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An infant with congenital micrognathia and upper airway obstruction was diagnosed as Hutchinson-Gilford progeria syndrome caused by a novel LMNA mutation: Case report and literature review

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ABSTRACT

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare disease characterized by appearance of premature aging, including the skin, bones, heart, and blood vessels caused by LMNA mutation. In this study, the patient presented with congenital micrognathia and progressively aggravated upper airway obstruction as the initial symptom, which required bilateral mandibular distraction osteogenesis (MDO) surgery intervention. This was not commonly described in the literature, and the primary clinical diagnosis of Pierre Robin sequence (PRS) was made. However, other clinical features included sclerotic skin, dry skin, growth failure, lipoatrophy, joint stiffness, prominent scalp veins, small ear lobes, hair loss, and craniofacial disproportion gradually emerged, the diagnosis of HGPS was preferred when the patient was 5 months old. The genetic testing result with a novel and de novo LMNA mutation (c.1968 + 3_1968+6delGAGT) further confirmed the diagnosis and expanded the clinical and mutational spectrum of HGPS. During the 12-month follow-up period after surgery, the patient no longer suffered dyspnea. Complications of other organs and systems have not happened at the moment. In addition, the pathogenesis, the role of LMNA gene mutation, the progress in clinical treatment, and breakthrough studies about genetic treatment in animals of HGPS are described in the literature review.

1. Introduction

HGPS (OMIM#176670) is an extremely rare genetic disorder caused by a heterozygous mutation in the LMNA gene, with an incidence rate of 1 in 8 million to 1 in 4 million [1,2]. It was first described by Hutchinson in 1886. Then a more specific definition was suggested by Gilford in 1904. HGPS is mainly characterized by accelerating aging, causing multi-system alterations such as severe growth retardation, characteristic skin manifestation, and complications of cardiovascular and cerebral ischemic disease. It is reported

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that the average life expectancy of HGPS patients was about 14 years, while cardiovascular complications have been reported as the leading cause of death [3]. HGPS is still poorly recognized because of its rarity.

To increase the awareness of this disease and evaluate its clinical manifestations and genetic features, we reported an unusual case of HGPS patient caused by a new mutation in the LMNA gene with initial manifestations of micrognathia and upper airway obstruction. Combined with the literature, the detailed clinical information, radiological images, genetic features, and treatment progress were analyzed and discussed.

1.1. Case report

An 11-week-old female was admitted to the Intensive Care Unit (ICU) in Beijing Children's Hospital owing to intermittent difficulty in breathing for seven week's duration. She was the 2100-g product of a 34-week and 3-day pregnancy of a 44-year-old mother. The first complaint of dyspnea occurred at four weeks after birth. It worsened progressively, while the patient's initial conservative treatment, including prone positioning, nasal catheter, oropharyngeal airway, and nasal continuous positive airway pressure (CPAP), failed. With circumoral cyanosis, labored breathing, feeding difficulties, and decreased oxygen saturation, the airway dysfunction became a life-threatening emergency for the patient.

Physical examination revealed a stunted, malnourished, and delirious baby with a weight of 3kg and a length of 55cm. Transcutaneous oxygen saturation could not be detected due to severe inspiratory dyspnea, accompanied by obvious circumoral cyanosis, micrognathia, glossoptosis, and high-arched palate. The primary diagnosis was "Dyspnea, Pierre Robin sequence". First-aid measures included cardiopulmonary resuscitation, urgent trachea intubation and mechanical ventilation. Computer tomography (CT) scanning of the head, maxilla, mandible, airway, and chest showed no organ diseases or tumors. Nasopharyngofiberscope (NPF) and CT multiple planar reconstruction of airway ruled out nasopharyngeal obstruction and lower airway anomalies. Computed tomography image showed craniofacial disproportion and widened cranial suture of this patient (Fig. 2a).

The patient was evaluated comprehensively by a multi-disciplinary team (MDT), including ICU physicians, otolaryngology & head and neck surgeons, respiratory physicians, anesthesiologists, and oral& maxillofacial surgeons. After discussion, they agreed that surgery of bilateral MDO was to be taken for the patient under general anesthesia by oral& maxillofacial surgeons. With preoperative virtual surgical planning, a skin incision in the submandibular area was performed, and bilateral internal subperiosteal devices were fixed (Fig. 1a). The operation was performed under general anesthesia with nasotracheal intubation for airway management. Postoperative mandibular distraction was taken as planned (Fig. 1b). Dyspnea was relieved and the patient was extubated on postoperative day 11, while the distraction plan was completed on day 14. The patient's condition of micrognathia and glossoptosis was alleviated, which contributed to the relief of life-threatening upper airway obstruction.

At a 3-month follow-up after surgery, the patient was noticed to have sclerotic skin, growth failure, dry skin, lipoatrophy, joint stiffness, prominent scalp veins, small ear lobes, hair loss, and craniofacial disproportion (Fig. 2b and c). Diagnosis of HGPS was taken into consideration. Then 2mL of peripheral blood was collected from the child and her parents using ethylenediaminetetraacetic acid (EDTA)-anticoagulation tube for genetic testing after informed consent. DNA was extracted from the white blood cells of a 200 μL blood sample. Whole exome capture procedure was performed with an Agilent SureSelect Human All Exome V6 kit. Whole exome sequencing was conducted on an Illumina Hiseq X sequencing platform. The pathogenicity of the variants was assessed according to the ACMG guidelines. The results showed a *de novo* variant in gene LMNA in the proband: c.1968 + 3_1968+6delGAGT (Fig. 3a). No mutation was found in the proband's parents (Fig. 3b and c).

Internal mandibular distractors were removed under general anesthesia in the fourth month postoperatively. During the 12-month follow-up period, the patient no longer suffered dyspnea. Complications of other organs and systems have not happened at the moment. The patient hasn't received any specific treatment for progeria till now.

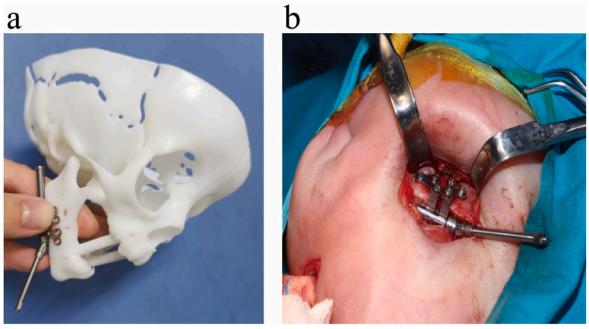

Fig. 1. The preoperative planning and the operation. (a) Before MDO surgery, a 3-dimensional model of skull and craniofacial was established using CT data, and virtual surgical planning was made. (b) Individualized internal mandibular distractors were fixed during surgery.

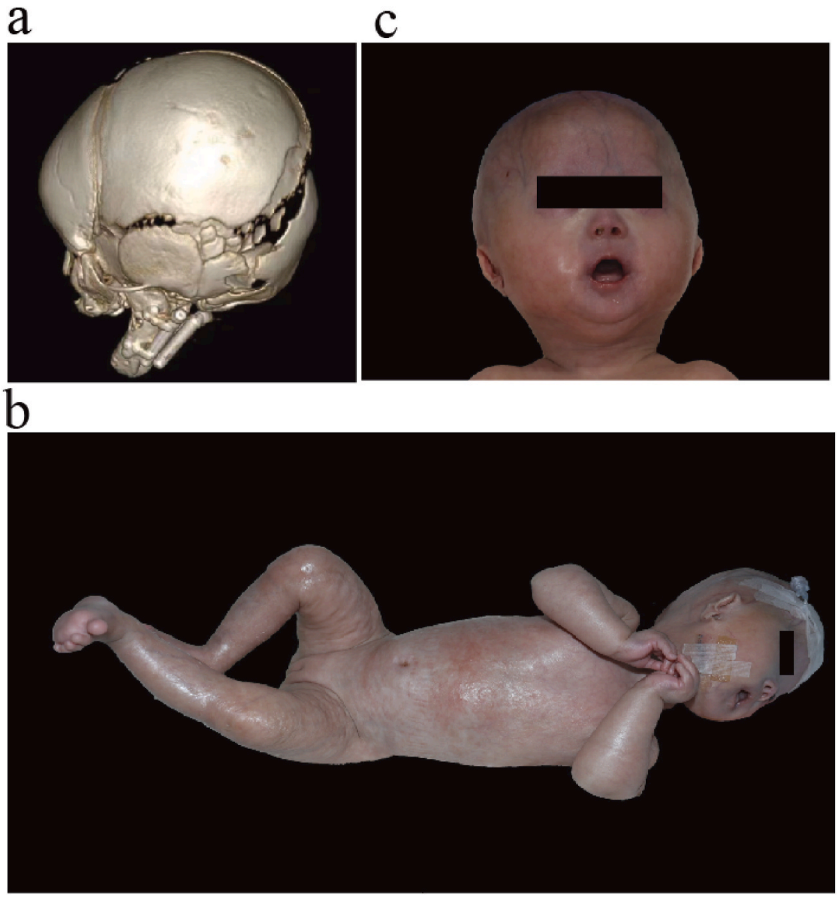

Fig. 2. Computed tomography image and appearance of progeria of the patient. (a) Computed tomography image showed craniofacial disproportion and widened cranial suture of the patient. (b) The patient was noticed to have sclerotic skin, dry skin, lipoatrophy, and joint stiffness when she was at five months of age. (c) Manifestations of head and neck included prominent scalp veins, small ear lobes, hair loss, and craniofacial disproportion.

2. Discussion

2.1. Pathogenesis and the role of LMNA gene mutation

HGPS can be categorized into classical HGPS and atypical HGPS according to the clinical characteristics and pathogenic genes. Classical HGPS is usually diagnosed around two years of age, and most patients seek medical treatment because of clinical manifestations, such as abnormal facial appearance, slow growth, and skin sclerosis. In 2003, Eriksson et al. proposed the molecular pathogenesis of classical HGPS (90 % of children with progeria) [4]. The mutation (GGC-GGT) in exon 11 (c.1824 C > T) in the LMNA (Lamin A) gene on chromosome 1 in humans activates a cryptic splice site on the mRNA and is the main cause of classical HGPS. It results in transcriptional abnormalities that prevent the precursor lamin A (prelamin A) (progerin) from becoming mature lamin A. In atypical HGPS, a splicing mutation in exon 11 of the LMNA gene or a mutation site in intron 11 of the LMNA gene that produces progerin is the main cause. Progerin gradually accumulates in tissue cells, resulting in abnormal tissue development as well as accelerating tissue damage, leading to the clinical manifestations of progeria [5–7].

The severity and speed of progression of disease in HGPS patients mainly depend on the spliceosome recognition of cryptic donors by specific germline LMNA mutations and the resulting accumulation of progerin in vivo [8]. It is reported that children with the C. 1968+1G > A mutation soon after birth developed severe joint contracture, skin tightness of limbs and trunk, ear dysplasia, severe minor mandibular deformity, and speedy aging. Eventually, they died of gastroenteritis and pneumonia at the age of 3.5 [9]. There are some other reports of severe cases related to mutations c.1968+1G > C, c.1821G > A, c.1822G > A, etc. [10,11] On the contrary, several patients with mutations C. 1968G > A and C. 1968+5G > A showed only mild symptoms. They are milder than those in classical patients in terms of hair loss, height and weight gain, and joint contracture [12]. The result of our patient showed a novel and de novo mutation in the gene LMNA with c.1968 + 3_1968+6delGAGT, which did not appear in the regular population databases, such as gnomAD_exome, ExAC, 1000 Genomes, etc. The mutation was *inferred to be pathogenic* based on characteristic clinical manifestations of the patient, similar pathogenic mutation site as previously reported, and abnormal splicing considered by splicing predictive

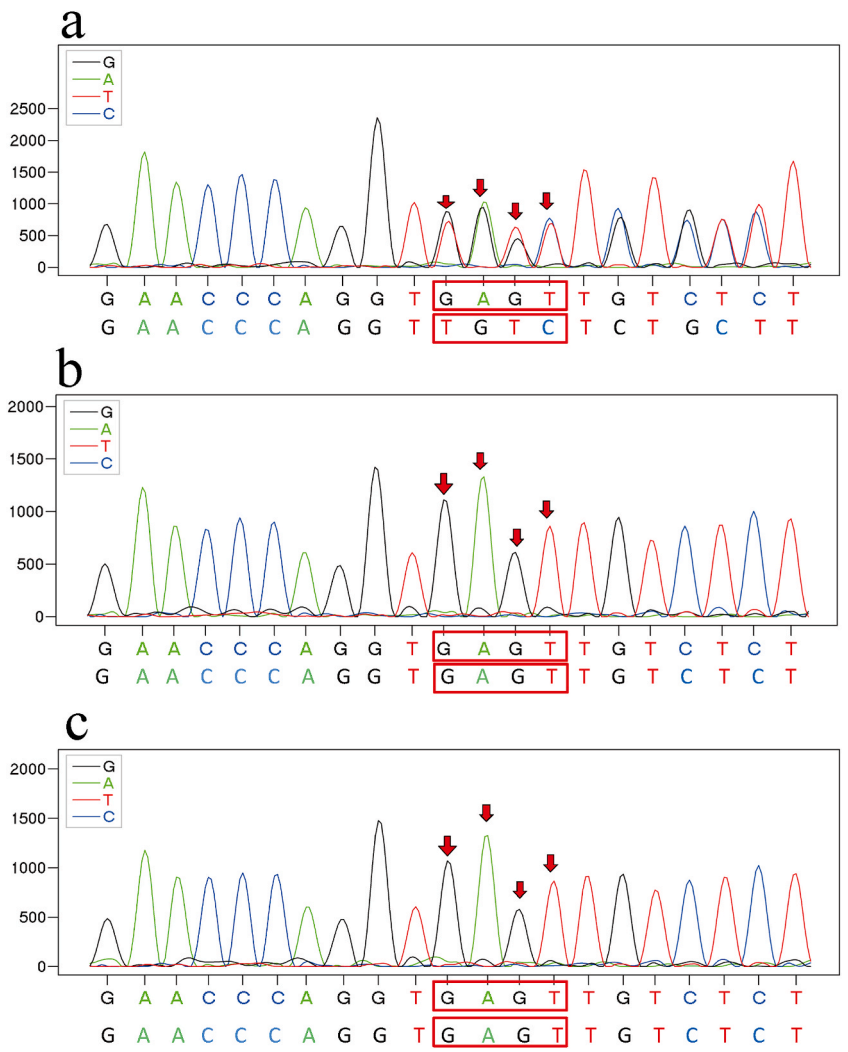

Fig. 3. The results of genetic testing. (a) DNA sequencing analysis revealed a heterozygous c.1968 + 3_1968+6delGAGT mutation in the LMNA gene in the patient. (b) No mutation was found in the patient's father. (c) No mutation was found in the patient's mother.

analysis. In addition, the patient's symptoms were found to be more severe than classical type and similar to the severe type caused by the c.1968+1G > A mutation mentioned above. It should be noted that one limitation of our study is the lack of mRNA sequencing of LMNA, resulting in a lack of conclusive evidence for the mutation's pathogenicity.

2.2. Process of diagnosis

For this patient, progressively aggravated upper airway obstruction seemed to be the first manifestation and finally became a life-threatening emergency that needed MDO surgery. This was not commonly described in the literature. The initial manifestation of reported HGPS patients was mostly sclerotic skin, which appeared as early as one month after birth. Other clinical manifestations always gradually progressed depending on age [3,13,14]. The primary clinical diagnosis of this baby was Pierre Robin sequence (PRS), characterized by micrognathia, glossoptosis, and upper airway obstruction. PRS can occur as an isolated condition or as part of a syndrome or multiple-anomaly disorder [15]. When the baby was 5 months old, other clinical features included sclerotic skin, dry skin, growth failure, lipoatrophy, joint stiffness, prominent scalp veins, small ear lobes, hair loss, and craniofacial disproportion gradually emerged. These symptoms were essential to make a diagnosis of HGPS. Genetic detection confirmed the diagnosis when the patient was 6 months old, much earlier than 2–3 years in most articles, but later than three months reported by S. Wang et al. in China [3]. When the patient was analyzed retrospectively, it was found that subcutaneous adipose tissue was thinner than a normal infant at the first visit. Meanwhile, the initial diagnosis of PRS also covered up other manifestations, making the diagnosis process difficult and time-consuming. As with our patient, the micrognathia associated with HGPS might initially be classified as PRS. Other craniofacial abnormalities included J-shaped sellas, a mottled appearance and increased vascular markings of the calvaria, abnormally configured

mandibular condyles, hypoplastic articular eminences, small zygomatic arches, prominent parotid glands, and optic nerve kinking summarized by N.J. Ullrich et al. may be helpful for clinical diagnosis [16].

2.3. MDO surgery

MDO is increasingly used for neonates and infants with upper airway obstruction secondary to micrognathia. For this patient who had failed conservative treatments, MDO surgery was taken after an overall and comprehensive assessment to exclude tumors, nasopharyngeal obstruction, and lower airway anomalies [17]. Before surgery, 3-dimensional model of skull and craniofacial was established using CT data, virtual surgical planning was made, and individualized internal mandibular distractors were prepared. The operation was successful, and postoperative distraction of 15mm length for bilateral mandible was completed in 14 days as planned. The patient's respiratory status improved within a few days and extubation was achieved, avoiding long-term tracheal intubation or tracheostomy. The patient's parents were satisfied with the treatment outcome. In literature, MDO has a success rate of approximately 95 % in preventing tracheostomy and is generally safe [17,18]. However, the patient was only 3kg weight at MDO, which was an absolute challenge for both anesthesiologists and surgeons [19]. Meanwhile, MDO on early HGPS infants was first reported in this article and might also help to recognize and understand HGPS with life-threatening upper airway obstruction. Other oral and maxillofacial surgical considerations for HGPS included mandibular and maxillary hypoplasia, delayed tooth eruption, dental treatment and orthodontic treatment [20]. Another limitation in our study should be noted is that our findings may not be generalizable to other patients.

2.4. Progress of research in treatment

In addition to symptomatic treatments, Farnesylation inhibitors (FTIs) are generally administered as a systemic drug treatment for HGPS by inhibiting the farnesylation of A-type lamin precursors, thereby avoiding cytotoxicity. However, FTIs can only improve the symptoms and cannot completely cure the progeria phenotype. Clinical trials conducted for more than two years suggested that the FTI lonafanib results in weight gain, reduces arterial pulse wave velocity and carotid artery echo density, increases bone stiffness and sensory nerve hearing, and reduces the prevalence of stroke, transient ischemic attack, and the frequency and prevalence of headache. Lonafanib was approved by the US FDA on November 20, 2020. Adverse effects of the drug include diarrhea, nausea, vomiting, decreased appetite, fatigue, infection, etc. In addition, the drug is currently recommended only for patients with body surface area (BSA) greater than 0.39 m^2 and older than 12 months. The BSA of our patient was lower than 0.39 m^2; therefore, the drug was not recommended [21,22]. A Rapalog (rapamycin) mTOR inhibitor was shown to improve the phenotype of fibroblasts in HGPS patients and increase fibroblast autophagy and prolong the lifespan of laminin A-deficient mice, suggesting that it may show potential in treating HGPS. However, the clinical trial results are still unclear and need further exploration [23,24].

Researchers have also made progress in gene editing and transcription blockade. It has been reported using animal experiments that the use of antisense peptide-conjugated phosphodiformyl morpholino oligomers can block the pathogenic splicing of mutant transcripts and significantly prolong the lifespan of HGPS transgenic mice and prevent the loss of vascular smooth muscle cells in large arteries [25]. In addition, studies have shown that morpholino antisense oligonucleotide can prevent the splicing of pathogenic LMNA and significantly reduce the accumulation of Progerin in HGPS patient cells [26]. In conclusion, blocking abnormal splicing using antisense peptides provides an important theoretical basis for the effective treatment of HGPS. In addition, it has been reported that the use of adenine base editors can correct pathogenic HGPS mutations in fibroblasts obtained from progeria children and HGPS mouse models by 87 %–91 %, reduce RNA misspellings, reduce progerin levels, and correct nuclear abnormalities [27]. A few studies based on CRISPR/CAS9 gene editing tools infected fibroblasts of children with HGPS with Streptococcus pyogenes lentivirus vector containing sgRNA designed upstream of Exon 11 of LMNA and found that it could significantly reduce progerin expression and the number of abnormal nuclei [28]. In conclusion, HGPS is a genetic disease, and potentially effective treatment is early diagnosis and gene therapy. We think that these gene editing-related studies can be applied to the clinic soon, and better therapeutic or curative effects can be achieved through the combination of gene therapy and drug application.

3. Conclusions

The diagnosis of HGPS is a gradual process along with typical clinical manifestations gradually emerge as patients grow. For the cases of suspected multiple organ abnormalities of preterm birth, it is recommended to perform genetic testing as early as possible to help find the cause and determine the prognosis. Micrognathia is one of the potential clinical manifestations of HGPS, and the dyspnea caused by it may be one of the earliest symptoms. In this study, MDO surgery received by the patient effectively improved airway obstruction and avoided tracheotomy. However, it is necessary to remind surgeons that as the related systematic treatment drugs for HGPS have not been approved for marketing in China, if HGPS has been diagnosed, sufficient communication with the patient's guardian about the prognosis is important, and treatment decisions should be made prudently based on multiple factors.

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Data availability statement

Data will be made available on request.

Ethics statement

Written informed consent was obtained from the parents for publication of this case report.
Informed consent and patient details statement.
A written consent for publication was obtained from the parents to publish all clinical details and any accompanying images.

CRediT authorship contribution statement

Duojiao Xu: Writing – original draft, Data curation, Formal analysis, Methodology. **Yujiao Guo:** Writing – original draft, Data curation, Formal analysis, Methodology. **Zhan Qi:** Data curation, Methodology. **Chanjuan Hao:** Data curation, Methodology. **Guoxia Yu:** Funding acquisition, Writing – review & editing, Conceptualization, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

HGPS	Hutchinson-Gilford progeria syndrome
MDO	mandibular distraction osteogenesis
WES	whole-exome sequencing
ICU	Intensive Care Unit
CPAP	continuous positive airway pressure
CT	Computer tomography
NPF	Nasopharyngofiberscope
MDT	multi-disciplinary team
PRS	Pierre Robin sequence
HGMD	Human Gene Mutation Database
FTIs	Farnesylation inhibitors
BSA	body surface area

References

[1] S. Gonzalo, R. Kreienkamp, P. Askjaer, Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations, Ageing Res. Rev. 33 (2017) 18–29.
[2] R. Kreienkamp, S. Gonzalo, Hutchinson-gilford progeria syndrome: challenges at bench and bedside, Subcell. Biochem. 91 (2019) 435–451.
[3] S. Wang, Z. Yang, Z. Xu, Y. Chu, Y. Liang, L. Wei, B. Zhang, Z. Xu, L. Ma, Clinical and genetic features of children with hutchinson-gilford progeria syndrome: a case series and a literature review, J. Eur. Acad. Dermatol. Venereol. 35 (6) (2021) e387–e391.
[4] M. Eriksson, B. Wt, G. Lb, G. Mw, J. Singer, L. Scott, et al., Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome, 423, Nature 423 (6937) (2003) 293–298.
[5] M. Catherine, Gordon, Leslie B. Gordon, Brian D. Snyder, Ara Nazarian, Nicolle Quinn, Susanna Huh, et al., Hutchinson-Gilford progeria is a skeletal dysplasia, J. Bone Miner. Res. 26 (7) (2011) 1670–1679.
[6] Marie Gerhard-Herman, Leslie B. Smoot, Nicole Wake, Mark W. Kieran, Monica E. Kleinman, David T. Miller, et al., Mechanisms of premature vascular aging in children with Hutchinson-Gilford progeria syndrome, Hypertension 59 (1) (2012) 92–97.
[7] Andy Tsai, Patrick R. Johnston, Leslie B. Gordon, Michele Walters, Monica Kleinman, Tal Laor, Skeletal maturation and long-bone growth patterns of patients with progeria: a retrospective study, Lancet Child Adolesc. Health 4 (4) (2020) 281–289.
[8] F.M. Hisama, D. Lessel, D. Leistritz, K. Friedrich, K.L. McBride, M.T. Pastore, et al., Coronary artery disease in a Werner syndrome-like form of progeria characterized by low levels of progerin, a splice variant of lamin A, Am. J. Med. Genet. 155A (12) (2011) 3002–3006.
[9] C.L. Moulson, L.G. Fong, J.M. Gardner, E.A. Farber, G. Go, A. Passariello, et al., Increased progerin expression associated with unusual LMNA mutations causes severe progeroid syndromes, Hum. Mutat. 28 (9) (2007) 882–889.
[10] J. Reunert, R. Wentzell, M. Walter, S. Jakubiczka, M. Zenker, T. Brune, et al., Neonatal progeria: increased ratio of progerin to lamin A leads to progeria of the newborn, Eur. J. Hum. Genet. 20 (9) (2012) 933–937.
[11] V. Gonzalez-Maestro, E. Monteagudo-Vilavedra, J. Rodriguez-Antuna, M. Lendoiro-Fuentes, M.S.B. Gomez, E.M. Mino, Carotid artery dissection in Hutchinson-Gilford Progeria: a case report, BMC Pediatr. 22 (1) (2022) 135.

[12] D.Z. Bar, M.F. Arlt, J.F. Brazier, W.E. Norris, S.E. Campbell, P. Chines, et al., A novel somatic mutation achieves partial rescue in a child with Hutchinson-Gilford progeria syndrome, J. Med. Genet. 54 (3) (2017) 212–216.
[13] W.F. Lai, W.T. Wong, Progress and trends in the development of therapies for Hutchinson-Gilford progeria syndrome, Aging Cell 19 (7) (2020), e13175.
[14] N. Sato-Kawano, M. Takemoto, E. Okabe, K. Yokote, M. Matsuo, R. Kosaki, et al., The clinical characteristics of Asian patients with classical-type Hutchinson-Gilford progeria syndrome, J. Hum. Genet. 62 (12) (2017) 1031–1035.
[15] C.C. Breugem, K.N. Evans, C.F. Poets, S. Suri, A. Picard, C. Filip, et al., Best practices for the diagnosis and evaluation of infants with Robin sequence: a clinical consensus report, JAMA Pediatr. 170 (9) (2016) 894–902.
[16] N.J. Ullrich, V.M. Silvera, S.E. Campbell, L.B. Gordon, Craniofacial abnormalities in Hutchinson-Gilford progeria syndrome, AJNR Am. J. Neuroradiol. 33 (8) (2012) 1512–1518.
[17] O. Breik, D. Tivey, K. Umapathysivam, P. Anderson, Mandibular distraction osteogenesis for the management of upper airway obstruction in children with micrognathia: a systematic review, 769-82, Int. J. Oral Maxillofac. Surg. 45 (6) (2016).
[18] D.J. Lam, M.E. Tabangin, T.A. Shikary, A. Uribe-Rivera, J.K. Meinzen-Derr, A.D. Alarcon, et al., Outcomes of mandibular distraction osteogenesis in the treatment of severe micrognathia, JAMA Otolaryngol. Head Neck Surg. 140 (4) (2014) 338–345.
[19] Z. Taufique, B. Ebert, E.C. Smith, H. Zavala, A.R. Scott, B.B. Roby, The safety and efficacy of mandibular distraction osteogenesis among infants less than 3 kg, Laryngoscope 132 (6) (2022) 1295–1299.
[20] M.D. Batstone, A.W.G. Macleod, Oral and maxillofacial surgical considerations for a case of Hutchinson-Gilford progeria, Int. J. Paediatr. Dent. 12 (6) (2002) 429–432.
[21] L.B. Gordon, H. Shappell, J. Massaro, R.B. D'Agostino, J. Brazier, S.E. Campbell, et al., Association of lonafarnib treatment vs No treatment with mortality rate in patients with hutchinson-gilford progeria syndrome, JAMA 319 (16) (2018) 1687–1695.
[22] S. Dhillon, Correction to: lonafarnib: first approval, Drugs 81 (5) (2021) 619.
[23] V. Cenni, C. Capanni, M. Columbaro, M. Ortolani, M.R. D'Apice, G. Novelli, et al., Autophagic degradation of farnesylated prelamin A as a therapeutic approach to lamin-linked progeria, Eur. J. Histochem. 55 (4) (2011) e36.
[24] K. Cao, C.D. Blair, D.A. Faddah, J.E. Kieckhaefer, F.S. Collins, Progerin and telomere dysfunction collaborate to trigger cellular senescence in normal human fibroblasts, J. Clin. Invest. 121 (7) (2011) 2833–2844.
[25] M.R. Erdos, W.A. Cabral, U.L. Tavarez, K. Cao, F.S. Collins, A targeted antisense therapeutic approach for Hutchinson–Gilford progeria syndrome, Nat. Med. 27 (3) (2021) 536–545.
[26] K. Harhouri, C. Navarro, C. Baquerre, N. Da Silva, C. Bartoli, F. Casey, et al., Antisense-based progerin downregulation in HGPS-like patients' cells, Cells 5 (3) (2016) 31.
[27] L.W. Koblan, M.R. Erdos, C. Wilson, W.A. Cabral, D.R. Liu, In vivo base editing rescues Hutchinson–Gilford progeria syndrome in mice, Nature 589 (7843) (2021) 608–614.
[28] O. Santiago-Fernandez, F.G. Osorio, V. Quesada, F. Rodriguez, S. Basso, D. Maeso, et al., Development of a CRISPR/Cas9-based therapy for Hutchinson-Gilford progeria syndrome, Nat. Med. 25 (3) (2019) 423–426.