Mental Retardation, Unusual Facies, and Abnormal Nails Associated with a Group-G Ring Chromosome

A Case Report on Two Unrelated Cases

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This is a report on two unrelated male children with a stable ring chromosome of the G group, associated with severe mental retardation, an unusual facies, and pachyonychia congenita of the toe nails. The facial appearance was so strikingly similar, that the diagnosis in the second case was suspected clinically.

Although there have been a number of reports of ring formation, simple deletion, or monosomy in the G-group autosomes (Lejeune *et al.*, 1964; Reisman *et al.*, 1966; Al-Aish *et al.*, 1967; Hall, Fredga, and Svenningsen, 1967; Hoefnagel *et al.*, 1967; Schulz and Krmpotic, 1968; Weleber, Hecht, and Giblett, 1968; Blank and Lorber, 1969), our two patients do not entirely resemble any of the previously reported cases, as far as can be judged from the clinical descriptions and published photographs.

Case Reports

Case 1 (Nigel N., born 16.12.56). He is the only child of healthy, unrelated parents. The father and mother were 32 and 30 years of age, respectively, at the time of his birth. Pregnancy was normal and there was no exposure to drugs or radiation.

The birthweight was 3630 g at full term. In the newborn period he had an unexplained jaundice for 10 days which was not investigated. In early infancy his hair was very blonde and at one time he was likened to an albino (Fig. 1).

He was first referred at the age of 2½ years because of delay in development. He had sat unsupported at 1 year and walked at 22 months. When assessed at 2½ years his intellectual development was considered to be less than a 15-month level. He still had very fair hair. The phenistix test on the urine for phenylketonuria was negative.

When assessed at 10½ years he was still severely subnormal, his IQ falling in the ineducable range (<50). He had no intelligible speech, but was able to make himself understood by simple gestures. He could feed him-

self and use the toilet. He was continent of urine by day only.

He had an unusual facies with large prominent ears (Fig. 2). His eyebrows came to a point about one-third of the way from the lateral end, and almost formed a whorl. The palate had a high arch. His build was thin and lanky. His length was 144 cm and weight 30.5 kg which were at the 80th and 50th centile respectively for his age. His head circumference was 54 cm.

There was pachyonychia of the nails of both large toes (Fig. 3). His mother said they had always been thick

FIG. 1. Case 1, aged 16 months. Note the fair hair and wide nasal bridge.

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FIG. 2. Case 1, aged 10½ years, showing unusual facies with large ears, and lanky build.

FIG. 3. Case 1. Feet showing thickening of nails of both halluxes and to lesser extent of left second toe.

and hard and did not grow normally. From time to time the nail dropped off while another formed beneath it. The left second toe showed a similar abnormality but of lesser degree. All other toe and finger nails were normal.

He had an unsteady, ataxic gait. He had difficulty going up and down steps, which he negotiated one at a time. There was no obvious weakness on assessment of individual muscle groups, although it was difficult to get full co-operation in view of his retardation. The tone was normal; tendon reflexes were present but sluggish and the plantar response flexor.

He had an apical mid-diastolic rumbling murmur of the mitral stenotic type and also a soft systolic murmur. There was no history of rheumatic fever.

Chromosomes. Two samples of blood were taken from the propositus on separate occasions and chromosome preparations made by culturing the separated leucocytes. Thirty cells were scored and analysed from the first preparation and found to be of the chromosome constitution 46,XY,Gr. Fifty cells from the second preparation showed 48 with the constitution 46,XY,Gr (Fig. 4) and two with 45,XY,G-. The chromosome complement of the parents was normal (father = 46,XY; mother = 46,XX).

Skin. This failed to grow satisfactorily in culture. Cells tended to clump and many died, and analysis was impossible. A second attempt was made to culture the skin but growth was again slow and irregular, and to date no harvest has been possible.

Dermatoglyphs. The digits of the right hand showed: first a radial loop; second a radial loop; third an arch; fourth an arch; fifth an ulnar loop. The left hand showed: first an ulnar loop; second an ulnar loop; third a radial loop; fourth an ulnar loop; fifth an ulnar loop. In both palms the triradius r' was normally placed. The hallucal area in both feet showed a simple fibular loop.

Nerve conduction velocity. The ulnar nerve velocity was 58.9 m/sec and the posterior tibial nerve velocity was 50.0 m/sec (both normal).

Electromyography. There was no spontaneous activity at rest and full interference pattern on voluntary activity with normal motor units.

Blood. Plasma protein was 7.7 g/100 ml; electrophoresis showed a slight increase in α_2 globulin. Immunoglobulins: IgG 875 mg/100 ml; IgA 52 mg/100 ml; IgM 60 mg/100 ml. Phenylalanine 3.7 mg/100 ml (in September 1968); tyrosine 1.0 mg/100 ml; amino-acid chromatography was normal; creatine phosphokinase 1.5 μ M/ml/hr and aldolase 3.0 m IU/ml (both normal). Ca 10.2 mg/100 ml; P 4.5 mg/100 ml; Na 140 mEq/l; K 5.1 mEq/l; urea 33 mg/100 ml. Wassermann, Kahn, and Reiter tests were negative; the blood count was normal.

Urine. Routine microscopy was normal, there was no albumin or sugar, and amino-acid chromatography was normal.

Cerebrospinal fluid. Cell count was 1/mm³, protein 20 mg/100 ml, and sugar 50 mgm/100 ml.

FIG. 4. Case 1 (left column) and Case 2 (right column). Partial karyotype of G-group chromosomes showing ring morphology.

Radiography. Chest x-ray showed slight cardiomegaly with prominent pulmonary artery and lung vasculature. Skeletal x-ray showed spina bifida occulta of L5. There were no other abnormalities of skeletal system. The bone age was consistently commensurate with chronological age.

Blood groups and marker studies. Studies on the proband and his parents were not informative with respect to loci on the abnormal G-group chromosome (see Table I).

Case 2 (Ian C., born 1.8.64). He was the second child of healthy, unrelated parents. The maternal and paternal ages were 30 and 38 years respectively. Birth weight was 2900 g at term. Pregnancy was normal. The mother had an x-ray of the abdomen 14 days before delivery.

He first presented at the age of 17 months because of delay in walking. At that time he was noted to have an unusual facies with a fair complexion, prominent ears, and widely spaced eyes with an antimongoloid slant (Fig. 5). He was relatively tall (89 cm/97 centile) and slender (11 kg/25 centile). He was found to be retarded in all his developmental milestones. A phenistix test on the urine was positive and he was admitted for further investigation. Plasma phenylalanine levels

were slightly elevated up to 7.5 mg/100 ml, on several occasions. Plasma tyrosine never exceeded 1.7 mg/100 ml. No orthohydroxyphenylacetic acid was demonstrable in the urine and repeated two-dimensional chromatography on urine and plasma were normal. A phenylalanine load (1.2 g) produced a peak phenylalanine level of 9.9 mg at 1 hour with no significant rise in plasma tyrosine and only trace amounts of phenylalanine in the urine. A positive reaction with phenistix was only demonstrable on the one occasion.

He was re-admitted at age 3 years because of haematuria. Intravenous pyelography revealed a duplex kidney on the left and poor excretion on the right. No further investigations were undertaken at that time. There were still marked retardation of all milestones and his height was above the 97th centile.

Eight months later he was again admitted, with a left-sided abdominal mass, marked weight loss and dehydration. At laparotomy a large nephroblastoma was resected together with the left half of a horseshoe kidney. Radiotherapy was commenced but because of his poor general condition was not completed. It was on this admission that the facial similarity to case 1 was observed (Fig. 6) and inspection of the feet revealed pachyonychia (Fig. 7). A karyotype was then done. The further course was one of gradual deterioration and he died at the age of 3 years and 11 months. Necropsy revealed generalized spread of metastases.

TABLE I

DETAILS OF SERUM PROTEINS, RED CELL ENZYME TYPES, AND RED CELL ANTIGENS IN CASE 1 AND HIS PARENTS

	Age	Serum Types		Red Cell Enzyme Types								Red Cell Antigens									
		Hp	Tf	AcP	PGM ₁	AK	Ada	Peptidases				ABO	Rh	MNSs	P ₁	K	Le	Lu	Fy	Jk	
								A	B	C	D										
Case 1	13	2-1	C	BA	1	1	1	1	1	1	1	A	CcDee	NNss	+	a-	a-b+	a-	a+	a+b+	
Father	45	2-1	C	BA	1	1	1	1	1	1	1	O	CCDee	MNSs	+	a+b+	a-b+	a-	a-	a-b+	
Mother	43	1-1	C	BA	1	1	1	1	1	1	1	A	ccDEe	NNss	+	a-	a-b+	a-	a+	a+b-	

Chromosomes. One sample of blood only was taken from the propositus since the child was very ill. Chromosome preparations were made by culturing separated leucocytes. Thirty cells were scored and analysed, twenty-nine of which were of the constitution 46,XY,Gr (Fig. 4) and one with 45,XY,G-. The chromosome complement of the father, mother, and a phenotypically normal sib showed no abnormality (father=46,XY; mother=46,XX; sib=46,XY).

Dermatoglyphs. The hands showed whorls on all digits and a normally placed triradius t' . Both feet showed whorls on the hallual areas.

Discussion

These two unrelated male patients presented a similar picture of severe mental retardation, an unusual facies with large ears, and pachyonychia of the big toe nails.

Chromosome study showed that in both individuals there was a ring chromosome in the G group which was smaller than the other chromosomes of the group. The ring was constant in size in relation

to the rest of the G group and was only rarely missing altogether, indicating stability of behaviour. It is therefore likely that these two cases showed partial monosomy of the G group uncomplicated by duplications and/or subsequent deletions, as would be produced by a breakage-fusion-bridge cycle. This contrasts with the recent case in Sheffield of Blank and Lorber (1969), where the ring was variable in size, so that in at least some of the cells partial trisomy was presumed.

Skin culture in case 1 was unsuccessful at two attempts. The cells tended to clump and growth was slow and irregular. This may well be due to the presence of the ring chromosome, as in our experience it is unusual to find such difficulty in the culture of skin fibroblasts. It was not possible to do any studies of the skin on the second case.

The parents in both instances had a normal karyotype as did the sib of case 2.

Marker studies done in case 1 and his parents failed to demonstrate any loci associated with the abnormal G-group chromosome.

TABLE II
MAIN CLINICAL FEATURES IN CASES WITH PARTIAL

	Lejeune <i>et al</i> , 1964 Broyer <i>et al</i> , 1966	Reisman <i>et al</i> , 1966	Thorburn and Johnson, 1966	Al-Aish <i>et al</i> , 1967	Hall <i>et al</i> , 1967
Sex	M	M	F	F	M
Karyotype	45,XY,G- / 46,XY,Gf	46,XY,Gf	45,XX,G-	45,XX,G-	45,XY,G-
Birthweight (g)	2100	2040		3200	2660
Maternal age	27	18	18	22	30
Paternal age	28	23	30	24	32
Mental retardation	+	+	+	+	
Tall stature	+			+	
Dwarfism	+			+	
Large ears	+	+	+	+	
Antimongoloid slant	+	+	+	+	+
Hypertelorism	+	+	+	+	
Prominent nasal bridge	+	+		+	
Broad or flat nasal bridge	+	+		+	
Micrognathia	+	+	+	+	
Koilonychia/nail dystrophy	+	+		+	
Pachyonychia	+	+		+	
Hypertonia	+	+	+	+	
Hypotonia	+	+	+	+	
Cardiac murmur	+	+	+	+	+

FIG. 5. Case 2, aged 17 months, showing fair complexion, prominent ears, hypertelorism and antimongoloid slant to eyes.

The clinical features in these two children differ in certain respects from any of the previous reports on either ring chromosome, partial deletion or monosomy of a G-group chromosome (see Table II). None of the previous cases have had their tall

stature and there has also been no previous record of pachyonychia or onychogryphosis, although some cases have had other anomalies of the nails, such as koilonychia or dystrophic change. On the other hand mental retardation has been a constant feature, and large ears have also been present in a number of cases. In addition, our second patient also showed the antimongoloid slant and wide spacing of the eyes, which have been features of some previous cases. There was also a suggestion of widening of the nasal bridge in our first case. Lejeune *et al* (1964) observed that some of the features of a male child with deletion of part of a G-group chromosome were the opposite of those seen in mongolism and suggested the term *contre-type* mongolism for this phenotype. Reisman *et al* (1966) used the term 'antimongolism' for a similar male infant with partial monosomy of chromosome 21. However, Reisman *et al* (1967) subsequently studied another male child with partial deletion of G-group chromosome whose features were very unlike the cases of 'antimongolism'. There have also been a number of reports on apparent monosomy of a G-group autosome. The infant described by Hall *et al* (1967) was thought to have some of the features of 'antimongolism' while the case of Thorburn and Johnson (1966) had an antimongoloid slant to the eyes but none of the other features of the case of Hall *et al*. The two cases with monosomy G mosaicism described by Schulz and Krmpotic (1968) were dissimilar in phenotype, and one of them resembled the published cases of 'antimongolism'. Of the case reports with a ring chromosome in the G-group, the 5-month-old infant described by

OR COMPLETE LOSS OF G-CHROMOSOME MATERIAL

Schulz and Krmpotic, 1968		Blank and Lorber, 1969	Hoefnagel <i>et al</i> , 1967	Reisman <i>et al</i> , 1967	Weleber <i>et al</i> , 1968	Dubowitz <i>et al</i>	
F	M	F	F	F	F	M	M
45,XX,G- /46,XX 2200 31	45,XY,G- /46,XY 2500 20	45,XX,G- /46,XX,Gr 2850 26 44	46,XX,Gr 2850 24 23	46,XX,Gr 1360 29 26	46,XX,Gr 2980 2980 23 24	46,XY,Gr 3630 30 32	46,XY,Gr 2900 30 38
+	+	+	+	+	+	+	+
+	-	-	-	+	+	+	+
+	+	-	+	+	-	+	+
+		-	-	-	+	-	-
+		-	+	-	-	-	-
		-	+	+	-	+	+
		-	-	-	-	+	-
		-	-	-	+	+	-

FIG. 6. Case 2, aged 3 years 9 months, showing the unusual facies and large ears. (Cachexia associated with nephroblastoma.)

Hoefnagel *et al* (1967) had a fairly normal facies apart from a broad nasal bridge, while the case of Weleber, Hecht, and Giblett (1968) was said to resemble that of Reisman *et al* (1967). In contrast Blank and Lorber (1969) noted some resemblance to mongolism in the facial characteristics of a child with a mosaic of 45,XX,G- / 46,XX, Gr. The ring chromosomes had a diameter equivalent to the length of the long arm of the largest G chromosome, thus suggesting it contained more genetic material than the normal G chromosome, rather than less.

The clinical feature of these reported cases with complete or partial monosomy in the G-group are summarized in Table II. It is of interest to note the marked variation in phenotype even in cases with a ring chromosome. A possible explanation is that superimposed on the original breakage-reunion phenomenon leading to the ring formation, there may be disturbance of the division of such chromosomes, so that daughter cells may show either duplication or loss of segments of the remainder of the chromosomes. Whereas those indi-

FIG. 7. Case 2. Feet showing thickening of nails of first and second toes bilaterally.

viduals with 'stable rings', as in our two cases, may be expected to show only clinical features associated with loss of G material, individuals with 'unstable' rings, may show features characteristic of excess G material as well. It would therefore be expected that not all individuals with a ring chromosome would show the same spectrum of effect, even where the chromosome involved is the same.

Summary

Two unrelated male children are described with an unusual facies with large prominent ears, severe mental retardation and pachyonychia congenita of the hallux and to a lesser extent of other toe nails. Both children had a stable ring chromosome with karyotype 46,XY,Gr. The parents in both cases were phenotypically normal and had a normal karyotype. Marker studies in case 1 and his parents failed to demonstrate any loci referable to the abnormal G group chromosome.

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REFERENCES

- Al-Aish, M. S., de la Cruz, F., Goldsmith, L. A., Volpe, J., Mella, G., and Robinson, J. C. (1967). Autosomal monosomy in man. Complete monosomy G (21-22) in a four-and-one-half-year-old mentally retarded girl. *New England Journal of Medicine*, **277**, 777-784.
- Blank, C. E. and Lorber, J. (1969). A patient with 45,XX,G- / 46,XX,Gr mosaicism. *Journal of Medical Genetics*, **6**, 220-223.

- Hall, B., Frega, K., and Svenningsen, N. (1967). A case of monosomy G?. *Hereditas, genetiskt arkiv*, **57**, 356-364.
- Hoefnagel, D., Schroeder, T. M., Benirschke, K., and Allen, F. H. (1967). A child with a group-G ring chromosome. *Human-genetik*, **4**, 52-58.
- Lejeune, J., Berger, R., Réthoré, M.-O., Archambault, L., Jérôme, H., Thieffry, S., Aicardi, J., Broyer, M., Lafourcade, J., Cruveiller, J., and Turpin, R. (1964). Monosomie partielle pour un petit acrocentrique. *Comptes rendus hebdomadaires des séances de l'Académie des sciences*, **259**, 4187-4190.
- Reisman, L. E., Kasahara, S., Chung, C-Y, Darnell, A., and Hall, B. (1966). Anti-mongolism—Studies in an infant with a partial monosomy of the 21 chromosome. *Lancet*, **1**, 394-397.
- Reisman, L. E., Darnell, A., Murphy, J. W., Hall, B., and Kasahara, S. (1967). A child with partial deletion of a G-group autosome. *American Journal of Diseases of Children*, **114**, 336-339.
- Schulz, J., and Krmpotic, E. (1968). Monosomy G mosaicism in two unrelated children. *Journal of Mental Deficiency Research*, **12**, 255-268.
- Thorburn, M. J. and Johnson, B. E. (1966). Apparent monosomy of a G autosome in a Jamaican infant. *Journal of Medical Genetics*, **3**, 290-292.
- Weleber, R. G., Hecht, F., and Giblett, E. R. (1968). Ring-G chromosome, a new G-deletion syndrome? *American Journal of Diseases of Children*, **115**, 489-493.