CLINICAL QUIZ (p199-200) ANSWER

What is the diagnosis?

In view of global developmental delay, hypotonia and subtle dysmorphic facial features, chromosome microarray (aCGH) was arranged for the child. Deletion of the most distal band of the short arm of chromosome 1 (1p36) was detected. The abnormality is characterised by a copy loss of 4.51 Mb in the region of 1p36.33-p36.31 (Genomic Coordinates [hg18]: Chr1:825513-5332232). Reviewing the clinical features of the child together with the chromosome microarray result, the diagnosis of 1p36 deletion syndrome was made. The result of the chromosome microarray is shown in Figure 2.

What is 1p36 deletion syndrome?

1p36 deletion syndrome[1] accounts for 0.5% to 1.2% of idiopathic intellectual disability.[2] It is considered to be one of the most common microdeletion syndromes. Our patient has typical craniofacial features of 1p36 deletion syndrome, including straight eyebrows, deep set eyes, broad nasal root/bridge, midface hypoplasia, long philtrum and pointed chin. Other features, that could also manifest in affected individuals, include microbrachycephaly and large, late – closing anterior fontanelle. Brachydactyly and short feet are common (Table 1). Developmental delay and intellectual disability are universal to all children suffering from this syndrome. Majority are in the range of severe to profound mental retardation. Affected children are particularly weak at language expression. Behavioural disorders are present in 50% of affected individuals. These include poor social interaction, temper tantrums, self-biting, stereotypies and less commonly hyperphagia. Congenital hypotonic is present in 95% of children with this microdeletion syndrome. Nearly all had EEG abnormalities but only 44%-58% had clinical seizures.[3] The onset was at a median of 2.75 months old. About 22% of children with seizure developed infantile spasm at a median age of 5 months old. EEG abnormalities include hypsarhythmia to paucity of rhythmic activities.[3] About 88% of affected individuals had central nervous system defects – mainly dilatation of lateral ventricles and subarachnoid spaces; cortical atrophy, diffuse brain atrophy; and hypoplasia, thinning or absence of corpus callosum. Cardiac involvement is very common (43-71%). Other findings include eye/vision problems (52%), hearing loss (47%), skeletal anomalies (41%), abnormalities of external genitalia (25%) and renal abnormalities (22%).

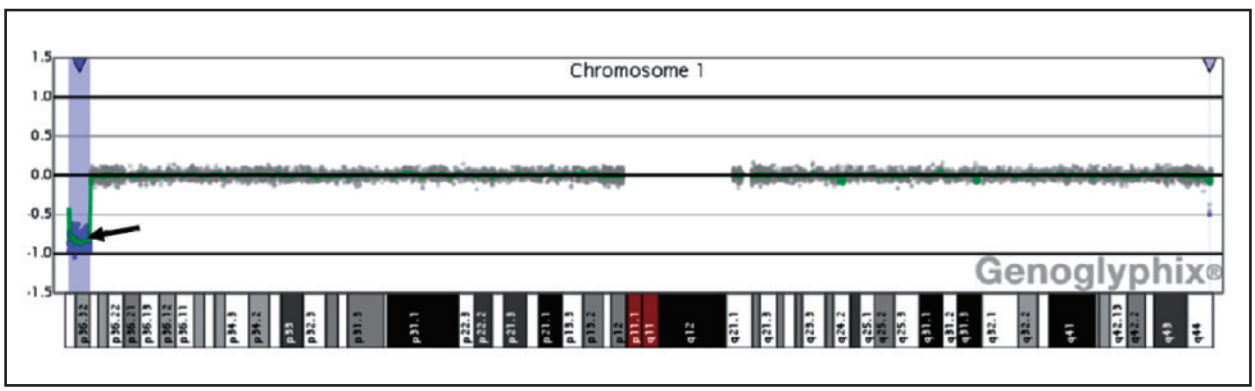

Figure 2 Result of the chromosome microarray, the 1p36 deletion is indicated by the arrow. [Courtesy of Dr Anita Kan, whole genome aCGH testing service, Prenatal Diagnostic & Counselling, Tsan Yuk Hospital]

Table 1 Clinical findings in 1p36 deletion syndrome. Further delineation of deletion 1p36 syndrome in 60 patients: a recognisable phenotype and common cause of developmental delay and intellectual disability[1]

	Number	Percentage	Our Proband
Dysmorphic craniofacial features			
Microbrachycepahly	39	65	
Large, late closing anterior fontanelle (N=39)	30	77	
Straight eyebrows	60	100	*
Deep-set eyes	60	100	*
Epicanthus	30	50	
Broad nasal root/bridge	60	100	*
Midface hypoplasia	60	100	*
Posterior rotated/low set/abnormal ears	20	40	
Long philtrum	60	100	*
Pointed chin	60	100	*
Limb/skeletal defects			
Brachydactyly/camtodactyly	48	80	
Short feet	48	80	
Skeletal anomalies(N=32)	13	41	
Visceral anomalies			
Congenital heart defects (N=48)	34	71	
Noncompaction cardiomyopathy (N=48)	11	23	
Dilated cardiomyopathy (N=48)	2	4	
Gastrointestinal anomalies (N=18)	5	28	
Anal anomalies	2	3	
Genitourinary tract defects			
Renal abnormalities (N=18)	4	22	
Abnormalies of external genitalia	15	25	
Neurological findings			
Congenital hypotonia	57	95	*
Seizures	26	44	
EEG abnormalities (N=34)	34	100	
Brain abnormalities (US/CT/MRI) (N=49)	43	88	
Eye/vision problems (N=44)	23	52	
Visual inattention (N=44)	28	64	
Sensorineural deafness (N=32)	9	28	
Developmental findings			
Developmental delay	60	100	*
Intellectual disability (formally evaluated)	52	100	*
Espressive language (poor/absent)	60	100	*
Behaviour disorders	28	47	

N.B. The total number of patients equals 60 unless otherwise noted. US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging

(Modified from Battaglia A, Hoyme HE, Dallapiccola B, et al. Further delineation of deletion 1p36 syndrome in 60 patients: a recognisable phenotype and common cause of developmental delay and mental retardation. Pediatrics 2008;121:404-10)[1]

What are the cardiac implication(s) of 1p36 microdeletion syndrome?

Congenital cardiac anomalies are very common. These consist of atrial septal defects (28%), ventricular septal defects (23%), patent ductus arteriosus (12.8%), valvular anomalies (20.5%), Tetralogy of Fallot (7.7%), Coartation of aorta (5.1%) and Ebstein anomaly (2%). In particular, cardiomyopathy is unusually common in this group of patient (27%) – majority is of the "non-compaction" type; the rest is of the dilated type. Parents have to be counselled on the possible risk of cardiomyopathy as the condition could lead to devastating sequelae. The high incidence of cardiac problems warrants a thorough cardiac evaluation, including auscultation, electrocardiogram and echocardiography, for all children with 1p36 deletion syndrome.

What are the genetic implications of 1p36 deletion syndrome?

There are several mechanisms that can lead to deletion of 1p36 chromosome.[4] More than 50% of affected individuals have *de novo* terminal 1p36 deletion. Approximately 29% have an interstitial deletion. Approximately 12% have complex rearrangements of chromosomes that may involve more than one 1p36 deletion or a 1p36 deletion with duplication. Approximately 7% have a derivative chromosome 1, where the 1p telomere region is replaced by another chromosome end. Risks to family members depend on the mechanism of the deletion. Prenatal testing is available for families who have had a child with 1p36 deletion syndrome or a family in which one parent is a known carrier of a chromosome rearrangement involving 1p36.

Acknowledgements

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References

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