

A PARTIAL TRISOMY 9 CASE WITH DICENTRIC CHROMOSOME DUE TO THE ADJACENT-2 SEGREGATION OF MATERNAL RECIPROCAL TRANSLOCATION

MATERNAL RESİPROKAL TRANSLOKASYONUN ADJACENT-2 SEGREGASYONUNA BAĞLI OLUŞAN DİSENTRİK KISMİ TRİZOMİ 9 OLGUSU

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ABSTRACT

Duplication of the short arm (p) of chromosome (Chr.) 9 is a frequently seen abnormality while duplication of both p and long arm (q) is a rare chromosomal rearrangement derived mostly from parental translocations or inversions. The unbalanced products of the translocations are mostly derived from the 2:2 segregation of adjacent-1 division while the ones due the adjacent-2 patterns are rare. Here, a dysmorphic infant with a pure duplication of 9pter to 9q22.31 is reported due to the product of the adjacent-2 segregation of maternal reciprocal translocation between the 9q22.31 and 22p11.1. The affected infant had two normal and one derivative/dicentric Chr.9 (carrying the centromere regions of both Chr.9 and Chr.22) with one normal Chr.22. These results were confirmed by the fluorescence *in situ* hybridization technique. Array-comparative genomic hybridization confirmed the breakpoints precisely and revealed a 61.75 megabases duplication of Chr.9 consisting of many genes such as *BICD2*, *NTRK2*, *HNRNPK*, and *SMARCA2*, which are mostly related to developmental delay and growth retardation. Additionally, the infant had ear abnormalities, microcephaly, and extremity abnormalities, which were the other findings of trisomy 9. In sum, the case has presented as a rare example of adjacent-2 division of 2:2 segregation and a pure partial trisomy of 9pter to 9q22.31.

Keywords: Partial trisomy 9, reciprocal translocation, adjacent-2 segregation, dicentric chromosome, chromosomal rearrangement, growth retardation, fluorescence in situ hybridization, array-comparative genomic hybridization

ÖZET

Kromozom (Chr.) 9'un kısa koluna (p) ait duplikasyon sık olarak görülmele birlikte hem kısa hem de uzun kolun (q) duplikasyonu daha çok ailesel translokasyonlar ve inversiyonlara bağlı oluşan ve nadir olarak görülen bir kromozomal yeniden düzenlenmedir. Ailesel translokasyonlara bağlı oluşan dengesiz gebelik ürünleri daha çok 2:2 segregasyonun adjacent-1 aktarımı ile oluşmakta iken, adjacent 2 aktarımı nadir bir durumdur. Bu çalışmada, annenin 9q22.31 ve 22p11.1 bölgeleri arasındaki resiprokal translokasyonuna bağlı 9pter ile 9q22.31 bölgeleri arasında duplikasyonu olan disomorfik bir çocuk sunulmaktadır. Etkilenmiş çocuk iki normal Chr.9, bir derivatif/disentrik Chr.9 (hem Chr.9, hem de Chr.22'nin sentromerini taşıyan), bir tane de normal Chr.22'ye sahiptir. Tüm bu sonuçlar floresan *insitu* hibridizasyon tekniği teyit etmiştir. Kırk bölgelerini doğru olarak belirleyen array-karşılaştırmalı genomik hibridizasyon tekniği *BICD2*, *NTRK2*, *HNRNPK* ve *SMARCA2* gibi büyüme gelişme geriliğine eşlik eden genleri de kapsayan kromozom 9'a ait 61,75 megabazlık duplikasyonu ortaya çıkarmıştır. Ek olarak mikrosefali ve ekstremitte anomalileri gibi trizomi 9'a eşlik eden diğer bulgular da olguda bulunmaktadır. Özetle bu olgu, adjacent-2 tipi segregasyonun ve sadece 9pter-9q22.31 bölgelerini kapsayan kısmi trizomi 9'un nadir bir örneği olarak sunulmaktadır.

Anahtar Kelimeler: Kısmi trizomi 9, resiprokal translokasyon, adjacent-2 segregasyonu, disentrik kromozom, kromozomal yeniden düzenlenme, büyüme geriliği, floresan in situ hibridizasyon, array-karşılaştırmalı genomik hibridizasyon

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INTRODUCTION

Complete trisomy 9 is a quite rare but well-known syndrome with distinctive clinical features, with more than 150 cases reported in the database of the National Organization for Rare Disorders (NORD) up to today (1). The vast majority of the cases are mosaic due to the postzygotic error at any time in early development, or, rarely, due to the meiotic nondisjunction with subsequent loss of the trisomic cell line. The assumed complete trisomy 9 is a rare aneuploidy (which might represent a sampling error of variable tissue mosaicism) that is worthy of consideration (2). The partial trisomy of chromosome (Chr.) 9 (involving short; p and/or long; q arm) is mostly derived from a parental reciprocal translocation and is accompanied by a concurrent deletion or duplication of another chromosome due to the 2:2 or 3:1 segregation mechanisms (2, 3). The present partial trisomy 9 (pter to q22.31) case resulted from adjacent-2 segregation of the maternal reciprocal translocation between Chr.9 and Chr.22. Since the breakpoint was at the centromere of the Chr.22, the derivative chromosome 9 had two centromeres, and a dicentric chromosome [dic(9;22)] had been formed. This rare reciprocal translocation was inherited to the child with adjacent-2 segregation, which led to disomy 22 and partial trisomy 9 (pter to q22.31) and this unique case gave us the opportunity to delineate the accurate genotype-phenotype correlation of the duplication for this relevant segment of chromosome 9. Furthermore, we believe that this case will increase the familiarity of the geneticist with the unusual segregation pattern and also emphasize the importance of the usage of different techniques such as cytogenetic, fluorescence *in situ* hybridization (FISH) and array-comparative genomic hybridization (array-CGH) studies to determine the breakpoints of the chromosomal rearrangements.

CASE PRESENTATION

The 13-month-old girl patient was the first child born to a non-consanguineous 27-year-old mother and a 34-year-old father. At the 36th week of pregnancy, oligohydramnios was detected and an emergency C-section delivery was performed. At birth, her measurements were in the normal range for her birth week: 2160 g weight (10th centile), 44 cm length (10-25th centile), and 33 cm head circumference (75th centile). After the birth, the hypotonic baby was hospitalized in the neonatal intensive care unit for 53 days and was intubated for 23 days due to respiratory distress syndrome. One month after she was discharged from the hospital she started vomiting 6-7 times a day, and her weight gain stopped after the 7th month.

Developmental milestones were delayed: she was able to hold her head up at the age of 8 months. Physical examination at 13 months of age revealed that her measurements were small for her age (6200 g weight

(3.47 SD), 68 cm length (-2.81 SD) and 40.5 cm head circumference (-4.81 SD). Brachydactyly was found (hand 8 cm and 3rd finger 3 cm, below the lowest percentile line). She had microcephaly and facial dysmorphic features such as hypertelorism, low set and cup-shaped ears, broad nasal root and bulbous nose, low hanging columella, short philtrum, thin and tented upper lip, and downturned corners of the mouth (Figure 1a, b). She also had a single transverse palmar crease in both hands and fifth finger clinodactyly. Both of her second toes were shorter than the others, and both of her feet were deviated laterally (Table 1). She could not sit without assistance, talk, or walk at time of physical examination.

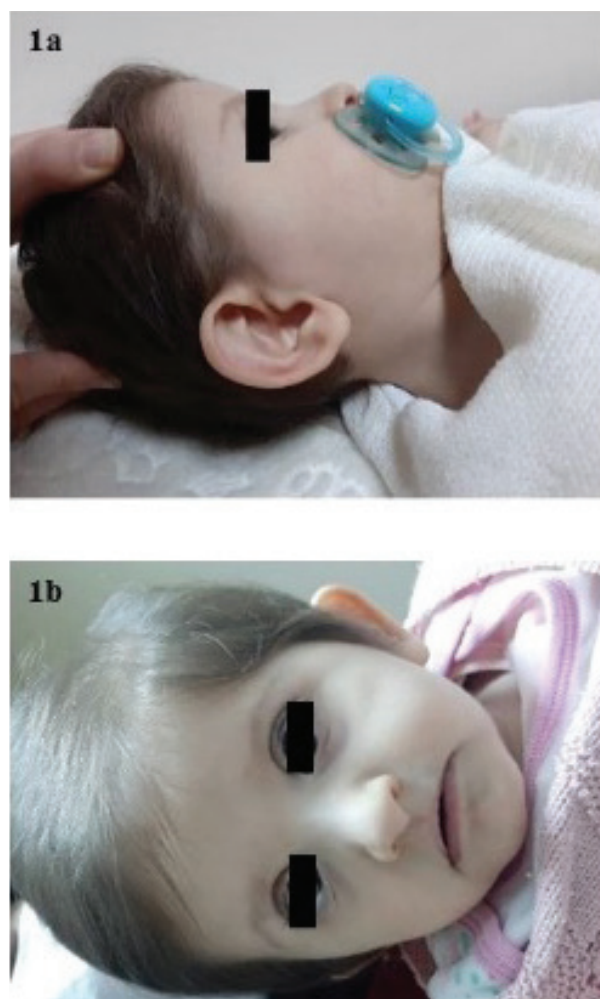


Figure 1: Dysmorphic signs of the patient (a,b): hypertelorism, bulbous nose, broad nasal root, low hanging columella, short philtrum, tented upper lip, downturned corners of the mouth, cup shaped ears

Abdominal ultrasonography (USG) at two months showed mild renal pelvis dilatation with renal pelvic AP with a diameter of 4-4.5 mm. Brain MRI findings were compatible with ventriculomegaly, which was evaluated as benign

Table 1: The comparison of the clinical findings, conventional cytogenetic and array studies in patients with partial trisomy 9 (pter to q22~q32)

	Karyotype	Chromosome 9 duplicated region	Other duplicated or deleted region	Array	Facial dysmorphism	Other clinical findings	Extremity abnormalities	Radiological findings	Age
Present case	46,XX,+9,dic(9;22)(9pter→9q22.31::2q11.1→22qter)mat	Trisomy 9pter to 9q22.31	No other chromosomal trisomy or monosomy	arr[hg19] 9p24.3p13.1(211,086-38,741,437)x3 9q21.1q22.31(71,069,763-94,291,138)x3.	hypertelorism, esotropia, bulbous nose, broad nasal root, low hanging columella, short philtrum, tented upper lip, downturned corners of the mouth, cup shaped ears	hypotonia, developmental delay, growth retardation, sacral dimple	laterally deviated feet, joint laxity, brachydactyly, bilateral single transverse palmar creases, clinodactyly of fifth finger, secondly shorter second toes	Abdominal US: mild renal pelvis dilatation and renal stones ECHO: mitral valve prolapse, secundum atrial septal defect Brain MRI: ventriculomegaly	15 months old (living)
Dhangar S, et al. (2019)	46,XX,+der(9)(t(9;14)(q22.1;q11.2)pat,-14	Trisomy 9pter to 9q22.1	Monosomy 14pter to 14q11.2	arr[GRCCh38] 9p24.3q22.1(203861-87860633)x3 pat	Mild macrocephaly, prominent forehead, low hair line, downward slanting of the eyes epicanthic folds, hypertelorism, low set ears, large pinnae, long face, bulbous nose, thin upper lip, long philtrum, high arched palate	webbed neck, kyphoscoliosis, pilonidal sinus, delayed speech development and poor fine motor development, bilateral hearing loss	rocker bottom feet, short middle interphalangeal elongated foot, clinodactyly of fifth finger	MRI and CT scan of brain: generalized cerebral atrophy, dilated ventricles and arachnoid cyst 2D-ECHO: tiny patent ductus arteriosus US of abdomen: small size of both kidneys	5 years old (living)
von Kaisenberg CS, et al. (2000)	47,XX,+der(9)t(7;9)(q35;q22.2)mat	Trisomy 9pter to 9q22.2	Trisomy 7q35 to 7qter	N/A	micrognathia, hypertelorism, deep-set, posteriorly rotated ears, bulbous nose	postmortem examination: caudal hypoplasia and dysplasia of the cerebellar vermis, dilated foramen magnum, enlarged cisterna magna micropolygyria female sex abnormalities	bilateral simian creases	US at 23 weeks of gestation: hypoplasia of the cerebellar vermis, marginal dilatation of the cisterna magna and the lateral ventricles X-ray; presence of only 11 ribs	23 weeks of gestation (termination of pregnancy)
Sutherland GR et al. (1976)- Case1	47,XX,+der(9)t(7;9)(p21;q32)mat	Trisomy 9pter to 9q32	Trisomy 7pter to 7p22	N/A	microcephaly, low hair line, low set ears, micrognathia, hypertelorism, microphthalmos, pinpoint pupils, large mouth, downturned corners of the mouth	widely open sagittal suture, palpable metopic suture, short, prominent sternum, sacral dimple Autopsy findings: persistent left superior vena cava, patent ductus arteriosus, bilobed right lung, small kidneys, hypoplastic cerebellar vermis, dilated fourth ventricle	flexion deformities of the arms and hands, bilateral simian creases, absence of the terminal phalanges of the thumb and index fingers, hyperconvex nails, fixed dislocation of the hips, unstable dislocated knees, talipes calcaneovalgus	bilateral hypoplasia of the pubic bones and an angulated ischia, dislocation of the head of the radius, hypoplasia of the distal humerus and fibulae, hypoplasia of the ala of the sacrum with poorly developed sacro-iliac joints	17 days (exitus)
Lopez-Felix J, et al.(2017)	47,XX,+der(9)t(8;9)(p21.3;q22.3)mat	Trisomy 9pter to 9q22.3	Trisomy 8pter to 8p21.3	N/A	Absent nasal bone		claw-like hands	US at 15.1 weeks of gestation: CRL (crown-rump length) of 77.6 mm (which accorded to 13.6 gestational weeks) US at 20 weeks of gestation: a fetus of 18 weeks, thickness and dilatation of right cardiac walls, echogenic focus in left ventricle	20 weeks of gestation (termination of pregnancy)
Metzke-Heidemann S, et al. (2004)-patient 2	47,XX,+der(9)t(7;9)(q35;q22.2)mat	Trisomy 9pter to 9q22.2	Trisomy 7q35 to 7qter	N/A	Unilateral cleft lip and cleft of both hard and soft palate				N/A

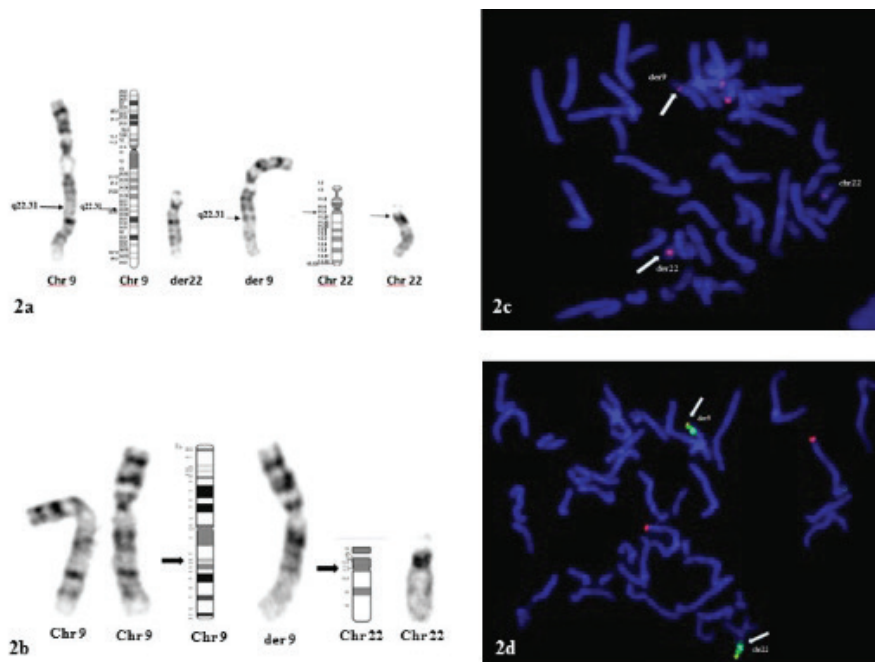


Figure 2: Partial karyotypes and FISH images of mother and proband. Partial karyotype of the mother showing the breakpoints of normal and derivative (der) chromosome 9s and 22s (a), partial karyotype of the proband showing two normal and one derivative chromosome 9 and one normal chromosome 22 (b). Arrows indicate the breakpoint regions. In **figure 2c**, the cep14/22 (red) painting of mother's metaphase is demonstrated. The occurrence of centromere region on der 9 (up) is confirmed via cep14/22 probe. Arrows indicate der9 (up), normal 22 (down) and der22 (right middle). In **figure 2d**, proband's chr 22q11 (LSI bcr: blue), qter regions of ch22 (yellow) and whole chromosome paintings of ch22 (green) are demonstrated on der9 (up) and normal chr22 (down) (the red signals show the 3qter regions and green signals show the 3pter regions as control probes). Arrows indicate der 9 (up) and normal 22 (down).

external hydrocephalus. An echocardiogram at ten months revealed a mitral valve prolapse and secundum atrial septal defect (Table 1).

Cytogenetics and molecular cytogenetics

Cytogenetic analysis was performed in the proband and later in the parent with their consent (4). Proband karyotype was 46,XX,+der(9)(9pter->9q22.31::22q11.1->22qter),-22. Paternal cytogenetic analysis revealed a normal result (46,XY), while the mother had a reciprocal translocation between Chr.9 and Chr.22 [46,XX,t(9;22)(q22.31;q11.1)] (Figure 2a, 2b) (Table 1).

FISH analyses were carried out for both the proband and the mother using the centromere, telomere (9p: pVYS234B, 9q: pVYS235B) and whole chromosome painting probes of Chr.9 and Chr.22 (Cytocell, Cambridge UK), and ToTelVysion™ Multi-colour DNA probe mixture 3 [(22q11 (LSI bcr), 22qter (pVYS207M)] with chromosome 3pter and 3qter as controls) (Vysis, Downer's Grove, IL, USA) (Figure 2c, d). The existence of centromere

region of Chr.22 (p11.1q11.1) on derivative Chr.9 was detected via FISH analysis (Figure 2c, d), and the final karyotype of the proband with dicentric chromosome was 46,XX,+9,dic(9;22)(9pter->9q22.31::22p11.1->22qter) mat,ish dic(9;22)(9pter+,9qter-, D14Z1/D22Z1+,LSI BCR+,22qter+,wcp22+) (Figure 2b, d). Array-CGH (Human Genome G3 SurePrint 8x60K ISCA Array; Agilent Technologies, Santa Clara, California) confirmed the breakpoints of the alteration and revealed a duplication in size of 61.75 megabases of Chr.9, consisting of the *BICD2*, *NTRK2*, *HNRNPK* and *SMARCA2* genes with no gain or a loss of chromosome 22 [(arr[hg19] 9p24.3p13.1(211,086-38,741,437)x3,9q21.1 1q22.31(71,069,763-94,291,138)x3] (Figure 3).

DISCUSSION

After the first example of trisomy 9 shown via quinacrine mustard fluorescence and trypsin banding techniques by Feingold and Atkins in 1973, numerous cases of partial trisomy 9 with a concomitant partial monosomy/trisomy

were reported (Table 1) (3, 5-9). In those cases, the phenotypic effects of the concomitant partial monosomy/trisomy could not be excluded. However, the present case was derived from the adjacent-2 of 2:2 segregation in meiotic disjunction of maternal translocation and her

clinical findings were demonstrative for pure duplication of 9pter to 9q22.31 without any other concurrent imbalance. Contrary to what is known about the dicentric chromosomes, which are almost always unstable in the cell division with the centromeres pulled to the opposite poles of the cell at anaphase, dicentric chromosome [dic(9;22)] of our case was stable in the cell cycles. The steadiness of this chromosome might be because of the formation of a pseudo dicentric chromosome in which only one centromere is active, and presumptively the active centromere belongs to Chr.9 (10).

The present case (adjacent-2 segregation product) is one of the few options for the infant to be born alive with dysmorphic signs as adjacent-1 segregation will be ended with the trisomy/monosomy of Chr.22 with a partial deletion/duplication of chromosome 9. In 3:1 segregation, there are two options of disomy 22 with duplication and deletion of Chr.9 derived from tertiary monosomy/trisomy segregation pattern, while the vast majority of the gestational products will be monosomic or double trisomic for the chromosome 9 and 22 (interchange monosomy/trisomy products). The family was informed about all the options of the segregation via videotaping consultation, and notified about the preimplantation and prenatal diagnosis in future pregnancies (11).

Low-set/malformed ear is a common facial abnormality seen in almost all patients with the regular or partial trisomy 9 cases, concordant with ours (Figure 1a) (2, 7, 12-14). While our case and the Sutherland GR *et al.* case were presented with microcephaly, the Dhangar S *et al.* case had macrocephaly (Table 1) (3, 6). Different extremity deformities, most frequently talipes or rocker bottom feet, were also reported in cases with complete or partial trisomy 9 (2, 3, 6, 15). The present case had laterally deviated feet, joint laxity, clinodactyly of fifth finger, and relatively shorter second toes (2, 3). Heart defects (valve defects and atrial septal defects) were presented in those cases and a mitral valve prolapse and a secundum atrial septal defect were detected in our infant's echocardiogram at 10 months of age (2, 13).

The genes located on the long arm of chromosome 9, like *BICD2*, *NTRK2*, *HNRNPK*, and *SMARCA2*, which are mostly associated with autosomal dominant developmental delay and growth retardation, were found to be duplicated in our case. The *BICD2* gene is associated with childhood-onset muscle weakness and atrophy, while the *HNRNPK* gene is associated with a complex syndromic neurodevelopmental disorder, which explains hypotonia, delayed psychomotor development, and the sacral dimple in our patient. *SMARCA2* and *NTRK2* genes are related to microcephaly, and our case also has this finding (Table 1).

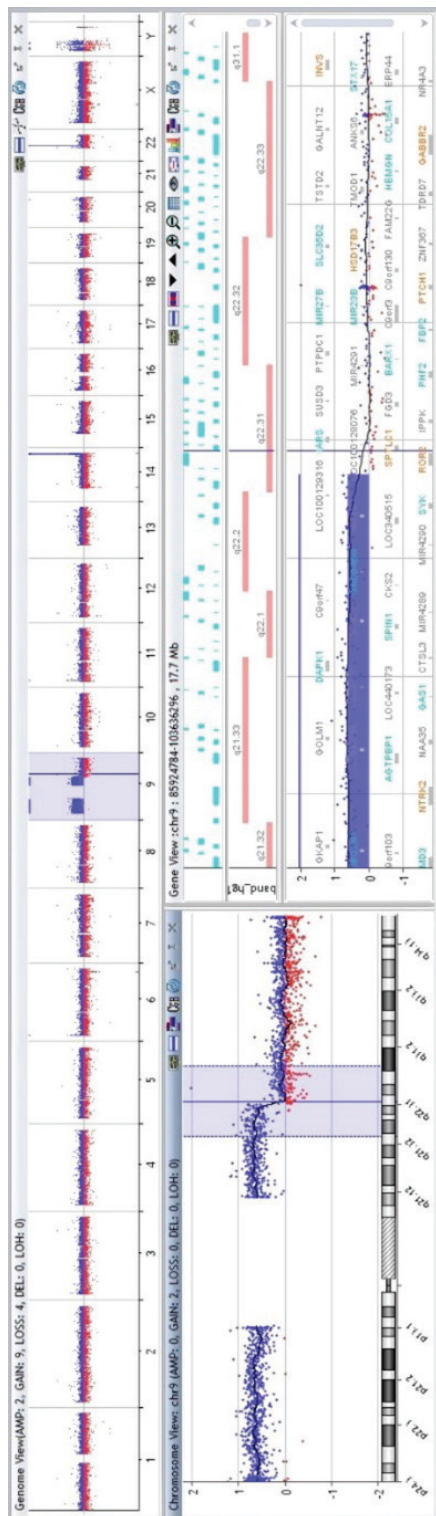


Figure 3: Array-CGH image of the proband. The breakpoint region is 9q22.31. There is a duplication of chromosome 9 (61,751 kilobases) but no gain or loss of chromosome 22 (Human Genome G3 SurePrint 8x60K ISCA Array)

In conclusion, this case with pure partial trisomy of chromosome 9 has allowed us to describe the accurate phenotype-genotype correlation of this duplication and the proper counselling. It must be kept in mind that the identification of the breakpoints, the size of the duplication or the deletion and the identification of the genes encompassed in the imbalances are important, and all laboratory techniques, such as cytogenetic analysis, FISH and array-CGH studies, should be applied to get a reliable result.

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