# A case of dyskeratosis congenita with prominent splenomegaly, portal hypertension, and hypoxemia

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**Research Article**

**Keywords:** Dyskeratosis congenita, Splenomegaly and portal hypertension, Hypoxemia, Esophageal stricture, Case report

**Posted Date:** April 7th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1485606/v1

# Abstract

**Background**: Dyskeratosis congenita is a rare hereditary disease. A correct diagnosis of this disease might be delayed due to its rarity. Therefore, a deep understanding of the characteristics of this condition is necessary to assist in early diagnosis.

**Case presentation**: A 16-year-old male was admitted to the hospital with the complaint of abdominal pain. The patient was examined to consider the diagnosis of acute portal vein thrombosis. In the previously-consulted hospital, the patient was diagnosed with "splenomegaly, portal hypertension, and hypoxemia" and treated with splenic resection. After surgery, he began developing portal vein thrombosis. Since the patient had the classic triad of reticulate hyperpigmentation, nail dystrophy, and leukoplakia, these observations in combination with the patient's genetic testing report for hereditary diseases prepared outside our hospital led to the diagnosis of congenital dyskeratosis in our hospital.

**Conclusion**: In the absence of any other evident reasons, when the patient presents with changes in the skin, nails, leukoplakia, etc., and multiple organ functions are affected at the same time, a diagnosis of dyskeratosis congenita should be suspected. A better understanding of the genetics underlying this rare disease condition would assist in improving its diagnosis and better monitoring disease progression and treatment.


# Core Tip

Here, a rare case of dyskeratosis congenita with splenomegaly, portal hypertension, hypoxemia, and esophageal stenosis is reported. It is recommended to conduct multidisciplinary consultation and genetic testing to provide further insight into the disease condition for better diagnosis and treatment of rare diseases.

# Background

Dyskeratosis congenita (DC) is a rare inherited and progressive multisystemic disease that was first described as Zinsser-ColeEngman syndrome in 1906 [1]. Approximately 80%–90% of the typical DC patients exhibit abnormal skin and mucous membranes, which manifest as the classic triad of skin reticular pigmentation, nail (toe) atrophy, and oral mucosal leukoplakia [2]. Other clinical manifestations which may precede the skin and mucosal abnormalities include non-skin and mucosal abnormalities, such as bone marrow failure, pulmonary fibrosis, and tumor susceptibility. These other abnormalities render the early diagnosis of patients with atypical clinical manifestations further difficult. According to the literature, the inheritance of DC occurs via three routes, namely X-linked recessive inheritance, autosomal recessive inheritance, and autosomal dominant inheritance [3]. Previous studies have reported that the main causes of death in patients with DC are bone marrow failure (60%~70%), pulmonary complications (10%~15%), and malignant tumors (10%) [4].

Owing to the rarity of dyskeratosis congenita, its genetic heterogeneity, and the variability in its expression [5], the correct diagnosis of this disease condition might be delayed [1,6]. The present report discusses the clinical and genetic characteristics of a DC patient who presented with splenomegaly, portal hypertension (PH), and hypoxemia as the initial manifestations of his condition at our hospital. The objective is to improve the understanding of the disease to facilitate early diagnosis and provide timely assistance for effective treatment of the condition.

## Case Presentation

A 16-year-old man was admitted to the Department of Gastroenterology at our hospital with the complaint of acute abdominal pain. After conducting relevant clinical examinations of the patient, the diagnosis of acute portal vein thrombosis was considered. The abdominal pain was relieved gradually after the anticoagulation treatment using low molecular weight heparin. Afterward, the patient was being administered oral warfarin anticoagulation. However, several doubts remained. The medical history of the patient revealed that he had previously visited another doctor a year ago with the complaint of skin cyanosis and exertional dyspnea. The complete examination at that time had revealed no evidence of congenital heart disease on echocardiography, although routine blood tests had revealed leukopenia and thrombocytopenia. When a blood gas analysis was conducted at the nasal cannula inhalation rate of 1–2 L/min of oxygen, the results were as follows: clac, 1.9 mmol/L; pO2(Aa)e, 70.8 mmHg; FShumte, 44.7%; SBEc, −6.7 mmol/L; AGK+c, 9.6 mmol/L; PH, 7.44. These findings suggested that type I respiratory failure and $pO_2(Aa) \geq 15$ mmHg should be considered for the diagnosis of oxygenation dysfunction and hypoxemia. Lung HRCT revealed no evident manifestations of bilateral interstitial pneumonia. In order to further evaluate the patient's condition, Contrast-enhanced computed tomography (CT) was conducted, which revealed splenomegaly (Fig. 1). Improved bone marrow biopsy and other tests were also conducted, which could not identify any other cause. In order to determine whether splenomegaly was caused due to liver cirrhosis, a liver biopsy was performed, which revealed no evidence of liver cirrhosis (unfortunately, since the liver biopsy was performed in other hospitals, pathological images were not available for our examination). Meanwhile, a hepatic venous manometry was also performed, which indicated that the hepatic venous manometry was 14.5 mmHg and the HVPG calculation was 15 mmHg. According to these findings, combined with the patient's previous visits and perfect results in the relevant laboratory examinations, it was considered that the patient had splenomegaly, PH, and arterial oxygenation disorder, and, therefore, the diagnosis of hepatopulmonary syndrome (HPS) was established. In terms of etiology, the left and right branches of the portal vein and the splenic vein of abdominal CTA were considered to be widened. On the basis of this diagnosis, a splenectomy was performed in the other hospital. The specific situation, however, remained unknown, and the pathology exhibited congestive splenomegaly. After surgery, the patient began developing portal vein thrombosis. The physical examination conducted at our hospital also revealed short stature, nail dystrophy, leukoplakia, and hypopigmentation of the cervical reticularis (Fig. 2). According to the skin condition, a skin biopsy was performed, which revealed the hyperkeratosis of the squamous epithelium on the surface of the submitted skin tissue, an increase in the number of pigmented cells, dilation of the superficial

dermis, and infiltration of a few chronic inflammatory cells around it (refer to Pigment Incontinence in Fig. 3). The endoscopic examination revealed esophageal stricture as another abnormal point (Fig. 4). A review of the literature was conducted, based on which the triad of nail dystrophy, vitiligo, and skin examination was considered for the clinical suspicion of dyskeratosis congenita. Moreover, it was learned that the patient had previously undergone genetic testing at Peking Union Medical College Hospital, which had revealed the mutation site NHP2 (Fig. 5). After consultation with a multidisciplinary diagnosis and treatment team at our hospital, the final diagnosis of dyskeratosis congenita was established for the patient.

## Discussion And Conclusions

The clinical manifestations of DC are mainly the triad of skin reticular pigmentation, oral leukoplakia, and nail deformity and atrophy. The main diagnostic feature of DC is mottled or gridded hyperpigmentation or hypopigmentation of the skin. In the case presented here, the patient had typical skin reticular pigmentation, mainly in the regions of the body that are exposed to the sun, such as the face, neck, and upper limbs, which is consistent with previous reports in the literature [7]. The leukoplakia of this patient was located mainly on the tongue, which is also one of the characteristics of DC, as reported in the literature that approximately 80% of DC patients have leukoplakia[7]. Since the body location where leukoplakia occurs is a high-incidence region for cancer, it is recommended that in addition to regular monitoring, patients also maintain decent levels of oral hygiene. Moreover, the nails of this patient were characterized by longitudinal ridges, deformities, and atrophy, and these features were more evident in the fingernails than in the toenails, which is consistent with previous research reports [7].

DC is a highly heterogeneous disorder in terms of clinical characteristics and its pattern of inheritance [8,9]. In the case reported here, the patient's presentation with oxygenation disturbance had been attributed to HPS, which is caused due to pulmonary vasodilation and arterial oxygenation disturbance arising from various liver diseases of severe nature[10]. The condition is characterized by the triad of primary liver disease, pulmonary vasodilation, and arterial oxygenation disorders. Recent studies have demonstrated that HPS causes dyspnea in several patients with DC, a few of which have PH without clear evidence of liver disease, a condition referred to as non-cirrhotic portal hypertension (NCPH) [11,12]. NCPH exhibits several characteristics that distinguish it from the other causes of PH [1,13,14]. For instance, the first symptoms and complications in most NCPH patients are primarily PH-related rather than related to the liver. In these patients, despite their hypoxemia due to HPS, transaminase levels were normal or only mildly elevated, and the liver pathology findings were non-specific, similar to that observed in our patient's first biopsy and other examinations such as CT. The common evidence of initial PH includes dilated portal veins and splenomegaly rather than ascites and varicose veins. In a previous study on a symptomatic case, our patient's presentation was consistent with HPS due to NCPH. However, in clinical practice, severe HPS without the evidence of proportional liver injury is often not accepted by physicians as a cause of hypoxemia and may lead to delay in liver transplantation (LT). The present case report, therefore, re-emphasizes that HPS should be suspected early in DC patients with dyspnea, even if multiple liver biopsies for this patient have not revealed specific findings. Since DC is characterized by

premature aging of various organs[15], with the development of the disease, organs such as the liver may also be damaged. Therefore, a close follow-up, detection, and active timely intervention are necessary to prevent any further damage to these organs in these patients.

Other clinical manifestations of DC include ectodermal abnormalities, such as alopecia, eyebrows and eyelashes, immature gray hair, profuse sweating, hyperkeratosis of palms and soles, and dermatophytosis. Concomitant severe bone marrow failure, myelodysplastic syndrome, acute myeloid leukemia, or solid tumors are also poor prognostic factors. Bone marrow failure is one of the leading causes of death, with approximately 70% of deaths being related to bleeding and opportunistic infections. Patients with DC have a higher susceptibility to tumors and a higher prevalence of malignant mucosal tumors [7]. The most common kind of tumor is the head and neck squamous cell carcinoma, followed by skin and anorectal tumors, which are more common in vitiligo [16]. Other reported malignancies include Hodgkin's lymphoma, gastrointestinal adenomas, and bronchial and laryngeal cancers. Malignant tumors are reported to occur over the age of 30 years [17]. In certain cases, the skeletal system, digestive system, and genitourinary system may also become involved, such as in the form of osteoporosis, genitourinary malformations, etc. In the case presented here, no evidence of the involvement of these systems was observed. However, gastroscopy revealed the stricture of the esophagus, although there were no symptoms of dysphagia. It is reported that 17% of patients with dyskeratosis congenita have esophageal strictures. A few of these patients required endoscopic dilation due to dysphagia [7]. A close follow-up and endoscopic dilation therapy are performed when necessary.

It is difficult to establish a correct diagnosis of DC due to its clinical and genetic heterogeneity. There are three inherited forms of DC, namely, X-linked, autosomal dominant, and autosomal recessive. In clinical practice, DCs may be misdiagnosed as other diseases, such as aplastic anemia (AA), as DCs may present with varying degrees of cutaneous and non-cutaneous features [9]. Besides the typical triad, the diagnosis of DC relies mainly on genetic monitoring. Eight genes have been confirmed to cause DC, namely CTC1, DKC1, TERC, TERT, TINF2, WRAP53, NHP2, and NOP10. The genetic testing of the patient case presented here revealed two heterozygous variants in the autosomal recessive dyskeratosis congenita type 2 (AR)-related gene NHP2 – c.265G>A (p. E89K) and c.110C>G (p. P37R) – neither of which has been reported previously. The results of pedigree verification revealed that the double heterozygous variant was received from the patient's parents, and was a compound heterozygous variant. Patients with this condition may also overlap with other genetic syndromes that prevent an accurate diagnosis and subsequent management of DC, thereby requiring a classic evaluation of dyskeratosis congenita in patients based on the clinical features of dyskeratosis congenita. In addition to the genetic and telomere length measurements, genetic analysis of USB1, LIG4, and GRHL2, among others, is required [17]. This has important implications for establishing a genetic diagnosis when new patients present to the clinic.

So far, no ideal treatment plan is available for DC, and mainly symptomatic or palliative treatments are adopted, which do not produce an ideal treatment effect, and the prognosis of patients is poor. Certain studies have reported improvement in bone marrow involvement upon treatment in a few cases.

Allogeneic hematopoietic stem cell transplantation may be the only cure for bone marrow failure, although it neither alters the symptoms that have developed in the other systems of the patient's body nor does it change the propensity to develop the malignant form of the disease in adulthood. Other treatments are to be evaluated in further investigation.

According to the cases reported in the literature, DCs may involve multiple organs and manifest various clinical features. Therefore, even in the case presented here, the patient could have had certain manifestations that were not identified and required further investigation and treatment. The present case emphasizes the need to consider every suspicious sign and symptom that might assist in the diagnosis and treatment. If necessary, a multidisciplinary team (MDT) should be consulted to assist with the diagnosis and treatment.

# Abbreviations

DC: Dyskeratosis congenita; CT: Computed tomography; PH: Portal hypertension; HPS: Hepatopulmonary syndrome; NCPH: Non-cirrhotic portal hypertension; MDT: Multi-disciplinary team.

# Declarations


### Acknowledgments

Not applicable.


### Authors' contributions

Li-juan Liu and Cheng-xian Yong: Manuscript writing, literature research. Qiong Niu and Yu Gao: Management of the case, editing the manuscript. Cheng-xia Liu: Manuscript writing, management of case and final approval of manuscript. All authors have read and approved the manuscript.


### Funding

None.


### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

### Ethics approval and consent to participate

Ethics approval by committee was not required for this case report.

### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Competing interests

The authors declare that they have no competing interests.

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# Figures

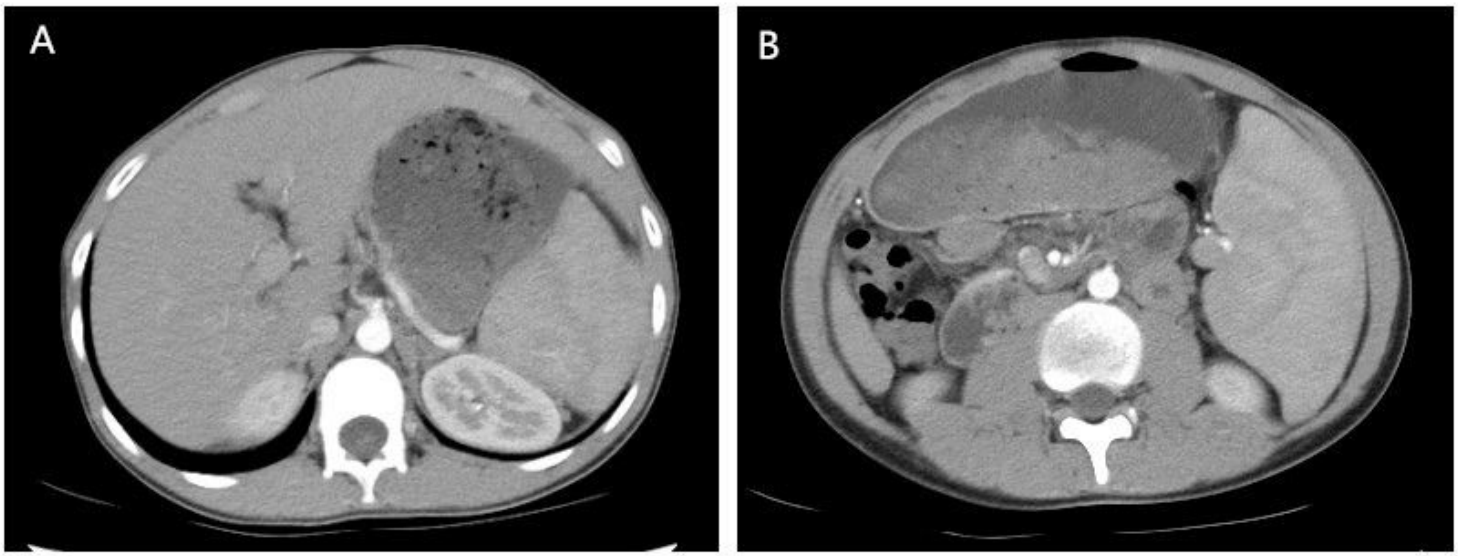



**Figure 1**

Contrast-enhanced computed tomography (CT) revealed that (A) the liver was in good shape and (B) the enlarged spleen could be observed in the lower pole of the left kidney.

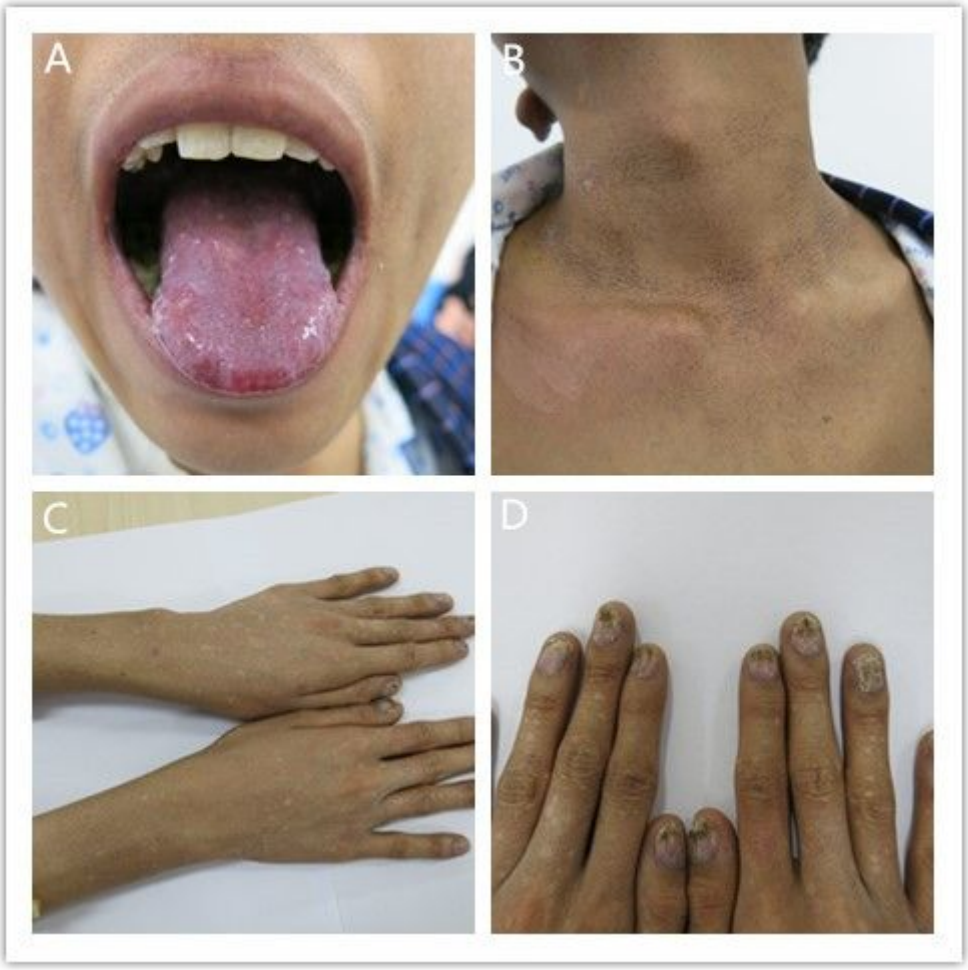



**Figure 2**

Physical examination revealed (A) oral leukoplakia and (B and C) skin reticular hyperpigmentation of the neck and upper extremities. (D) The higher magnification revealed nail dystrophy.

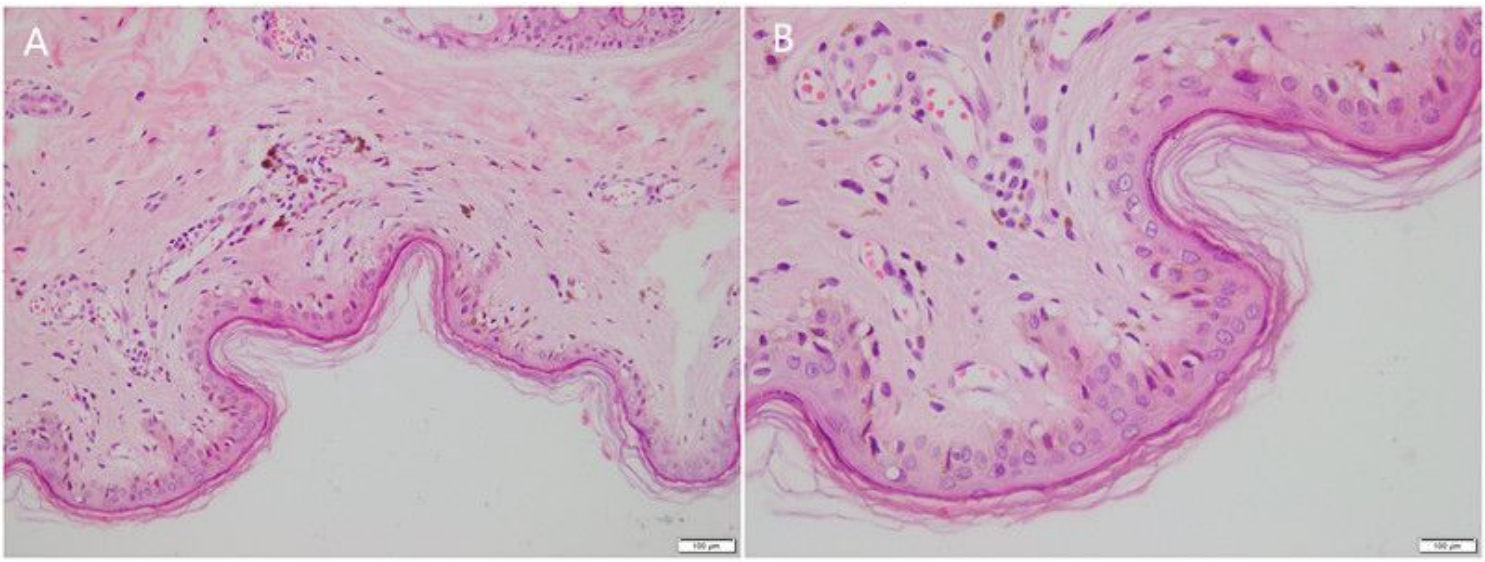



**Figure 3**

Skin biopsy pathology revealed dyskeratosis and pigment incontinence.

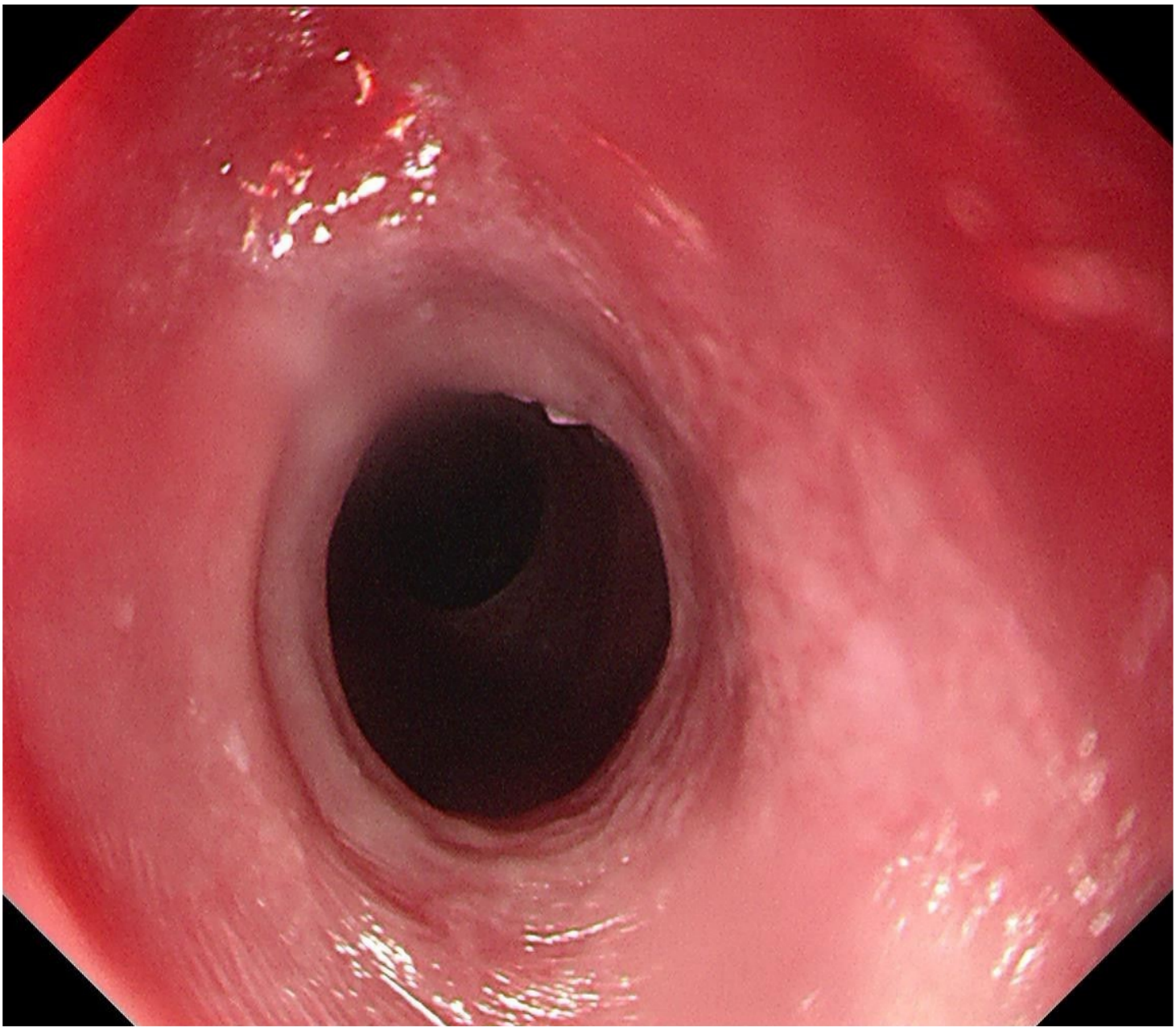
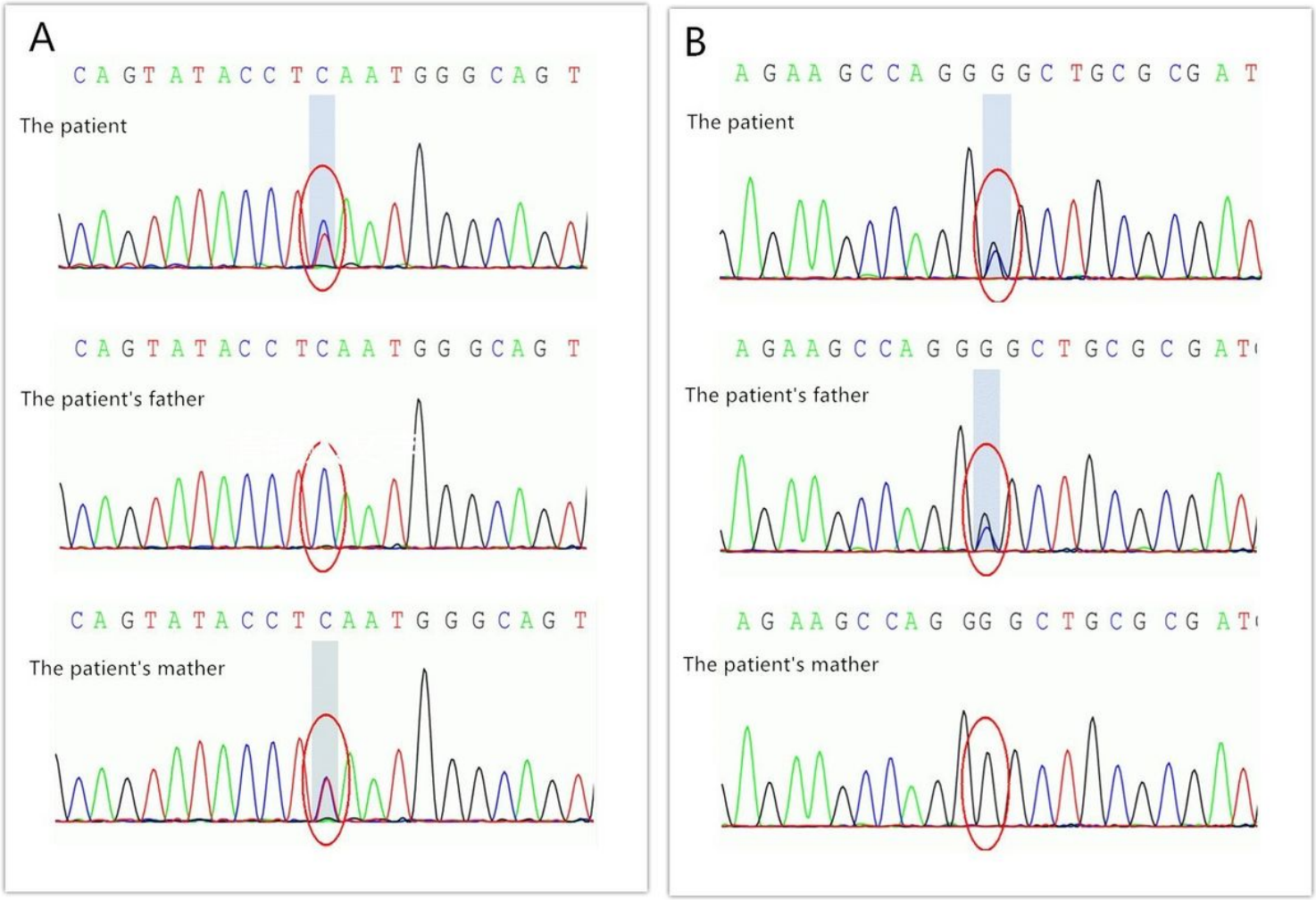


**Figure 4**

Gastric endoscopy revealed annular stenosis of the esophageal lumen approximately 17 cm from the incisors.




## Figure 5

The NHP2 sequencing maps for the patient, the patient's father, and the patient's mother. The red circle indicates the mutated base. Patient A and the patient's mother had a heterozygous variant (antisense strand) of c.265G>A in chr5:177577960, while no variant (antisense strand) was detected in chr5:177577960 of the patient's father. Patient B and the patient's father had a heterozygous mutation (antisense strand) of c.110C>G in chr5:177580709, while the patient's mother had no mutation (antisense strand) in chr5:177580709.