Chromosome aberration

Deletion of 3.2Mb on chromosomeband 4q24

Patient

A girl with mild facial dysmorphisms, a speech delay and a postaxial polydactyly minimus. She was referred to a clinical geneticist because of mild developmental delay at the age of 4 years and 6 months.

Background information

Polydactyly is a common congenital defect with an incidence between 1 in 1000 and 1 in 3000 newborns [38]. Most often it occurs to be isolated, however sometimes it is associated with other congenital anomalies.

Clinical details

- Last age of examination: 4 years and 6 months
- Perinatal history: The patient was born after an uneventful pregnancy at 39 weeks gestation. Birth weight was 2920 g.
- Congenital anomalies: Postaxial polydactyly minimus at the left hand.
- Psychomotor development: somewhat retarded, she was sitting independently at 14 months and walking unassisted at the age of 22 months. At the age of 3 yrs and 8 months her IQ was 85. She was referred to the paediatrician at the age of four because of poor speech development. Hearing and vision is normal.
- Dysmorphic features at 4 years and 6 months: thin hair, narrow palpebral fissures, long eyelashes, a dysplastic outward turned helix, a broad nasal bridge and nasal base, a small mouth, a double canine in the lower jaw, small teeth and a broad uvula. At the extremities a digitus minimus was seen at the left fifth finger, clinodactyly of digiti IV and V and depressed foot arches. There were no toe nails on both digits IV and she had pathological feet reflexes. Hyperlaxity of joints (beightonsscore 7/8) was noted. She had two small café au lait spots, one on the abdomen and one on the leg.

- Other investigations: MRI of the brain and EEG showed no abnormalities

Cytogenetic details

The karyotype was normal (46,XX). Fragile X and a 22q11 deletion were excluded.
DNA of this patient was analyzed with a 32K BAC array. A 3.2 Mb loss (102.98-106.50) was found on chromosome 4, located completely within band 4q24.

The deletion was confirmed with four different FISH probes. FISH investigations on parental DNA showed that the deletion occurred de novo in this patient.

Summary of other patient with a deletion including choromosome 4q24

Deletion breakpoints	Schinzel 4q21-q25	Rose 1991 4q21-q25	Kulharya 1995 4q21.1-q25	Mitchell 1981 4q21.1-q25	Hegmann 1996 4q21.2-q25	Schinzel 4q21.3-q25	Mitchell 1981 4q21.3-q26	Campbell 1986 4q21-q27	Butler 1987 4q22-q25	Schinzel 4q22-q26	Serville 1977 4q24-q32	**Our patient**
Development												
Developmental delay	Newborn	2 months old	Died at 5 months	Died at 8 months	+	newborn	+	Prenatal diagnosis	Died at 3 months	Prenatal diagnosis	+	**+**
Growth												
Growth delay			+	+	+						+	**-**
Skull												
hydrocephaly		+	+	+								**-**
Microcephaly			-		+						+	**-**
Delayed closure of surtures and fontanelles		+	+	+					+		+	**-**
Eyes												
Narrow palpebral fissures		+							+			**+**
Upward slant		+							+			**-**
Epicantic folds							+		+		-	**-**
Nose												
Broad nose											+	**+**
Upturned nose									+			**+**
Small nose			+	+	+				+			**-**
Mouth												
Small mouth									+			**+**
Short/hypoplastic philtrum		+			+						+	**+**
Extra teeth												**+**
Clefting anomalies, incl. High palate	+							+	+		+	**-**
micrognathia	+	+	+	+	+		+					**-**
Extremities												
Abnormal palmar crease					+			+			+	**-**
Polydactyly										+		**+**
Clinodactyly	+	+					+		+			**+**
Hypoplastic nails		+										**+**
brachydactyly			+	+						+		**-**
Neurological												
Hypotonia		+		+	+							**-**
Seizures			+	+								**-**
Abnormal reflexes				+								**+**
Other congenital defects												
Vertebral anomalies		+	+									**-**
Anterior placed anus			+	+							+	**-**
Renal malformation		+							+		+	**-**
Hypospadia					+					+		**-**
Intestinal malrotation									+		+	**-**
Hypoplastic thymus						+						**-**
Heart												
Cardiac defects	ASD				VSD, dilated cardiomyopathy	+	VSD	complex		+	+	**-**

Empty spaces indicate there is no information on this feature.
Level of developmental delay: 4q21.2-q25: 8 months level at age 15 months, 4q21.3-q26: 9 months level at age 1 yr, 4q24-q32: 10 week level at age 16 months

The deletion found in our patient is unique in its small and well defined size which is the result of the newer technique used to detect this deletion, in comparison to the overlapping deletions. Patients with larger deletions seem to be more severely retarded.

Additional

A candidate gene for this postaxial polydactyly minimus is *CXXC4* as it inhibits the Wnt-signaling pathway and subsequently *GLI3* transcription, a gene associated with postaxial polydactyly. Small deletions or mutations in this gene could be responsible for polydactyly in more patients, even in those with apparently isolated forms.