合も再評価は必要。心臓超音波による先天性心疾患の検索は不可欠である。著しい脳奇形などは報告されていないが、新生児脳超音波検査も必要である。新生児聴覚検査（ALGO）検査で難聴が指摘される場合には、言語聴覚専門士、小児耳鼻咽喉科専門医による評価が必要となる。新生児期にはほとんど目をあけることがなく、眼瞼裂狭小もあり、眼科的評価が極めて難しい。小児眼科専門医師の評価が不可欠である。症状の組み合わせから、比較的早い段階でヤング・シンプソン症候群を鑑別の一つに挙げるべきである。ただし、除外診断は重要で、他の奇形症候群や染色体異常症を各種の検査解析で否定したのちに、ヤング・シンプソン症候群の診断を下すことが望ましい。上述のように新生児乳児期から医療管理を必要とされることが多いために、両親の理解を得るためにも早い段階での診断は重要であるが、医療サイドには慎重な対応が求められる。

乳児期

親の疾患理解と、各専門領域の合併症管理が本格的に進む時期である。耳鼻咽喉科では難聴評価とそれに対する補聴器の作成、整形外科では内反足に対するギプス固定と難治例に対する観血的修復術の計画策定、眼科では積極的な眼科的評価が求められる。新生児期の哺乳障害は、乳児期には改善傾向が認められ、経口哺乳練習も組み入れて行く。リハビリテーションの参加も自宅での生活リズムが安定した時点で考慮すべき問題である。新生児からこの乳児期までは、強いそり返りとそれと矛盾する筋緊張低下が目立つので、小児リハビリテーション専門医の評価と訓練は重要である。不明熱を繰り返す場合には、泌尿器系合併症を疑い、小児泌尿器の専門医の評価を受ける。また、外性器異常（停留精巣など）についても同様である。

幼児期

このころから自閉的傾向から人懐こい行動への大きな変化が目立ってくる。社会性の獲得が進むことと一致しているかもしれない。集団療育への参加も社会性獲得の手段として重要である。内反足手術と治療の結果、歩装具での立位歩行が促される。運動能力の拡大がみられる時期である。言語も含めた多方面からの療育訓練が求められる。眼科では正確な評価が可能となり、本格的な眼鏡処方がなされることになる。

幼児期後期から学童期

手術を要する医療管理も一段落の時期となる。身辺自立を目指した生活指導も重要となる。表出言語と理解言語の差が極めて大きいことは考慮すべきことで、

様々な表現手段を用いての理解を促すことも重要かもしれない。就学については地域の状況や親の意向、合併症の程度も考慮して総合的に対応する。歩行の不安定性はこの時期も目立つために、安全面は重視する。第二次性徴の発来は男女ともに認めるが、男児でやや遅い傾向がある。調査数が少ないため限定されるが、二次性徴の発来時期とパターンは一般健常集団との差は小さい。しかし、女児では不順月経などが目立つことがある。

青年期以降

青年期以降の情報は乏しいが、退行や能力低下などは目立っていない。医療管理としては専門医による定期医療管理が必要である。

【結語】

ヤング・シンプソン症候群の医療管理指針についてまとめた。上記は、臨床診断に基づいた症例に関する調査によるものであり、今後遺伝子レベルでの診断が可能となったことから、遺伝子型と症状の相関関係に関する情報が蓄積され、医療管理指針の見直しも必要となる。我が国においては、ヤング・シンプソン症候群の疾患概念はまだ確立されて間もないために周知されておらず、潜在的未診断例が多く存在することが予想される。生涯にわたる医療管理指針の策定および分子レベルでの病態の解明が重要課題である。

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主催：「ヤング・シンプソン症候群の病態解明と医療管理指針作成に関する研究」（研究代表者：黒澤健司）
平成23年11月23日
神奈川県立こども医療センター

ヤング・シンプソン症候群
―研究成果、そして、これからの課題―

地方独立行政法人神奈川県立病院機構
神奈川県立こども医療センター　遺伝科
黒澤健司

この研究グループで行ったこと

平成22年度

1. 全国1次調査
2. 発生頻度の推定
3. 診断基準の作成
4. 原因遺伝子同定を目指した
   エクソーム（Exome）解析
5. ホームページ開設（現在作成中）

この研究グループで行ったこと

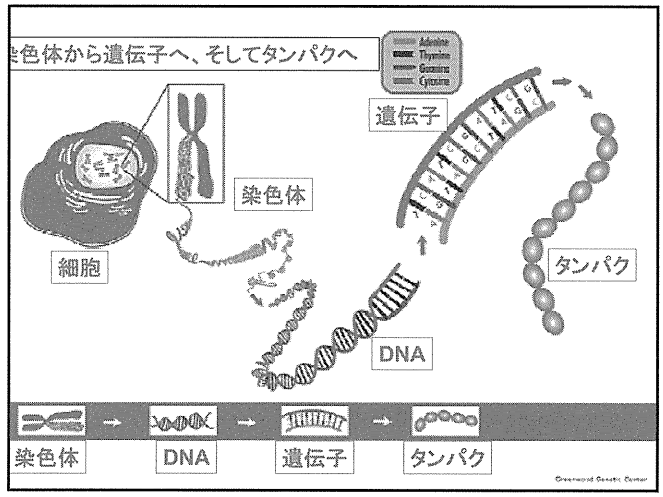
平成23年度

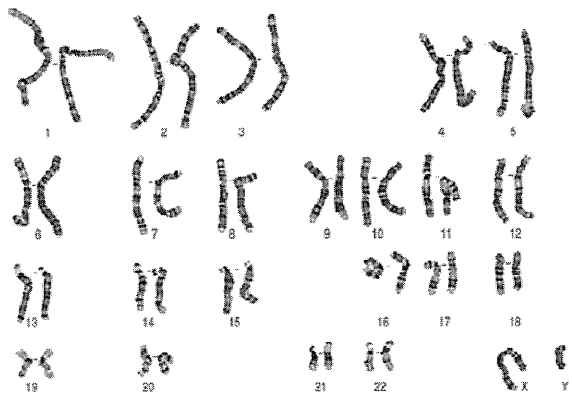
1. Exome解析
2. 全国二次調査
3. 自然歴に基づいた医療管理指針作成
4. 情報還元
   Webサイトの充実
   公開セミナー

1. Exome解析研究
エクソーム

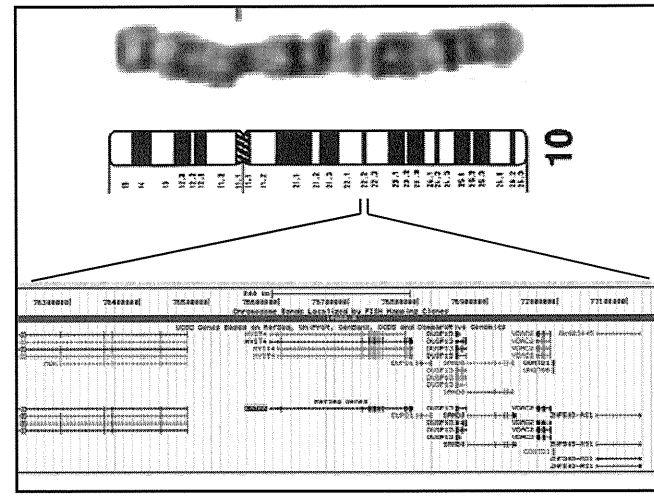
Exome（エクソーム）解析

ヒトの遺伝子（全部で約25000個くらい）のなかにあって、タンパク質に翻訳される領域（暗号部分）をエクソン（exon）とよぶ。エクソーム解析は、このすべての遺伝子についてエクソンを解読すること。





男性の染色体



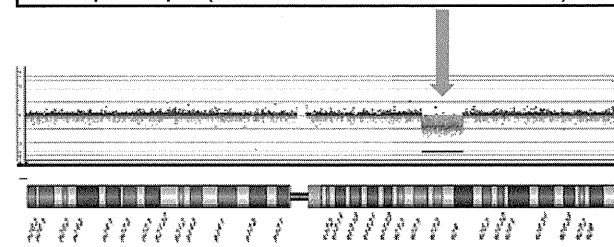
「原因となる遺伝子を明らかにする」ことの意義

Q なぜ、遺伝子を探すことが重要なのですか？

- ✓診断が確実になる
- ✓遺伝子の機能から病気の本質がわかる
- ✓何らかの治療への手掛かりが得られる
- ✓遺伝カウンセリングに応用できる

1）マイクロアレイCGH法

arr 3q22.1q24(131,875,994 –145,644,805)×1



Chromosome 3

2）エクソーム（Exome）解析

次世代シーケンサーでひとり分のすべての遺伝子（約25000個くらい）を読み解く

↓

コンピューターを使って、その中から患者特有の変化を見つけだす

約25,000個の遺伝子（暗号として30,000,000文字）を数十回繰り返して読み解くと
約20,000個の疑わしい変化が見つかる

↓

アミノ酸変化をもたらすもの：5,000個

↓

400個の変化 → 既によく知られた誰にでもある1字の変化を除外

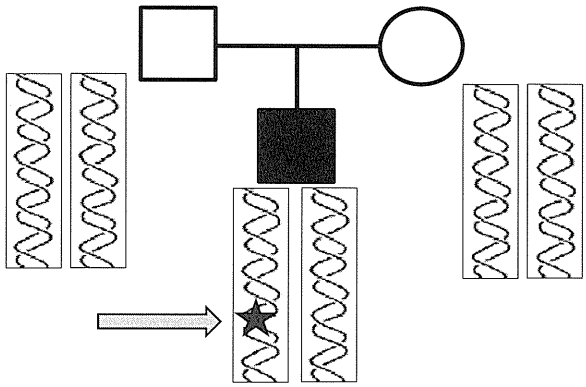
↓

数個の遺伝子変化 ← 既に両親が持っている1字の変化を除外

↓

複数の患者さんに共通に見られる遺伝子の変化：1個

トリオ解析



Q. どうして、トリオ解析で遺伝子の異常を見つけ出せるの？

1世代で全ゲノムの中の暗号の変化は約70個

親と70か所の違いがある
（父親から35個、母親から35個）

そのうち、遺伝子のエクソンの中には1個程度

中間報告

トリオ解析

2584か所の親子で矛盾する変化を確認

↓

173個の遺伝子に絞り込み

↓

機能的に可能性がありそうな遺伝子
数十個に絞り込み

緊急速報

REPORT

Whole-Exome-Sequencing Identifies Mutations in Histone Acetyltransferase Gene *KAT6B* in Individuals with the Say-Barber-Biesecker Variant of Ohdo Syndrome

Jill Clayton-Smith,[1,4] James O'Sullivan,[1] Sarah Daly,[1] Sanjeev Bhaskar,[1] Ruth Day,[1] Beverley Anderson,[2] Anne K. Voss,[2,3] Tim Thomas,[2] Leslie G. Biesecker,[4] Philip Smith,[1] Alan Fryer,[5] Kate E. Chandler,[1] Bronwyn Kerr,[1] May Tassabehji,[1] Sally-Ann Lynch,[6] Malgorzata Krajewska-Walasek,[7] Shane McKee,[8] Janine Smith,[9] Elizabeth Sweeney,[5] Sahar Mansour,[10] Shehla Mohammed,[11] Dian Donnai,[1] and Graeme Black[1]

イギリスのグループが、ヤング・シンプソン症候群の原因遺伝子を発見したことを報告（2011.11月号）

これからの課題

遺伝子レベルで原因を解明

- 遺伝子変異の違いで症状の違いが生じるのか？
- 本当に、この遺伝子が原因か？
- 他に原因遺伝子はないのか？
- 日本の患者さんと海外の患者さん症状の違いは？

課題：医療管理指針の作成

診断基準の作成

1）精神遅滞
2）眼症状
　眼瞼裂狭小を必須として付随する弱視・鼻涙管閉塞
3）骨格異常
　内反足など
4）内分泌学的異常
　甲状腺機能低下症
5）外性器異常
　主に男性で停留精巣および矮小陰茎
6）除外診断：
　他の奇形症候群あるいは染色体異常症を除外できる

診断基準の作成

補助項目：
- 羊水過多
- 新生児期の哺乳不良
- 難聴
- 行動特性
- 泌尿器系異常

症状に合わせての治療指針の作成

- 整形外科
- 眼科
- 内分泌科
- 泌尿器科
- 耳鼻咽喉科
- 新生児科
- 遺伝科

ご協力ありがとうございます。

得られた結果は、各患者さまによりよい医療がなされるように、少しでも生活の質が向上するように、還元してゆきたいと思います。
引き続き宜しくお願い申し上げます。

Ⅳ．研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
近藤達郎		近藤達郎	ダウン症者・家族が幸せに暮らすために	晃洋書房	京都	2011	近藤達郎

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Soneda A, Teruya H, Furuya N, Yoshihashi H, Enomoto K, Ishikawa A, Matsui K, Kurosawa K.	Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a children's hospital.	Eur J Pediatr.	171	301-305	2012
Kurosawa K, Masuno M, Kuroki Y	Trens of occurrence of twin births in Japan.	Am J Med Genet Part A	158A	75-77	2012
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近藤達郎	染色体検査結果の評価. A. 染色体異常の種類.	遺伝子分析科学		188-197	2011
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Naiki M, Mizuno S, Yamada K, Yamada Y, Kimura R, Oshiro M, Okamoto N, Makita Y, Seishima M, Wakamatsu N.	MBTPS2 mutation causes BRESEK/BRESHECK syndrome	Am J Med Genet A		Epub ahead of print	2011

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Liang JS, Shimojima K, Takayama R, Natsume J, Shichiji M, Hirasawa K, Imai K, Okanishi T, Mizuno S, Okumura A, Sugawara M, Ito T, Ikeda H, Takahashi Y, Oguni H, Imai K, Osawa M, Yamamoto T.	CDKL5 alterations lead to early epileptic encephalopathy in both genders.	Epilepsia	52(10):	1835-42	2011
Adachi M, Soneda A, Asakura Y, Muroya K, Yamagami Y, Hirahara F.	Mass Screening of Newborns for Congenital Hypothyroidism of CentralOrigin by Free Thyroxine Measurement of Blood Samples on Filter Paper.	European Journal of Endocrinology		Epub ahead of print	2012
曽根田明子, 安達昌功, 室谷浩二, 朝倉由美,住吉好雄,春木英一, 山上祐次	神奈川県における先天性中枢性甲状腺機能低下症の疫学的調査第一報	日本マス・スクリーニング学会誌	21(1)	23-28	2011

Ⅴ．研究成果の刊行物・別刷

Eur J Pediatr (2012) 171:301–305
DOI 10.1007/s00431-011-1534-2

ORIGINAL PAPER

Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a children's hospital

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Abstract Genetic disorders and birth defects account for a high percentage of the admissions in children's hospitals. Congenital malformations and chromosomal abnormalities are the most common causes of infant mortality. So their effects pose serious problems for perinatal health care in Japan, where the infant mortality is very low. This paper describes the reasons for admissions and hospitalization at the high-care unit (HCU) of a major tertiary children's referral center in Japan. We retrospectively reviewed 900 admission charts for the period 2007–2008 and found that genetic disorders and malformations accounted for a significant proportion of the cases requiring admission to the HCU. Further, the rate of recurrent admission was higher for patients with genetic disorders and malformations than for those with acquired, non-genetic conditions. Over the past 30 years, admissions attributed to genetic disorders and malformations has consistently impacted on children's hospital and patients with genetic disorders and malformations form a large part of this facility. These results reflect improvements in medical care for patients with genetic disorders and malformations and further highlight the large proportion of cases with genetic disorders, for which highly specialized management is required. Moreover, this study emphasizes the need for involvement of clinical geneticists in HCUs at children's hospitals.

Keywords Malformation · Genetic disease · High-care unit · Children's hospital · Mortality

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Introduction

Genetic disorders and birth defects account for a high percentage of the admissions to children's hospitals [4, 13]. In 2008 [5], the Ministry of Health, Labor and Welfare in Japan reported that congenital malformations, chromosomal abnormalities, and genetic diseases are the leading causes of death in children during the first year of life. As per that report, 999 infants under the age of 1 year died of congenital malformations and chromosomal abnormalities; this corresponds to 35.7% of the total number of deaths in this age group. Since 1985, congenital malformations and chromosomal abnormalities have remained the leading causes of infant mortality in Japan [5]. Indeed, in USA it

has been found that patients with genetic disorders had a greater need for hospital admission and were hospitalized for longer durations than were those without genetic disorders [14].

However, recent advances in treatment are likely to improve the survival of individuals with congenital malformations, which, in turn, is likely to increase the rates of readmission to pediatric intensive care units (PICUs) [16]. Several studies have assessed the role of genetic disorders in pediatric mortality and hospitalization [2, 6, 7, 16]. Congenital malformations and chromosomal abnormalities pose serious challenges for perinatal health care in this country, as they are the leading contributors to the infant mortality rate in Japan.

In this study, we assessed the reasons for admissions and hospitalization to the high-care unit (HCU) of a major tertiary children's referral center in Kanagawa Prefecture, Japan, and compared our findings to those of a study of this unit 30 years ago. To elucidate the impact and contribution of birth defects and genetic diseases on pediatric hospitalization, we studied the reason for hospitalization, underlying diagnoses, and duration of hospitalization in this children's hospital in Japan.

Materials and methods

Permission for the study was obtained from the Ethical Committee of our medical center.

We retrospectively analyzed the cases of children hospitalized at the HCU of Kanagawa Children's Medical Center (KCMC) between June 2007 and December 2008. KCMC is a major tertiary children's referral center for pediatric cardiology, surgery, and cancer cases and serves a large area in Kanagawa Prefecture, Japan. It has an institute for the severely handicapped, a PICU, a neonatal intensive care unit, and an HCU. In contrast to the PICU, which admits patients who have undergone cardiovascular or neurosurgery, the HCU specializes in pediatric patients with other acute conditions. All of the patients were included if they were admitted to the HCU from the emergency room, operating room, or inpatient ward. KCMC, with 419 beds, is the only specialized pediatric hospital in Kanagawa Prefecture, where the total number of births is 80,000 annually [8, 9]. About 8,500 patients (male/female, 1:1) were admitted to KCMC in 2007, and the average of hospital stay was 15.3 days.

We summarized and reviewed the medical charts of all patients admitted to the HCU. The charts and summaries were reviewed for age, sex, duration of hospitalization, underlying disease, and reason for admission. Subcategories were created for the underlying diseases and reason for admission.

The underlying disease was classified into two main categories: genetic conditions and acquired (non-genetic) conditions. Genetic conditions were considered to include chromosomal abnormalities, recognizable malformation and dysplasia, multiple malformations, isolated malformations (e.g., those related to the heart, central nervous system (CNS), and respiratory and gastrointestinal tracts), other single-gene defect-related conditions, mitochondrial diseases, and metabolic disorders (Table 1). All cases of chromosomal abnormalities and multiple malformations were examined using standard karyotyping. Cases of recognizable malformation/dysplasia were ascertained by clinical dysmorphologists (H.Y., N.F., and K.K.). Acquired conditions were considered to include perinatal complications, trauma, neoplasm, and sequelae of severe infectious conditions.

The reasons for admission were classified as problems of the respiratory system, CNS, heart, gastrointestinal tract, kidneys and urinary tract, infectious diseases, post-operative management, and unknown condition. Those cases that did not fall into these categories were placed into a category called "others."

Statistical analyses were performed to compare the duration of hospitalization and the age distribution, using StatView version 5.0 (SAS Institute, Inc; Cary, NY). Categorical data were reported as counts and percentages, and continuous data as mean (SD) or median values. Statistical differences for categorical variables were determined by using chi-squared analyses. Median differences were compared by Mann–Whitney *U* test.

Results

A total of 900 admissions, consisting of 687 individual cases with 200 recurrent admissions, were reviewed. Sixteen admissions were excluded from the study because of insufficient information regarding the underlying causes for admission.

The median age at admission was 3.5 years (range, 1 day–32.5 years), and the sex ratio was 1.36 (396 males and 291 females). The median lengths of hospitalization in the HCU were 4 days. Table 2 shows the distribution of the 884 admissions across the different categories of causes for admission. Most patients were admitted for common medical problems, including respiratory problems, post-operative management, and CNS problems. Of the 298 admissions for respiratory problems, most cases involved respiratory infection, including pneumonia and bronchitis. Admissions for post-operative management accounted for 30.7% cases (271 of 884 admissions), while CNS problems such as convulsions, encephalitis, and meningitis accounted for 16.3% (144 of 884 admissions).

Table 1 Definitions of categories

Category	Examples
Chromosomal syndromes	Down syndrome, trisomies 13 and 18, cri du chat syndrome, and Wolf–Hirschhorn syndrome
Recognizable malformation/dysplasia	22q11.2 deletion syndrome, CHARGE syndrome, and VATER association, Lowe syndrome, achondroplasia, Crouzon syndrome, Noonan syndrome, and Treacher–Collins syndrome
Multiple malformations	
Isolated malformations	
Congenital heart diseases	VSD ASD, AVSD, TGA, and DORV
Central nervous system malformations	Schistorrhachis, hydrocephalus, and meningoencephalocele
Gastrointestinal malformations	Diaphragmatic hernia, biliary atresia, and congenital intestinal obstruction
Respiratory system malformations	CCAM and tracheal stenosis
Other isolated malformations	Cleft palate and cleft lip
Single-gene defect	Metabolic diseases, spinal muscular atrophy, and spinocerebellar degeneration
Mitochondrion	

The classification of the underlying conditions of the 687 patients is shown in Table 3. In 13 cases, the data for identifying the underlying disease were insufficient (e.g., charts were missing). These cases were categorized as "unknown condition." Of the total 687 patients, 372 (54.1%) had genetic disorders and the remaining 302 (44.0%) had acquired conditions unrelated to genetic disorders, including perinatal complications, neoplasm, and trauma. Among the 372 patients with genetic disorders, 72 had chromosomal abnormalities, with Down syndrome (29 cases) being the most common underlying disorder. Seventy patients had recognizable malformations and dysplasia, with conditions such as osteogenesis imperfecta, 22q11.2 deletion syndromes, CHARGE syndrome, and VATER association. Multiple malformations with unrecognizable patterns were present in 38 cases while isolated malformations, including CNS malformation, congenital heart disease, and gastrointestinal malformation were present in 160 cases.

We also summarized the reasons for the total of 884 admissions, according to the underlying condition (genetic or acquired). Of these admissions, 200 were readmissions. Patients with genetic disorders and malformations had a greater tendency to be hospitalized repeatedly as compared with those with acquired conditions (Fig. 1). In both genetic and acquired condition categories, respiratory disease, post-operative management, and CNS problems were the major medical problems leading to admission.

We further compared age distribution and the lengths of hospitalization between the groups with genetic and acquired disorders (Table 4). The patients with genetic

Table 2 Medical problems for admission (N=884)

Causes for admission	Number	Percent
Respiratory problems	298	33.7
Post-operative management	271	30.7
CNS problems	144	16.3
Gastrointestinal problems	35	4.0
Cardiac diseases	23	2.6
Other infectious state	23	2.6
Examination	21	2.4
Kidney and urinary tract problems	14	1.6
Other	55	6.2
Total	884	100.0

Table 3 Classification of underlying diseases in 678 patients

Underlying diseases	Number	Percent
Genetic disorders and malformations (subtotal)	372	54.1
Chromosomal abnormalities	(72)	10.5
Recognizable malformation/dysplasia	(70)	10.2
Multiple malformations	(38)	5.5
Isolated malformations	(subtotal:160)	23.3
Central nervous system malformation	(71)	10.3
Congenital heart disease	(35)	5.1
Gastrointestinal malformation	(32)	4.7
Respiratory system malformation	(9)	1.3
Other isolated malformations	(13)	1.9
Single-gene defect	(26)	3.8
Mitochondrion	(6)	0.9
Acquired non-genetic conditions (subtotal)	302	44.0
Perinatal complications	(66)	9.6
Neoplasm	(38)	5.5
Trauma(non-accidental and accidental)	(27)	3.9
Infection	(16)	2.3
Other	(155)	22.6
Unknown	13	1.9
Total	687	100.0

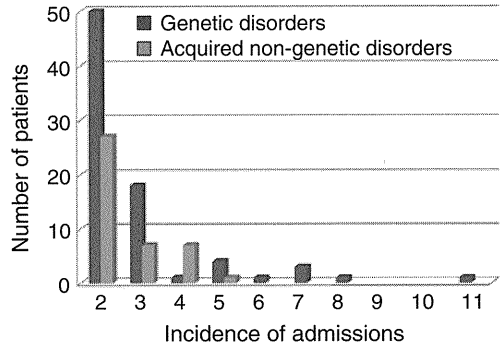

Fig. 1 Comparison of the incidence of admission between the groups with genetic disorders and acquired disorders. In both groups, a total of 200 patients were readmitted. The group with genetic disorders generally required frequent readmission

disorders were significantly younger than those with acquired conditions (median age, 2.0 vs. 4.9 years; $P<0.0001$). There is no significant difference in the length of hospitalization between the patients with genetic disorders and those with acquired conditions (median, 4 vs. 4 days; $P=0.26$), but some patients with genetic disorders had much longer hospitalization (mean, 13.0 vs. 7.0 days; $P=0.007$; range, 1–979 days). Among the reasons for admission, respiratory problems tended to have a longer duration of hospitalization for patients with genetic disorders than for those with acquired conditions (median, 7 vs. 5 days; $P=0.17$).

Discussion

Our study shows that genetic disorders and malformations account for a significant proportion of cases requiring admission to the HCU. Additionally, the rate of recurrent admission was higher among patients with genetic disorders and malformations than among those with acquired non-genetic conditions. This finding is in agreement with those of previous reports for other countries [4, 13].

Several studies from different countries have previously suggested that genetic conditions and malformations and the associated mortality and morbidity have a significant impact on the cost burden for society and the patients' families. Cunniff et al. reported that 19% of deaths in a PICU were in cases of heritable disorders [1]. Stevenson and Carey reported that the 34.4% of deaths in a children's hospital were due to malformations and genetic disorders [15]. On the basis of a population-based study, Yoon et al. reported that the overall rate of hospitalization was related to birth defects and genetic diseases, and varied with age and race/ethnicity [16]. McCandless et al. reported the enormous impact of genetic disease on inpatient pediatrics and the health care system in both admission rates and the total hospital charges [11]. These studies emphasize the importance of understanding the impact that genetic diseases have on mortality and healthcare strategies [15]. Furthermore, it is also clear that early recognition of the underlying disorders is necessary for optimal management of patients with genetic disorders.

Our study highlights another aspect related to the impact of genetic disorders and malformations. In 1981, Matsui et al. analyzed the cases of 18,736 children of total admission during 1975–1979 to KCMC and found that 44% had genetic disorders and malformations [10]. Although our study period and ward are limited to those in the HCU, the patients with genetic disorders and malformations had consistently significant impact in KCMC during the ensuing three decades. Further, it emphasizes that medical care for acute conditions and surgical procedures frequently requires highly specialized knowledge of unusual disease conditions and should be provided in consultation with specialists such as clinical geneticists.

Table 4 Comparison of patients with genetic disorder vs. acquired condition on ages at admission and lengths of stay

	Genetic disorders		Acquired conditions		
	Median (range)	*n*	Median (range)	*n*	*P*
Ages	2.0 years (1 day–27.0 years)	372*	4.9 years (9 days–32.5 years)	302*	<0.0001
Length of hospitalization (days)					
Respiratory problem	7 (1–979)	182	5 (1–97)	109	0.17
CNS	4 (1–54)	73	4 (1–207)	68	0.61
Cardiovascular	4 (2–11)	13	4 (2–24)	8	0.94
Gastrointestinal	5.5 (1–37)	22	5 (2–15)	12	0.60
Kidney and urinary tract	3 (2–12)	5	8 (2–12)	9	0.32
Sepsis	3.5 (2–9)	14	7 (2–20)	9	0.19
Post-operative care	2 (1–49)	174	2 (1–62)	93	0.18
Total	4 (1–979)	518	4 (1–207)	366	0.26

*For the patients who have recurrent admissions, the only first admission was calculated

Although the strategies for management of respiratory infection, by means of newly developed antibiotics and mechanical ventilators, and surgical intervention for infants with malformations, have improved, the general strategies for the medical treatment of genetic disorders and malformations remain to be clarified. Hall commented on the report by Yoon et al. [16] and emphasized the significance of basic research on the human genome and developmental genetics [3]. As shown in Table 2, genetic disorders and malformations include rare diseases, which, although uncommon, remain an important public-health issue and a challenge for the medical community [12].

Our study had the limitations of genetic studies and evaluation in cases with multiple malformations and other isolated malformations. The underlying conditions of most patients in this study were ascertained by clinical geneticists, but high-resolution genome analysis with arrays using comparative genomic hybridization was applied in only limited cases. Recently, research attention has focused to a large extent on rare genetic disorders and Mendelian diseases, because of their significant effect on human health, with the aim of identifying disease-related genetic variations. Re-evaluation and classification of underlying disorders, especially in the case of multiple congenital anomalies in undiagnosed patients, are required for further analysis.

Another limitation of our study is estimation of the financial burden of the group of patients with a genetic background. McCandless et al. showed that the disorders with genetic determinant account for 81% of the total hospital charges [11]. Their results are consistent with those of Hall et al. in 1978 [4]. Further analysis of financial burden in our study may provide useful information for improvement of health care systems.

In conclusion, we report here the proportion of genetic disorders and malformations among cases encountered at the HCU of a tertiary children's medical center in Japan. Over 30 years, the proportion of admissions attributed to genetic disorders and malformations has impact and currently accounts for more than half of admissions to this facility. These results firstly indicate improvements in medical care for patients with genetic disorders and malformations and further highlight the large proportion of cases with genetic disorders. As these cases require highly specialized management, the involvement of clinical geneticists in HCUs at children's hospitals is crucial. Eventually, a better fundamental understanding of genetic disorders and malformations may lead to further improvements in medical care and may reduce the impact of these conditions on the patients and their families.

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Conflict of interest The authors declare no conflict of interest.

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Trends in Occurrence of Twin Births in Japan

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The rise in the rate of multiple births since the 1980s is due to the effect of advanced maternal age and increased use of assisted reproductive technology (ART). To determine the trends of prevalence in twin births, we studied the data of a population-based birth defects monitoring system during 26 years in Kanagawa Prefecture, Japan. A total of 15,380 twins from 7,690 deliveries were ascertained from 990,978 births in the Kanagawa Birth Defects Monitoring Program (KAMP) during 1981–2008. From the start of KAMP in 1981, the incidence of twin births had been consistently increasing from 57.0 to 98.6 per 10,000 deliveries until 2003, but after this time, the incidence declined to 78.5 in 2007. While the rate of monozygotic twins has been stable (~40 per 10,000 deliveries) after 1990, that of dizygotic twins increased from 25.3 to 57.3 per 10,000 deliveries until 2002, and recovered to 40.1 in 2007. These results showed the most recent tendency of twin births and indicated that the single embryo transfer method can provide protection and reduction of perinatal risk caused by multiple births.

Key words: assisted reproductive technology (ART); twin; Kanagawa Birth Defects Monitoring Program (KAMP); zygosity

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INTRODUCTION

Multiple births including twin births have several implications for maternal and child health care. Twin pregnancy is associated with an increased incidence of anomalies [Bahtiyar et al., 2007; Glinianaia et al., 2008; Hardin et al., 2009a], a higher risk of perinatal mortality, and preterm births with low birth weight [Helmerhorst et al., 2004; McDonald et al., 2005] compared with singleton pregnancy. A tendency for an increasing rate of twin delivery has been observed in 14 out of 16 countries in Europe, Canada, Australia, Singapore, and Hong Kong [Imaizumi 1998]. This tendency has also been observed in Japan [Imaizumi 2000]. The rise in the rate of multiple births is due to the effect of advanced maternal age and increased use of assisted reproductive technology (ART) [Bondel and Kaminski, 2002]. In the USA and Europe, between 20 and 30% of deliveries following ART are twin births compared with 1% following spontaneous conception [Andersen et al., 2008; Wright et al., 2008]. However, the rate of twin pregnancies in the USA has stabilized at 32 per 1,000 births in 2006 [Chauhan et al., 2010]. In Australia, recent data indicated that the proportion of twin deliveries decreased in 2006 [Wang et al., 2008].

To determine the trends of prevalence in twin births, we studied the data of a population-based birth defects monitoring system during 26 years between 1981 and 2008 in Kanagawa Prefecture, Japan. Kanagawa Prefecture, which is adjacent to Tokyo, includes Yokohama City with a total population 3,687,000. To investigate the effects of ART, we analyzed the data of twins according to the zygosity during the study period.

MATERIALS AND METHODS

A total of 15,380 twins from 7,690 deliveries were ascertained from 990,978 births in the Kanagawa Birth Defects Monitoring Program (KAMP). This program has been in operation since October 1981 as the first population-based monitoring system in Japan. Details of KAMP are described elsewhere [Kuroki et al., 1982; Kuroki and Konishi, 1984, 1992; Kuroki, 1988; Kurosawa et al., 1994; Yuan et al., 1995]. KAMP covers one-half of the total births (40,000 births annually) in Kanagawa Prefecture. All live births and stillbirths are screened for 44–48 marker malformations (only surface anomalies), arranged in 10–11 groups, and they are examined by general obstetricians or occasionally by general pediatricians within 7 days after birth. During the study period between 1981 and 2008, the KAMP was divided into four stages according to a minor modification in marker anomalies and registration systems. The first two stages, for 1981–1983 and 1984–1988, had total birth registration systems including all the malformed infants, normal

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infants, and all multiple births. However, in the last two stages, 1989–2000 and 2001–2008, all malformed infants as well as all multiple births were registered with two consecutive normal infants. Information on zygosity is not available in the KAMP, and therefore, we used Weinberg's differential rule for zygosity estimation [Fellman and Eriksson, 2006; Hardin et al., 2009b]. The incidence of twin births was defined as the number of twin pairs per total deliveries.

RESULTS

During the period of analysis, the incidence of malformed infants was 0.88% in live births and 17.24% in stillbirths. The sex ratio was 1.05. From the start of KAMP at 1981, the incidence of twin births had been consistently increasing from 57.0 to 98.6 per 10,000 deliveries until 2003 (Fig. 1). This tendency is consistent with the results of previous studies [Imaizumi, 1998, 2000]. The incidence of twin births peaked at 98.6 per 10,000 deliveries in 2003, but after this time, the incidence declined to 78.5 per 10,000 deliveries in 2007. The incidence of monozygotic twins fluctuated during the first 10 years, but after 1990 the incidence was stable at 40 per 10,000 deliveries. The incidence of dizygotic twins increased from 25.3 to 57.3 per 10,000 deliveries in 2002, but rapidly decreased to 40.1 in 2007, while the incidence of monozygotic twins was stable (Fig. 2). These results indicated that the incidence of twins is directly affected by the rate of dizygotic twins, and that the incidence of dizygotic twin births has already reached its peak, at least in the urban area of Japan.

DISCUSSION

Our study found that during the last 20 years, the incidence of twin births increased from 57 to 98 per 10,000 deliveries, but after it reached a peak in 2003, it recovered to 78.5 per 10,000 deliveries in 2007. Our study demonstrated that the trend in twin births was affected by the incidence of dizygotic twins. The incidence of monozygotic twins was stable at 40 per 10,000 deliveries, while that of dizygotic twin births attained a peak in 2002 with 57.3 per 10,000 deliveries, and it declined to 40.1 after this time. To the best of our knowledge, this is the first report describing the trends of a decrease in the rate of twin births in Japan. Because the rates of monozygotic twins are thought to be constant throughout the world, our results on the tendency of the rates of monozygotic twins have implication of the accuracy of the study. In the USA, between 1980 and 2006, the rate of twin pregnancies consistently increased from 18.9 to 32.1 per 1,000 births [Chauhan et al., 2010]. However, the rapid rise appeared to end in 2004 and the rate stabilized in 2006. A rise in the prevalence of twin births has also been observed in Austria, Finland, Norway, Sweden, Canada, Australia, Hong Kong, Israel, and Singapore [Imaizumi, 1997]. The rate of twin births in these countries stabilized between 2004 and 2006, and recent trends of a decreasing rate has been reported in some countries [Wang et al., 2008].

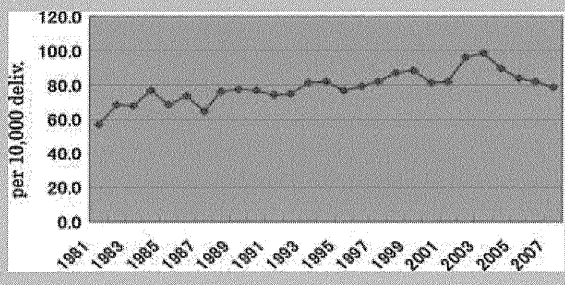

FIG. 1. Trends of the incidence of total births of twin pairs per total deliveries in Japan. The rate of twin births consistently increased from 57.0 per 10,000 deliveries in 1981 to 98.6 in 2003, but after this time, the rate recovered to that of the 1990s.

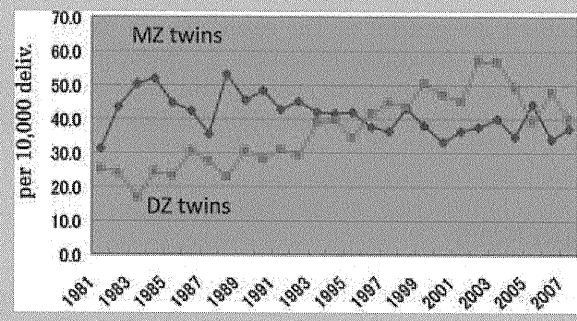

FIG. 2. Comparison of the rate of twin births between monozygotes and dizygotes. In the first 10 years, the fluctuation was remarkable in the rate of births in monozygotic twins for unknown reasons, but during the last 20 years, the rate was stable at approximately 40 per 10,000 deliveries. However, the rate of dizygotic twins consistently increased to reach a peak in 2003, and it then rapidly decreased.

Clearly, the use of ART has contributed to the changes in the rate of twin pregnancies [Wright et al., 2008; Hansen et al., 2009]. ART twins have a greater risk of adverse perinatal outcome including preterm birth, low birth weight, and cerebral palsy compared with spontaneously conceived twins and singletons [Hansen et al., 2009]. The use of single embryo transfers reduces multiple birth rates and the risks of these adverse outcomes following ART. According to a report from the European Society of Human Reproduction and Embryology, compared with the number of cycles in 2003, fewer embryos were transferred in Germany in 2004, but there were still huge differences between countries [Andersen et al., 2008]. This transfer policy had a considerable impact in Belgium, Finland, Sweden, and several other countries [Andersen et al., 2008], and therefore, a reduced rate of twin births may be observed within a few years in these countries. In the case of Japan, the reduction of the rate was rapid, but a stable rate was not observed at the end of the study period. The rate of twin births may be stabilized when there is a balance between maternal age distribution in reproductive generation and establishment of technical standardization of single embryo transfer. Further analysis on the rates of multiple births based on the population-based monitoring system is required to determine the impact of ART.

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death for type II and type III patients was 10.7 months and 17.6 months, respectively.[6] Our patient had a very severe form of the disease and died when she was 8 months old. Immunoblot analysis of DBP revealed the absence of the 79 and 45 kDa bands of DBP with trace amounts of the 35 kDa component which strongly suggests that the proband can be classified as a type 1 deficient patient.

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Miller syndrome with novel dihydroorotate dehydrogenase gene mutations

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Key words dihydroorotate dehydrogenase (*DHODH*) gene, Miller syndrome, postaxial acrofacial dysostosis.

Miller syndrome (postaxial acrofacial dysostosis; OMIM #26375) was described by Miller *et al.* in 1979;[1] it is characterized by postaxial limb deficiency, cup-shaped ears, and malar hypoplasia. The etiology of this syndrome, which is the mutation of the dihydroorotate dehydrogenase (DHODH) gene, was established in 2010.[2] Here we report a Japanese girl with Miller syndrome, probably the first case in Japan, with novel compound heterozygous mutations of the *DHODH* gene.

Case report

The patient, a 2-year-old Japanese girl, was the first child of nonconsanguineous healthy parents. The pregnancy course was uneventful. The mother and father were 20 and 25 years old, respectively, when the girl was born. She was born at 38 weeks of gestational age by normal vaginal delivery with weight and length of 3480 g (+1.0 SD) and 50.0 cm (+0.6 SD), respectively. Her weight was 10.5 kg (+1.0 SD) and height 77.2 cm (mean) at the age of 15 months. At the age of 2 years and 5 months, her weight was 13.0 kg (+ 0.7 SD), height 87.6 cm (mean), and head circumference 46.7 cm (−0.7 SD). She was referred to a pediatric department because of her limb anomalies.

She had mild micrognathia, mild malar hypoplasia, sparse eyebrows and eyelashes, hypertelorism, down-slanting short palpebral fissures, lower eyelid clefts, protruding and low set small, cup-shaped ears, long philtrum, conical teeth, and ankyloglossia (Fig. 1a). Her cleft palate was not seen. She also had pectus excavatum and an accessory nipple near her left underarm. Postaxial limb deficiencies included absence/hypoplasia/dysplasia of the fifth digits in all limbs, without short forearms (Fig. 1b–e). Bone X-rays of her hands showed the absence of

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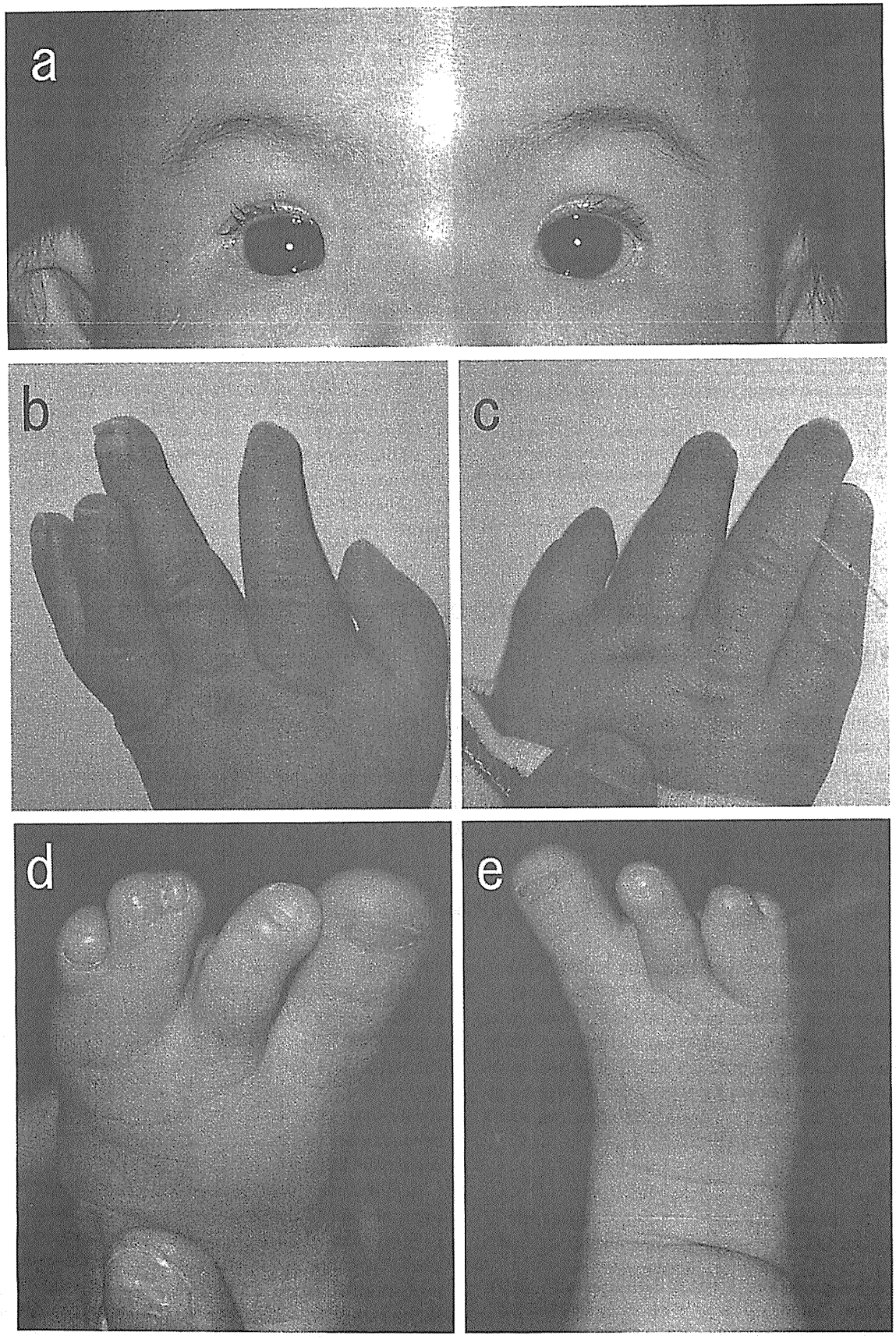

Fig. 1 (a) Front facial image. The patient has short palpebral fissures, ectropion of lower lids, and cupped ears. (b) The left hand with split hand and syndactyly. (c) Absence of the fifth digit of the right hand. (d, e) Bilateral syndactylies involving the third to fifth toes.