diagnosed as having a fetus with neonatal disease requiring surgery between January 2000 and December 2009, and who had delivered their children, received treatment, and/or were observed at our hospital. The anonymous questionnaires were sent by mail and the responses from those who consented to participate in our survey were compiled. The respondents were questioned regarding the diagnosis of the fetal abnormality, gestational age at diagnosis, whether they had obtained information from the internet or not, the type of information they had obtained, their assessment of the information, their comparison between such information and the explanations provided by their physicians, whether they would wish to use such information if they were faced with the same situation again, and the type of information they would wish to obtain. Our questionnaire mostly involved single-answer questions, with a few multiple-answer questions. This study was approved by our institutional review board (IRB Approval No. 09252).

Results

Demographics of the respondents

The response was obtained from 75 out of 155 (48.4%) pregnant patients or their families. The response rate did not significantly differ between years. The neonatal surgical diseases comprised: 25 with alimentary tract diseases, 14 with a congenital diaphragmatic hernia, 11 with cystic lung disease, 8 with an ovarian cyst, 7 with a tumor, 4 with an abdominal wall defect, and 6 with other diseases. The median gestational age at the first diagnosis of the neonatal surgical diseases was 29 weeks of gestation (between 12 and 39 weeks of gestation). There were 11 patients (14.7%) who were diagnosed before 22 weeks of gestation, the period in which a termination of pregnancy is legally permitted in Japan [3].

Forty-three out of the 75 cases (57.3%) had used medical information from the internet during their pregnancy. The proportion of using the internet for medical information varied between the patients who had fetuses with different diseases. Among the patients who had been diagnosed with a fetal congenital diaphragmatic hernia, 13 patients (93%) had used the internet, in contrast to 9 patients (36%) who had used it among the cases with alimentary tract diseases. Eight out of 11 patients who were diagnosed before 22 weeks of gestation had used medical information from the internet about their children's diseases. Among these, five patients answered that they had experienced difficulty in deciding whether to continue the pregnancy or not, and 4 patients answered that they had referred the information on the internet when deciding whether to continue the pregnancy or not.

The history of internet use and the present desire to use the internet

The proportion of pregnant patients who became pregnant until 2003 and who had used the internet to obtain medical information during their pregnancy was approximately 30%. However, the proportion began to increase among those who became pregnant around 2007, exceeding 90% in the last 2 years (Fig. 1a). On the other hand, the proportion of pregnant patients who would use the internet to obtain medical information, if they were prenatally diagnosed as having a fetus with a neonatal surgical disease exceeded 90% in all of the 2 year increments (Fig. 1b). The 43 patients and their families who had used the internet to obtain medical information were asked about the type of information they had actually referred to and what type of information they would presently use (Table 1). 88% of the subjects had used search engines to search for the information about the diseases. The people who would presently wish to read blogs on the lives of other people, who had children with the same disease was low compared to the number of people who had actually read such blogs. On the other hand, the people who wished to join an internet forum

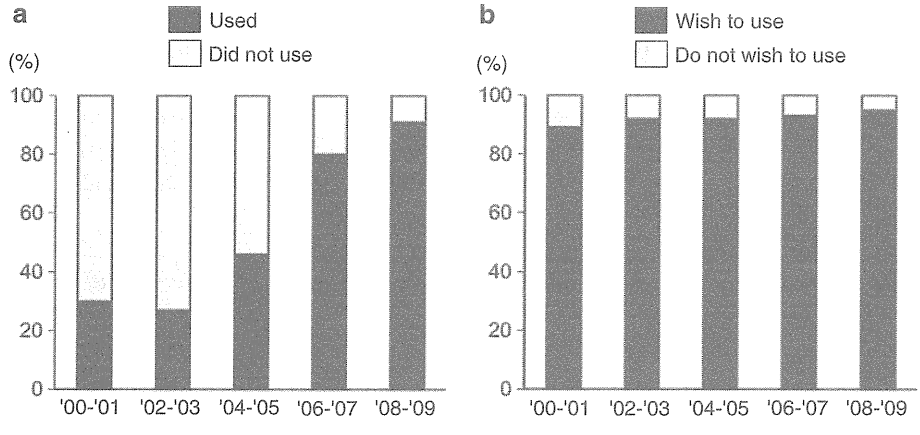

Fig. 1 The proportion of pregnant patients who had used the internet to obtain medical information during their pregnancy (**a**), and the proportion of patients who would use it if they were faced with the same situation (**b**), are shown for 2 year increments

Table 1 The type of internet information that was actually used, and is currently desired, by pregnant Japanese patients with a prenatal diagnosis of a neonatal surgical disease

Type of internet information	Actually used (%)	Presently desire (%)
Using search engines to learn about the disease	88	71
Reading a family blog about a child with the same disease	72	50
Visiting a website of a medical society or institution to learn about the disease	51	67
Reading a medical web dictionary to learn about the disease	49	57
Looking at a personal website to learn about the disease	40	31
Joining a communication site for families who have a child with the same disease	37	55
Checking a website of a hospital to learn about the hospital	35	64
Contacting a family who has a child with the same disease	9	17
Sending an e-mail to a physician or medical institution	2	21

for patients' families and who would wish to contact the family of patients with the same disease was found to have increased compared to the actual use of such forums. Although only one-third of the families had checked hospital websites to learn about the diseases, two-thirds of the people stated that they wished to check them at present. Therefore, the proportion of people who wished to access personal websites tended to decline, while the proportion of people who wished to obtain information from public institutions tended to increase. 21% of the patients answered that they would wish to consult physicians and medical institutions by e-mail [4, 5].

The usefulness and comprehensibility of the information on the internet and physicians' explanations

A total of 75.5% of the respondents answered that the internet was useful for learning about the child's disease, while 17.1% answered that it was not useful. A total of 73.2% answered that they had understood more about their child's disease based on the information from the internet, while 98.7% answered that they had understood about their children's disease based on their physician's explanations. With regard to the comprehensibility of the medical information on the internet and the physicians' explanations, 75% of respondents answered that their physicians' explanations were easier to understand, while 5.0% answered that the information on the internet was easier to understand (Fig. 2).

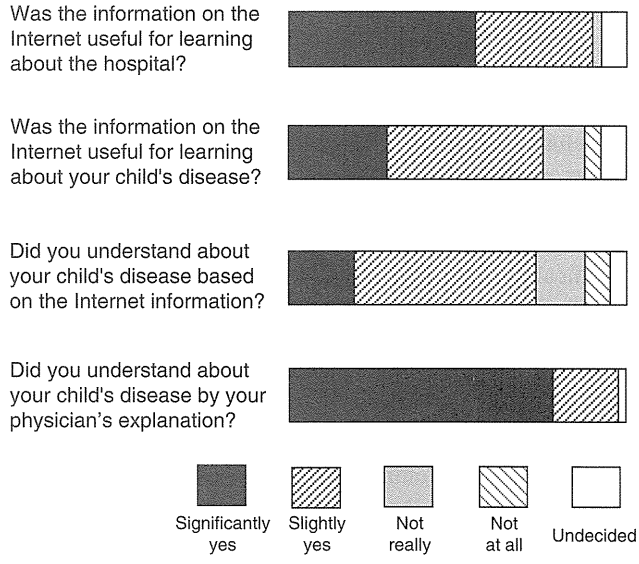

Fig. 2 The usefulness and comprehensibility of the information on the internet and the physician's explanation

Comparison between the information available on the internet and the physicians' explanations

In total, 62.5% of the respondents answered that their knowledge and impression of the disease differed based on the information available on the internet with that provided by their physician's explanation. With regard to the impression of the severity of the disease, 60% had felt the disease to be more severe after viewing the information on the internet, while 17.5% had felt it to be more severe on hearing their physician's explanation. In fact, 73.1% of subjects had felt more anxious upon reading the medical information on the internet, while 24.4% of subjects were more anxious due to their physician's explanation. In contrast, 12.2% of respondents were relieved by the medical information available on the internet, while 63.4% were more relieved due to their physician's explanation. Concerning the degree of anxiety, 65.9% of the subjects had experienced a stronger sense of anxiety over the information on the internet, and 12.2% had experienced a stronger sense of anxiety based on their physician's explanation (Table 2).

Recognition of the medical information on the internet

The proportion of respondents who answered that the medical information on the internet is reliable was 9.5%.

Table 2 Comparison between the information on the internet and the physician's explanation

Did the knowledge or the impression of the disease differ between that on the internet and that of your physician's explanation?	Very different	Slightly different	Almost the same	Same	Undecided
	25.0%	37.5%	32.5%	0.0%	5.0%
Which type of information gave you a more severe impression of your child's disease?	Internet, significantly	Internet, slightly	Almost the same	Physician's explanation, slightly	Physician's explanation, significantly
	35.0%	25.0%	22.5%	7.5%	10.0%
Did you become anxious about your child's disease due to the information on the internet?	Very anxious	Slightly anxious	Slightly relieved	Very relieved	Undecided
	58.5%	14.6%	12.2%	0.0%	14.6%
Did you become anxious about your child's disease due to your physician's explanation?	Very anxious	Slightly anxious	Slightly relieved	Very relieved	Undecided
	17.1%	7.3%	51.2%	12.2%	12.2%

The proportion of respondents who answered that it is unreliable was also 9.5%. A total of 66.2% of the respondents answered that the reliability of medical information on the internet should be judged by the viewer him/herself. The proportion of the respondents who answered that medical information on the internet should be provided by public institutions was 31.1%.

Discussion

The internet is becoming indispensable in daily life for many people throughout the world, and its use has spread rapidly in the recent years. Today, anyone can easily obtain high-level medical information on the web [1, 2, 6]. Under such circumstances, it is a matter-of-course for pregnant patients with a prenatal diagnosis of a fetal abnormality and their families, to use the internet to obtain medical information about their children's diseases. It became apparent through this survey that the use of the internet to obtain medical information has rapidly increased among pregnant patients prenatally diagnosed as having a fetus with a neonatal surgical disease in our country. Although the proportion of internet use was only approximately 30%, 10 years ago, 90% of them answered that they would wish to use it if they were faced with the same situation at present. Therefore, the use of the internet is likely to continue.

Most of the people who responded to our study had used search engines as a way to learn about the diseases. Generally, the search results appear in the order of the frequency of access. However, high-frequency access does not necessarily mean high-level reliability. It is suspected that the users inevitably tend to access the search results in the order of their appearance due to the difficulty for majority of the internet users to judge the reliability of the search results. The accuracy and neutrality of the information on the web is rarely evaluated by impartial observers, even among the websites serving the interests of the public. Furthermore, such information is prone to be subjective and self-righteous, as the information senders take the initiative in framing their websites. It is therefore, difficult for the viewers to judge the reliability of such information. Four out of five pregnant patients who had experienced trouble over deciding whether to continue the pregnancy or not after the prenatal diagnoses answered that they had referred to the information on the web, thus suggesting an increasing need for neutrality and accuracy concerning internet-based medical information that can influence the patients' important decisions [1, 3]. A code of ethics [7] may need to be established in the future to ensure the accuracy of medical information.

As it has become easy for individuals to disseminate information to society through the internet, there are many cases in which people who have developed serious diseases and their families report their experiences under treatment on blogs. Such blogs have the advantage of encouraging other patients with the same diseases and their families. On the other hand, due attention must be paid to the fact that many such blogs report cases of severe illness, which catch the viewers' attention more effectively, thus resulting in a bias, and blogs reporting more severe cases receive higher viewing numbers, making them easier to find using search engines. In addition, it is feared that such blogs may cause the viewers to develop a bias and overly negative images regarding the diseases [3], as reports of severe illness leave a stronger impression than reports about less severe disease. This might be the reason for the lower proportion of subjects who answered that they wished to view the blogs of other people with children who had the same disease, compared to the proportion of people who had viewed such blogs in the

past. Internet forums about disease also may lack neutrality and fairness due to their administrators' thoughts, as well as to biases held by some members. Such websites may also suffer from various ethical issues, such as prejudice, slander, and the disclosure of personal information.

Many of the respondents felt that the knowledge or the impression that they obtained from the internet differed from those provided through their physician's explanation. It has been clarified that the information on the web is likely to be less comprehensible, present the disease as more severe, and cause more anxiety compared to a physician's explanation. The information on the web, which was obtained to ease anxiety through learning more about the diseases [1], conversely resulted in increased anxiety. Since the anxiety of many respondents decreased on hearing their physician's explanations, a proper explanation by a physician seems to be very important for subjects with a prenatal diagnosis of a neonatal surgical disease. Those who had previously used the internet to obtain information showed a stronger tendency to desire information from public institutions, such as medical institutions and academic societies, rather than from personal websites. As many people also answered that information about diseases should be provided by public institutions, academic societies and medical institutions should therefore, play an even more important role in the future by providing accurate medical information on the web.

Along with receiving proper explanations by a physician and accurate medical information from public institutions, some of the new websites, nevertheless do sometimes provide useful information for pregnant patients. Websites providing peer-reviewed collaborative information and the forums providing accurate medical information on the web may gradually result in an improvement in the quality of medical information available on the web. Strong warnings that medical information on the web may be misinterpreted by people not familiar with a special medical field and websites, which stress the importance of carefully interpreting medical information, may help to avoid misunderstandings by pregnant patients and their families.

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ORIGINAL ARTICLE

Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia

Noriaki Usui · Yoshihiro Kitano · Hiroomi Okuyama · Mari Saito · Nobuyuki Morikawa · Hajime Takayasu · Tomoo Nakamura · Satoshi Hayashi · Motoyoshi Kawataki · Hiroshi Ishikawa · Keisuke Nose · Noboru Inamura · Kouji Masumoto · Haruhiko Sago

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Abstract
Purpose An accurate prenatal assessment of the patients' severity is essential for the optimal treatment of individuals with congenital diaphragmatic hernia (CDH). The purpose of this study was to clarify the reliability of the lung to thorax transverse area ratio (L/T) as a prenatal predictive parameter.
Methods A multicenter retrospective cohort study was conducted on 114 isolated CDH fetuses with a prenatal diagnosis during the period between 2002 and 2007 at five participating centers in Japan. The relationship between the gestational age and the L/T was analyzed. The most powerful measurement point and accurate cutoff value of the L/T was determined by an analysis of a receiver operating characteristic curve, which was verified by comparing the patients' severity.
Results There was a negative correlation between the gestational age and the L/T in the non-survivors, and no correlation in the survivors. There were significant differences in the parameters which represented the patients' severity including the respiratory and circulatory status, the surgical findings, and the final outcomes between the groups divided at 0.080 in the minimum value of the L/T during gestation.
Conclusion The L/T was not strongly influenced by the gestational age, and it was found to be a reliable prenatal predictive parameter in fetuses with isolated CDH.

Keywords Congenital diaphragmatic hernia · Prenatal diagnosis · Predictive parameter · Prognostic factor · Pulmonary hypertension · Severity

N. Usui (✉)
Department of Pediatric Surgery,
Osaka University Graduate School of Medicine,
2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: usui@pedsurg.med.osaka-u.ac.jp

Y. Kitano · N. Morikawa · H. Takayasu
Division of Surgery, National Center for Child Health and Development, Tokyo, Japan

M. Saito
Division of Clinical Research,
National Center for Child Health and Development,
Tokyo, Japan

T. Nakamura · S. Hayashi · H. Sago
Division of Maternal-Fetal and Neonatal Medicine,
National Center for Child Health and Development,
Tokyo, Japan

H. Okuyama
Department of Pediatric Surgery,
Hyogo College of Medicine, Hyogo, Japan

M. Kawataki · H. Ishikawa
Department of Perinatal Care, Kanagawa Children's Medical Center, Yokohama, Japan

K. Nose
Department of Pediatric Surgery,
Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

N. Inamura
Department of Pediatric Cardiology,
Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

K. Masumoto
Department of Pediatric Surgery,
Kyushu University, Fukuoka, Japan

Introduction

Postnatal mortality and morbidity of fetuses with congenital diaphragmatic hernia (CDH) mainly depends on the severity of the pulmonary hypoplasia. An accurate prenatal assessment of pulmonary hypoplasia is essential to plan an optimal treatment strategy for individual cases before birth. Many prenatal prognostic parameters, which are estimated by ultrasonography or MRI, such as fetal lung size [1–4], liver or stomach position [5–7], signal intensity of the fetal lungs [8], and pulmonary artery blood flow [9] have been previously proposed by various investigators. The lung area to head circumference ratio (LHR) [1, 10] and the lung to thorax transverse area ratio (L/T) [2, 11] are the predictive parameters in which the fetal lung size is measured by ultrasonography. However, several investigators have been skeptical about the reliability and usefulness of LHR in predicting the outcome of the fetuses with CDH [12–14]. It is necessary for the LHR to be standardized by the normal values obtained from normal fetuses, because the LHR increases significantly with gestational age in fetuses with CDH [11, 15] as well as in normal fetuses [15, 16]. Therefore, the LHR value is no longer considered independently predictive of survival [6]. In contrast, L/T was originally reported to be a constant parameter throughout the gestational period in the normal fetuses [2]. However, it is unclear whether the L/T changes significantly with gestational age in fetuses with CDH [15]. The purpose of this study was to clarify the reliability of the L/T by an analysis of the change in the L/T with gestational age and to identify the most accurate cutoff value of the L/T for a prediction of patients' postnatal severity in isolated CDH.

Materials and methods

Study population

This multicenter retrospective cohort study included the prenatally diagnosed, isolated CDH fetuses that were born at five participating centers during the period between January 2002 and December 2007. The National Center for Child Health and Development, Kanagawa Children's Medical Center, Osaka Medical Center and Research Institute for Maternal and Child Health, Kyushu University Hospital, and Osaka University Hospital participated in this study. Patients with serious associated anomalies such as major cardiac anomaly and unfavorable chromosomal abnormalities were not included in this study. Cases with bilateral diaphragmatic hernia and cases where neither the LHR nor L/T was measured were also excluded from this study. All patients were inborn and managed by immediate resuscitation followed by neonatal intensive care including gentle ventilation with high-frequency oscillatory ventilation. To successfully carry out the gentle ventilation strategy, the goals of the arterial blood gas data were set at $PaCO_2 < 70$ mmHg and preductal $SpO_2 \geqq 90\%$/preductal $PaO_2 \geqq 70$ mmHg. Once these gas data were obtained, the ventilator settings including FiO_2 and the mean airway pressure decreased immediately. Inhaled nitric oxide (NO) was used in the patients with persistent pulmonary hypertension of the newborn. This study was approved by the institutional review board of each participating center.

Collected data

The primary outcome measures were the overall survival, which was defined as surviving until the end of the observation period, and intact discharge, which was defined as being discharged from the hospital without any need for home treatment such as ventilatory support, oxygen administration, tube feeding, and parenteral nutrition. The postnatal factors including the Apgar scores at 1 and 5 min, highest PaO_2 and lowest $PaCO_2$ in the pre-ductal artery within 24 h after birth, duration of NO inhalation, duration of ventilatory support, duration of oxygen inhalation, need for extra corporeal membrane oxygenation (ECMO), need for prostaglandin E_1 administration [17], surgical findings and survival time were also collected. The L/T and the LHR were measured at the transverse section containing the four-chamber view of the heart by ultrasonography. The L/T was defined as the area of contralateral lung divided by the area of the thorax [11]. The LHR was defined as the ratio of the contralateral lung area, which was the product of the longest two perpendicular linear measurements, to the head circumference [1, 18]. The L/T and the LHR values were collected up to three measurement times according to the gestational age at diagnosis; the earliest measurement before 30 weeks of gestation, the earliest measurement between 30 and 35 weeks of gestation, and the earliest measurement after 35 weeks of gestation.

Analysis of relationship and determination of cutoff value in L/T and LHR

The relationship between the gestational age with the L/T and the LHR was analyzed by subgroups divided according to the outcomes. Logistic regression models were used with the survival and intact discharge as response variables to explore the most powerful measurement point of the L/T and LHR for a prediction of outcomes. The explanatory variables were the earliest value, the latest value, the minimum value, and the maximum value during the gestation. Then the receiver operating characteristic (ROC) curves was calculated to examine the performance of each

value. The area under the ROC curve (AUC) was used as an index of global performance, with an AUC of 0.5 indicating no discrimination ability. The efficacy of a screening test is dependent not only on its overall accuracy assessed by the AUC, but also on the consequences of misclassification associated with sensitivity and specificity. The point maximizing the difference between the sensitivity and the false-positive rate was evaluated as the most accurate cut off point of L/T and LHR for discriminating the survival and intact discharge. The patients' postnatal profiles, including the parameters which represented the severity concerning respiratory status, circulatory support, surgical findings, and prognosis, were compared between the groups divided at the accurate cutoff value to assess the usefulness of the adequate cutoff value of appropriate L/T.

Statistical analysis

The median and interquartile range or the mean and standard deviation were used to describe continuous variables; frequency and percentages were used to describe the categorical data. Either the Wilcoxon rank sum test or Student's *t* test was used for comparison of continuous variables. Fisher's exact test was used for analysis of categorical data. The log-rank test and Kaplan–Meier method were used to compare the duration of respiratory managements and survival time. *p* values of less than 0.05 were considered to indicate statistical significance.

Results

The L/T or LHR were measured at least one time in 114 patients with isolated unilateral fetal CDH who were managed in the participating centers in the study period. Eighty-seven infants (73.3%) were alive until the end of the observation period and 74 infants (64.9%) were discharged from the hospital without any home treatment. The median survival time of the survivors was 1,052 (595–1,496) days, and the median survival time of the non-survivors was 12 (2–57) days. Among them, the L/T was measured 211 times in 103 patients, the LHR was measured 200 times in 100 patients and both of them were measured simultaneously 168 times in 89 patients.

Relationship between L/T and LHR with gestational age

No correlation was observed between the gestational age and the L/T in survivors, although there was a negative correlation between those variables in non-survivors. On the other hand, there were positive correlations between the gestational age and the LHR both in survivors and non-survivors (Fig. 1; Table 1). A negative correlation was observed only between the gestational age and the L/T in infants who died or needed home treatment. On the contrary, a positive correlation was recognized only between the gestational age and the LHR in patients with intact discharge (Fig. 2; Table 1).

Determination of most appropriate cutoff value in L/T for discriminating the outcome

The AUC for discriminating the survivors demonstrated the maximum when the minimum value of the L/T was applied (Table 2). In contrast, the AUC for discriminating the survivors demonstrated the maximum when the maximum value of LHR was applied (Table 2). The difference between the sensitivity and the false-positive rate was maximized with the cutoff value of 0.080 for the minimum L/T and with the cutoff value of 2.04 for the maximum LHR (Table 2). The best AUC in the L/T was greater than the best AUC in the LHR (Table 2; Fig. 3). The AUC for discriminating the intact discharge also demonstrated a maximum when either the minimum value of the L/T was applied or the maximum value of LHR was applied (Table 3). The difference between the sensitivity and the false-positive rate of the minimum L/T was also maximized with the cutoff value of 0.080 (Table 3).

Comparison of the patients' severity in each predictive group divided by the cutoff value of the L/T

The patients were divided into two predictive groups according to the cutoff value of 0.080 in the minimum value of the L/T. Although there was no significant difference in the patients' demographic profiles between the two groups, there were statistically significant differences in the respiratory status such as Apgar scores, arterial blood gas data, and the duration of respiratory support, in the necessity of circulatory support such as ECMO and prostaglandin E_1 administration, in the surgical findings such as operability, diaphragmatic defect size and the need for patch closure and in the final outcomes (Table 4). There was also a significant difference in the survival curve between the two groups (Fig. 4).

Discussion

Although the original definition of the L/T was calculated from both areas of the contralateral lung and ipsilateral lung [2], the L/T was calculated as the ratio of the contralateral lung area to the thorax area in this study, as it has been used in the measurement of the LHR and has also been reported previously in the measurement of the L/T [11]. It seems to

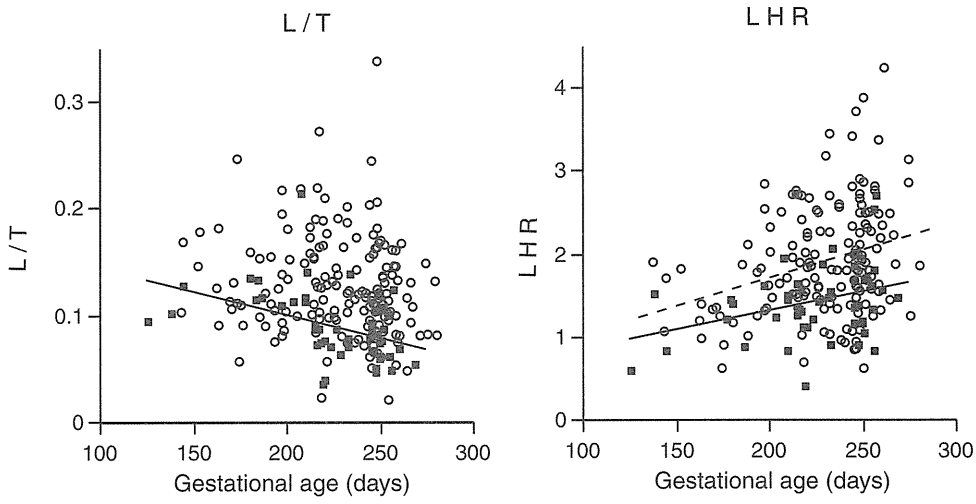

Fig. 1 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia by survival and non-survivors. The *open circles* and *dashed regression line* (LHR = 0.344 + 0.00677GA) represent the survivors and the *closed squares* and *solid regression lines* (L/T = 0.187 − 0.000434GA, LHR = 0.386 + 0.00455GA) represent the non-survivors. *GA* gestational age

Table 1 Relationship between the gestational age, the lung to thorax transverse area ratio (L/T), and the lung area to head circumference ratio (LHR) in the fetuses with congenital diaphragmatic hernia according to survival and intact discharge

Outcome	Gestational age with L/T			Gestational age with LHR		
	n	CC	*p*	*n*	CC	*p*
Survival	166	−0.141	0.056	151	0.296	<0.001
Non-survival	45	−0.411	0.001	49	0.301	0.022
Intact discharge	139	−0.113	0.163	126	0.356	<0.001
Died or needed home treatments	72	−0.343	0.001	74	0.172	0.109

CC correlation coefficient

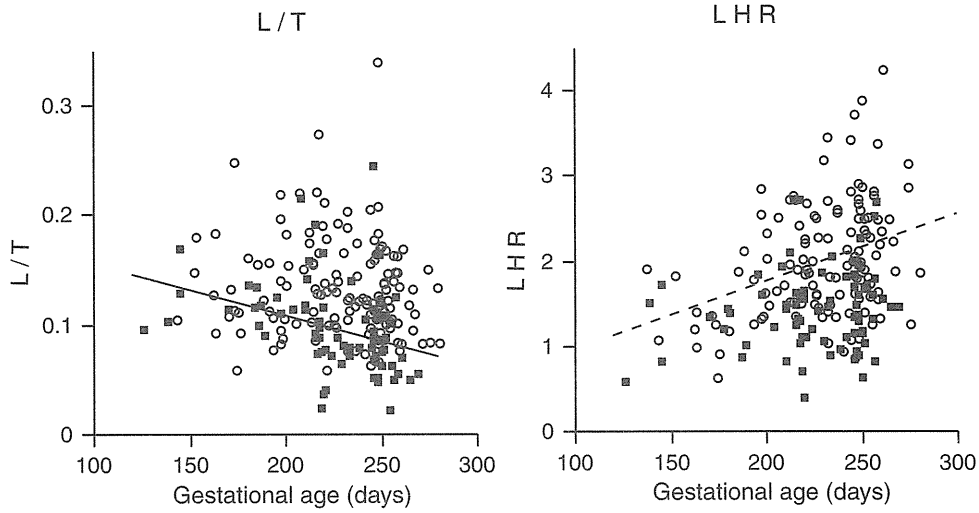

Fig. 2 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia according to intact discharge and non-intact discharge. The *open circles* and *dashed regression line* (LHR = 0.159 + 0.00796GA) represent the infants with intact discharge and the *closed squares* and *solid regression line* (L/T = 0.201 − 0.000469GA) represent the infants without intact discharge. *GA* gestational age

be reasonable to use only the contralateral lung area for determination of the L/T, because the ipsilateral lung is invisible in many cases at the transverse section containing the four-chamber view of the heart because of cranial dislocation of the ipsilateral lung [11]. There is also a possibility of over-estimation in measuring the ipsilateral lung area because of the close similarity of ultrasonographic appearance of the ipsilateral lung and the intestine or spleen. A manual tracing of the limit of the lungs, which is conducted in the measurement of the L/T, has been reported to be the most reproducible measurement rather than a multiplication of lung diameters for the assessment of lung area [16, 18].

The present study found that the LHR were increased according to the gestational age both in the subgroups of survivors and non-survivors, as it has been previously

Table 2 The AUC and the best cutoff value for survival which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

Representative value of L/T and LHR	AUC	Difference between sensitivity and false-positive rate	The best cutoff value
L/T			
The earliest value	0.721	0.347	0.077
The latest value	0.761	0.457	0.107
The minimum value	0.776[a]	0.521	0.080
The maximum value	0.739	0.444	0.142
LHR			
The earliest value	0.735	0.498	1.59
The latest value	0.729	0.441	1.85
The minimum value	0.746	0.476	1.59
The maximum value	0.750[a]	0.459	2.04

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

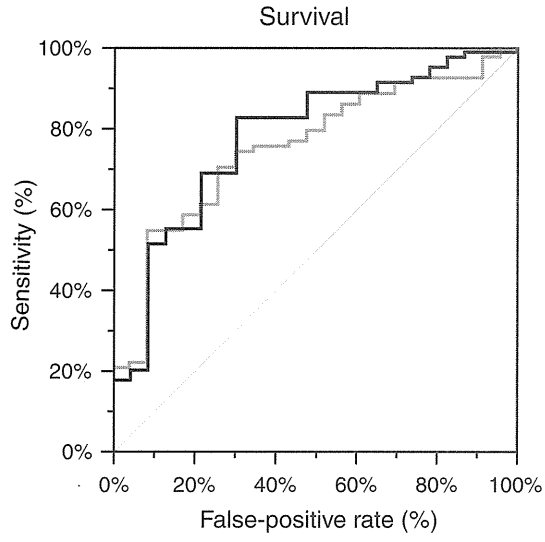

Fig. 3 The ROC curve for discriminating the outcome of survival based on the minimum L/T (*solid line*) and the maximum LHR (*light line*). The AUC for survival in L/T and LHR was 0.776 and 0.750, respectively

reported in normal fetuses [16] and in the fetuses with CDH [11, 15]. The reason for the increase of LHR with the gestational age is due to the difference in the rate of the increase of the lung area and head circumference. Peralta reported that there was a fourfold increase in the LHR between 12 and 32 weeks of gestation in normal fetuses because of these differences [16]. This explains the difficulty in identifying a common cutoff value in LHR which is able to predict the survival, independently of the timing of prenatal assessment. Standardizing the LHR by using the expected LHR has been proposed to provide a constant value throughout period of gestational and thus excellent performance of the ROC curve [15]. However, determining the observed to expected LHR requires the expected LHR in normal fetuses for a standardizing in each population, and thus it has less availability in each population.

On the other hand, the L/T has been reported to be a constant parameter in normal fetuses, [2] and in fact, it had no correlation with gestational age in the survivors or in the patients with intact discharge. The L/T in non-survivors or patients who needed home treatment decreased according to the gestational age, but it may imply that there is a possibility to determine the most powerful measurement point of the L/T to predict poor outcomes. The latest L/T should be theoretically more reliable than the earliest L/T for the prediction of outcome because the L/T had a downward trend in those patients with poor prognosis. In

Table 3 The AUC and the best cutoff value for intact discharge which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

Representative value of L/T and LHR	AUC	Difference between sensitivity and false positive rate	The best cutoff value
L/T			
The earliest value	0.740	0.367	0.080
The latest value	0.784	0.465	0.092
The minimum value	0.798[a]	0.511	0.080
The maximum value	0.729	0.372	0.142
LHR			
The earliest value	0.790	0.474	1.59
The latest value	0.819	0.556	1.72
The minimum value	0.804	0.559	1.59
The maximum value	0.835[a]	0.372	1.79

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

Table 4 Patient demographics and the postnatal severity of the fetuses with isolated congenital diaphragmatic hernia in the groups divided by the L/T at 0.080

	n	L/T < 0.080 (*n* = 30)	L/T ≥ 0.080 (*n* = 73)	*p*
Gender (M/F)	103	19/11	39/34	0.390
Side of hernia (left/right)	103	28/2	71/2	0.578
Gestational age at diagnosis (weeks)[a]	103	27.8 ± 5.0	29.0 ± 5.9	0.305
Gestational age at birth (weeks)[a]	103	38.0 ± 1.2	38.0 ± 2.0	0.952
Body weight at birth (kg)[a]	103	2.60 ± 0.50	2.81 ± 0.52	0.063
Polyhydramnios (%)	103	36.7	27.4	0.356
Apgar score at 1 min[a]	101	3.28 ± 1.67	4.88 ± 2.18	<0.001
Apgar score at 5 min[a]	99	4.64 ± 2.04	5.76 ± 2.24	0.024
Highest pre PaO_2 (mmHg)[b]	90	116 (45–237)	266 (177–374)	<0.001
Lowest pre $PaCO_2$ (mmHg)[b]	103	36.7 (29.2–51.4)	31.2 (26.0–43.7)	0.041
Duration of NO inhalation (days)[b]	95	19 (14–40)	8 (5–13)	<0.001
Duration of ventilatory support (days)[b]	103	35 (28–545)	19 (11–31)	<0.001
Duration of O_2 inhalation (days)[b]	103	251 (42–555)	30 (16–53)	<0.001
Need for ECMO (%)	103	33.3	5.5	<0.001
Need for PGE_1 administration (%)	103	60.0	23.3	<0.001
Inoperable cases (%)	103	23.3	5.5	0.013
Over 75% defect of diaphragm (%)	83	89.5	37.5	<0.001
Need for patch closure (%)	92	82.6	36.2	<0.001
Intact discharge rate (%)	103	26.7	82.2	<0.001
Overall survival rate (%)	103	46.7	90.4	<0.001

NO nitric oxide, *ECMO* extra corporeal membrane oxygenation, *PGE_1* prostaglandin E_1

[a] Mean ± standard deviation

[b] Median with interquartile range

fact, the AUC of the latest L/T was greater in comparison to the AUC of the earliest L/T (Table 2). However, the AUC indicated a maximum sensitivity when the L/T was represented by the minimum value during gestation. This may be related to a measurement deviation of L/T and there may be a limit of reliability of this methodology. An earlier assessment of the infants is more desirable to determine the indications for fetal intervention [19, 20]. Neither the LHR nor the L/T may independently be sufficient to determine the indications for fetal intervention; thus, a combination of these and other prenatal factors such as liver position may be necessary, because the liver position has been reported to be one of the most predictive factors [1, 5, 21–23].

Although the LHR increased according to the gestational age in the patients with intact discharge, there is no increase of the LHR in infants without intact discharge. The LHR may be a beneficial indicator for discriminating the favorable patients who can be discharged from hospital without any home treatment. In fact, the best AUC for intact discharge in the LHR was greater than the best AUC for intact discharge in the L/T (Table 3). Interestingly, the most powerful measurement point and accurate cutoff value of L/T for discriminating the outcome of intact discharge was the same value in the same explanatory variable as that used to discriminate the survivors, namely 0.080 in the minimum L/T (Table 3).

The groups divided by a cutoff value of a minimum L/T of 0.080 demonstrated a significant difference in the postnatal severity including respiratory status, need for

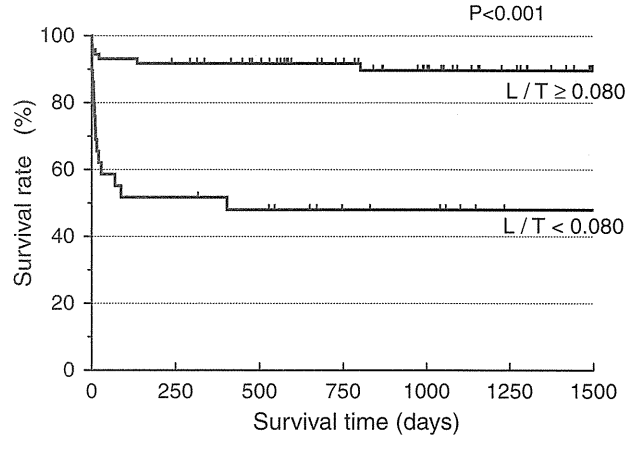

Fig. 4 Survival curves in the patients with isolated congenital diaphragmatic hernia divided by the minimum L/T at 0.080

respiratory support, need for circulatory support, surgical findings, and prognosis, which seems to be reflected in pulmonary hypoplasia. Therefore, the L/T was able to accurately estimate the severity of the infants in the perinatal and perioperative period, and we may be able to develop several different treatment programs in terms of perinatal and perioperative management to adjust for the predicted severity as estimated by the L/T.

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ORIGINAL ARTICLE

The utility of muscle sparing axillar skin crease incision for pediatric thoracic surgery

Tomoaki Taguchi · Kouji Nagata · Yoshiaki Kinoshita · Satoshi Ieiri · Tatsuro Tajiri · Risa Teshiba · Genshiro Esumi · Yuji Karashima · Sumio Hoka · Kouji Masumoto

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Abstract
Background Posterolateral or standard axillar incisions for the pediatric thoracic surgery are occasionally associated with poor motor as well as cosmetic results, including chest deformities and large surgical scars. A muscle sparing axillar skin crease incision (MSASCI) was initially proposed by Bianchi et al. (in J Pediatr Surg 33:1798–1800, 1998) followed by Kalman and Verebely (in Eur J Pediatr Surg 12:226–229, 2002) resulting in satisfactory cosmetics. However, they performed operations through the third or fourth intercostals space (ICS), therefore the target organs were restricted in the upper two-thirds of the thoracic cavity.
Patients and methods Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old). There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. A thoracotomy was performed through the appropriate ICS (from third to eighth).
Results In all patients, the expected procedures, including pulmonary lower lobectomy, were successfully performed by MSASCI throughout the thoracic cavity. A good operational field was easily obtained in neonates and infants. Most of the patients achieved excellent motor and aesthetic outcomes.
Conclusions MSASCI may become the standard approach for the thoracic surgery for small children.

Keywords Axillar skin crease · Thoracotomy · Pulmonary lobectomy · Neonate · Infant

Introduction

Advances in antenatal diagnosis, surgical technique and perioperative care have improved survival rate for neonatal surgical diseases. The mortality rate has become less than 10% [1]. It is now important to consider the long-term good "quality of life" (QOL) in neonatal surgical disease. Therefore, surgeons have sought to establish procedures that leave no scars, using the natural skin crease such as axillar crease and umbilical crease [2–4].

Posterolateral or standard axillar incisions for the pediatric thoracic surgery sometimes cause poor functional as well as cosmetic results, including chest deformities (scoliosis, shoulder deformity, and winged scapula) and large surgical scars. Muscle sparing axillar skin crease incision (MSASCI) was initially proposed for neonates by Bianchi et al. [5] in 1998, and then Kalman and Verebely [6] extended this approach for children in 2002, thus resulting

T. Taguchi · K. Nagata · Y. Kinoshita · S. Ieiri · T. Tajiri · R. Teshiba · G. Esumi
Department of Pediatric Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

T. Taguchi (✉)
Department of Pediatric Surgery, Reproductive and Developmental Medicine, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
e-mail: taguchi@pedsurg.med.kyushu-u.ac.jp

Y. Karashima · S. Hoka
Department of Anesthesiology and Critical Care Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

K. Masumoto
Department of Thoracic, Endocrine, and Pediatric Surgery, Fukuoka University School of Medicine, Fukuoka, Japan

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in a good postoperative cosmetic results. However, they performed surgery through the third or fourth intercostals space (ICS), therefore the performed operations were restricted in the upper two-thirds of the thoracic cavity.

Patients and methods

Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old) from December 2006 to February 2011. There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. The performed operations were 10 primary esophageal anastomoses, 12 pulmonary lobectomies (including lower lobectomies) or partial resections, 2 subtotal neuroblastoma resections, 1 diaphragmatic repair, 1 pulmonary biopsy, and 1 exploratory thoracotomy.

This study was performed, according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan on 30 July 2003 and complies with the Helsinki Declaration of 1975 (revised 1983). Regarding this retrospective study, properly informed consent was obtained from the parents.

The patient was placed in the lateral position. The uppermost arm was extended to about 130°, drawn forward, and placed on an arm-rest. A pulse-oxymeter was applied on hand of the extended arm.

A skin incision was made just on the axillar skin crease, and the pectoralis major and latissimus dorsi muscles were retracted superiorly and medially, respectively. Either of these muscles could be partially incised in case. The incision was deepened and the axillary fat pad and lymph nodes were pushed upward. The long thoracic nerve was preserved in the posterior part of the wound (Fig. 1). The anterior serratus muscle was split along its fibers just on the targeted costa. The thoracic cavity was entered through the appropriate ICS. The peripheral pulse was monitored by the pulse-oxymeter of the extended arm avoid a circulatory failure of the arm.

Thoracotomy for esophageal atresia was performed through the fourth ICS and the upper and lower esophagus was exposed via an extrapleural approach. After cutting The azygos vein was cut and the Tracheoesophageal fistula (TEF) was closed by 5-0 polydioxanon (PDS) transfixing sutures and cut. Esophageal end-to-end anastomosis was performed with one layer stitch sutures. Both lateral sides were approximated using 5-0 PDS, and a transanastomotic tube was inserted from the nose to the stomach through the anastomosis. The anterior and the posterior aspects were sutured with 6-0 PDS in stitch.

One-lung ventilation was attempted in order to obtain adequate operational field for pulmonary lower lobectomy [7]. Briefly, bronchial blockade with a 4Fr or 5Fr Fogarty embolectomy catheter was attempted in each case. Children were initially intubated with a Fogarty embolectomy catheter under direct laryngoscopy. Then, immediately, an endotracheal tube was placed alongside the catheter in the trachea. After securing the tube, a pediatric fiberoptic bronchoscope (2.2 mm in diameter) was passed through to set a Fogarty embolectomy catheter to the mainstem bronchus. And then, bronchial blockade was performed with its balloon inflated with an appropriate volume of normal saline. Thoracotomy was done through the fifth or sixth ICS, and then the lung was deflated. The pulmonary arteries were ligated and cut and then the bronchus was cut and closed with 5-0 PDS sutures. Finally, the pulmonary vein was doubly ligated and cut, and the pulmonary ligament was dissected.

One-lung ventilation was also performed for the pulmonary sequestration. Thoracotomy was performed via the seventh or eighth ICS in order to approach the abnormal artery in pulmonary ligament at first. One-lung ventilation allowed lower lobe to be easily lifted for the dissection of pulmonary ligament and the ligation of abnormal artery. This abnormal artery was ligated, before ligation of pulmonary vein in order to avoid lung volume expansion.

A rolled vicryl sheet was inserted between the costa during thoracic closure, in order to avoid bony adhesion in some cases. Both the thoracic and subcutaneous tubes were inserted through both ends of wound; therefore, no additional wounds were necessary for tubes.

Results

Thoracotomy was successfully done through from the third and eighth ICS using MSASCI. All of the expected procedures, including pulmonary lower lobectomies, were able to be performed adequately. A good operational field was easily obtained in neonates and infants in comparison to that in elder children. The incision was extended caudally, about 1 cm in only one infant with pulmonary sequestration. Two patients died due to the severe cardiopulmonary anomalies, and one patient with right diaphragmatic hernia showed recurrence and required reoperation using an abdominal approach. The other patient with a right diaphragmatic hernia showed no right lung; therefore, no procedure was performed (exploratory thoracotomy).

Surgical complications included wound disruption in the four cases and transient arm paralysis in the two cases. The wound disruptions were treated by vacuum therapy and healed about 1 week, and the transient arm paralysis

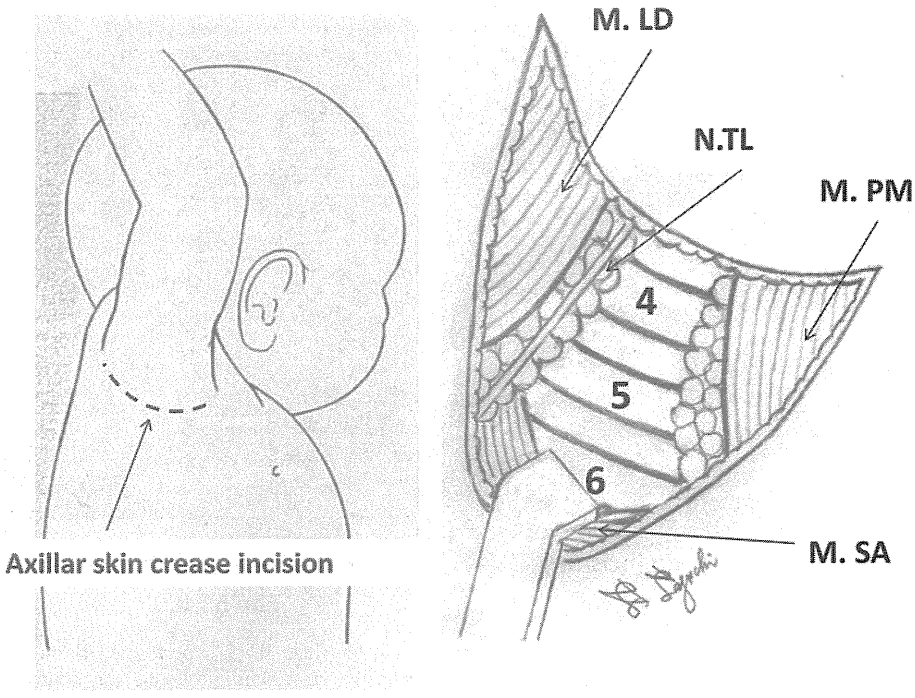

Fig. 1 Operation schema for MSASCI. *M.LD* lattismus dorssi muscle, *N.TL* long thoracic nerve, *M.PM* pectoralis major muscle, *M.SA* serratus anterior muscle, The *numbers* are labeling in the individual ribs.

recovered spontaneously in a few weeks. All of the patients showed uneventful postoperative course and achieved excellent motor and aesthetic outcomes after 1 month. The surgical scar was almost hidden by the axillar skin crease in a year (Figs. 2, 3). So far, there have been no patients showing thoracic deformity, in a relatively short-term follow-up (no more than 4 years). The outcome of each patient is shown in Table 1.

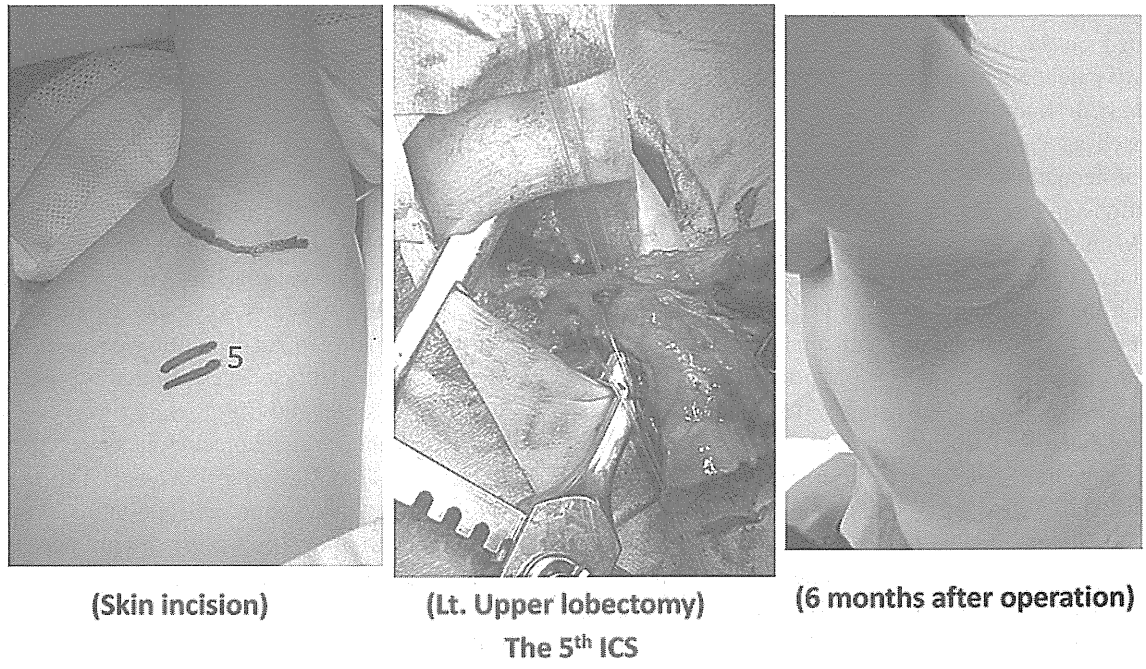

Fig. 2 Pre, intra, and postoperative appearance of Case 15. Congenital cystic adenomatoid malformation in Lt. upper lobe. *Left* skin incision on the axillar crease. *Middle* Lt. upper lobectomy of lung was performed through the fifth ICS at 1-month old. *Right* operative wound was almost hidden 6 months after operation

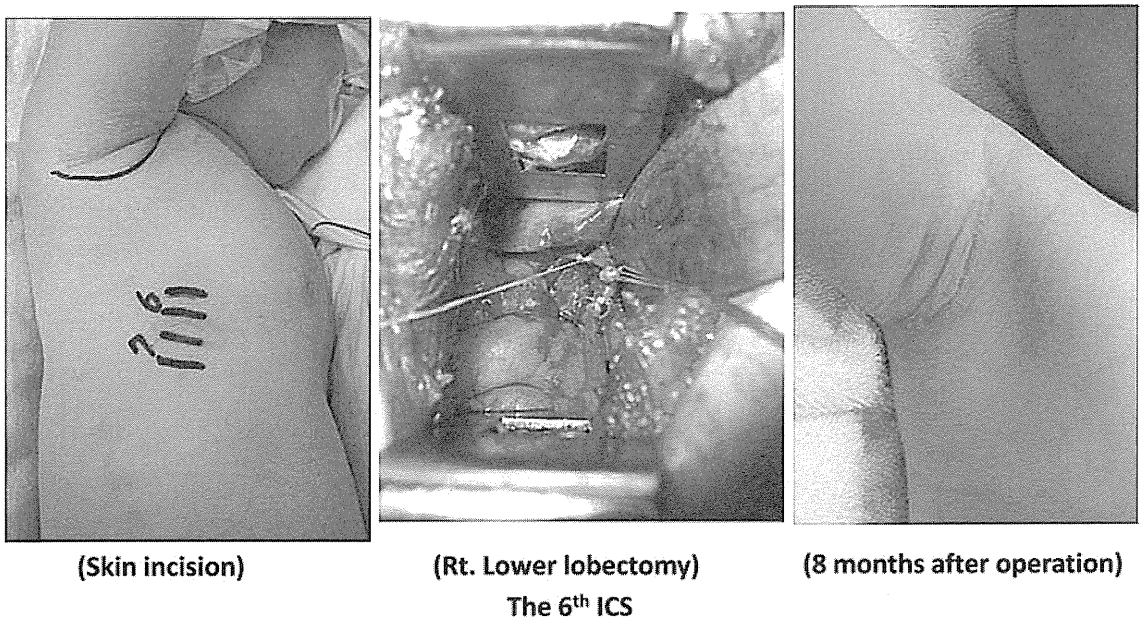

Fig. 3 Pre, intra, and post operative appearance of Case 17. Intralober lung pulmonary sequestration in Rt. lower lobe. *Left* skin incision on the axillar crease. *Middle* Rt. lower lobectomy of lung was performed through the sixth ICS at 3-month old. *Right* operative wound was almost hidden 8 months after operation

Discussion

Axillary skin crease incision for thoracic surgery was initially reported by Atkinson as "peraxillary approach" for dissection of the upper thoracic and stellate ganglia through the second ICS in adult in 1949 [8]. Bianchi et al. [5] reported using "high axillary skin crease, muscle-sparing to right lateral thoracotomy" for children in 1998. They operated on 29 neonates including 27 esophageal atresia and two patent ductus arteriosus (PDA) through the third or fourth ICS. Kalman and Verebely [6] also reported this approach as "axillary skin crease incision" for thoracotomy of neonates and children in 2002. They performed 17 operations in neonates (8 esophageal atresia, 8 PDA, 1 CCAM) and 9 operations in children (3 neuroblastoma, 1 teratoma, 5 pulmonary operations including lobectomies) through the third or fourth ICS. The oldest patient of this report was a 15-year-old girl with a large teratoma from the anterior mediastinum. They performed five pulmonary operations including one biopsy for histiocytosis, one marsupialization of an inflammatory cyst, one cystectomy of a congenital cyst and two pulmonary resections for bronchiectasia (one S2-3-4 trisegmentectomy on the left side and one middle lobe lobectomy). They concluded that it ensured unrestricted access to the upper two-thirds of the thoracic cavity through the third or fourth ICS. They did not perform any pulmonary lower lobectomies.

These reports indicate that the term MSASCI is appropriate. The approach was extended downward up to the eighth ICS in the current series to perform the expected procedures in all cases, including pulmonary lower lobectomy and intralobular pulmonary sequestration. This technique is feasible for almost all kinds of pediatric thoracic surgery from third to eighth ICS. The appropriate ICS for thoracotomy depends on the target organ. For example, the fourth ICS is used for esophageal atresia, the fifth ICS is for standard pulmonary lobectomy, and the seventh or eighth ICS for pulmonary sequestration. We experienced technical difficulties in patch closure of right diaphragmatic hernia in one case. The medial margin of diaphragmatic defect was difficult to be exposed for suturing, because liver and intestine interfered to the operation field. Right diaphragmatic hernia might not be indication for MSASCI from our restricted experience.

There were initially several complications, such as wound disruption and transient arm paralysis. In 18 out of the 27 patient, thoracotomy was performed below the fourth ICS. The wound disruption occurred in four cases (Cases 5, 7, 9 and 26). These four were operated through fifth, fourth, sixth, and fifth ICS, respectively. Three out of four cases underwent thoracotomy below the fourth ICS. Therefore, downward hyperextension of skin by metal retractor may cause wound disruption. In addition, the case five was extremely premature infant and the modified gestational age at operation was 40 weeks. Cases 7, 9 and 26 were operated in their neonatal period. And the three out of these four cases showed cyanosis in perioperative period due to their congenital heart disease and the subsequent pulmonary hypertension. Therefore, hyperextension of the skin as well as vulnerable factors of each child may cause

Table 1 Summary of 27 pediatric patients performed thoracotomies with MSASCI

Case	Sex	Diagnosis	Type or site	Age at op.	Operation	Intercostal space	Complication	Prognosis
1	M	EA	Gross type A	1 year 3 month	Esophageal EEA	Rt. 4th intercostal	Minor leakage	Alive
2	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	Stenosis	Alive
3	M	EA, AA, TAC	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
4	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	None	Alive
5	F	EA, ELBWIPA stenosis	Gross type C	3 months	Esophageal EEA	Rt. 5th intercostal	TEF recurrence wound disruption	Died[b]
6	F	EA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
7	M	EA, TA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	Wound disruption transient paralysis	Died[c]
8	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 5th intercostal	Stenosis	Alive
9	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 6th intercostal	Wound disruption	Alive
10	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
11	M	CCAM	Rt. middle lobe	8 months	Partial resection	Rt. 5th intercostal	None	Alive
12	M	LPS	Rt. lower lobe	4 days	LPS resection	Rt. 5th intercostal	None	Alive
13	F	CCAM	Lt. upper lobe	1 month	Partial resection	Lt. 5th intercostal	None	Alive
14	F[a]	LPS	Lt. lower lobe	8 months	LPS resection	Lt. 8th intercostal	None	Alive
15	M	CCAM	Lt. upper lobe	1 month	Lt. upper lobectomy	Lt. 5th intercostal	Pneumothorax	Alive
16	F	CCAM	Lt. lower lobe	4 months	Lt. lower lobectomy	Lt. 5th intercostal	None	Alive
17	M	LPS	Rt. lower lobe	3 months	Rt. lower lobectomy	Rt. 6th intercostal	None	Alive
18	F	CTA with LPS	Lt. lower lobe	4 months	Rt. lower lobectomy	Rt. 6th intercostal	Transient paralysis	Alive
19	M	CCAM	Lt. lower lobe	3 months	Lt. lower lobectomy	Lt. 6th intercostal	None	Alive
20	M	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Rt. 5th intercostal	None	Alive
21	M	LPS	Lt. lower lobe	7 months	LPS resection	Lt. 7th intercostal	None	Alive
22	F	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Lt. 5th intercostal	None	Alive
23	M	Mediastinal NB	Lt. upper lobe	6 years 1 month	Subtotal excision	Lt. 4th intercostal	None	Alive
24	F	Mediastinal NB	Lt. upper lobe	9 years 4 months	Subtotal excision	Lt. 3th Intercostal	None	Alive
25	M	Pulmonary HT	Lt. upper lobe	5 years 11 months	Biopsy	Lt. 6th intercostal	None	Alive
26	M	Rt. CDH		5 days	Repair	Rt. 5th intercostal	Wound disruption CDH recurrence	Alive
27	F	Rt. CDH Rt. lung agenesis		5 days	Exploratory thoracotomy	Rt. 7th intercostal	None	Alive

EA esophageal atresia, *AA* anal atresia, *TAC* truncus arteriosus communis, *ELBW* extremely low birth weight infant, *PA* pulmonary artery, *TA* tricuspid atresia, *CCAM* congenital cystic adenomatoid malformation, *LPS* lung pulmonary sequestration, *CTA* congenital tracheal atresia, *NB* neuroblastoma, *CDH* congenital diaphragmatic hernia, *HT* hypertension, *EEA* end to end anastomosis, *TEF* tracheoesophageal fistula

[a] Incision was extended caudally about 1 cm

[b, c] Two patients died due to the severe cardio-pulmonary anomalies

the wound disruption. In order to prevent this complication, a wound retractor XS has been currently applied to protect the surgical wound. This instrument can prohibit skin and subcutaneous tissue damage during surgery. Postoperative subcutaneous negative-pressure drainage is also an effective for avoiding or treating wound disruption.

The transient arm paralysis occurred in the case 7 and 18. They were operated through the fourth ICS and the sixth ICS, respectively. Therefore, the transient paralysis is not considered to be related to the level of thoracotomy. Actually, there were no complications in the patients operated from the seventh to eighth ICS. Currently, a pulse-oxymeter has been applied, on the hand, of the extended arm for monitoring peripheral blood pulse and saturation of oxygen. During operation blood pulse and saturation of oxygen has been kept in normal range. Since then, no patient has experienced transient arm paralysis. Therefore, transient arm paralysis is considered to be vascular origin caused by the hyperextension of arm or the hyperextension of wound.

The surgical field is relatively small; therefore, there are a few technical methods in order to overcome this disadvantage. One-lung ventilation is required for pulmonary lower lobectomy during the dissection of the pulmonary ligament and pulmonary vein. Furthermore, one-lung ventilation provides adequate operative field in ligation of the abnormal artery during surgery of pulmonary sequestration. One-lung ventilation has been technically feasible in infant, using Fogarty embolectomy catheter [7]. Hemoclips facilitate the ligation of pulmonary arteries. The proximal site is ligated by 3-0 or 4-0 silk suture and the distal site is closed by a hemoclip, to provide sufficient distance for a safe cut. A long and fine-tip needle holder and forceps are required for dissection of the TEF and anastomosis of the esophagus in esophageal atresia. Fine monofilament absorbable 5-0 or 6-0 PDS with the two needles in both ends are useful for full thickness stitch suture using an inside-to-outside and inside-to-outside manner.

In conclusions, MSASCI for pediatric thoracic surgery resulted in excellent motor and aesthetic outcomes. MSASCI may become the standard approach for thoracic surgery for the small children, especially for neonates and infants.

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ORIGINAL ARTICLE

Identification of *TCTE3* as a gene responsible for congenital diaphragmatic hernia using a high-resolution single-nucleotide polymorphism array

Risa Teshiba · Kouji Masumoto · Genshiro Esumi · Kouji Nagata · Yoshiaki Kinoshita · Tatsuro Tajiri · Tomoaki Taguchi · Ken Yamamoto

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Abstract
Purpose Congenital diaphragmatic hernia (CDH) is a birth defect of the diaphragm associated with pulmonary hypoplasia. Although genetic factors have been suggested to play a role, the etiology of CDH is still largely unknown. In this study, we analyzed copy number variants (CNVs) using a single-nucleotide polymorphism (SNP) array to examine whether microdeletions contribute to the pathogenesis of this disease.
Methods A total of 28 CDH patients, including 24 isolated and 4 non-isolated cases, were available. We performed CNV analysis using high-resolution SNP arrays (370K, 550K, 660K; Illumina Inc.) and CNstream software. Deletions in loci that have been suggested in previous studies to contain candidate genes affecting CDH were analyzed.
Results We detected 335, 6 and 133 deletions specific for patients in 14 (350K array), 3 (550K) and 11 (660K) cases, respectively. Among these deletions, no segments included the previously suggested candidate genes with the exception of an 18-kb deletion observed in the candidate locus 6q27 in two non-isolated patients. This deleted region contains exon 4 of the *t-complex-associated-testis-expressed 3* (*TCTE3*) gene.
Conclusion Because *TCTE3* encodes a putative light chain of the outer dynein arm of cilia and human diseases caused by ciliary dysfunction show various phenotypes including skeletal defect, *TCTE3* may be a genetic candidate influencing CDH.

Keywords Congenital diaphragmatic hernia · Copy number variation · Microdeletion · Single-nucleotide polymorphism array · TCTE3

Introduction

Congenital diaphragmatic hernia (CDH) is a relatively common birth defect characterized by an abnormality in the integrity of the diaphragm. In a meta-analysis, its prevalence was calculated to be approximately 1/4,000 births [1]. CDH cases can be divided into two phenotypic categories—isolated and non-isolated—based on the presence of additional non-hernia-related anomalies. The non-isolated type makes up 30–40% of CDH cases [1–3], and some patients with this type show anomalies that are strongly suggestive of a recognized genetics syndrome such as Fryns syndrome (MIM 229850). In addition to a genetic syndrome within CDH, more than 50 CDH multiplex families have been reported [2]. These observations have implicated genetic factors in the condition's etiology.

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R. Teshiba · K. Yamamoto (✉)
Division of Genome Analysis, Research Center for Genetic Information, Medical Institute of Bioregulation, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: kyama@bioreg.kyushu-u.ac.jp

R. Teshiba · K. Masumoto · G. Esumi · K. Nagata · Y. Kinoshita · T. Tajiri · T. Taguchi
Department of Pediatric Surgery, Reproductive and Developmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

K. Masumoto
Division of Thoracic, Endocrine and Pediatric Surgery, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

Chromosomal aberrations have been identified as an important etiological factor in non-isolated CDH [4]. However, the majority of the cases were analyzed by low-resolution approaches, such as a combination of G-banded chromosome analysis and FISH. In recent years, array-based techniques have been widely used to detect small chromosomal changes that cannot be detected by traditional karyotype analysis, and a role for rare copy number variants (CNVs) in the etiology of diseases has gained considerable attention [5]. In non-isolated CDH, array-based analysis has detected several microchromosomal changes and delimited critical regions [6–10]. Those hotspot regions are of great interest because they may harbor genes associated with the development of CDH. However, the exact etiology of most cases of CDH still remains unknown.

In the present study, we screened CNV regions in CDH patients using a high-resolution single-nucleotide polymorphism (SNP) array to analyze the association of CNVs in both hotspot loci and candidate genes involved in retinoid signal pathways [11–13] with the disease.

Materials and methods

Subjects

This study was approved by the Ethics Committee at Kyushu University, Fukuoka, Japan. All patients or their parents were fully informed and agreed to participate in the study. DNA samples were obtained from 28 CDH patients; 24 had isolated CDH and 4 had CDH with additional anomalies. Non-isolated CDH cases were complicated with horseshoe kidney in one case, tracheal stenosis and double-outlet right ventricle (DORV) in one case, facial anomalies (low-set ears, micrognothia, saddle-nose) and cryptorchism in one case and Fryns syndrome in other case. The sides of defect were left-sided in 26 patients, right-sided in 1 patient and bilateral in 1 patient (Table 1). Patients with chromosomal aberrations already detected by karyotype analyses were excluded.

Table 1 Patient characteristics

Characteristic	Number of cases
Isolated	24
Non-isolated	4
Horseshoe kidney	1
Tracheal stenosis and double-outlet right ventricle	1
Fryns syndrome	1
Facial anomalies (low-set ears, micrognothia, saddle-nose) and cryptorchism	1
Defect side	
Left	26
Right	1
Bilateral	1
Total number of cases	28

DNA isolation and CNV analysis

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Midi Kit (QIAGEN) and was adjusted to a final concentration of 50 ng/μl for array analyses. The Illumina Human CNV370K-Duo, 370K-Quad, 550K-Duo or 660K-Quad Array and the Illumina BeadStation 500G SNP genotyping system were employed to obtain signal intensities of probes according to the manufacturers' protocols. To evaluate experimental quality, SNP genotypes were determined using BeadStudio Genotyping Analysis Module 3.3.7 software. All samples showed call rates greater than 0.99 (the average was 0.997; see supplemental Table S1).

CNstream was used to estimate CNVs from X and Y channel intensities loaded from the BeadStudio Genotyping data [14]. Input files for CNstream consisted of 14 patients into the 370K array, 3 into the 550K array and 11 into the 660K array, and each file also included 100 samples from normal controls. The numbers of markers for all autosomes were 334,515 in the 370K array, 547,405 in the 550K array and 639,815 in the 660K array. Those SNP and CNV markers successfully genotyped in <95% of cases were discarded. There were thus 345,359 markers remaining in the 370K array, 561,123 markers remaining in the 550K array and 656,308 markers remaining in the 660K array. Markers of sex chromosome were excluded from this study owing to inaccuracy of the computed result. CNVs were calculated using the CNstream program under the following parameters: maximum segment length (= 100 kb), number of probes per segment (= 5), minimum number of probes in one segment that must exceed the threshold for identifying an amplification/deletion (= 3), deletion threshold (= 1.65) and amplification threshold (= 2.7). The results of computation included the segments of CNV (bp), the percentage of amplifications and deletions over the samples (%) and the copy number assigned to each sample. CNstream could also perform an association analysis using Fisher's exact test and provide odds ratio and *P* values via a chi-squared case/control association test. The result was filtered by the percentage of amplification/deletion in cases and controls, and we selected deleted segments observed in case but not control samples. Selected segments were compared with the following sequences: (1) the candidate genes within the regions of chromosomal aberrations reported in CDH, the genes associated with the retinoid signaling pathway, and the genes whose mutations were reported in CDH; (2) the causative

genes of known syndromic CDH; and (3) the loci in which chromosomal abnormities were frequently reported. Physical position was obtained from the UCSC genome browser (http://www.genome.ucsc.edu/cgi-bin/hgGateway: NCBI36/hg18). Subsequently, the segments overlapping with those genes and loci were selected, and the logR ratio and B allele frequency of those segments checked using the BeadStudio genome viewer to exclude experimental artifacts.

Results

The CNstream program calculated the estimated amplification and deletion regions in both patients and control subjects, and a total of 21,366 segments were obtained in the 370K array, 1,945 segments were obtained in the in 550K array and 6,377 segments were obtained in the in 660K array (including redundant regions, Table 2). We presumed that the deletions not observed in the general population were relevant to the development of CDH. Therefore, deletions obtained in patients but not controls were subjected to evaluation. The numbers of such deletion segments were 335 in the 370K array, 6 in the 550K array and 133 in the 660K array.

Table 2 Output result of CNstream

SNP-array version	370K	550K	660K
Case/control	14/100	3/100	11/100
Number of markers	334,515	547,405	639,815
Segment of Amp./Del.			
Total number of detected segments	21,366	1,945	6,377
Amp. Case(+)/Control(−)[a]	20,333	682	1,224
Del. Case(+)/Control(+)[b]	540	73	2,064
Del. Case(+)/Control(−)[c]	335	6	133
(Per case)	(24)	(2)	(12)

Amp. amplification, *Del.* deletion

[a] Segments of amplification in cases but not in controls

[b] Segments of deletion in cases and controls

[c] Segments of deletion in cases but not in controls

The results of the comparison between the locations of deletion segments and candidate genes are shown in Table 3. With the exception of *HLX* and *DISP1*, these genes are associated with the retinoid signaling pathway. One mutation in and two variants of the *FOG2* gene were reported in isolated CDH [15, 16]. *HLX* is a homeobox gene transcription factor, and four variants were reported in isolated CDH as well [17]. The mutation of *DISP1* was reported in a CDH patient with additional malformations, and this gene is known to interact with sonic hedgehog [11]. So far, sequencing analyses have found no mutations in *COUP-TFII* [7, 9]. Deletion segments did not overlap with these genes.

Then, we compared these segments with genes known to be causative of monogenic syndromes (Table 4). Patients with these syndromes, which include Cornelia de Lange syndrome and Denys–Drash syndrome, are known to exhibit a higher incidence of CDH than the general population. However, the deletion segments did not overlap with the positions of these genes.

Table 3 Candidate genes for CDH and numbers of patients with detected deletion segments

Candidate gene (OMIM)	Band	Mutation (human)[a]	Study author	Number of patient with deletion segment[b]		
				370K	550K	660K
HLX (142995)	1q41	CDH−	Slavotinek et al. [17]	0/14	0/3	0/11
DISP1 (607502)	1q41	CDH+	Pober et al. [11]	0/14	0/3	0/11
RBP1 (180260)	3q23	–		0/14	0/3	0/11
RBP2 (180280)	3q23	–		0/14	0/3	0/11
LRAT (604963)	4q32.1	–		0/14	0/3	0/11
ALDH8A1 (606467)	6q23.3	–		0/14	0/3	0/11
GATA4 (600576)	8p23.1	–		0/14	0/3	0/11
FOG2 (603693)	8q23.1	CDH−	Bleyl et al. [15] Ackerman et al. [16]	0/14	0/3	0/11
RBP5 (611866)	12p13.31	–		0/14	0/3	0/11
RAIG1 (604138)	12p13.1	–		0/14	0/3	0/11
CRABP1 (180230)	15q25.1	–		0/14	0/3	0/11
COUP-TFII (107773)	15q26.2	Not found	Slavotinek et al. [7] Scott et al. [9]	0/14	0/3	0/11

CDH− isolated CDH, *CDH+* non-isolated CDH

[a] Reported mutations in human

[b] Number of patients in whom deletions for each gene were calculated by the CNstream program