KATHOLIEKE UNIVERSITEIT
LEUVEN

Variability in expression of chr14q22.1-22.2 microdeletion

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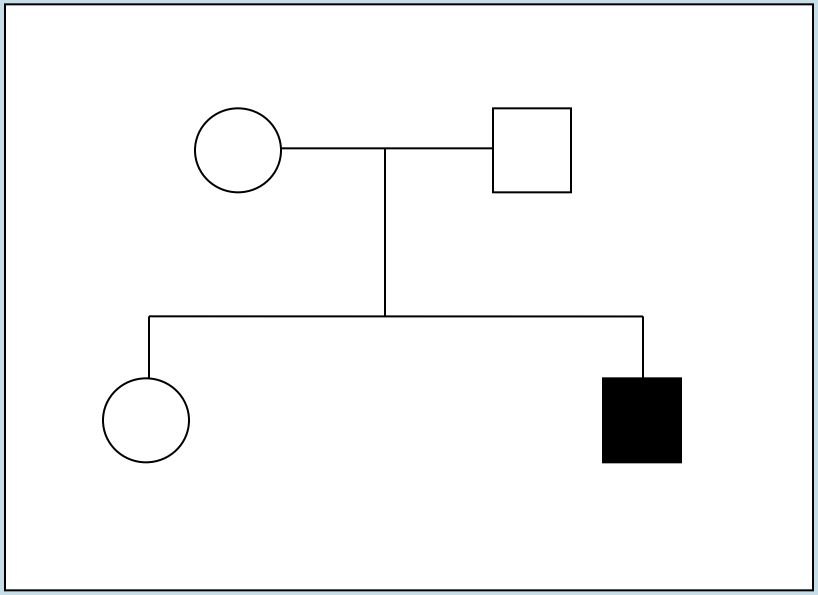
Case 1

- gestational age 39 wks
- Cesarean for weak heart tones
- Normal intra-uterine growth
  - Weight: 3500 g (P75),
  - Length: 51 cm (P75),
  - OFC : 37 cm (1 cm above P90).
- APGAR: 6/7
- Cyanosis after birth.



Anophthalmia

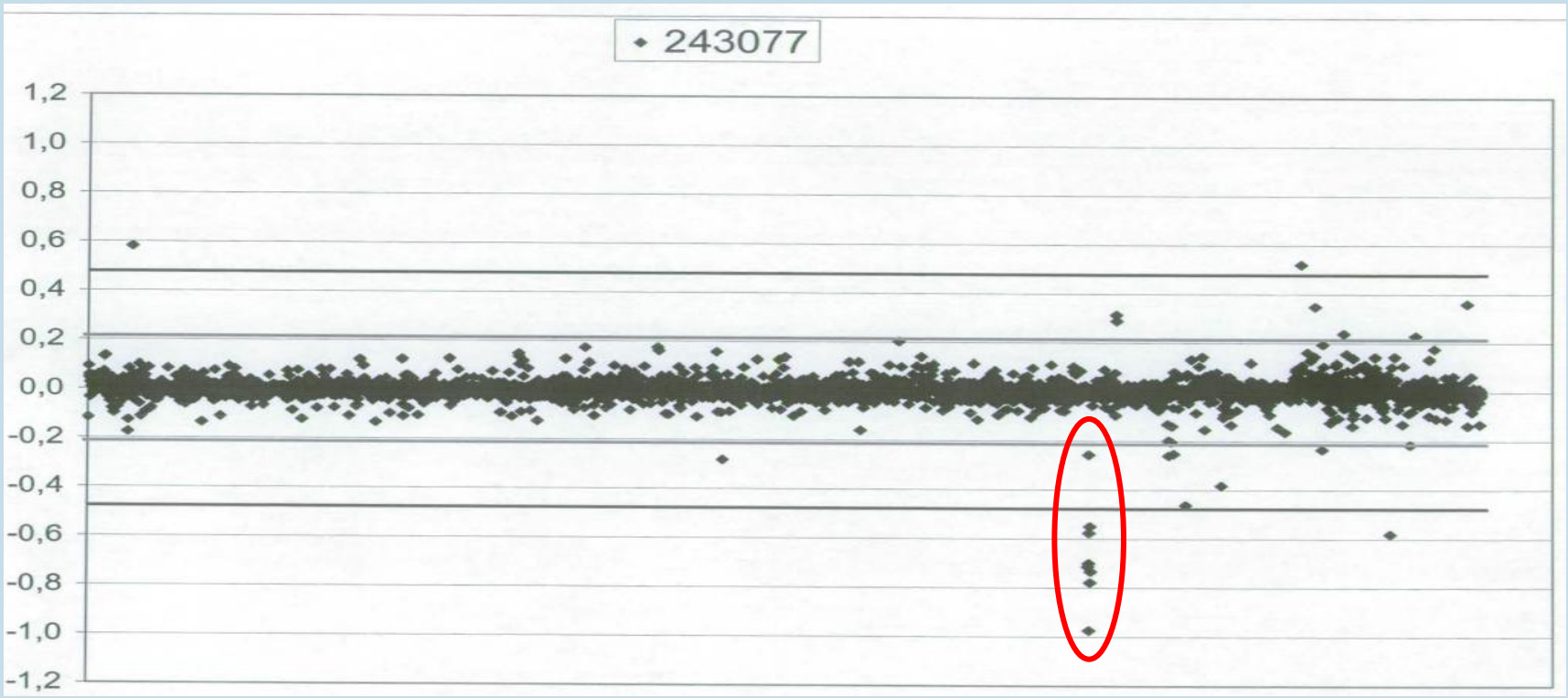
Microtia

Postaxial polydactyly

Cryptorchidism (right testis), Transposition great arteries.

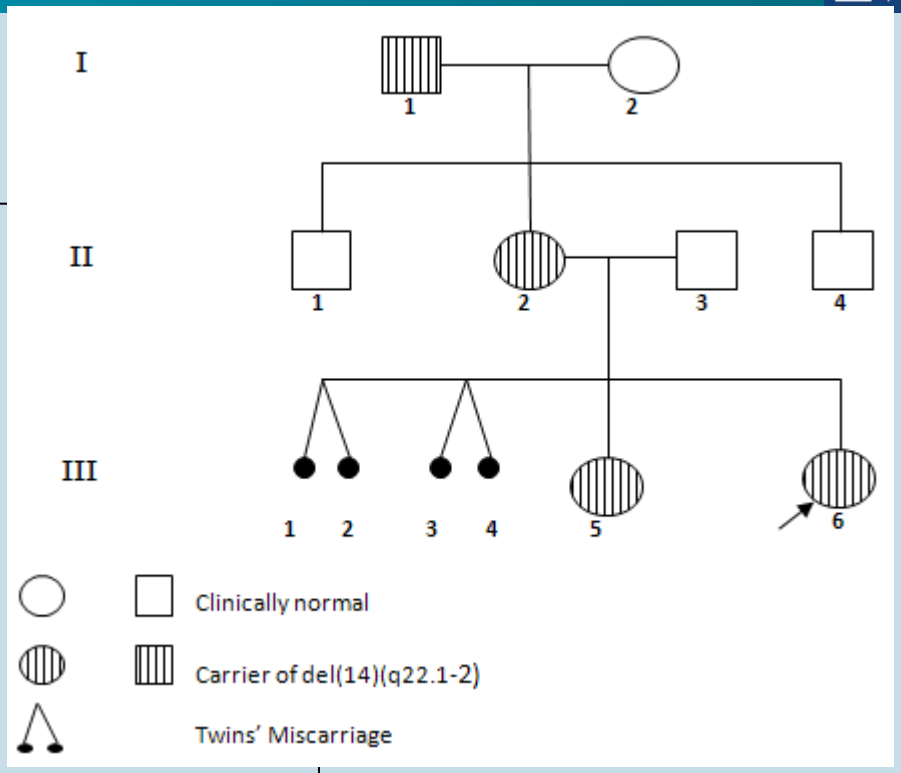
- 1 Mb Array-CGH
- 6 Mb de novo del(14)(q22.1q23.1)

- Normal parents (FISH)

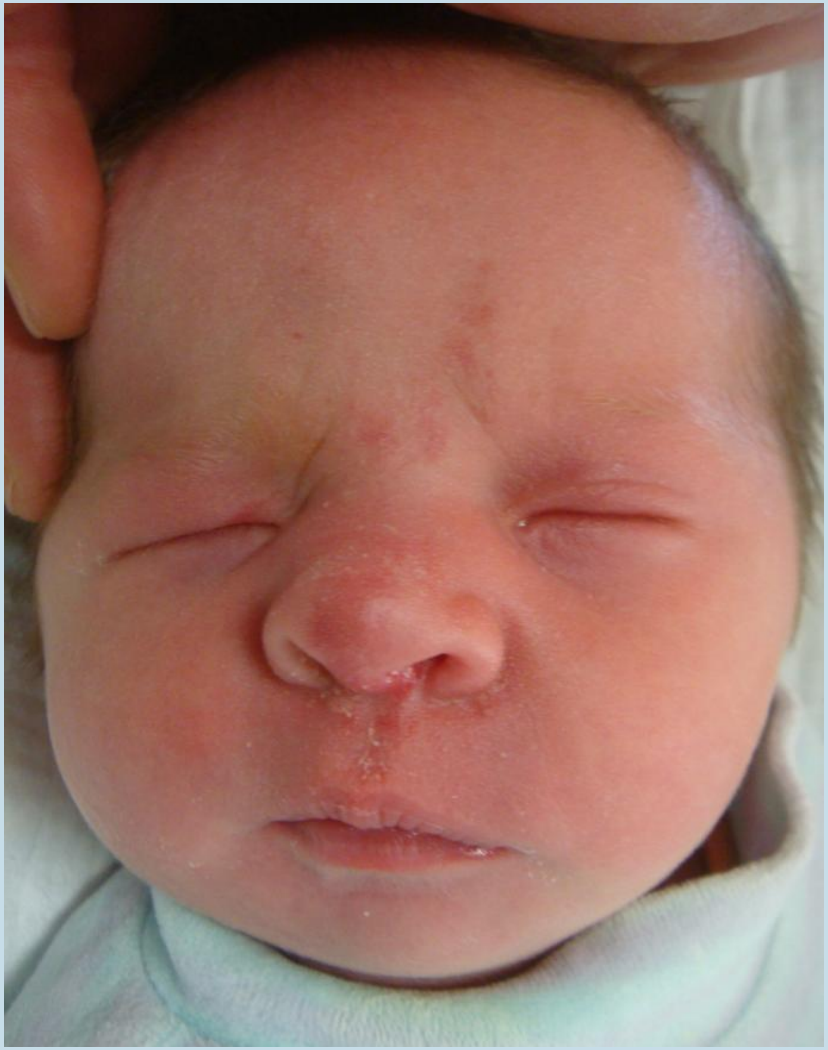


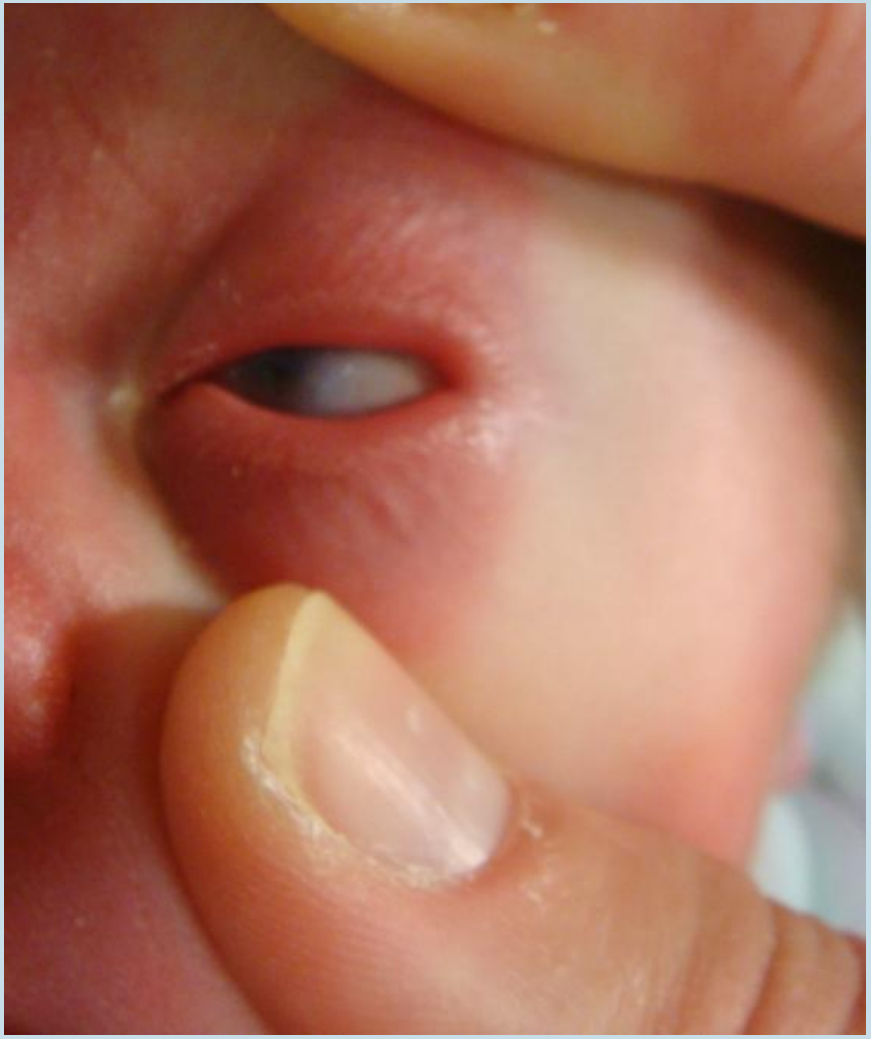
Case 2

- Delivery after induction (41 wks)
- Neonatal distress
- Intra-uterine growth retardation
  - Weight: 2930g (P5)
  - Length: 47 cm (<P3)
  - OFC : 35 cm (P50)
- Bilateral post-axial polydactyly (postminimus)

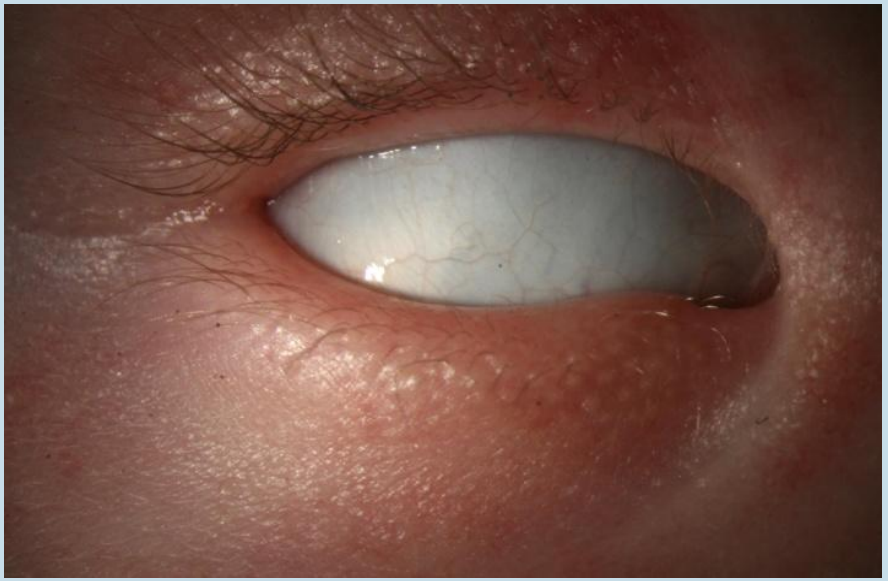


Microphthalmia

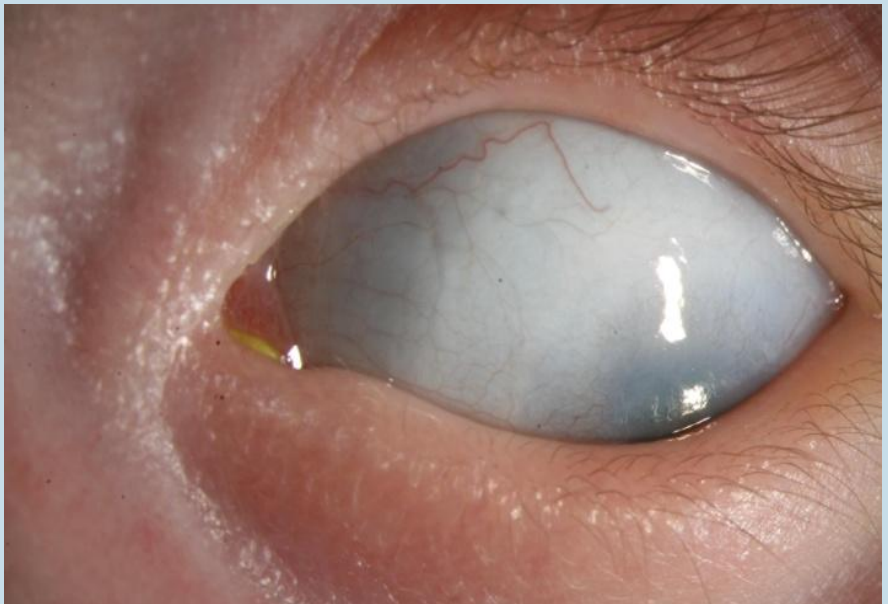




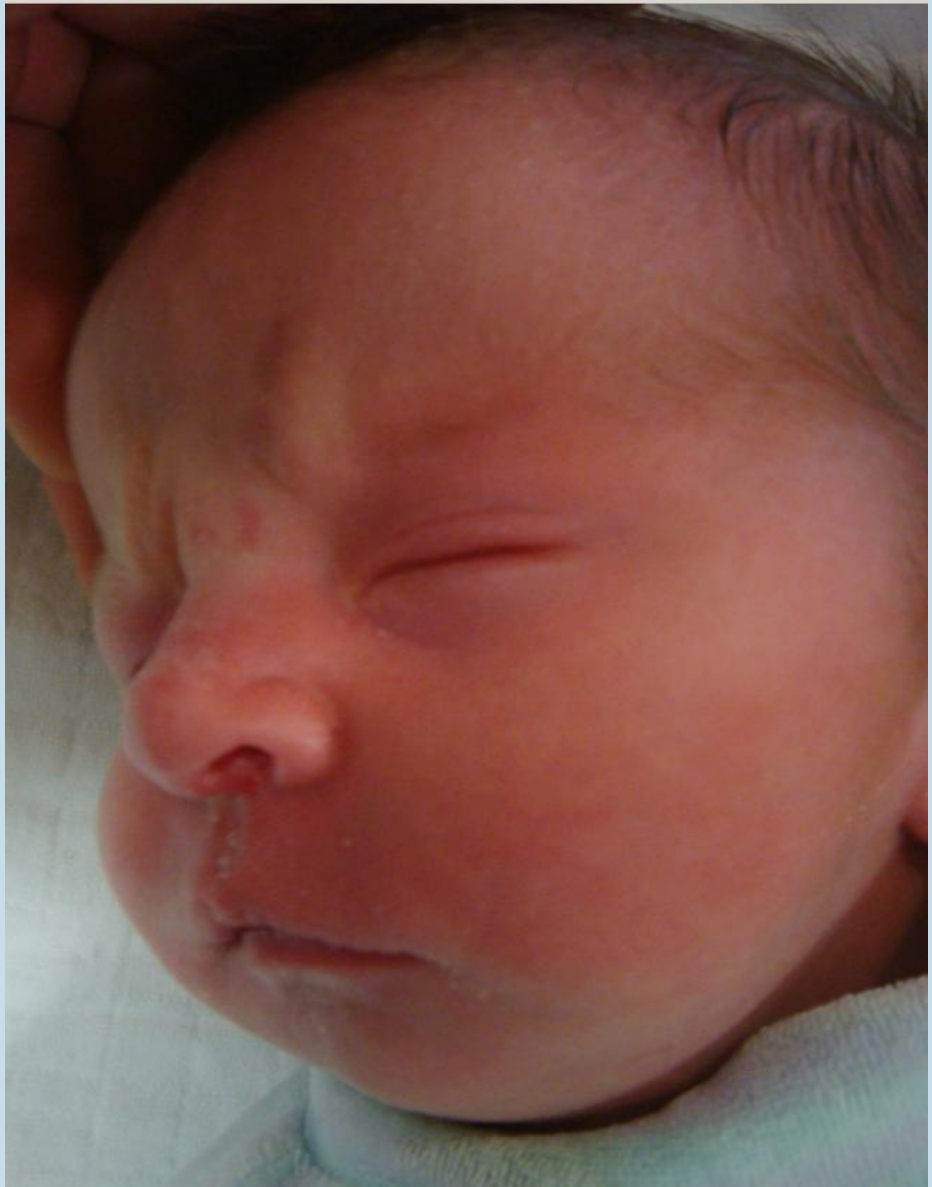
Right eye: complete sclerocornea with no visualization of anterior segment structures.

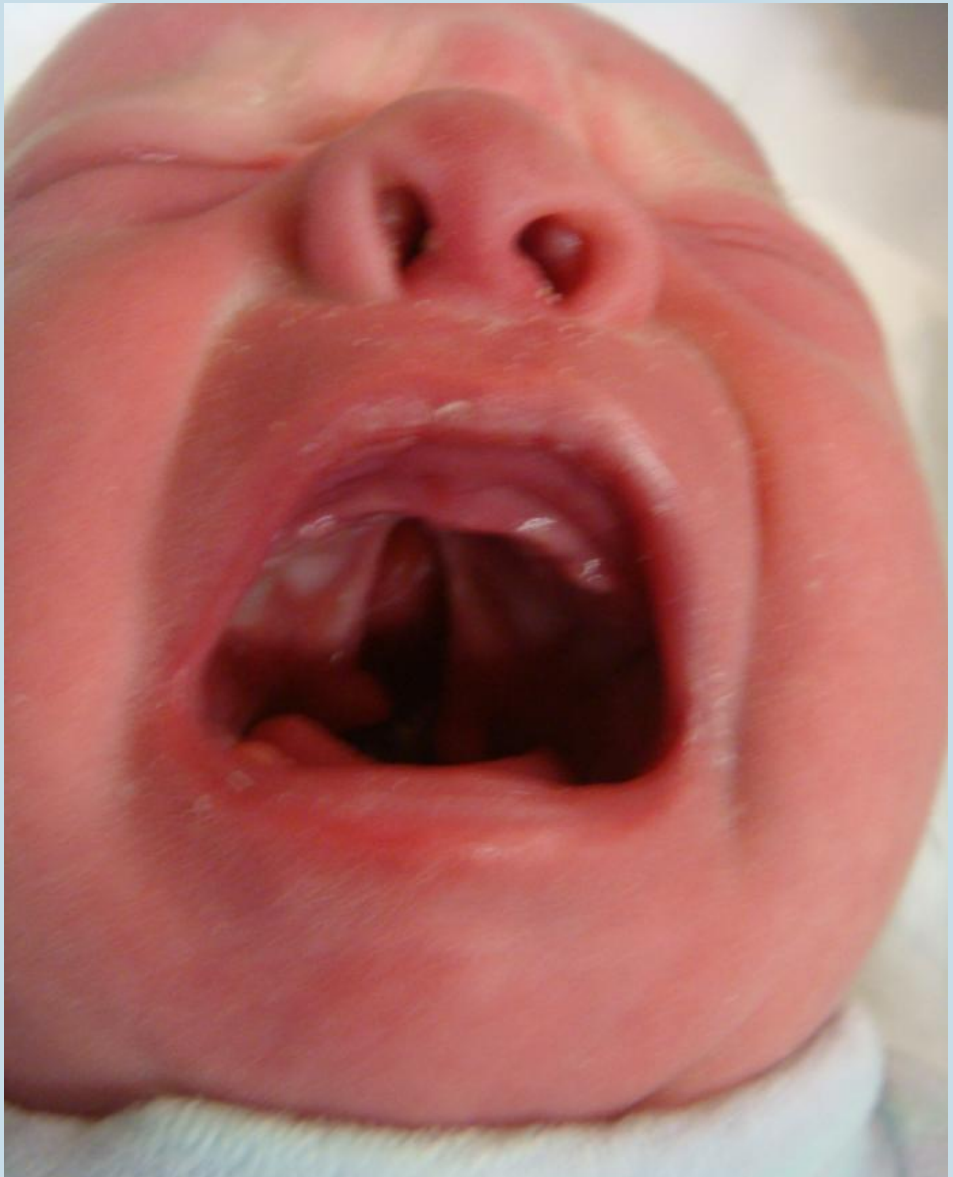


Left eye: partial sclerocornea and a poorly defined anterior segment.

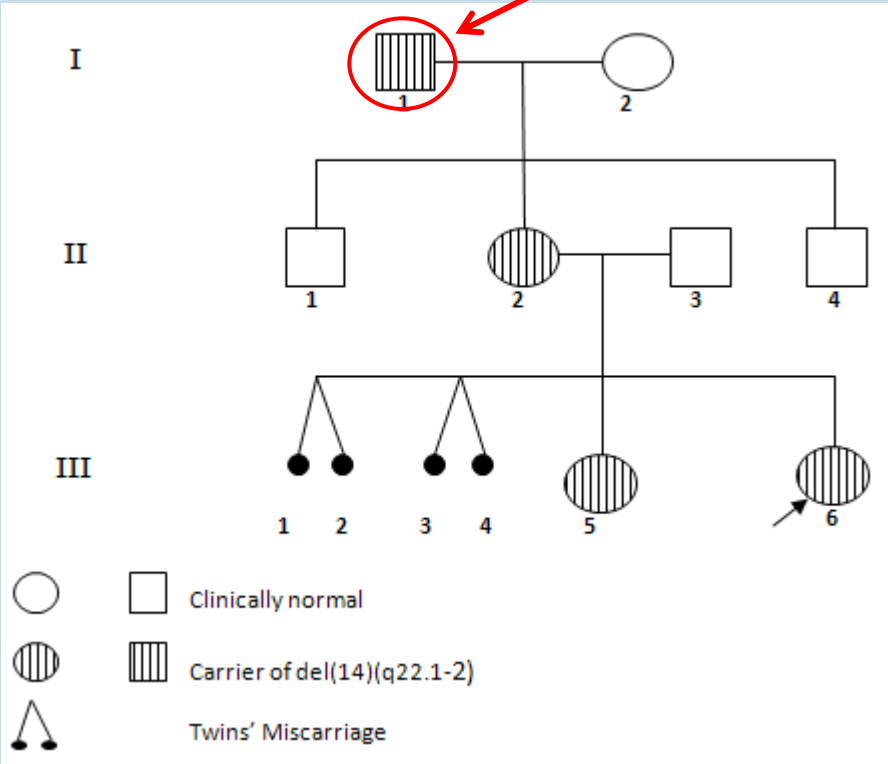


Robin sequence



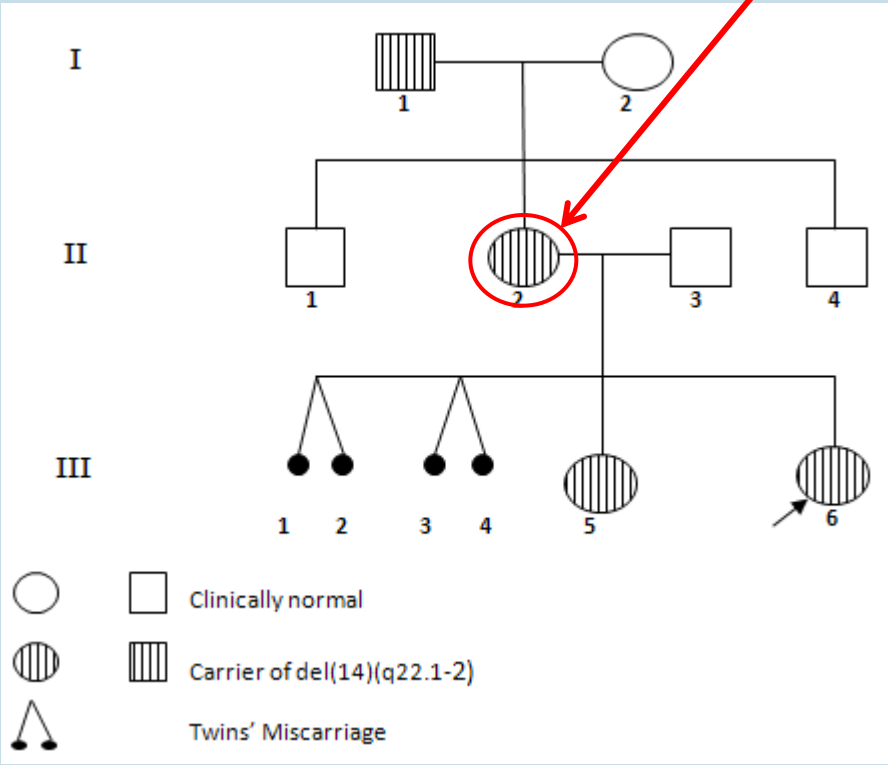


- Growth delay at 11 months
  - weight 6.7 kg (<P3),
  - length 69.9 cm (<P3),
  - OFC was 42.9 cm (P3-10).
- Mental delayed (mental development of 7m ¾).



Maternal grandfather

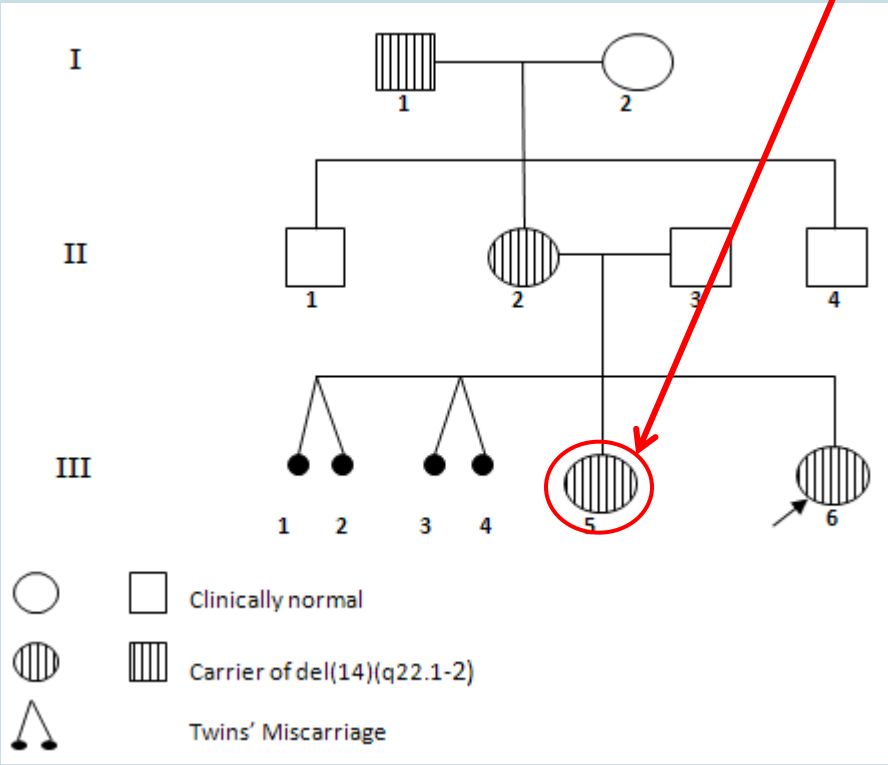
- Postaxial polydactyly (left foot)
- Height 165 cm
- Ocular surgery for cataracts at age 38 years
- normal intelligence
- no additional medical manifestations.



Mother

- 2 unexplained miscarriages (twins)
- Height 159 cm
- Bilateral cutaneous syndactyly of toes IV-V

  Partial duplication of 5th toe
- no eye manifestations
- Normal intelligence.



Sibling

- Born gestational age 35 weeks
- Postnatal growth delay

  age 3,5 yrs

  weight 10,6 kg (< P3)

  length 88,0 cm (< P3)

  OFC 48,8 cm (P25-P50)
- developmental delay

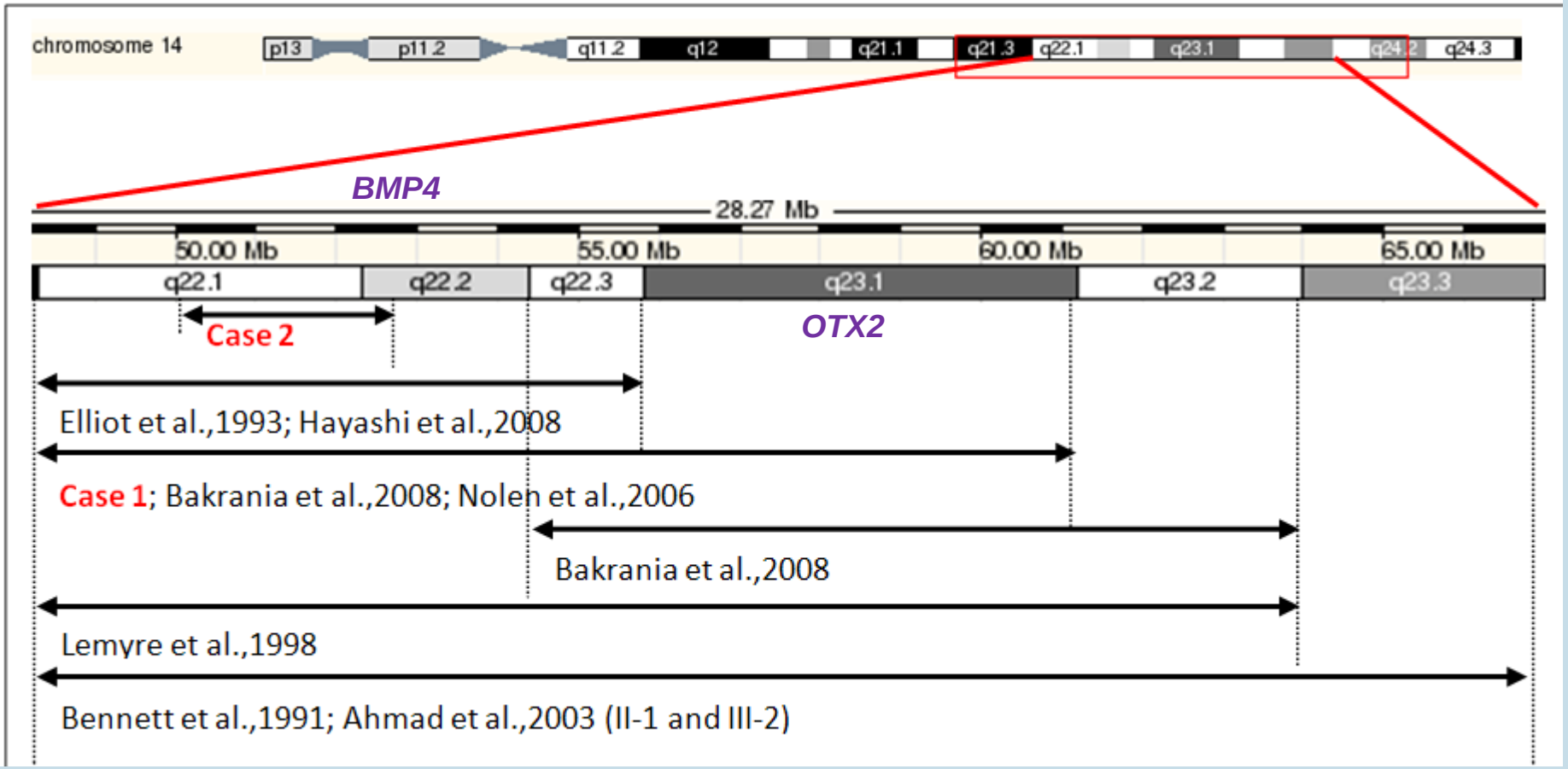
  (= 2yrs10months)
- hypertelorism, small ears,

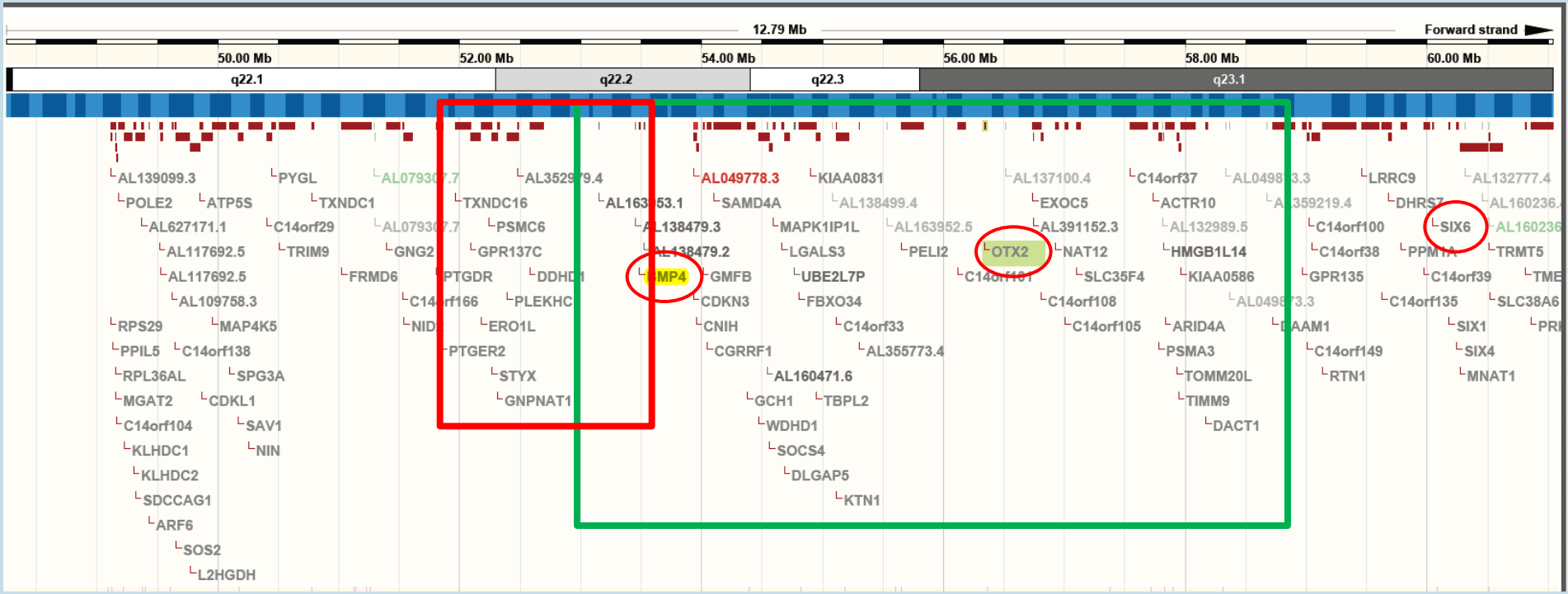
  mild retrognathia, cleft uvula

- Array-CGH 180k Oligonucleotides OGT platform
  - ✓ 2.79 Mb del14q22.1-22.2, (nt 50705004-53497565), EnsEMBL Homosapiens version 53.36 (NCBI36-Mar 2009).
- FISH using the probe RP11-463J10:
  - ✓ mother, sister and maternal grandfather were also carriers of the deletion.

Discussion

Overview of the deletions encompassing q22-23 in the literature.




12.79 Mb
Forward strand
50.00 Mb
52.00 Mb
54.00 Mb
56.00 Mb
58.00 Mb
60.00 Mb
q22.1
q22.2
q22.3
q23.1
AL139099.3
PYGL
AL079307.7
AL352979.4
AL049778.3
KIAA0831
AL137100.4
C14orf37
AL049873.3
LRRC9
AL132777.4
POLE2
ATP5S
TXNDC1
TXNDC16
AL163953.1
SAMD4A
AL138499.4
EXOC5
ACTR10
AL359219.4
DHRS7
AL160236.4
AL627171.1
C14orf29
AL079307.7
PSMC6
AL138479.3
MAPK1IP1L
AL163952.5
AL391152.3
AL132989.5
C14orf100
SIX6
AL160236
AL117692.5
TRIM9
GNG2
GPR137C
AL138479.2
LGALS3
PELI2
OTX2
NAT12
HMGB1L14
C14orf38
PPM1A
TRMT5
AL117692.5
FRMD6
PTGDR
DDHD1
TIMP4
GMFB
UBE2L7P
C14orf181
SLC35F4
KIAA0586
GPR135
C14orf39
TME
AL109758.3
C14orf166
PLEKHC
CDKN3
FBXO34
C14orf108
AL049873.3
C14orf135
SLC38A6
RPS29
MAP4K5
NID
ERO1L
CNIH
C14orf33
C14orf105
ARID4A
DAAM1
SIX1
PRI
PPIL5
C14orf138
PTGER2
CGRRF1
AL355773.4
PSMA3
C14orf149
SIX4
RPL36AL
SPG3A
STYX
AL160471.6
TOMM20L
RTN1
MNAT1
MGAT2
CDKL1
GNPNAT1
GCH1
TBPL2
TIMM9
C14orf104
SAV1
WDHD1
DACT1
KLHDC1
NIN
SOCS4
KLHDC2
DLGAP5
SDCCAG1
KTN1
ARF6
SOS2
L2HGDH

CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2010.01450.x

Short Report

OTX2 microphthalmia syndrome: four novel mutations and delineation of a phenotype

Schilter KF, Schneider A, Bardakjian T, Soucy J-F, Tyler RC, Reis LM, Semina EV. *OTX2* microphthalmia syndrome: four novel mutations and delineation of a phenotype.
Clin Genet 2011: 79: 158–168. © John Wiley & Sons A/S, 2010

KF Schilter[a,b], A Schneider[c], T Bardakjian[c], J-F Soucy[d], RC Tyler[a], LM Reis[a] and EV Semina[a,b]

34 OTX2 point mutation carriers

- Anophthalmia 13 (38.24 %)
- Microphthalmia 20 (58.82 %)

	BMP4 mutations		
	Bakrania et al. (2008)	Reis et al. (2011)	Total
Number of patients reported	12	3	15
Deletion or mutation	c.226del2AG; c.278A>G; c.370+28G>A; c.1217+88C>T	c.529C>T; c.171dupC; c.362A>G	
-Microphthalmia	10	1	11
-Anophthalmia	2	3	5
-Sclerocornea	2	1	3
-Cataract	3	-	3
-Glaucoma	1	-	1
-Polydactyly	2	1	3
-Syndactyly	1	-	1
-Ears/hearing anomalies	4	1	5
-ID or DD	5	-	5

Table 1. Clinical comparison of deletions encompassing *BMP4* but not *OTX2* vs deletions with both *BMP4* and *OTX2*

Features	**Case 2 and his family**				Reis et al. (2011)		Hayashi et al. (2008)	Elliot et al. (1993)	**Case 1**	Bakrania et al. (2008)		Nolen et al. (2006)	Lemyre et al. (1998)	Bennett et al. (1991)	Ahmad et al. (2003)	
Deleted regions on 14q	q22.1-22.2				q22.2		q22.1-22.3	q22.1-22.3	q22.1-23.1	q22.2-23.1	q22.3-23.2	14q22.1-23.1	q22.1-23.2	q22-23	q22-23	
Genes supposed to be involved	*BMP4*				*BMP4*		*BMP4*	*BMP4, OTX2???*	*BMP4, OTX2, SIX6*	*BMP4, OTX2*	*OTX2*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	
Patient's number in the report	I-1	II-2	III-5	III-6	1	2	1	1	7	2	1	1	1	1	II-1	III-2
Clinical features:																
-Microphthalmia	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	+
-Anophthalmia	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
-Sclerocornea	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
-Glaucoma	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-
-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
-Cryptorchidism	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	-
Presumed inheritance	AD	AD	AD	AD	NR	NR	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	AD? AR?	AD? AR?

CHD = Congenital heart defect; ID or DD = Intellectual disability or Developmental Delay; *BMP4 = Bone Morphogenic Protein-4*; *OTX2= Orthodenticle homeobox*; *SIX6= SIX homeobox 6*; NR= not reported; AD=Autosomal Dominant; AR=Autosomal Recessive; Microcornea has been associated to microphthalmia for this review.

BMP4 internal modifier for eyes anomalies

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Deleted regions on 14q	q22.1-22.2				q22.2		q22.1-22.3	q22.1-22.3	q22.1-23.1	q22.2-23.1	q22.3-23.2	14q22.1-23.1	q22.1-23.2	q22-23	q22-23	
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-Anophthalmia	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
-Sclerocornea	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
-Glaucoma	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-
-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
-Cryptorchidism	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	-
Presumed inheritance	AD	AD	AD	AD	NR	NR	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	AD? AR?	AD? AR?

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Genes supposed to be involved	*BMP4*				*BMP4*		*BMP4*	*BMP4, OTX2???*	*BMP4, OTX2, SIX6*	*BMP4, OTX2*	*OTX2*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	
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-Anophthalmia	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
-Sclerocornea	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
-Glaucoma	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-
-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
-Cryptorchidism	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	-
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Genes supposed to be involved	*BMP4*				*BMP4*		*BMP4*	*BMP4, OTX2???*	*BMP4, OTX2, SIX6*	*BMP4, OTX2*	*OTX2*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	
Patient's number in the report	I-1	II-2	III-5	III-6	1	2	1	1	7	2	1	1	1	1	II-1	III-2
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-Anophthalmia	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
-Sclerocornea	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
-Glaucoma	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-
-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
-Cryptorchidism	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	-
Presumed inheritance	AD	AD	AD	AD	NR	NR	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	AD? AR?	AD? AR?

CHD = Congenital heart defect; ID or DD = Intellectual disability or Developmental Delay; *BMP4 = Bone Morphogenic Protein-4*; *OTX2= Orthodenticle homeobox*; *SIX6= SIX homeobox 6*; NR= not reported; AD=Autosomal Dominant; AR=Autosomal Recessive; Microcornea has been associated to microphthalmia for this review.

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Features	**Case 2 and his family**				Reis et al. (2011)		Hayashi et al. (2008)	Elliot et al. (1993)	**Case 1**	Bakrania et al. (2008)		Nolen et al. (2006)	Lemyre et al. (1998)	Bennett et al. (1991)	Ahmad et al. (2003)	
Deleted regions on 14q	q22.1-22.2				q22.2		q22.1-22.3	q22.1-22.3	q22.1-23.1	q22.2-23.1	q22.3-23.2	14q22.1-23.1	q22.1-23.2	q22-23	q22-23	
Genes supposed to be involved	*BMP4*				*BMP4*		*BMP4*	*BMP4, OTX2???*	*BMP4, OTX2, SIX6*	*BMP4, OTX2*	*OTX2*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	
Patient's number in the report	I-1	II-2	III-5	III-6	1	2	1	1	7	2	1	1	1	1	II-1	III-2
Clinical features:																
-Microphthalmia	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	+
-Anophthalmia	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
-Sclerocornea	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
-Glaucoma	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-
-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
-Cryptorchidism	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	-
Presumed inheritance	AD	AD	AD	AD	NR	NR	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	AD? AR?	AD? AR?

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Genes supposed to be involved	*BMP4*				*BMP4*		*BMP4*	*BMP4, OTX2???*	*BMP4, OTX2, SIX6*	*BMP4, OTX2*	*OTX2*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	
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-Sclerocornea	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-
-Glaucoma	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-
-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
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Deleted regions on 14q	q22.1-22.2				q22.2		q22.1-22.3	q22.1-22.3	q22.1-23.1	q22.2-23.1	q22.3-23.2	14q22.1-23.1	q22.1-23.2	q22-23	q22-23	
Genes supposed to be involved	*BMP4*				*BMP4*		*BMP4*	*BMP4, OTX2???*	*BMP4, OTX2, SIX6*	*BMP4, OTX2*	*OTX2*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	*BMP4, OTX2, SIX6*	
Patient's number in the report	I-1	II-2	III-5	III-6	1	2	1	1	7	2	1	1	1	1	II-1	III-2
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-Microphthalmia	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	+
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-Cataract	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-Polydactyly	+	+	-	+		-	+	-	+	-	-	-	-	-	+	+
-Syndactyly	-	+	-	-		-	+	-	-	-	-	+	-	-	-	
-Growth delay/short stature	-	+	+	+	+	-	+	+	NR	NR	NR	+	+	NR	+	+
-Micro/retrognathia	-	-	+	+	+	+	-	+	-	-	-	+	+	+	-	-
-Cleft uvula/palate	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-
- Brain anomalies	-	-	+	+	-	NR	+	-	-	+	+	+	+	+	-	-
-ID or DD	-	-	+	+	+	+	+	+	-	+	-	+	+	NR	-	-
-Kidney anomalies	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
-Ears/hearing anomalies	-	-	+	-	-	+	-	-	+	+	-	+	+	-	-	-
-CHD	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
-Cryptorchidism	-	-	-	-	-	-	-	+	+	+	-	+	-	-	-	-
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KATHOLIEKE UNIVERSITEIT LEUVEN

BMP4 candidate gene for:

Eye anomalies

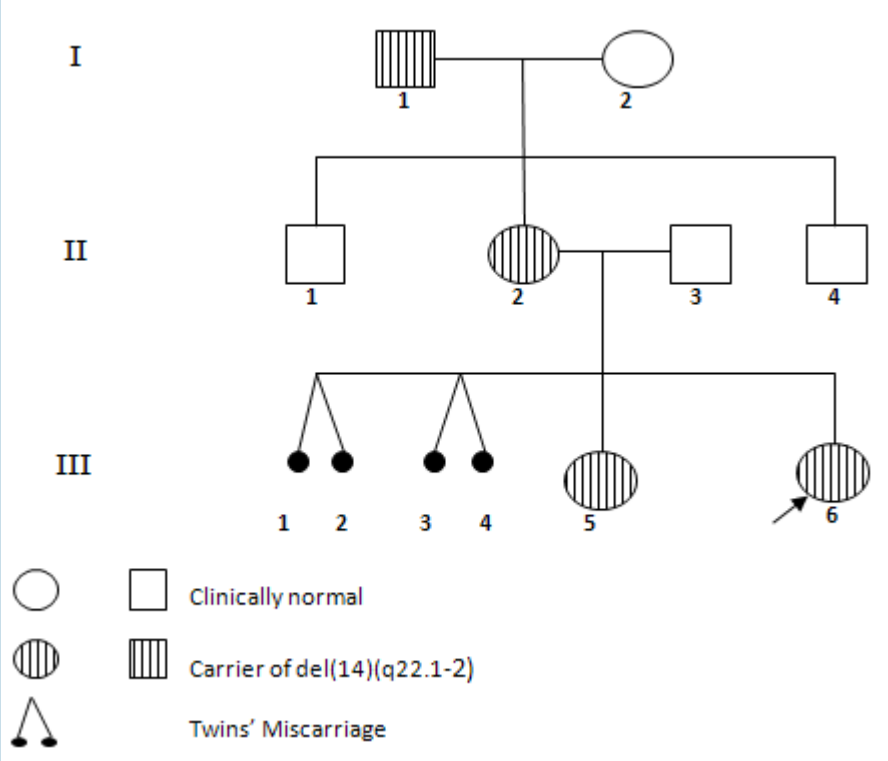
Poly/syndactyly

Intellectual disability

Retrognatia

Short stature

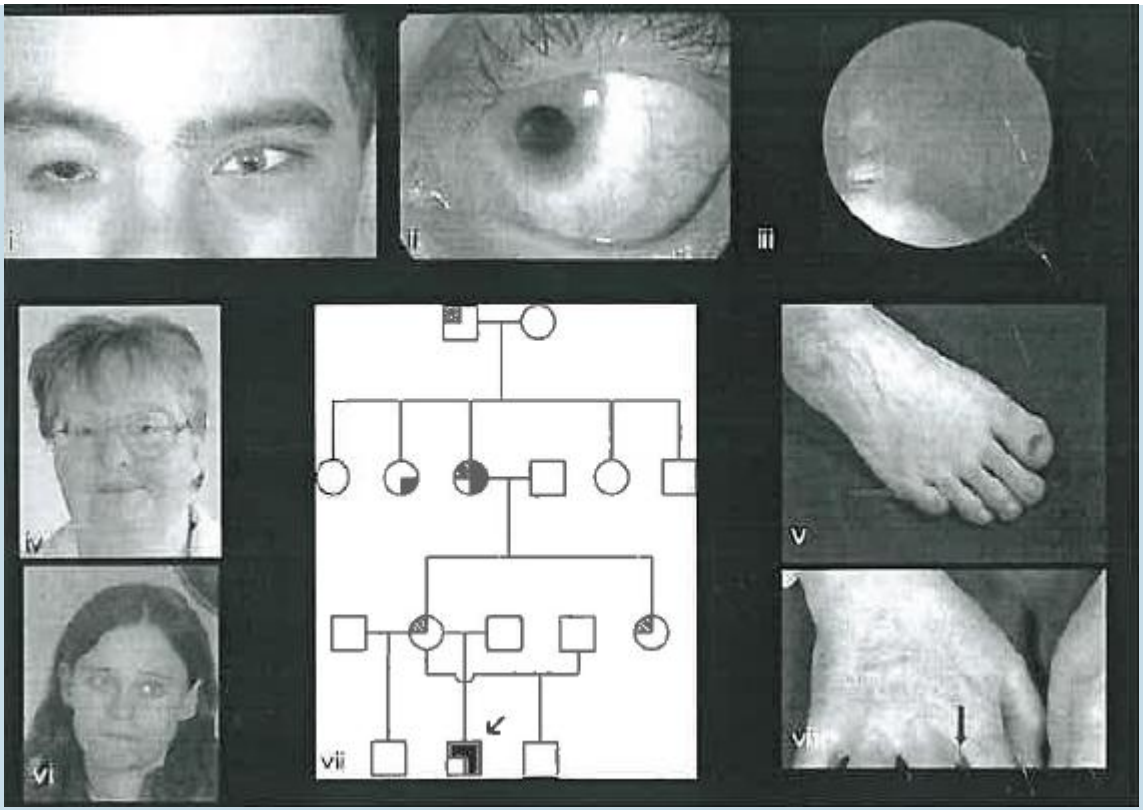
Intra-familial variability



Features	Case 2 and his family			
Deleted regions on 14q	q22.1-22.2			
Genes supposed to be involved	*BMP4*			
Patient's number in the report	I-1	II-2	III-5	III-6
Clinical features:				
-Microphthalmia	-	-	+	+
-Anophthalmia	-	-	-	-
-Sclerocornea	-	-	-	+
-Glaucoma	-	-	-	-
-Cataract	+	-	-	-
-Polydactyly	+	+	-	+
-Syndactyly	-	+	-	-
-Growth delay/short stature	-	+	+	+
-Micro/retrognathia	-	-	+	+
-Cleft uvula/palate	-	-	+	-
- Brain anomalies	-	-	+	+
-ID or DD	-	-	+	+
-Kidney anomalies	-	-	-	-
-Ears/hearing anomalies	-	-	+	-
-CHD	-	-	-	-
-Cryptorchidism	-	-	-	-
Presumed inheritance	AD	AD	AD	AD

Mutations in *BMP4* Cause Eye, Brain, and Digit Developmental Anomalies: Overlap between the *BMP4* and Hedgehog Signaling Pathways

Preeti Bakrania,[1] Maria Efthymiou,[2] Johannes C. Klein,[3] Alison Salt,[4,5] David J. Bunyan,[6,7] Alex Wyatt,[1] Chris P. Ponting,[1,8] Angela Martin,[1] Steven Williams,[9] Victoria Lindley,[10] Joanne Gilmore,[11] Marie Restori,[4] Anthony G. Robson,[4] Magella M. Neveu,[4] Graham E. Holder,[4] J Richard O. Collin,[4] David O. Robinson,[6,7] Peter Farndon,[10] Heidi Johansen-Berg,[3] Dianne Gerrelli,[2] and Nicola K. Ragge[1,4,12,*]



Conclusions

del(14)q22-23

Recognizable syndrome with variable expression

Many features are explained by BMP4 haploinsufficiency

Represents a contiguous gene deletion syndrome

* more severe eye defects in deletions including

BMP4 + OTX2

Thank you for your attention