Identification of hub genes, key pathways, and therapeutic agents in Hutchinson–Gilford Progeria syndrome using bioinformatics analysis

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Abstract

Background: Hutchinson–Gilford Progeria syndrome (HGPS) is a rare lethal premature and accelerated aging disease caused by mutations in the lamin A/C gene. Nevertheless, the mechanisms of cellular damage, senescence, and accelerated aging in HGPS are not fully understood. Therefore, we aimed to screen potential key genes, pathways, and therapeutic agents of HGPS by using bioinformatics methods in this study.

Methods: The gene expression profile of GSE113648 and GSE41751 were retrieved from the gene expression omnibus database and analyzed to identify the differentially expressed genes (DEGs) between HGPS and normal controls. Then, gene ontology and the Kyoto encyclopedia of genes and genomes pathway enrichment analysis were carried out. To construct the protein-protein interaction (PPI) network, we used STRING and Cytoscape to make module analysis of these DEGs. Besides, the connectivity map (cMAP) tool was used as well to predict potential drugs.

Results: As a result, 180 upregulated DEGs and 345 downregulated DEGs were identified, which were significantly enriched in pathways in cancer and PI3K-Akt signaling pathway. The top centrality hub genes fibroblast growth factor 2, decorin, matrix metallopeptidase2, and Fos proto-oncogene, AP-1 transcription factor subunit, were screened out as the critical genes among the DEGs from the PPI network. Dexamethasone and parthenolide were predicted to be the possible agents for the treatment of HGPS by cMAP analysis.

Conclusion: This study identified key genes, signal pathways and therapeutic agents, which might help us improve our understanding of the mechanisms of HGPS and identify some new therapeutic agents for HGPS.

Abbreviations: cMAP = connectivity map, DCN = decorin, uDEGs = upregulated DEGs, DEGs = differentially expressed genes, ECM = extracellular matrix, FGF2 = fibroblast growth factor 2, FOS = Fos proto-oncogene, AP-1 transcription factor subunit, GEO = gene expression omnibus, GO = gene ontology, HGPS = Hutchinson–Gilford Progeria syndrome, KEGG = Kyoto encyclopedia of genes and genomes, LMNA = lamin A/C, MMP2 = matrix metallopeptidase2, PPI = protein-protein interaction, uDEGs = upregulated DEGs.

Keywords: bioinformatics, differentially expressed genes, function enrichment analysis, progeria, protein-protein interaction network

1. Introduction

Hutchinson–Gilford progeria syndrome (HGPS, progeria) is an extremely rare premature and accelerated aging disease.\textsuperscript{[1]} HGPS patients generally appear physiological aging including thin skin with hyperpigmented lesions, loss of subcutaneous fat, alopecia, osteoporosis and severe generalized arteriosclerosis, leading to myocardial infarction in most cases, and the mean age of demise was 14.6 years.\textsuperscript{[2,3]} The leading cause of HGPS is the aberrant...
splicing of the lamin A/C (LMNA) gene. Lamina A and lamin C encoded by LMNA, are significant components of the nuclear lamina—a proteinaceous meshwork that underlies the inner nuclear membrane. It is necessary for proper nuclear architecture. Due to the mutations in the LMNA gene, the proper synthesis and maturation of lamin A are impaired and a truncated unprocessed lamin A protein called progerin is accumulated. Accumulation of progerin that disrupts the integrity of the nuclear lamina affects a whole repertoire of nuclear functions, causing faster cellular senescence, stem cell depletion and the progeroid phenotype, likely being the cause of the progressive nature of the disease. The cytological hallmark of HGPS involves nuclear morphological abnormalities, mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and chromosomal and telomere aberrations. HGPS cells have altered cell-cycle regulation and impaired DNA repair mechanisms, a higher apoptosis rate, and quicker cellular senescence. In HGPS, severe epigenetic alterations have been reported, including histone-covalent modifications, histone variants, DNA methylation, chromatin remodelers, chromatin architecture, and miRNAs.

Recently, numerous potential treatment strategies for HGPS have been developed, which mainly involve interfering with the processing of lamin A in the post-translational level; and thus promote the clearance of progerin, or directly target the HGPS mutation to diminish the progerin-producing alternative splicing of the LMNA gene. Farneysterol transferase inhibitors, statins or bisphosphonates, mono-aminopyrimidines have been found to interfere with prelamin A processing. The autophagy pathway is triggered by the administration of rapamycin, leading to the lysosomal degradation of progerin. Finally, mitochondrial dysfunction and biogenesis have been targeted by drugs with antioxidant effects such as Metformin, methylene blue, which resulted in improved mitochondrial function and reduction of ROS. Hence, HGPS is an excellent model to explore the accelerated aging with these striking features and similar mechanisms of normal aging. However, the mechanisms underlying cellular damage and senescence and accelerated aging in HGPS are incompletely understood.

Along with the development of bioinformatics, high-throughput tools such as microarray and sequencing have been widely used to explore the genetic variations which concern a variety of disorders, including cancer and aging. Mateos et al. used to explore the genetic variations which concerning a variety of diseases. Therefore, in this study, we aimed to screen relevant data to identify the DEGs that may play a role in HGPS. In addition, we assessed the functions and roles of screened candidate genes. Besides, the agents that maybe likely to rescue HGPS were also predicted and evaluated.

2. Materials and methods

2.1. Datasets and data preprocessing

The gene expression profiles GSE113648 and GSE41751 were obtained from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database in the National Center for Biotechnology Information. The former dataset has 4 progenitor lines: 2 HGPS patients and 2 control samples. And the latter one has 2 primary fibroblasts of HGPS patients and 2 healthy age-matched control samples.

The analysis of screening DEGs between HGPS and control samples was analyzed by GEO2R, respectively. Moreover, the threshold for the DEGs was set as $P$-value $< .01$ and $|\log2\text{foldchange (FC)}| \geq 1$.

2.2. Gene ontology (GO) and pathway enrichment analysis of DEGs

To analyze the functions of DEGs, GO enrichment and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis were carried out by using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) online tool. $P$-value $< .05$ was set as the cut-off point.

2.3. Protein-protein interaction (PPI) network construction and module selection

To investigate the possible hub genes/proteins that might play a significant role in the biological process, all DEGs were imported into STRING (https://string-db.org/) and Cytoscape to create network visualizations. A confidence score $> .4$ was defined as significant in STRING analysis to evaluate the interactive relationships. Then, we use Cytoscape to construct PPI networks and the Molecular Complex Detection (MCODE), a plugin for Cytoscape, to screen the modules of the PPI network. The default parameters were set as follows: degree cut-off $= 2$, node score cut-off $= 2$, $k$-core $= 2$, and maximum depth $= 100$.

2.4. Analysis of module and hub genes in the PPI network

The function and pathway enrichment analysis were carried out for DEGs in the modules. To explore key genes in the PPI network, 3 centrality methods: degree, closeness, and subgraph were calculated using a Cytoscape plugin CytoNCA.

2.5. Connectivity map (cMAP) database mining

With the aim of finding potential agents with molecular signatures that might reverse the transcriptional profiles of HGPS, we compared the observed gene expression profiles with the cMAP reference database (http://portals.broadinstitute.org/cmap/). DEGs between HGPS and control samples were used as query terms to submit to cMAP for analysis. The $P$-value $< .05$ was considered as the cut-off value. Small molecular compounds with negative connectivity enrichment scores were selected as potential therapeutic molecules for the treatment of HGPS.
3. Results

3.1. Identification of DEGs

HGPS patients and control samples in GSE113648 and GSE41751 dataset were analyzed to identify DEGs using the \( P < .01 \) and \( \mid \log2FC \mid \geq 1 \) criteria. Compared with control, a total of 1126 DEGs were identified from GSE113648 dataset, consisting of 472 upregulated DEGs (uDEGs) and 654 downregulated DEGs (dDEGs) in HGPS cells (Table S1, http://links.lww.com/MD/D706). As shown in Supplemental Table 2, http://links.lww.com/MD/D707, 1791 uDEGs and 1771 dDEGs have been generated from GSE41751 dataset. Moreover, 180 uDEGs and 345 dDEGs have been screened out in the intersections, respectively (Fig. 1, Table S3, http://links.lww.com/MD/D708).

3.2. Functional analysis of DEGs

Aiming to evaluate the functions of identified DEGs, we uploaded all DEGs to DAVID to identify significant GO categories and KEGG pathways. GO analysis showed that the DEGs were enriched in biological process, including positive and negative regulation of transcription from RNA polymerase II promoter, cell adhesion, positive regulation of GTPase activity and ECM organization (Table 1). For cellular components, DEGs were enriched in the plasma membrane, cytoplasm, extracellular exosome, extracellular region, and extracellular space (Table 1). Besides, for molecular function, the DEGs were enriched in transcription factor activity, sequence-specific DNA binding, calcium ion binding, protein homodimerization activity, sequence-specific DNA binding, and receptor binding (Table 1).

KEGG pathway analysis indicated that the DEGs were enriched in pathways in cancer, PI3K-Akt signaling pathway, focal adhesion, ECM-receptor interaction, and Ras signaling pathway (Table 2).

3.3. PPI network construction and modules selection

The PPI network of DEGs consisting of 206 nodes and 412 edges was constructed in the STRING database (version 11.0). Then it was visualized through Cytoscape (Fig. 2A). Furthermore, degree \( \geq 10 \) was set as the cut-off criterion. Based on the STRING database, the DEGs with the highest PPI scores identified by the 3 centrality methods are shown in Table 3. After repeated genes removing, the hub genes (shown in Fig. 2A, highlighted in yellow and shaped in diamond) were obtained using the 3 centrality methods, including fibroblast growth factor 2 (FGF2), decorin (DCN), matrix metalloproteinase2 (MMP2), Fos proto-oncogene, AP-1 transcription factor subunit (FOS), syndecan 4, early growth response 1, glial cell-derived neurotrophic factor, fibroblast growth factor receptor 2, syndecan 3, and ADAM metalloproteinase with thrombospondin type 1 motif 5.

Figure 1. Intersection of the uDEGs (1A) and dDEGs (1B) from GSE113648 and GSE41751 dataset respectively. The intersection included 180 upregulated and 345 downregulated genes. dDEGs = downregulated differentially expressed genes, uDEGs = upregulated differentially expressed genes.

| Category | Term/functions | Gene count | % | P-value |
|----------|---------------|------------|---|---------|
| BP       | Positive regulation of Transcription from RNA Polymerase II promoter | 52 | 10.0 | 8.0E-6 |
|          | Cell adhesion | 50 | 9.6  | 3.5E-16 |
|          | Negative regulation of Transcription from RNA Polymerase II promoter | 40 | 7.7  | 4.1E-5  |
|          | Positive regulation of GTPase activity | 37 | 7.1  | 2.5E-6  |
|          | Extracellular matrix organization | 32 | 6.1  | 2.4E-15 |
| CC       | Plasma membrane | 160 | 30.7 | 3.5E-7  |
|          | Cytoplasm     | 160 | 30.7 | 3.9E-2  |
|          | Extracellular exosome | 108 | 20.7 | 1.0E-4  |
|          | Extracellular region | 86  | 16.5 | 1.2E-9  |
|          | Extracellular space | 73  | 14.0 | 1.7E-5  |
| MF       | Transcription factor activity, Sequence-specific DNA binding | 45  | 8.6  | 2.7E-4  |
|          | Calcium ion binding | 36 | 6.9  | 3.7E-4  |
|          | Protein homodimerization activity | 30 | 5.7  | 1.9E-2  |
|          | Sequence-specific DNA binding | 29  | 5.6  | 2.9E-4  |
|          | receptor binding | 23  | 4.4  | 1.9E-4  |

Table 1
Gene ontology analysis of the differentially expressed genes (DEGs) associated with Hutchinson–Gilford Progeria syndrome.

BP = biological process, CC = cellular component, MF = molecular function.
3.4. cAMP analysis

The identified DEGs were selected and entered as a query signature in the cMAP database. It shows the top 5 hits with low connectivity scores (−0.863 to −0.738), indicating a high negative correlation with the HGPS signature (Table 5). These compounds may be capable of reversing or counteracting the gene expression pattern observed in HGPS and are thus candidate novel therapies. They were dexibuprofen, parthenolide, lomustine, PNU-0293363, and lincomycin.

4. Discussion

Despite advances in the present study and therapeutics, the molecular mechanisms underlying cellular damage and senescence and accelerated aging in HGPS have not been fully understood. In this study, DEGs in HGPS compared with normal controls were analyzed. The KEGG pathway analysis revealed that the DEGs were obviously enriched in pathways in cancer, PI3K-Akt signaling pathway, focal adhesion, and ECM-receptor interaction. As is known to us, cancer and progeria shared many molecular and cellular mechanisms, particularly in DNA damage. DNA damage has emerged as a significant cause in cancer and many diseases related to aging. HGPS and other premature aging disorders caused by mutations in DNA repair genes in biological process, including positive and negative regulation of transcription from RNA polymerase II promoter, cell adhesion, and positive regulation of GTase activity. RNA polymerase II Transcription is active in the lamin B deficient nuclear blebs of atypical progeria cells. In Werner syndrome, Werner syndrome protein is possibly a transcriptional activator in RNA polII transcription. In the meantime, Spann et al reported that disruption of normal lamin organization inhibits RNA polymerase II-dependent transcription. These may indicate that the screened DEGs may act on positive and negative regulation of transcription from RNA polymerase II. Hale et al reported that cell adhesion defects in Lmna−/− mouse (HGPS mouse model) adult fibroblasts and Lmna−/− mouse (Emery–Dreifuss muscular dystrophy mouse model) embryonic fibroblasts. Ran is a small ras-related GTase that controls the nucleocytoplasmic exchange of macromolecules across the nuclear envelope. The nuclear levels of Ran GTase are reduced. And the Ran protein gradient is disrupted in fibroblasts from HGPS patients, which causes a defect in generating nuclear γ-H2AX and DNA damage and ROS.

The PPI network was constructed with DEGs, and the top centrality hub genes were obtained: FGF2, DCN, MMP2, and FO8. FGF2 was identified as one of the hub genes with the highest degree of connectivity, the protein encoded by which is a member of the fibroblast growth factor (FGF) family. However, the relation between FGF2 and progeria has not been reported at present. The biosynthesis of the small proteoglycan decorin decreased in progeroid syndromes. MMP-2 messenger RNA showed a donor age-dependent decrease in HGPS fibroblasts, but levels of secreted protein were unchanged. The levels of proto-oncogene c-fos mRNA expression decreased in HGPS fibroblasts.

Module analysis of the PPI network showed that HGPS was associated with proteoglycans in cancer and GAG processes, such as biosynthesis, metabolic, and catabolic. Several patients with progeroid-like symptoms have been shown to have abnormalities in the biosynthesis of proteoglycans. O-glycosylation, the main type of protein glycosylation, is related to progeria. GAGs are an abundant structural component of the ECM. GAG hyaluronic acid (HA) was found excreted with an excessive amount in progeria patients. However, no conclusive evidence of HA being a primary effect in progeria has been found.

To predict the drugs that have the potential to rescue the HGPS biological process, DEGs were submitted to cMAP for analysis. Using this tool, a list of compounds that might reverse the DEGs profiles was screened out, of which 2 compounds (dexibuprofen and parthenolide) are particularly interested in our study. Mouse models that phenotypically recapitulate HGPS show increased activation of Nuclear Factor-kappa B (NF-kB) with a concomitant increase in interleukin-6 at the transcriptional and protein
Figure 2. Protein-protein interaction network of DEGs. (A) A total of 203 nodes and 346 interaction associations were identified. The nodes with the highest PPI scores were shaped as the diamond in yellow. (B) The most significant module from the PPI network. DEGs = differentially expressed genes, PPI = protein-protein interaction.
levels.\textsuperscript{[56]} João Ribas et al\textsuperscript{[57]} reported that HGPS smooth muscle cells showed an exacerbated inflammatory response and an increase in inflammation markers levels. Lovastatin and lonafarnib were able to ameliorate the exacerbated inflammatory response to strain in HGPS smooth muscle cells derived from human induced pluripotent stem cells (iPS-SMCs). Methionine restriction could prolong health span and longevity of 2 short-lived strains of HGPS mice by reducing inflammation and improving the DNA stability of HGPS.\textsuperscript{[58]} Dexibuprofen is a nonsteroidal anti-inflammatory drug, which works by preventing the oxidation of arachidonic acid by inhibiting the enzyme cyclooxygenase.\textsuperscript{[59]} Dexibuprofen may be a potential drug of age-related Alzheimer disease through reducing neuroinflammation.\textsuperscript{[60]} Further studies are required for the validation of Dexibuprofen as a potential compound of treatment of HGPS by anti-inflammatory effects.

Parthenolide is a sesquiterpene lactone found in the medicinal herb Feverfew. Parthenolide exhibits anti-inflammatory activity by inhibiting NF-κB activation, NF-κB altered signaling, which inhibition is an aging intervention strategy, has been causally linked to aging.\textsuperscript{[61]} Parthenolide could effectively inhibit the gene expression mediated by NF-κB and may be useful in preventing the skin photoaging.\textsuperscript{[62]} Parthenolide also inhibits HDAC1 protein without affecting other class I/II HDACs. HDAC

| Table 3 | The top 10 differentially expressed genes (DEGs) with higher scores, respectively, identified by the 3 centrality methods. |
|---|---|---|
| Subgraph | Degree | Closeness |
| FGF2 | 2093.965 | FGF2 | 28 | 0.6858 |
| DCN | 1203.585 | DCN | 22 | 0.6790 |
| MMP2 | 1137.531 | MMP2 | 21 | 0.6741 |
| FOS | 776.427 | FOS | 19 | 0.6719 |
| SDC3 | 492.079 | SDC4 | 13 | 0.6688 |
| SDC4 | 482.186 | EGR1 | 13 | 0.6685 |
| ADAMTS5 | 467.320 | GDNF | 13 | 0.6667 |
| FGFR2 | 392.824 | FGFR2 | 12 | 0.6667 |
| EGR1 | 373.374 | SDC3 | 11 | 0.6661 |
| GDNF | 363.072 | ADAMTS5 | 11 | 0.6661 |

ADAMTS5 = ADAM metallopeptidase with thrombospondin type 1 motif 5, DCN = decorin, EGR1 = early growth response 1, FGF2 = fibroblast growth factor 2, FGFR2 = fibroblast growth factor receptor 2, FOS = Fos proto-oncogene, AP-1 transcription factor subunit, GDNF = glial cell-derived neurotrophic factor, MMP2 = matrix metalloproteinase 2, SDC3 = syndecan 3, SDC4 = syndecan 4.

| Table 4 | Gene ontology (GO) and the Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis of genes in the selected module. |
|---|---|---|
| Category | Term/functions | Gene count | % | P-value |
| BP | Glycosaminoglycan Biosynthetic process | 6 | 0.4 | 1.9E-11 |
| | Glycosaminoglycan Metabolic process | 5 | 0.3 | 1.5E-9 |
| | Glycosaminoglycan catabolic process | 4 | 0.2 | 3.9E-7 |
| | Retinoid metabolic process | 4 | 0.2 | 5.4E-6 |
| | Extracellular matrix organization | 4 | 0.2 | 1.8E-4 |
| CC | Lysosomal lumen | 5 | 0.3 | 9.1E-8 |
| | Golgi lumen | 5 | 0.3 | 1.5E-7 |
| | Extracellular space | 5 | 0.3 | 4.3E-3 |
| | Extracellular region | 5 | 0.3 | 8.3E-3 |
| | Proteinaceous extracellular matrix | 3 | 0.2 | 9.0E-3 |
| MF | Coreceptor activity involved in the Wnt signaling pathway, planar cell polarity pathway | 2 | 0.1 | 3.2E-3 |
| | heparan sulfate proteoglycan binding | 2 | 0.1 | 9.6E-3 |
| | PATHWAY | Proteoglycans in cancer | 3 | 0.2 | 1.2E-2 |
| | Glycosaminoglycan biosynthesis – heparan sulfate/heparin | 2 | 0.1 | 2.1E-2 |

BP = biological process, CC = cellular component, MF = molecular function.

| Table 5 | The top 5 compounds with high negative correlations with Hutchinson–Gilford Progeria syndrome. |
|---|---|---|---|---|---|---|
| Rank | CMAP name | Mean | N | Enrichment | P | Percent non-null |
| 1 | Dexibuprofen | -0.432 | 4 | -0.863 | .00064 | 75 |
| 2 | Parthenolide | -0.225 | 4 | -0.797 | .00338 | 50 |
| 3 | Lomustine | -0.311 | 4 | -0.794 | .00366 | 50 |
| 4 | PNU-0293363 | -0.259 | 3 | -0.741 | .03961 | 66 |
| 5 | Lincomycin | -0.479 | 3 | -0.738 | .03702 | 66 |
inhibitors are new promising drugs in anti-aging research, which can recovery-associated functional declines, primarily the transcriptional levels of the biosynthetic and metabolic genes decreased. Krishnan et al. found that histone H4 acetylation impaired in the Zmpste24-deficient (HGPS mouse model) cells, using sodium butyrate (HDAC inhibitor) improved DNA repair and extend the life span of Zmpste24−/− mouse. Some of HDAC inhibitors have been recently examined in human clinical trials and recommended for the treatment of age-associated diseases.

Overall, dexibuprofen and parthenolide may be the promising drugs for the treatment of HGPS. Nevertheless, little evidence has shown the effect of HGPS or other premature aging disorders. Future validation investigations are needed to test their biological functions.

5. Conclusion
In conclusion, this study provides a preliminary study of the mechanisms underlying HGPS. DEGs were screened out and selected the interaction. Their possible functions were annotated by GO analysis and pathway analysis. The DEGs were mostly enriched in pathways in cancer and PI3K-Akt signaling pathway. Afterward, several key hub genes that may play key roles in HGPS have been screened out by PPI analysis. Using the cMAP tool, dexibuprofen, and parthenolide that might have the potential to reverse the progerin-induced biological process has been predicted. This study may provide a valuable clue for both prevention and treatment research of HGPS. Since HGPS is a rare disease and its incidence is very low, the data obtained is relatively limited in GEO database. Thus, it is necessary to have further studies with larger sample sizes. Our conclusions are based solely on the results of analysis of the gene expression profiles. Therefore, future validation experiments are warranted to examine the results.

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Author contributions
Dengchuan Wang, Shengshuo Liu, Shi Xu made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. Dengchuan Wang involved in drafting the manuscript or revising it critically for important intellectual content. Dengchuan Wang and Shi Xu gave final approval of the version to be published. Dengchuan Wang, Shengshuo Liu, Shi Xu agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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