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# Fibroadenoma in Beckwith–Wiedemann syndrome with paternal uniparental disomy of chromosome 11p15.5

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**Abstract** Herein is described a case of breast fibroadenomas in a 16-year-old girl with Beckwith–Wiedemann syndrome (BWS) and uniparental disomy (UPD) of chromosome 11p15.5. She was clinically diagnosed with BWS and direct closure was performed for an omphalocele at birth. Subtotal and 90% pancreatectomy were performed for nesidioblastosis at the ages 2 months and 8 years, respectively. Bilateral multiple breast fibroadenomas were noted at the age of 16 and 17 years. In this case, paternal UPD of chromosome 11p15.5 was identified on microsatellite marker analysis. The relevant imprinted chromosomal region in BWS is 11p15.5, and UPD of chromosome 11p15 is a risk factor for BWS-associated tumorigenicity. Chromosome 11p15.5 consists of imprinting domains of IGF2, the expression of which is associated with the tumorigenesis of various breast cancers. This case suggests that fibroadenomas occurred in association with BWS.

**Key words** 11p15, Beckwith–Wiedemann syndrome, breast tumor, fibroadenoma, uniparental disomy.

Beckwith–Wiedemann syndrome (BWS) is an overgrowth disorder with a potentiality for various embryonal tumors, such as Wilms tumor, hepatoblastoma, and a variety of other malignant and benign tumors.[1,2] BWS is caused by various epigenetic or genetic alterations associated with chromosome 11p15, such as uniparental disomy (UPD).[1] We report a case of breast fibroadenomas and ovarian adenofibroma in a 16-year-old girl with BWS and UPD of chromosome 11p15.5, and discuss the relationship between fibroadenoma, which is relatively common in adolescents, and BWS and paternal UPD on chromosome 11p15.5.

## Case report

The patient was a 16-year-old girl who was diagnosed with BWS at birth based on the following genetic characteristics: macrosomia, omphalocele, macroglossia, and hypoglycemia. Her birthweight was 4254 g. Direct closure was performed for the omphalocele immediately after birth.

At the age of 2 months, exploratory laparotomy was performed due to extremely high serum α-fetoprotein and intra-abdominal cystic lesion, which found a hepatic cyst and the tumor-forming type of nesidioblastosis.[2] Resection of the hepatic cyst and subtotal pancreatectomy were performed. Because the patient experienced hypoglycemic episodes 2–3 times per year, 90% pancreatectomy was again performed for nesidioblastosis at the age of 8 years.[2] Thereafter, she had no further hypoglycemic episodes. We previously reported on that course.[2]

At the age of 16 years, a right breast tumor was noticed, which grew over time. Extirpation was performed and histology confirmed breast fibroadenoma (Fig. 1a). Three months after extirpation of the breast tumor, the patient presented with lower abdominal distention; ultrasonography indicated that this was caused by an ovarian solid and cystic mass. The cystic lesion was resected, and histology confirmed adenofibroma (Fig. 1b).

At the age of 17 years, bilateral multiple tumors of the breasts were detected on follow-up ultrasonography, which were confirmed to be fibroadenomas on needle biopsy. The patient received no further intervention and has been followed up for 6 years.

Previously, we studied chromosome 11p for identification of the disorder using G banding, but no anomaly was detected. Recently, re-evaluation of chromosome 11p using microsatellite marker analysis indicated paternal UPD of chromosome 11p15.5. Although we analyzed three microsatellite markers, D11S2362, D11S1318 and TH01, only one microsatellite marker, D11S1318, provided useful information about the patient. The percentage mosaicism of paternal UPD in the patient's DNA was 98% and 69% from peripheral blood and saliva, respectively (Fig. 2).

## Discussion

Classically, BWS is diagnosed based on clinical features such as abdominal wall defects, macroglossia, and macrosomia.[1,2] BWS is the most common congenital overgrowth syndrome involving tumor predisposition and has a strong correlation with embryonal tumors such as Wilms tumor, hepatoblastoma, neuroblastoma, adrenocortical carcinoma, and a variety of other malignant and benign tumors.[1,2] The overall risk of tumor development has been

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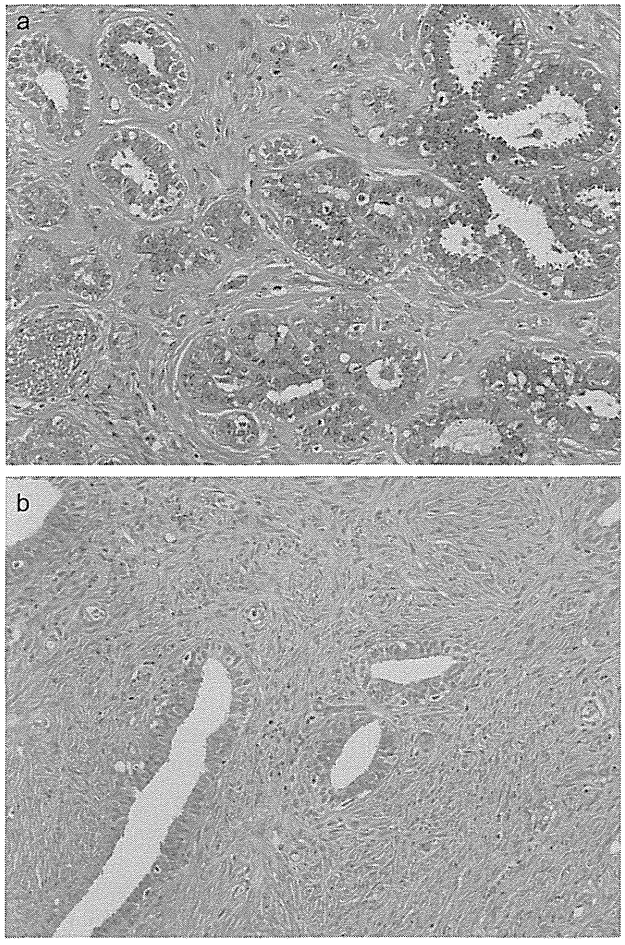


**Fig. 1** (a) Many ductular structures are visible, surrounded by moderately cellular stromal connective tissue. The stromal nuclei show little pleomorphism with infrequent mitosis. Breast fibroadenomas were diagnosed. (b) Proliferation of stromal cells and ductules is observed. Ductules are lined with ciliated high columnar epithelial cells. An ovarian adenofibroma was diagnosed.

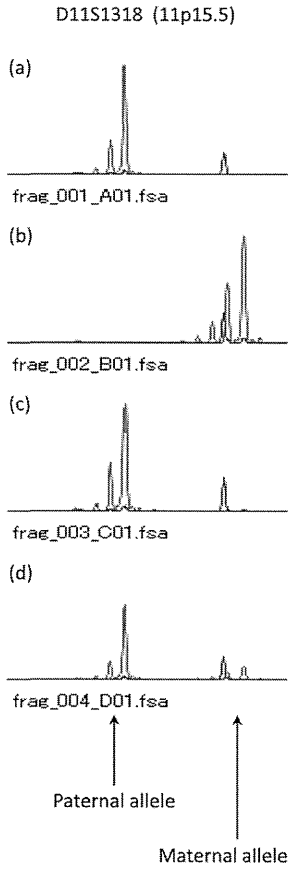


**Fig. 2** Microsatellite marker analysis. (a) Father; (b) mother; (c,d) patient DNA (c, peripheral blood; d, saliva). A microsatellite marker, *D11S1318*, from 11p15.5 was amplified and separated on electrophoresis using an Applied Biosystems 3130 genetic analyzer (Applied Biosystems, CA, USA); data were quantitatively analyzed using the GeneMapper software. The percentage mosaicism of paternal UPD was calculated as follows: % mosaicism = $(k - 1)/(k + 1) \times 100$, where k is the ratio of the peak height of the paternal to maternal alleles of the sample. The percentage mosaicism of paternal UPD in the patient's DNA was 98% and 69% from (c) peripheral blood and (d) saliva, respectively.

estimated at 7.5%.[1] Although there are no absolute unified criteria for the clinical diagnosis of BWS, the following criteria are generally accepted: presence of at least three major findings, or two major findings and one minor finding.[1] Major findings associated with BWS include abdominal wall defect, macroglossia, macrosomia, anterior ear lobe creases and/or posterior helical pits, visceromegaly intra-abdominal organ, embryonal tumor, hemihyperplasia, cytomegaly of adrenal fetal cortex, renal abnormalities, positive family history of BWS and cleft palate.[1] Minor findings include neonatal hypoglycemia, nevus flammeus, cardiac anomaly, diastasis recti, advanced bone age and pregnancy-related findings such as polyhydramnios, enlarged placenta and thickened umbilical cord.[1] The relevant imprinted chromosomal region in BWS is 11p15.5. Recently, with the development of molecular genetic analysis, several causative alterations in this region have been identified for sporadic cases of BWS. Paternal UPD of chromosome 11p15 is one such alteration and is found in 20% of BWS patients.[1] UPD occurs when an individual receives both copies of a chromosome or part of a chromosome from one parent. UPD can occur as a random event during the formation of egg cells or sperm cells, or may occur in early fetal development. Non-mosaic genome-wide paternal UPD, however, is known to be lethal.[3] Therefore, BWS patients with paternal UPD are mosaic for paternal UPD cells and normal biparental cells.[1] This indicates that somatic recombination occurs in the post-fertilization stage in BWS patients.[1] UPD of chromosome 11p15 is a reported risk factor for BWS-associated tumorigenicity.[1] The tumor risk for BWS patients with paternal UPD is estimated to be ≥25%.[1] In the present case, embryonal tumors did not develop, although multiple and recurrent fibroadenomas developed.

Although a fibroadenoma is a benign tumor that is relatively common in adolescents, a suspected correlation between BWS

and breast tumors is reported.[4–8] Seven cases, including the present one, of breast fibroadenomas probably associated with BWS have been reported in the literature (Table 1).[5–8] Patient age ranged from infancy, in one case,[4] to adolescence, in six cases.[3,5–8] Four of the seven patients presented with BWS-associated tumor lesions: three presented with Wilms tumors, adrenocortical carcinoma, adrenal pheochromocytoma, hamartoma of the liver, nesidioblastosis, and steroid cell tumor of ovary, whereas the current patient presented with nesidioblastosis, hepatic cyst, and ovarian adenofibroma.[3,5,7]

The chromosomal disorder was not detected in one of the seven patients, and was not mentioned in four of the seven patients. In the present case, paternal UPD of chromosome 11p15 was diagnosed on microsatellite marker analysis. Gogiel *et al.* reported that a 19-year-old woman with BWS, who was diagnosed as a carrier of a mosaic paternal UPD of chromosome 11p15, presented with fibroadenoma.[3] A BWS-associated chromosomal disorder of paternal UPD of chromosome 11p15 has been detected in two cases, including the present case of fibroadenoma with BWS.[3] Earlier in the present case, we used G banding for the detection of a chromosomal disorder on chromosome 11p, but no such disorder was detected using this method. Instead we identified the chromosomal disorder using microsatellite marker analysis. Microsatellites are tandem repeated nucleotide sequences. Individuals typically have two alleles per microsatellite. If the number of repeats for one allele is different from that of the other, two separate bands would be visible. If, however, the individual has a genetic deletion that includes the region containing the microsatellite, only one band would be visible. In the present case, only one band of paternal allele in chromosome 11p15.5 was amplified in the patient's DNA from peripheral blood and saliva (Fig. 2). This analysis indicated paternal UPD of chromosome 11p15.5. Early diagnosis of BWS is important because BWS patients have a predisposition to various tumors such as Wilms tumor, hepatoblastoma, and a variety of other malignant and benign tumors.[1] Therefore, we emphasize the need for additional molecular testing such as microsatellite marker analysis for the diagnosis of BWS if no chromosomal disorder has been detected by G banding.

In this case, we studied DNA only from the peripheral blood and saliva sample and not from the fibroadenoma tissue sample because of degradation of the sample tissue. Therefore, we could not conclude that paternal UPD of chromosome 11p15.5 was identified from the DNA of the fibroadenoma tissue sample. Gogiel *et al.* reported that analysis of breast tumor tissue DNA showed the same paternal UPD pattern as DNA from peripheral blood.[3] Thus, in the present case we could not confirm whether the association of fibroadenoma with BWS in this case was absolute or incidental. There is, however, a high probability of the association because of the unusual presentation of bilateral and multiple breast fibroadenomas, the coexistence of an ovarian adenofibroma, and the identification of paternal UPD of chromosome 11p15.5. In BWS patients, several mechanisms lead to an increased expression of *IGF2*.[1] BWS was one of the first syn-

**Table 1** Reported cases of breast fibroadenoma associated with BWS

| First author, year | Sex | Breast tumors | Other tumors | Chromosomal disorder | Hypertrophy |
|---|---|---|---|---|---|
| Müller, 1978[5] | F | 14 years old: FA of right breast | 3 years old: Wilms tumor<br>7 years old: Adrenocortical carcinoma | Not mentioned | Left leg right part of tongue |
| Raine, 1979[4] | F | 7 months old: FA of left breast<br>17 months old: Recurrence FA | None | Not mentioned | Right leg |
| Labrune, 1988[6] | F | 13 years old: FA of right breast<br>14 years old: Recurrence FA | None | Normal | Right side |
| Bemurat, 2002[7] | F | 14 years old: FA of bilateral breast | 20 years old: Adrenal pheochromocytoma | Not mentioned | Not mentioned |
| Poh, 2010[8] | F | 12 years old: FA of left breast | None | Not mentioned | Right side |
| Gogiel, 2013[3] | F | 18 years old: FA of breast | 1 month old: Hamartoma of liver<br>2 months old: Nesidioblastosis<br>14 years old: Steroid cell tumor of ovary | 11p15.5 paternal UPD | Left side |
| Present case | F | 16 years old: FA of right breast<br>17 years old: Recurrence of bilateral breast | At birth: Nesidioblastosis<br>16 years old: Adenofibroma of left ovary | 11p15.5 paternal UPD | None |

BWS-associated chromosomal disorder of paternal UPD of chromosome 11p15 was detected in two cases, including the present case of fibroadenoma with BWS. BWS, Beckwith–Wiedemann syndrome; FA, fibroadenoma; UPD, uniparental disomy.

dromes in which IGF2 expression was linked to a growth disorder, in addition to its association with the tumorigenesis of various breast cancers.[9,10] Sawyer *et al.* reported that extensive IGF2 overexpression was found in the majority of fibroadenomas.[11] The present case suggests that the development of multiple and recurrent fibroadenomas is associated with BWS-associated UPD of chromosome 11p15.5. We believe that the present case shows a strong correlation between BWS and fibroadenomas.

### *Conclusion*

We encountered a case of multiple and recurrent breast fibroadenomas and an ovarian adenofibroma associated with BWS in a patient diagnosed with paternal UPD of chromosome 11p15.5. Microsatellite marker analysis was useful to diagnose the case, which could not be diagnosed as BWS on G banding. BWS with paternal UPD of chromosome 11p15.5 presents not only as embryonal tumors but also as various benign and malignant tumors. Therefore, early diagnosis of BWS on molecular testing is helpful in screening for tumorigenesis.

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# Cyclic fluctuation of blood pressure in neonatal neuroblastoma


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**Abstract** Herein is described a case of neonatal neuroblastoma with cyclic blood pressure fluctuation and elevated catecholamines. The fluctuations stabilized after treatment with α-adrenergic blocker and the perioperative course was uneventful. The possibility of catecholamine-related symptoms including hypertension, heart failure, and blood pressure fluctuations should be considered in the treatment for neuroblastoma; if they are present, treatment with α-blockers is effective.



**Key words** catecholamine, cyclic fluctuation, hypertension, neuroblastoma, α-adrenergic blocker.


Although elevated epinephrine, norepinephrine, or dopamine were reportedly observed in approximately 20% of patients with neuroblastoma,[1] symptoms due to catecholamine excess are not common in neuroblastoma.[2] Among them, hypertension is relatively common and observed in approximately 10% of patients.[3] Hypertension can occur even in patients with ganglioneuroblastoma[4,5] or ganglioneuroma and is induced by catecholamine excess and for renovascular reasons.[5] Although hypertension is sometimes observed in patents with neuroblastoma,[5–7] the cyclic fluctuation of blood pressure is extremely rare and not reported in the literature. Here we describe a neonatal case of neuroblastoma with cyclic blood pressure fluctuations.


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# 神経症候群（第2版）

## —その他の神経疾患を含めて—

# IV

### VIII　先天異常/先天奇形

染色体異常・先天奇形症候群

## Hallermann-Streiff症候群

沼部博直

染色体異常・先天奇形症候群

# Hallermann-Streiff症候群

Hallermann-Streiff syndrome

沼部博直

Key words：先天性白内障，プロゲリア，眼・下顎・顔症候群，oculo-mandibulo-facial syndrome



## 1. 概念・定義

Hallermann-Streiff症候群(OMIM %234100)は，1948年にHallermann[1]が2例，1950年にStreiff[2]が1例の先天性白内障と小下顎や嘴(くちばし)状の鼻からなるいわゆる'鳥様顔貌(現在では用語として用いない)'を特徴として報告した症候群である．1958年にはFrançois[3]が自験例1例を加えた過去22例を総括して報告している．

眼・下顎・顔症候群(oculo-mandibulo-facial syndrome)とも呼ばれる．頭蓋・顔面の形成異常を伴う特徴的顔貌，先天性白内障，両側小眼球，歯牙の異常，疎な頭髪，萎縮した皮膚，均整の取れた低身長などを主症状とする症候群である(表1)[4]．頭髪や皮膚の外見印象はプロゲリア(早老progeria)，プロゲノイド(早老様progenoid)と表現されることがあるが，本症候群では実際の加齢推進は認められないことから本用語の使用はできるかぎり避けるべきである．

## 2. 疫　　学

性差は認められず[5]，明らかな家族例も認められていない[4]．1980年と1990年のHigurashiら[6,7]の東京におけるそれぞれ14,430人，27,472人の新生児の奇形症候群の調査によれば，各1例が本症候群であった．頻度は決して低くはないものと推定される．

表1　Hallermann-Streiff症候群の主症状の頻度(Cohen Jr.による150例の調査結果)(文献[4]より引用)

| 症　状 | % |
|---|---|
| 頭蓋・顔面形成異常 | 98-99 |
| 先天性白内障 | 81-90 |
| 小眼球症 | 78-83 |
| 歯牙異常 | 80-85 |
| 疎な頭髪 | 80-82 |
| 皮膚萎縮 | 68-70 |
| 均整の取れた低身長 | 45-68 |

## 3. 病因・病態

原因遺伝子ならびに病態はいまだに不明である．

Hallermann-Streiff症候群と眼・歯・指異形成症(oculodentodigital dysplasia: ODDD; OMIM #164200)の両疾患の症状が重複している1症例が，ODDDの病因として知られているコネキシン43をコードする*GJA1*遺伝子の変異のホモ接合体であったことが報告されているが[8]，同時に解析されたHallermann-Streiff症候群の典型例1例では変異は認められておらず，以降，*GJA1*遺伝子の変異症例の報告は本症候群ではなされていない．

また，疎な頭髪や萎縮した皮膚から得られる特徴的顔貌印象から，Hutchinson-Gilfordプロゲリア症候群(HGPS: OMIM #176670)や，

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下顎骨肢端骨異形成(mandibuloacral dysplasia; OMIM #248370)などのlaminin関連遺伝子の変異によるlaminopathieの一病型とも推測されたが，Hallermann-Streiff症候群における解析では，*LMNA*，*ZMPSTE24*，*ICMT*いずれの遺伝子の変異も認められていない[9]．

遺伝形式は，明らかな家族例が認められておらず，ほとんどが孤発例であることから，新生突然変異に基づく優性遺伝形式であると推測される．

## 4. 臨床像・診断

先天性白内障，両側小眼球，鳥様顔貌，均整の取れた小人症，歯牙の異常，貧毛症などを主徴とする症候群である．鳥様顔貌は小下顎症と嘴(くちばし)状の鼻により構成されるが，加齢とともに典型的となってくる．小下顎は新生児-乳児期の哺乳障害や上気道の狭窄による呼吸障害・呼吸器感染症を合併しやすい．

臨床像の詳細は下記のとおりである．

(1) 全身：上下肢の短縮や脊椎圧迫変形などを伴わない，四肢と体幹の長さの均整が取れた低身長(小人症)を呈する．

(2) 頭部：前頭部・側頭部の突出を伴う短頭．大泉門閉鎖遅延．

(3) 眼：先天性白内障(自然軽快することもある)，両側性小眼球．先天性白内障の頻度は1万出生あたり2.7と報告されており，子宮内感染や先天代謝異常症などでも生じるほか，本症候群を含む先天奇形症候群の症状としても認められることがある[10]．

本症候群には，これらのほかにも様々な眼科学的合併症が知られており(**表2**)，早期から眼科学的精査・治療管理が必要となる．また，先天性白内障の水晶体摘出術後の緑内障や網膜剥離の発生[11]も知られており，注意が必要である．

(4) 顔面：頬骨形成不全，小下顎．鼻は細く尖り，鼻軟骨の形成不全を伴い，加齢とともに特徴的顔貌を呈する．以前は，鼻が嘴状で，小さく後退した顎からなる横顔の輪郭から鳥様顔貌という用語が使われたが，現在は不適切な用語として使われないようになった．

**表2　Hallermann-Streiff症候群の眼科学的合併症**(Cohen Jr.による150例の調査結果)(文献[4]より改変)

| 症　状 | % |
|---|---|
| 先天性白内障 | 81-90 |
| 小眼球症 | 78-83 |
| 眼振 | 32-45 |
| 斜視 | 33-37 |
| 青色強膜 | 22-31 |
| 疎な睫毛と眉毛 | 29 |
| 眼底の異常 | 18-22 |
| 結膜の異常 | 11 |
| 角膜の異常 | 9-14 |
| 眼瞼裂斜下 | 12-13 |
| 眼圧上昇 | 7-11 |
| 虹彩萎縮 | 10-14 |
| 硝子体変性 | 8 |
| 眼瞼の異常 | 6 |
| 虹彩欠損 | 5 |
| 瞳孔膜遺残 | 5 |
| 眼球陥凹 | 2.5-4 |
| 内眼角贅皮 | 2-4 |
| 視神経乳頭コロボーマ | 1 |
| 脈絡膜コロボーマ | 1 |
| 眼瞼下垂 | 1-3 |
| 涙点低形成 | 2 |
| 眼球腫瘍 | 1 |
| 網膜色素変性症 | まれ |

(5) 歯牙：歯牙形成不全，歯列不整，先天歯，部分的欠歯症．

(6) 皮膚・毛：鼻尖部ならびに頭蓋縫合部に著明な皮膚萎縮．頭髪・眉毛・睫毛に著明な乏毛症．細く明るい毛髪．

(7) その他の低頻度の異常：舟状頭蓋，小頭症，扁平頭蓋底，皮膚性二重顎，合指症，翼状肩甲，脊椎前彎・側彎，二分脊椎，漏斗胸，精神発達遅滞，性腺機能低下，停留睾丸など様々な症状を伴うことが知られている(**表3**)．

先天性心疾患の合併はまれであるが，Imaizumiら[12]は心室中隔欠損の合併例を先天性心疾患の合併4例目として報告した．

## 5. 鑑別診断

mandibulofacial dysostosis(下顎顔面異形成症)はTreacher Collins症候群とも呼ばれ，

表3 Hallermann-Streiff症候群にみられる低頻度の症状(Cohen Jr.による150例の調査結果)(文献[1]より引用)

| 症 状 | % |
|---|---|
| 精神発達遅滞 | 15 |
| 神経学的症状 | まれ |
| 骨系統異常 | 10-50 |
| 性器奇形 | 10-12 |
| 先天性心疾患 | 2-9 |
| 耳の異常 | 9 |
| 造血器異常 | 7 |
| 肺奇形 | 3 |
| 消化器奇形 | 3 |
| 筋低形成 | 3 |
| 肝奇形 | 2 |
| 腎奇形 | 1-2 |

眼瞼裂斜下，眼瞼のコロボーマ，小顎症，小耳介を主徴とする症候群で，第1・第2鰓弓の発生異常が主たる病因である．'treacle'タンパクをコードする*TCOF1*遺伝子(OMIM *606847)のヘテロ変異で発症し本症候群の80-90％を占める1型(TCS1; OMIM #154500)，*POLR1D*遺伝子(OMIM *613715)のヘテロ変異で発症する2型(TCS2; OMIM #613717)，*POLR1C*遺伝子(OMIM *610060)のヘテロ変異で発症する3型(TCS3; OMIM #248390)に分類される．顔貌などはHallermann-Streiff症候群に類似するが，mandibulofacial dysostosisでは頭髪や皮膚の症状が認められない．

また，病因・病態の項目で挙げた本症候群の特徴的顔貌は，Hutchinson-Gilfordプロゲリア症候群(HGPS)などのプロゲリア症候群や，その他のプロゲリア様症候群に類似するが，先天的な眼科学的症状はHallermann-Streiff症候群に比較的特有であり，鑑別可能である．

眼・歯・指異形成症(oculo-dento-digital dysplasia，oculodentodigital dysplasia: ODDD)は，眼・歯・骨症候群(oculo-dento-osseous syndrome)とも呼ばれ，コネキシン34をコードする*GJA1*遺伝子のヘテロ変異により発症する常染色体優性遺伝疾患である．小眼球，小角膜，虹彩異常，白内障，鼻翼の低形成を伴った細く突出した鼻，歯牙欠損，小さな歯，歯牙エナメル質低形成，第IV・V指の合指(合指症III型)や屈指を主症状とする．Hallermann-Streiff症候群に極めて類似した症状を呈するが，指趾奇形はODDDに特徴的である．ODDDではほかに低身長，疎な頭髪，疎な眉毛，内眼角贅皮，歯列不整，口唇口蓋裂，心筋伝導障害も含む先天性心疾患などの症状がみられることがある．精神発達遅滞はまれであるが，約30％に伝音性難聴，構音障害，神経因性膀胱，失調，筋緊張低下，筋緊張亢進，痙攣などの神経学的異常を認めるとされる[13]．

## 6. 自然歴と予後

重篤な哺乳障害や呼吸障害のないかぎり，乳児期以降の生命予後は比較的良好である．

約15％に精神発達遅滞を伴うといわれているが，大部分は軽度である．主に視力障害に対する特別支援が必要となる．

生殖能力の低下を認めたとする報告もあるが，少なくとも女性では国内外で7回の挙児例がある[14]．

## 7. 治　　療

先天性白内障は自然軽快することもあるが，視力障害に基づく二次的精神運動発達遅滞を予防するためにも早期手術を要する．また，手術にもかかわらず，視神経乳頭欠損や網膜色素変性などにより矯正視力の得られないことがある．術後の合併症としての緑内障や網膜剥離の発生にも注意が必要である．

小下顎による上気道の狭窄により呼吸障害をきたす可能性があり気管切開を要する場合がある．閉塞性睡眠時無呼吸をきたす場合などには，経鼻的持続性陽圧呼吸(nasal CPAP)，舌の外科的挙上などが有効である．また，気管軟化症も伴うことがあり注意を要する．

歯牙異常に対しては，継続的な歯科学的診療が必要となる．

低身長や特異的な顔貌が精神的な影響を及ぼすことがあるので，対症的治療のみならず心理的な支援も必要となる[15]．

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