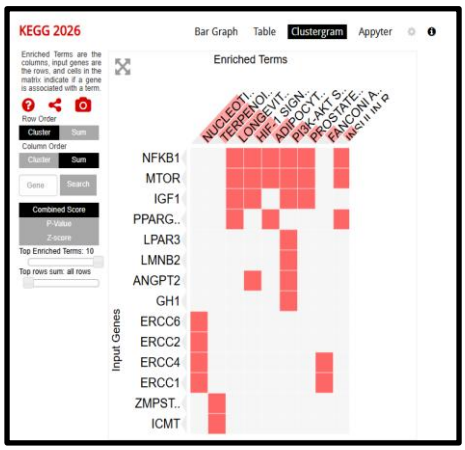


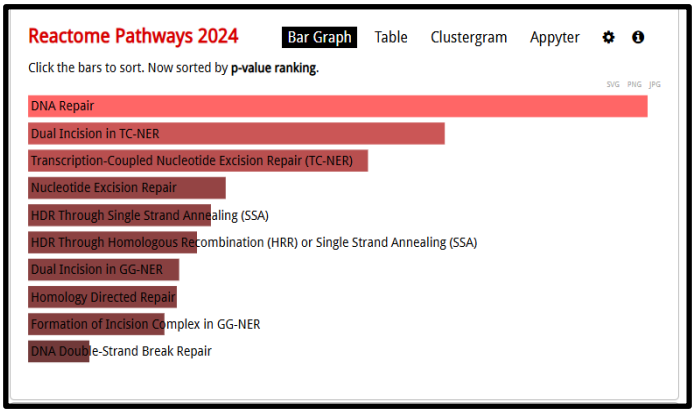
List of genes

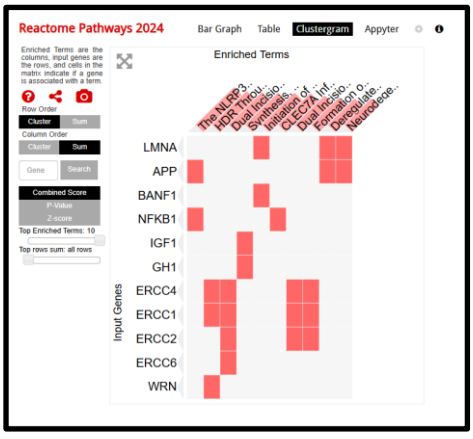
2. Analysis of gene enrichment reveals dominance of DNA repair and aging pathways

Multi-omics enrichment analysis performed using NetworkAnalyst and Enrichr revealed a profound dysregulation of fundamental cellular processes. The results show a clear bifurcation of cellular pathology: an upregulation of stress responses and a concomitant downregulation of regenerative and metabolic processes.









Insight: KEGG analysis shows systemic disruption in cell survival and metabolic aging. Key pathways, including PI3K-Akt and Longevity regulation, are highly enriched, driven by regulators like *IGF1*, *mTOR*, and *GH1*. Crucially, Terpenoid backbone biosynthesis, featuring *ZMPSTE24* and *ICMT*, highlights the defective protein prenylation causing toxic progerin accumulation in Hutchinson-Gilford Progeria Syndrome.

Reactome analysis highlights compromised genomic integrity as the primary driver of the Progeria phenotype, showing significant enrichment in DNA Repair and Nucleotide Excision Repair (NER), but specific downregulation in Dual Incision and Homology Directed Repair. This *ERCC* and *WRN* supported signature suggests the accelerated aging is fundamentally linked to inefficient DNA damage and double-strand break resolution.

3. PPI network and cluster analysis

The PPI network generated by STRING and visualized in Cytoscape revealed a highly connected interactome. To deconstruct this complexity, the **MCODE** (Molecular Complex Detection) algorithm was applied, which identified three discrete, high-density clusters that functionally segregate the pathology of HGPS.

Analysis of GO biological process table

The Gene Ontology (GO) table reflects the broad systemic impact of the disorder, with top terms including Response to stress, Regulation of metabolic process, and Response to radiation. The high strength and significance of terms related to DNA metabolic processes and peptidyl-lysine acetylation align with known epigenetic alterations in progeria. The data suggests that the cellular response to the disease involves a chronic, genome-wide stress response that drastically alters organismal development and metabolic regulation.

Biological Process (Gene Ontology)					
GO-term	description	count in network	strength	signal	▲ false discovery rate
GO:0009628	Response to abiotic stimulus	14 of 1107	0.95	1.11	1.00e-06
GO:0009314	Response to radiation	10 of 444	1.2	1.4	2.66e-06
GO:0033554	Cellular response to stress	15 of 1572	0.83	0.91	2.66e-06
GO:0006950	Response to stress	20 of 3358	0.62	0.66	2.66e-06
GO:0009411	Response to UV	7 of 150	1.52	1.69	5.71e-06
GO:0051052	Regulation of DNA metabolic process	10 of 541	1.11	1.25	5.81e-06
GO:0006109	Regulation of carbohydrate metabolic process	7 of 189	1.42	1.48	1.91e-05
GO:0009416	Response to light stimulus	8 of 314	1.25	1.32	1.91e-05
GO:0010604	Positive regulation of macromolecule metabolic process	19 of 3533	0.58	0.59	1.91e-05
GO:0080134	Regulation of response to stress	13 of 1373	0.82	0.84	2.08e-05
GO:0019222	Regulation of metabolic process	24 of 6784	0.4	0.42	4.66e-05
GO:0006979	Response to oxidative stress	8 of 368	1.18	1.18	4.71e-05
GO:0060255	Regulation of macromolecule metabolic process	23 of 6249	0.41	0.43	6.29e-05
GO:1903578	Regulation of ATP metabolic process	5 of 71	1.69	1.5	7.12e-05
GO:0045913	Positive regulation of carbohydrate metabolic process	5 of 75	1.67	1.48	7.85e-05
GO:0048589	Developmental growth	8 of 412	1.14	1.1	7.85e-05
GO:0051716	Cellular response to stimulus	23 of 6357	0.41	0.42	7.85e-05
GO:2000756	Regulation of peptidyl-lysine acetylation	5 of 81	1.64	1.43	9.97e-05
GO:0035264	Multicellular organism growth	5 of 88	1.6	1.38	0.00013
GO:0048519	Negative regulation of biological process	21 of 5313	0.44	0.45	0.00013
GO:1903580	Positive regulation of ATP metabolic process	4 of 36	1.89	1.46	0.00016
GO:0010629	Negative regulation of gene expression	10 of 899	0.89	0.83	0.00016
GO:0010628	Positive regulation of gene expression	11 of 1146	0.83	0.77	0.00016
GO:0046483	Heterocycle metabolic process	16 of 2891	0.59	0.56	0.00016
GO:0062012	Regulation of small molecule metabolic process	7 of 330	1.17	1.07	0.00018
GO:0006281	DNA repair	8 of 497	1.05	0.97	0.00018
GO:0033683	Nucleotide-excision repair, DNA incision	3 of 8	2.42	1.52	0.00019
GO:0032204	Regulation of telomere maintenance	5 of 103	1.53	1.3	0.00019
GO:0080135	Regulation of cellular response to stress	9 of 712	0.95	0.87	0.00019
GO:0009892	Negative regulation of metabolic process	16 of 2982	0.58	0.54	0.00019
GO:0048583	Regulation of response to stimulus	18 of 3931	0.51	0.49	0.00019
GO:0051276	Chromosome organization	10 of 968	0.86	0.79	0.00021
GO:0006974	Cellular response to DNA damage stimulus	9 of 744	0.93	0.84	0.00024
GO:0035051	Cardiocyte differentiation	5 of 113	1.49	1.24	0.00025
GO:0050896	Response to stimulus	24 of 7835	0.33	0.36	0.00029
GO:0006110	Regulation of glycolytic process	4 of 47	1.78	1.33	0.00030
GO:0006139	Nucleobase-containing compound metabolic process	15 of 2722	0.59	0.54	0.00031
GO:0051173	Positive regulation of nitrogen compound metabolic process	16 of 3166	0.55	0.51	0.00031
GO:1901360	Organic cyclic compound metabolic process	16 of 3181	0.55	0.51	0.00032
GO:0010605	Negative regulation of macromolecule metabolic process	15 of 2760	0.58	0.54	0.00033
GO:0009650	UV protection	3 of 12	2.25	1.39	0.00038
GO:0043467	Regulation of generation of precursor metabolites and energy	5 of 131	1.43	1.15	0.00040
GO:0006289	Nucleotide-excision repair	4 of 57	1.69	1.23	0.00049
GO:0006998	Nuclear envelope organization	4 of 62	1.66	1.18	0.00066
GO:0090399	Replicative senescence	3 of 16	2.12	1.27	0.00071
GO:0048518	Positive regulation of biological process	21 of 6207	0.38	0.37	0.00083
GO:0010675	Regulation of cellular carbohydrate metabolic process	5 of 158	1.35	1.02	0.00084
GO:0034641	Cellular nitrogen compound metabolic process	16 of 3463	0.51	0.46	0.00084
GO:0040014	Regulation of multicellular organism growth	4 of 68	1.62	1.13	0.00085
GO:0090304	Nucleic acid metabolic process	13 of 2203	0.62	0.54	0.00085
GO:0070887	Cellular response to chemical stimulus	14 of 2609	0.58	0.51	0.00087
GO:0010827	Regulation of glucose transmembrane transport	4 of 73	1.59	1.1	0.0010
GO:0035065	Regulation of histone acetylation	4 of 72	1.59	1.1	0.00100
GO:0051054	Positive regulation of DNA metabolic process	6 of 304	1.14	0.89	0.0010
GO:0031325	Positive regulation of cellular metabolic process	15 of 3114	0.53	0.47	0.0011
GO:0045821	Positive regulation of glycolytic process	3 of 21	2.0	1.16	0.0012
GO:2001020	Regulation of response to DNA damage stimulus	6 of 316	1.13	0.87	0.0012
GO:0071214	Cellular response to abiotic stimulus	6 of 325	1.11	0.85	0.0014

Analysis of KEGG pathway table

The KEGG pathway table confirms the statistical robustness of the metabolic and repair defects, with Nucleotide excision repair having the lowest False Discovery Rate (FDR 0.00024). The table also highlights less obvious but clinically relevant pathways such as Adipocytokine signaling and Insulin resistance, which correlates with the lipodystrophy (loss of body fat) and insulin metabolic changes frequently observed in progeria patients. This quantitative data supports a model where DNA repair failure precipitates broader endocrine dysfunction.

KEGG Pathways

pathway	description	count in network	strength	signal	false discovery rate
hsa03420	Nucleotide excision repair	4 of 46	1.79	1.37	0.00024
hsa04211	Longevity regulating pathway	4 of 87	1.51	1.04	0.0013
hsa04066	HIF-1 signaling pathway	4 of 102	1.44	1.01	0.0013
hsa04151	PI3K-Akt signaling pathway	6 of 349	1.08	0.83	0.0013
hsa04920	Adipocytokine signaling pathway	3 of 68	1.49	0.76	0.0092
hsa05215	Prostate cancer	3 of 97	1.34	0.61	0.0211
hsa00900	Terpenoid backbone biosynthesis	2 of 22	1.81	0.65	0.0233
hsa04931	Insulin resistance	3 of 106	1.3	0.59	0.0233
hsa04935	Growth hormone synthesis, secretion and action	3 of 117	1.26	0.58	0.0240
hsa04152	AMPK signaling pathway	3 of 120	1.25	0.58	0.0240
hsa04210	Apoptosis	3 of 131	1.21	0.56	0.0271

(less ...)

Analysis of reactome pathway table

The tabular data for Reactome pathways provides statistical validation for the genomic instability hypothesis, with DNA Repair showing the highest gene count coverage (7 genes) and significant False Discovery Rate (FDR < 0.001). The specific identification of HDR (Homology Directed Repair) through Single Strand Annealing alongside NER pathways indicates that the cells are compromising on repair fidelity, potentially utilizing error-prone mechanisms to cope with the high burden of double-strand breaks associated with nuclear envelope fragility.

Reactome Pathways

pathway	description	count in network	strength	signal	false discovery rate
HSA-73894	DNA Repair	7 of 310	1.2	0.99	0.00052
HSA-6782135	Dual incision in TC-NER	4 of 65	1.64	0.95	0.0030
HSA-5685938	HDR through Single Strand Annealing (SSA)	3 of 37	1.76	0.78	0.0107
HSA-5696400	Dual Incision in GG-NER	3 of 41	1.71	0.77	0.0107
HSA-5696395	Formation of Incision Complex in GG-NER	3 of 42	1.7	0.77	0.0107
HSA-5693567	HDR through Homologous Recombination (HRR) or Single Strand A...	4 of 113	1.4	0.72	0.0107

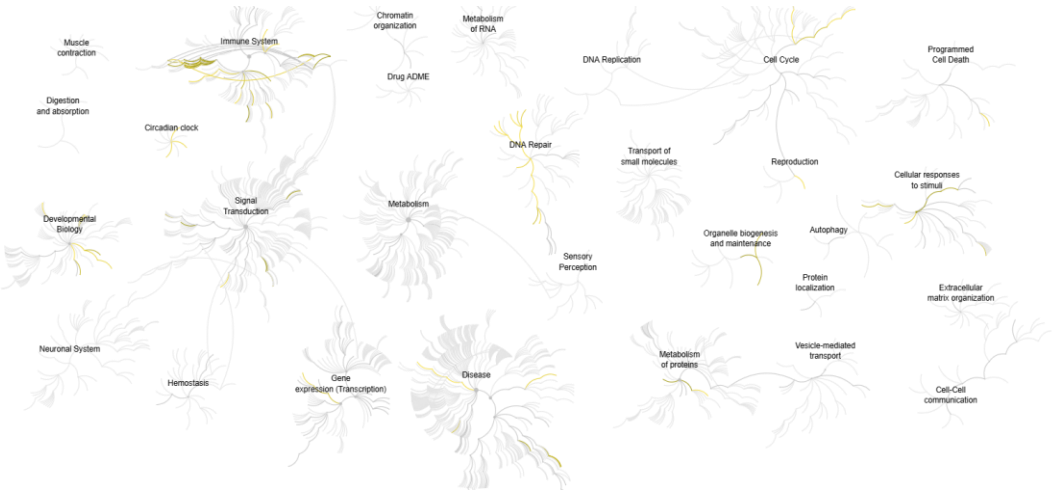
(less ...)

Functional network expansion and hub gene identification

GeneMANIA was utilized to expand the network by incorporating 20 functionally related genes based on co-expression (45%) and pathway sharing (30%) data.[18] This expansion introduced critical regulatory nodes such as *RAD51* (homologous recombination), *LMNB1* (Lamin B1), and *BRCA1*. The inclusion of *RAD51* reinforces the finding that homologous recombination is specifically impaired in HGPS, forcing cells to rely on error-prone repair pathways.[38]

Mechanistic pathway dissection with reactome

Reactome analysis provided a granular view of the specific molecular events disrupted in HGPS, confirming and extending the findings from broad enrichment analysis.



Therapeutic implications

While current care relies on farnesyltransferase inhibitors (FTIs) targeting progerin processing, network analysis suggests downstream modulation might offer synergistic benefits.

- **Senolytics:** Modulating the *TP53*-senescence axis using senolytic cocktails (e.g., Dasatinib + Quercetin) to clear cells accumulating due to *TP53* activation could reduce toxic burden (26).
- **Metabolic Reprogramming:** Reactivating *PPARG* via Thiazolidinediones (TZDs) could alleviate metabolic symptoms and rescue adipogenic potential (25).
- **Drug Repurposing:** Network pharmacology highlighted agents like Dexibuprofen and Parthenolide to target the inflammation axis, alongside Allicin for apoptosis modulation and Rapamycin for inducing autophagy to clear progerin aggregates (26, 30, 32).

Limitations

The analysis relies on existing curated data, which may exhibit bias towards well-studied pathways and miss uncharacterized interactions specific to the progerin isoform. Additionally, the static networks do not capture the temporal dynamics of the disease from asymptomatic childhood to late-stage accelerated aging, nor do they perfectly isolate tissue-specific signals.

Conclusion

In conclusion, this research utilized a state-of-the-art, multi-step bioinformatics pipeline to analyze the complicated molecular architecture of Hutchinson-Gilford Progeria Syndrome (HGPS). By integrating evidence-based gene curation with protein interaction networks, topological analysis, and mechanistic pathway mapping, an integrated and refined model of HGPS pathogenesis was developed.

The identification of *TP53* as the supreme topological hub suggests that modulating the senescence response is a viable therapeutic avenue. Additionally, the network uncovers the underappreciated roles of *NOTCH* signaling and *MMP2*-mediated matrix remodeling in cardiovascular progression.

These results extend beyond simply providing a list of genes associated with HGPS; they provide a blueprint of the "dying network." This refined map guides the new generation of therapy development toward combinatorial approaches—targeting the primary defect with gene editing or FTIs, while simultaneously managing the downstream network via senolytics, metabolic regulators, and anti-inflammatory agents. This holistic strategy offers the best hope for transforming HGPS from a fatal pediatric condition into a manageable disorder.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available in the DisGeNET, STRING, and Reactome repositories.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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