태아통합컨퍼런스

2019.08.19 (월)

삼성서울병원
소아청소년과
Fellow. 한예슬

CASE 조O희(42600472)

임신 22주경에 진단된
Multiple anomaly
(분만 후 진단명: Ring 4 chromosome syndrome, Wolf-Hirschhorn syndrome?)

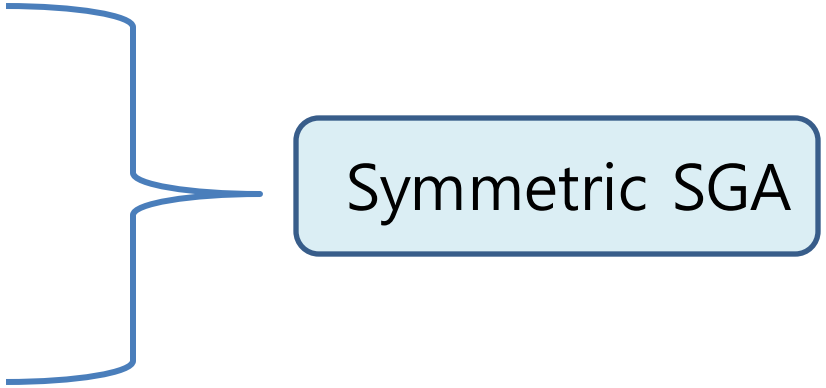
Present illness

- 산전 초음파 검사에서 **IUGR**, **multiple anomaly** (VSD, aortic arch hypoplasia, r/o Rt. Kidney agenesis, single umblical artery)있는 환아로 GA 37wks, 1300g, A/S 6/8, elective c/sec으로 출생함.

- 출생 당시 initial crying 있었고, HR target 이상이었으나 이후 점차 HR<100회, Spo2 target 미만으로 생후 2분째 PEEP 적용, 생후 3분 30초경 portable CPAP apply하며 NICU 입실함.

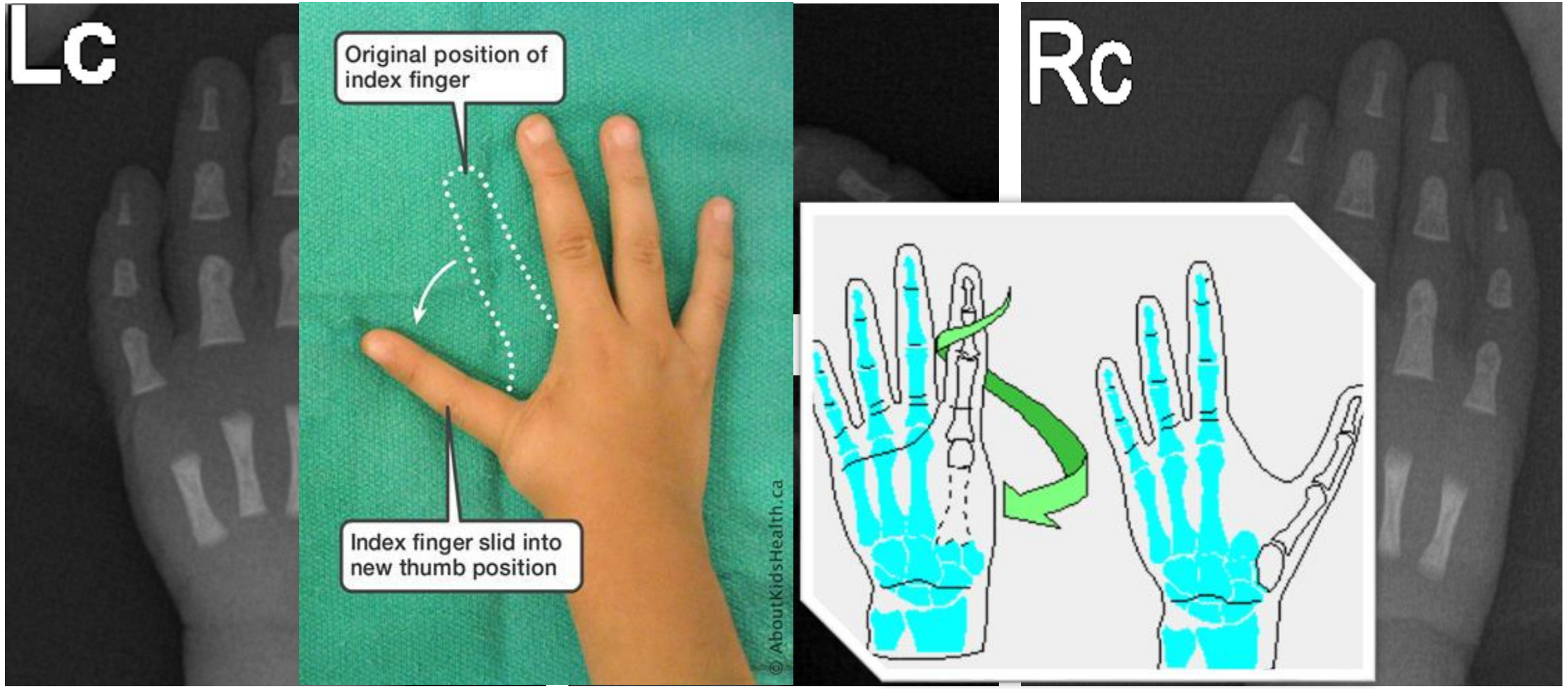
Patient information

- Date of Birth : 2019.07.02
- Inborn, normal pregnancy, 1st baby, Elective C/sec d/t severe IUGR
- Gestational age : 37weeks
- Birth weight : 1300g (<3p)
- Height : 37.5cm (<3p)
- Head circumference : 27.2cm (<3p)
- Ponderal index : 2.47
- Apgar score : 6/8



Morphologic feature

OS


Lc
Original position of index finger
Index finger slid into new thumb position
© AboutKidsHealth.ca
Rc

CNS

- Seizure (-)
- Brain USG (2019.07.05) HD #4

    1. Increased periventricular echogenicity.
    2. Ventricular wall contour undulation.

    --> R/O White matter injury cannot be excluded.

- Brain USG (2019.08.02) HD #32

    1. Persistently abnormal periventricular echogenicity.
    2. Basal ganglia vasculopathy.

BERA: both refer

-> 퇴원전 재검

ENT 협진 고려

OPH exam

(2019.07.08, initial)

Cornea B) clear

Lens B) clear

Fd B) flat

zone II ant.

plus (-) stage 1

no coloboma

(2019.07.22, HD#21)

Fd B) flat

zone III

plus (-)

stage 1 (temporal)

(2019.08.05, HD#35)

Fd B) flat, clear

full vascularization

regressed stage 1

-> observation

만 1세경 FU

Cardiovascular

Echo (2019.07.02) HD#1.

1) moderate 2' ASD with short post rim
   or
   r/o sinus venous ASD (4.7mm)
2) small - moderate MT VSD (bidirectional)
3) large PDA (about 4mm, bidirectional)
   minimally hypoplastic aortic arch
4) no significant AS, no AR
5) no RVOTO, no PS, good branch PAs
6) no MR, mild TR (PG 30mmHg)
7) normal pulmonary venous return
   normally arising both coronary arteries
8) dilated RV
9) good LV contractility

(2019.07.23) HD#22.

{S,D,S} left aortic arch
1) moderate secundum ASD (4.6 mm)
2) multiple MVSDs
   moderate low MT VSD (3.5x3.9 mm),
   bidirectional shunt through the VSDs
3) small to moderate left PDA (2.5-3.0 mm)
4) dilated RA & RV, squeezed LV
5) normal pulmonary venous return
6) normally arising both coronary arteries
7) good LV contractility

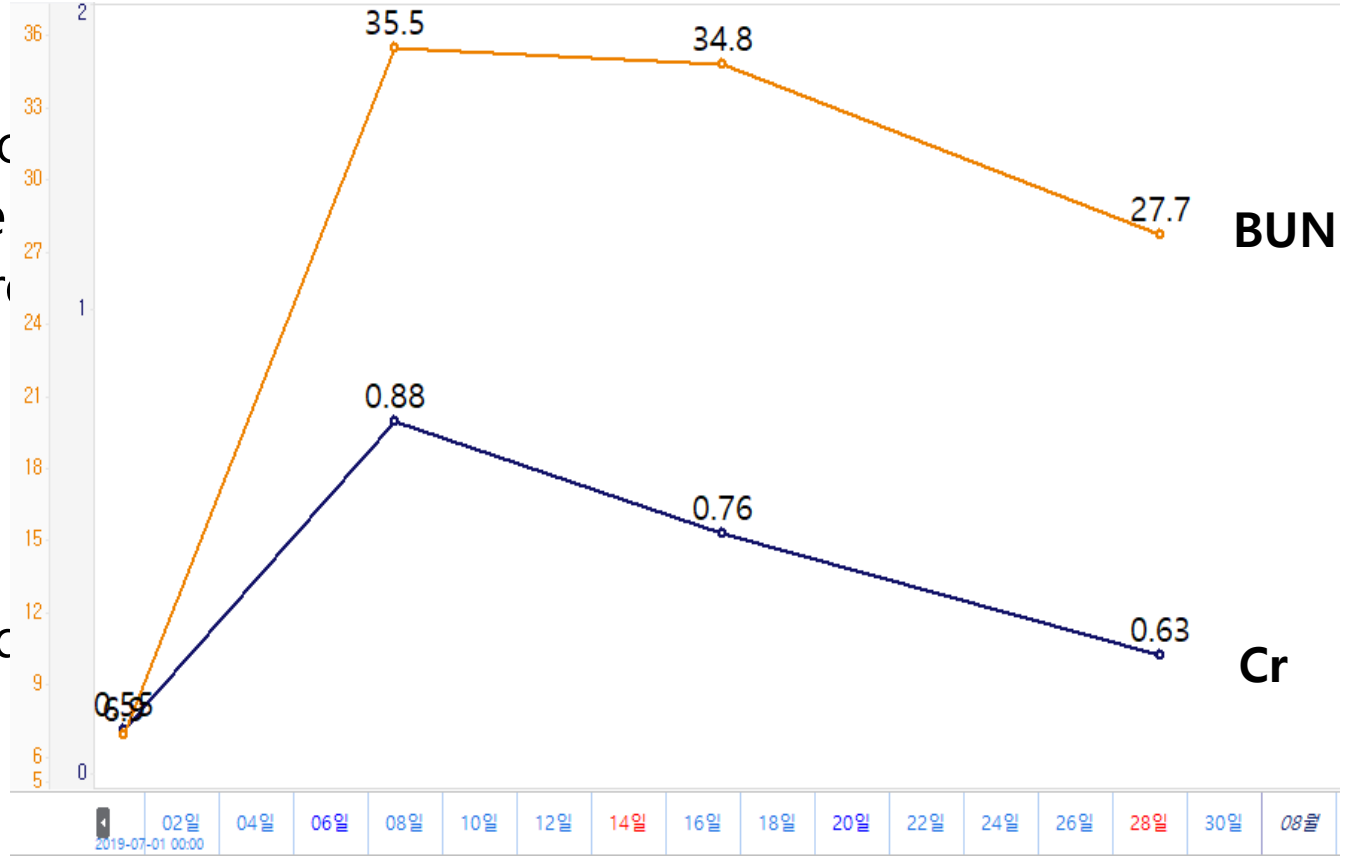
-> PDA ligation 예정

GI

- **Meconium pass (+) HD#1**
- **Full enteral feeding : HD#4**

- Abdomen US (2019.07.05, HD#4)
  1. Small GB with mild periportal echo
     --> R/O Biliary atresia can not be
  2. Bilateral renal hypoplasia with incr
  3. Hepatomegaly.
  4. Small sized spleen.

FU Abdomen US(2019.08.02, HD#32)
1. Normal appearance of the gallblac
2. Small echogenic both kidneys.
3. Small spleen. (2cm)



Spine US

- (2019.07.08) Normal spine US

Metabolic

- NST (2019.07.09, HD#8) normal
- TMS (2019.07.09, HD#8) normal

- TFT(2019.07.30) normal

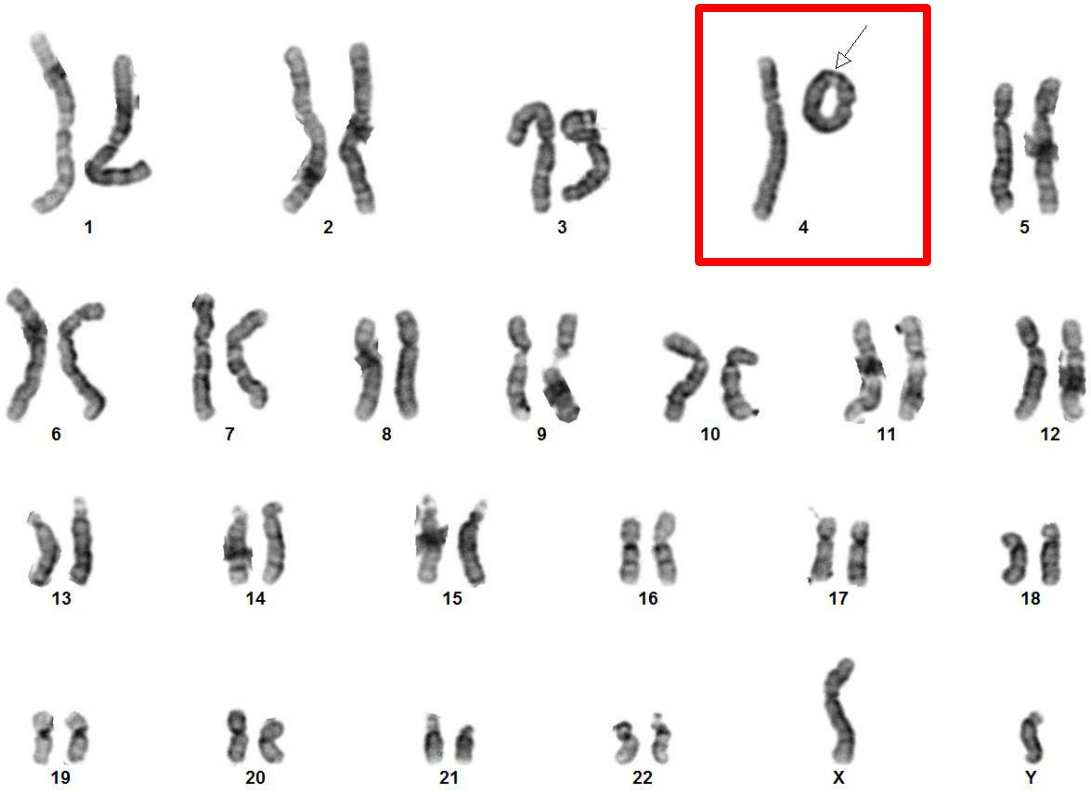
Gene study

- karyotype

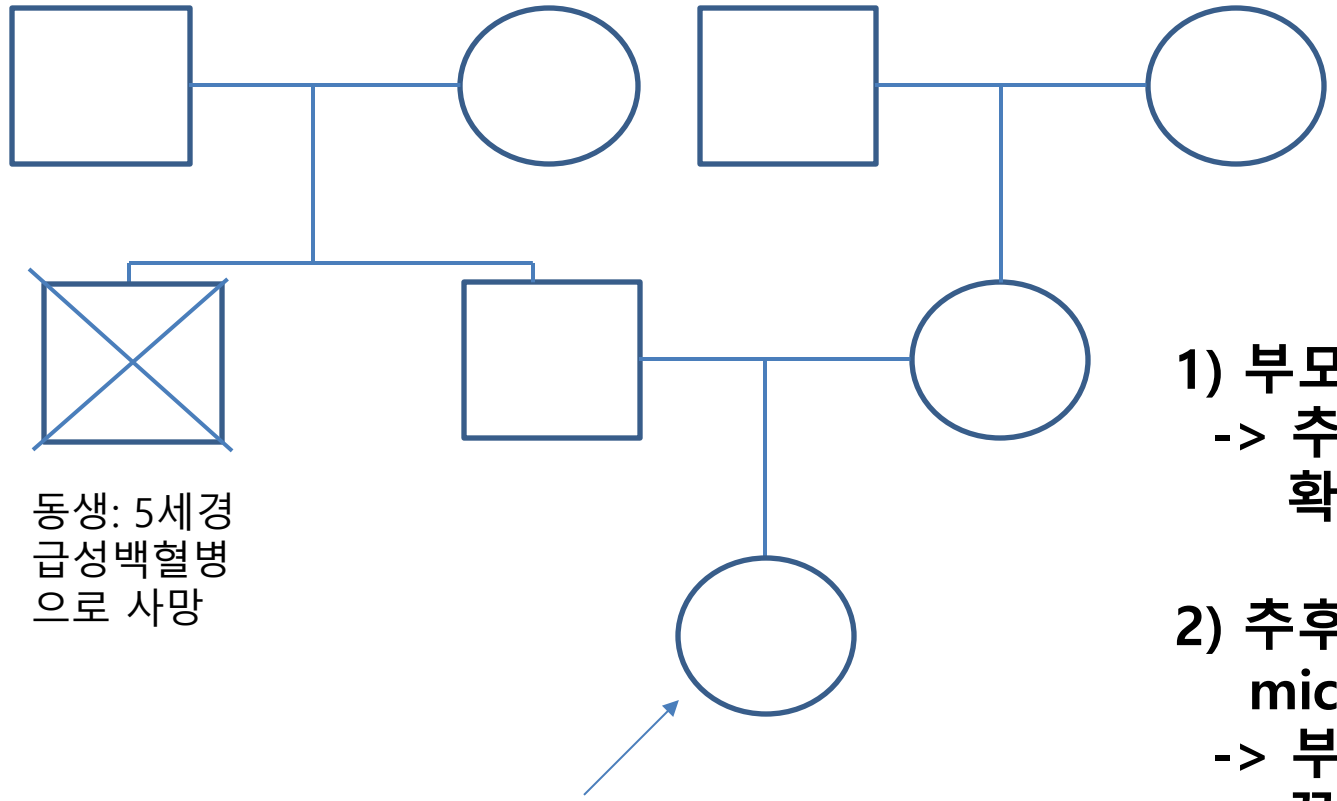
==========

Karyotype : 46,XY,r(4)(p16.3q35)

==========



Genogram

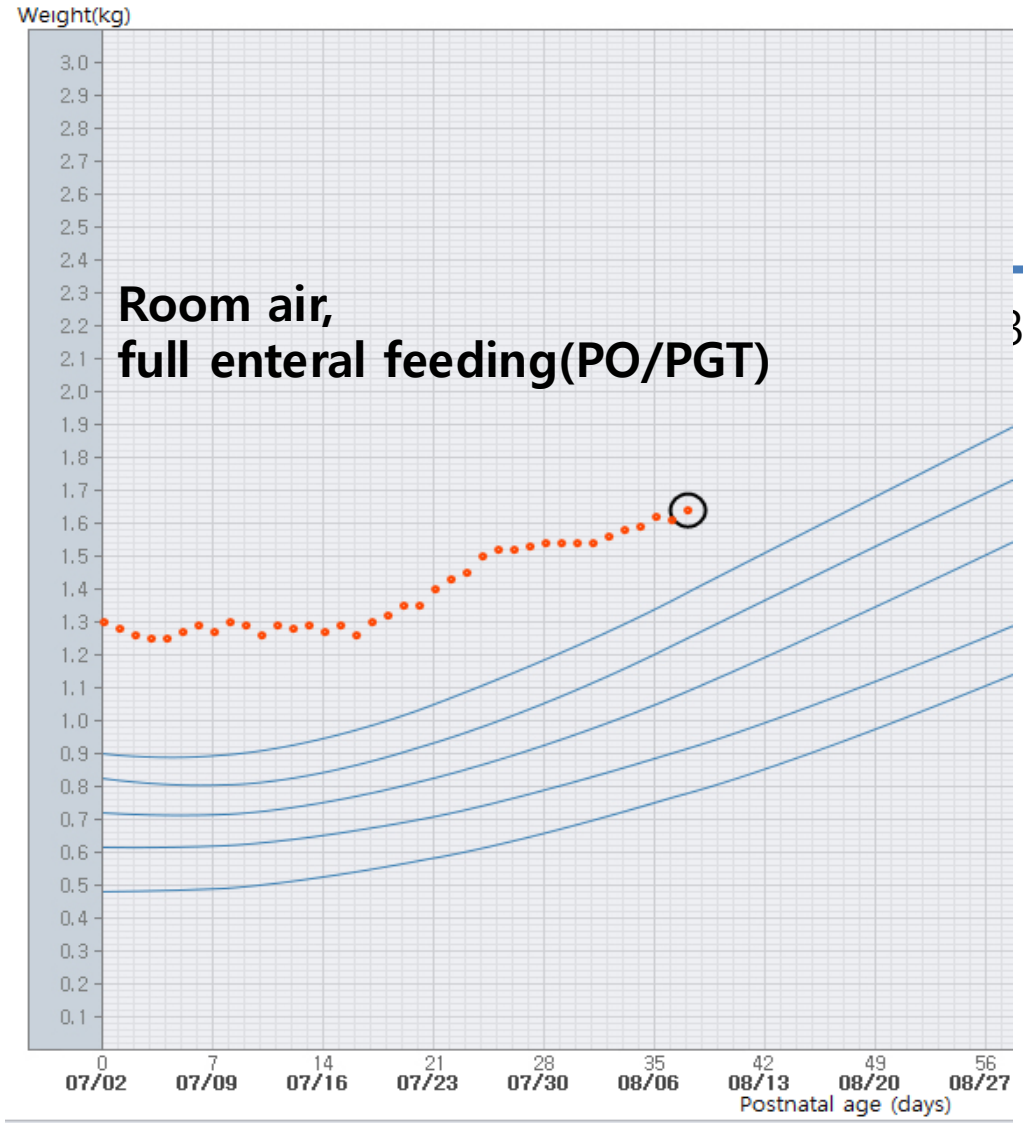


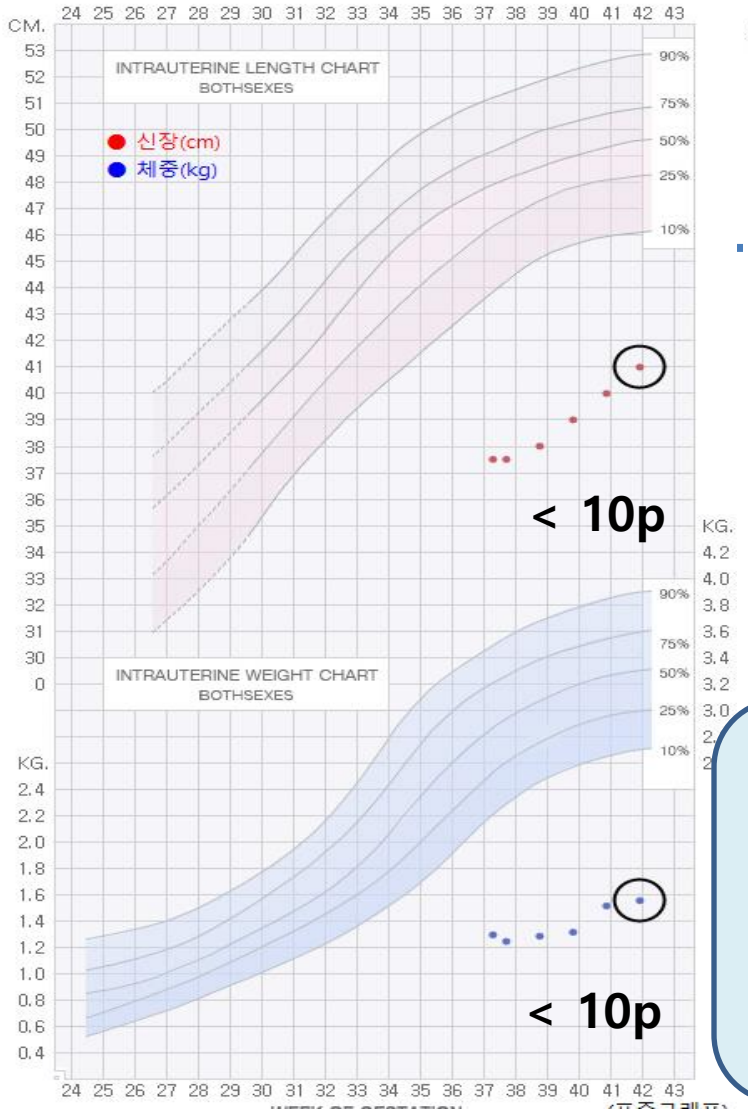
동생: 5세경
급성백혈병
으로 사망

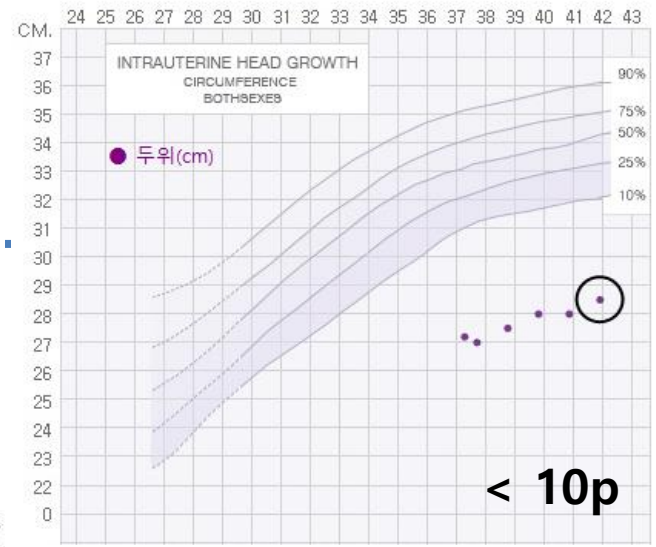
1) 부모 염색체 검사가 정상인 경우,
-> 추후 2세가 같은 질병에 이환될 확률은 일반 인구집단과 같음.

2) 추후 2세에서 착상전유전진단으로 microarray를 시행??
-> 부모에서 염색체 이상이 없을 시 꼭 필요한 것은 아님.

Hospital course





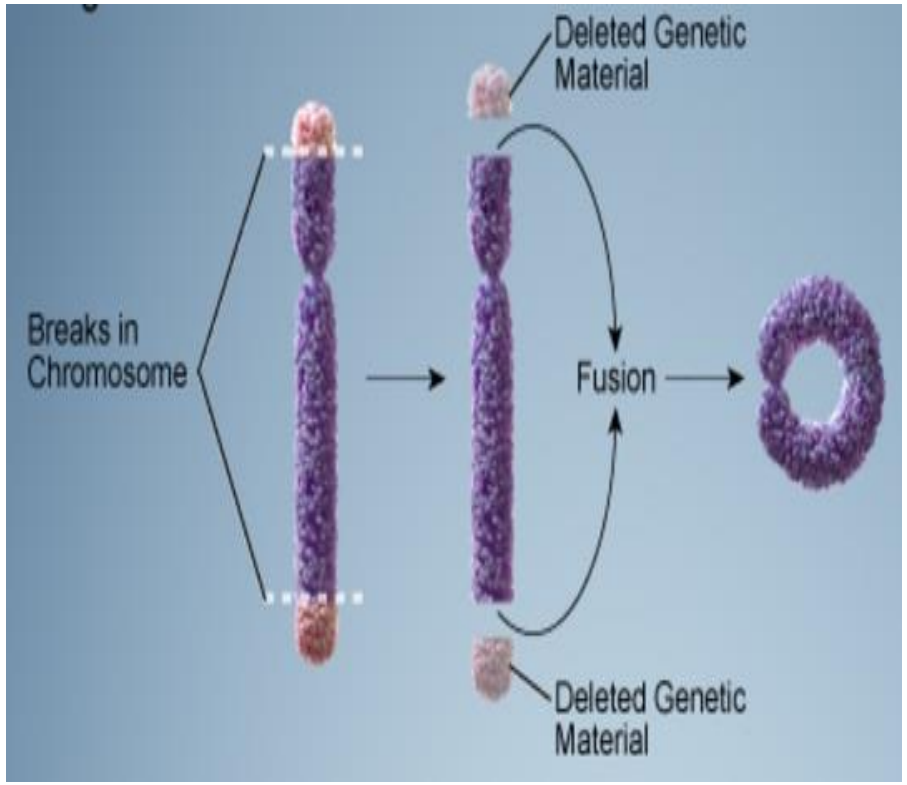


- Weight gain 및 full PO feeding 될 시 퇴원고려
- PDA ligation 예정

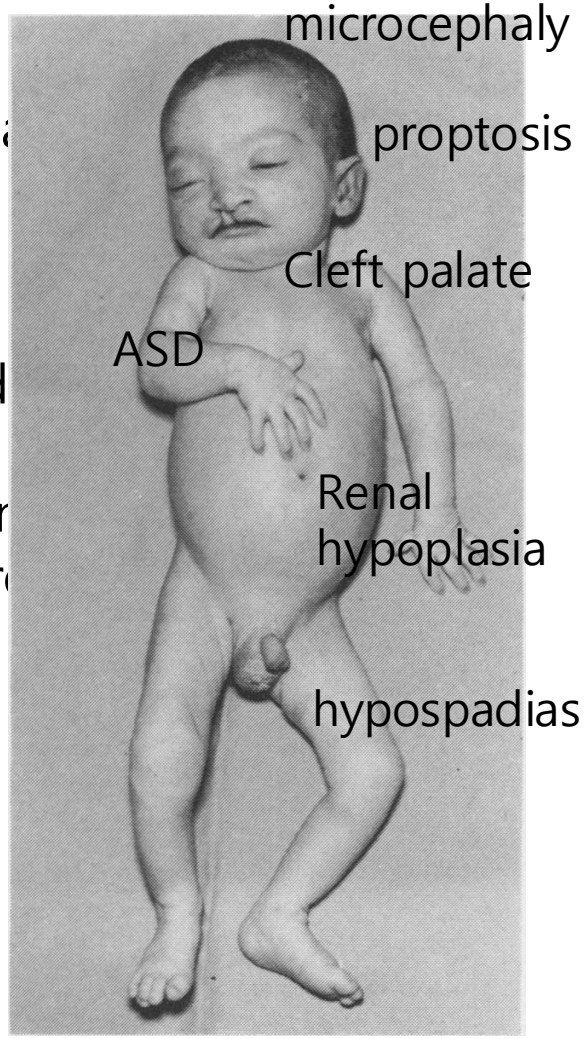
RING CHROMOSOME 4

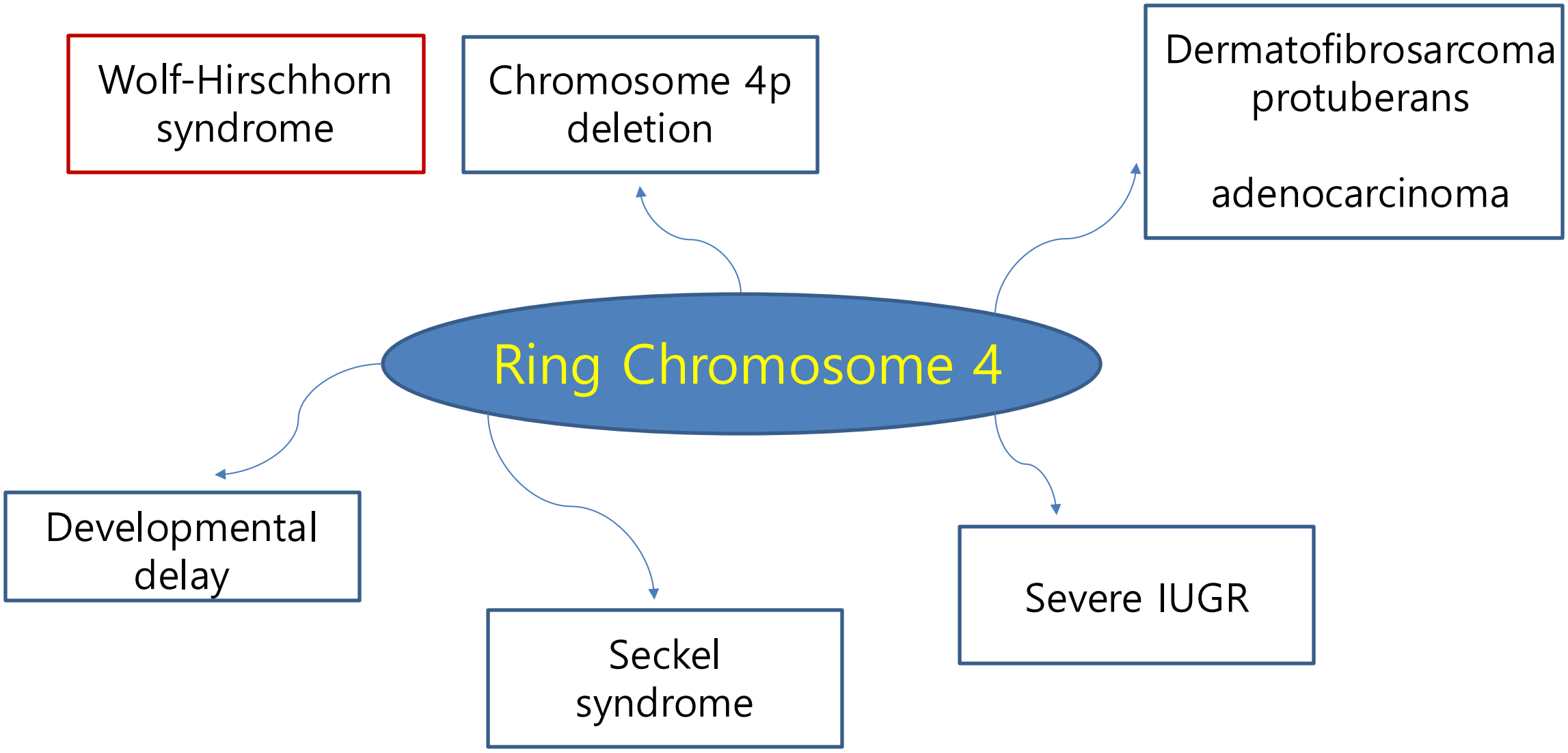
Wolf-Hirschhorn syndrome?

Ring chromosome 4



- a form of structural chromosoma
- 1/10,000,000 births
- Majority of the cases are sporad
- Phenotypic variation depends or
  - The size, stability of ring chr
  - Amount of genetic material
- 1st report (in 1969)




Wolf-Hirschhorn syndrome
Chromosome 4p deletion
Dermatofibrosarcoma protuberans
adenocarcinoma
Ring Chromosome 4
Developmental delay
Seckel syndrome
Severe IUGR

대한진단검사의학회지 제29권 제1호 2009
Korean J Lab Med 2009;29:77-81
DOI 10.3343/kjlm.2009.29.1.77

4p 아종말체의 결실을 동반한 모자익형 4번 환 염색체 1예

김정현[1] · 오필수[2] · 나혜연[2] · 김선희[1] · 조현찬[3]

성균관의대 삼성서울병원 진단검사의학과[1], 한림의대 소아청소년과학교실[2], 한림의대 진단검사의학교실[3]

A Case of Mosaic Ring Chromosome 4 with Subtelomeric 4p Deletion

Jeong Hyun Kim, M.D.[1], Phil Soo Oh, M.D.[2], Hye Yeon Na, M.D.[2], Sun-Hee Kim, M.D.[1], and Hyoun Chan Cho, M.D.[3]

Department of Laboratory Medicine[1], Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Departments of Pediatrics[2] and Laboratory Medicine[3], Hallym University School of Medicine, Seoul, Korea

Ring chromosome is a structural abnormality that is thought to be the result of fusion and breakage in the short and long arms of chromosome. Wolf-Hirschhorn syndrome (WHS) is a well-known congenital anomaly in the ring chromosome 4 with a partial deletion of the distal short arm. Here we report a 10-month-old male of mosaic ring chromosome 4 with the chief complaint of severe short stature. He showed the height of –4 standard deviation, subtle hypothyroidism and mild atrial septal defect/ventricular septal defect, and also a mild language developmental delay was suspected. Brain magnetic resonance imaging showed multifocal leukomalacia. Chromosomal analysis of the peripheral blood showed the mosaic karyotype with [46,XY,r(4)(p16q35)[84]/45,XY,-4[9]/91,XXYY, dic r(4;4)(p16q35;p16q35)[5]/46,XY,dic r(4;4)(p16q35;p16q35)[2]]. FISH study showed the deletion of the 4p subtelomeric region with the intact 4q subtelomeric and WHS region. Both paternal and maternal karyotypes were normal. We compared the phenotypic variation with the previously reported cases of ring chromosome 4. The ring chromosome 4 with the subtelomeric deletion of short arm seems to be related with the phenotype of short stature. *(Korean J Lab Med 2009; 29:77-81)*

Key Words : r(4) chromosome, Mosaic ring chromosome, Short stature

- a 10-month-old male
- Chief complaint : severe short stature
- Birth : 41wks, 2.8kg(AGA), C/S
- Echo) ASD(2-3mm), VSD(7mm) -> ASD(4mm)
- Brain MRI) multifocal leukomalacia
- Mild language developmental delay

4117명 -> ring chromosome abnormality 1.5%

Table 1: Karyotype and the clinical features of the present case and previously reported cases with ring chromosome 4.

	Present case	1 [10]	2 [13]	3 [14]	4 [3]	5 [15]	6 [16]	7 [17]	8 [18]
Karyotype	46,XX,r(4)	46,XY,r(4)	46,XY,r(4)	46,XY,r(4)	46,XY,r(4),(p16q35)	46,XY,r(4),(p15q35)	46,XX,r(4),(p16q35)	46,XY,r(4),(p16q35)	46,XY,r(4),(p16q35)
Preterm delivery	+								
Low birth weight	+	+	+	+	+	+	+	+	
Growth retardation	+	+	+	+	+	+	+	+	+
Developmental delay	NA			+	+			+	+
Mental retardation	NA	NA	+	+	+	NA	NA		+
Microcephaly	+	+	+	+	+		+	+	+
Hypertelorism	−		+			+	+		
Epicanthal folds	−		+			+			
Coloboma	−	+				+			
Ptosis	+			+					
Malformed ears	Low set	Large	Low set			Low set	+	+	
Abnormal nose	−	Flat, broad					Flat	Broad	
Cleft lip	+ (U/L)	+ (U/L)				+ (B/L)			
Cleft palate	+	+				+		+	
Micrognathia	−		+					+	
Abnormal spine	−								
Transverse palmar crease	−	+	+					+	
Clinodactyly	−		+	+	+	+			
Abnormal thumb	−	B/L hypoplasia		Hypoplasia	Long slender				Adducted
Feet deformity	+ B/L TEV	Overriding toes			Valgus deformity	Rocker-bottom, overriding toes	Valgus deformity	Overlapping toes	Syndactyly, hypoplastic toes
Sacral dimple	−		+		+				
Cardiac abnormalities	PDA	PFO					VSD		
Intestinal anomalies	−	Incomplete rotation							
Renal and urinary tract anomalies	Unilateral agenesis	Renal hypoplasia							
Hypospadias	NA	+	Epispadias	+			NA	+	
Cryptorchidism	NA		+	+			NA		+
Neurological abnormalities	−	Generalized hypoplasia of brain	Seizures			Hypotonia	Hypotonia abductors		
Early death	10 weeks	4 weeks				2nd week	3 days		

Preterm 4

hypertelorism 6

epicanthal folds 6

micrognathia 7

Early death 4

Wolf-Hirschhorn syndrome (-4p)

- Partial monosomy of the short arm of chromosome 4 (4p16.3)

- Incidence : 1/50,000 live births
- 85-90% de novo deletions

- Clinical features
  - Most are stillborn or die in infancy
  - Distinctive "greek helmet" facies
  - Cardiac defects in 60% (m/c, ASD)
  - Microcephaly, Mental retardation
  - **Developmental delay**

- Treatment : **no cure**, To manage the symptoms

Table 2: The comparison of clinical features of Wolf-Hirschhorn syndrome which were found in common in the present case and in previously reported cases of ring chromosome 4.

Clinical signs associated with WHS (Zollino et al., 2008 [25])	Number of reported cases of ring chromosome 4	Present case
Facial dysmorphism (2 or more abnormal facial features, excluding facial clefts)	11/17	+
Mental retardation	8/13	?
Seizures	2/16	-
Prenatal growth retardation	15/16	+
Postnatal growth retardation	16/16	?
Microcephaly	15/16	+
Hypotonia	2/16	-
Congenital heart defects	6/17	+
Cleft lip/cleft palate	5/17	-
Ocular colobomas	3/17	-
Hypospadias	4/11	-
Renal abnormalities	6/17	+
Skeletal abnormalities	11/17	+

WHS: Wolf-Hirschhorn syndrome. NA: not applicable.

- The exact chromosomal breakpoints can only be confirmed by the use of molecular cytogenetic methods
  - fluorescence *in situ* hybridization (FISH)
  - microarray

- Such techniques will allow the precise identification of the deleted chromosomal segments and the genes involved, which will help to improve the understanding of the phenotype-genotype correlation of this relatively rare structural chromosomal abnormality.

감사합니다.