Hum Genet (1981) 57:300–306

Human Genetics

Aniridia, Male Pseudohermaphroditism, Gonadoblastoma, Mental Retardation, and del 11p13

Catherine Turleau[1], J. de Grouchy[1], J. L. Dufier[2], Lè Hoang Phuc[2], P. H. Schmelck[3], R. Rappaport[3], Claire Nihoul-Fékété[4], and Nicole Diebold[5]

[1] U.173 I.N.S.E.R.M. and E.R. 149 C.N.R.S.
[2] Service d'Ophthalmologie
[3] Unité d'Endocrinologie Pédiatrique
[4] Clinique Chirurgicale Infantile
[5] Groupe de Pathologie Pédiatrique (I.N.S.E.R.M. U.77), Hôpital Necker-Enfants-Malades, 149, rue de Sèvres, F-75730 Paris Cedex 15, France

Summary. A 20-month-old male patient was referred because of severe growth and mental retardation, bilateral glaucoma, hypospadias, and cryptorchidism. Karyotyping revealed a de novo complex three-chromosome rearrangement as well as deletion of band 11p13:46,XY,t(4;7;15)(q212;p14;q26),del(11)(p13p14). Trabeculectomia revealed bilateral aniridia. Surgery on the genitalia revealed male pseudohermaphroditism and bilateral gonadoblastoma. The kidneys were normal. A deficiency in catalase (CAT) activity allowed the regional assignment of the CAT gene to band 11p13.

Introduction

Aniridia is most often an autosomal dominant trait with a frequency of about 1.8×10^{-5} and a mutation rate of about 4×10^{-6} per gamete per generation (McKusick 1975). Yet this condition may occasionally be part of a syndrome affecting psychomotor, renal, and genital development. The association of aniridia and nephroblastoma or Wilms' tumor, which is also known to be of genetic origin in some instances, was reported for the first time by Brusa and Torricelli (1953). In 1964 Miller et al. studied 440 cases of Wilms' tumor and found six cases of aniridia, i.e., an incidence of 1/76. This first observation was confirmed by numerous reports. In 1979 François et al. reviewed nearly 50 instances of the aniridia-Wilms' tumor association. A chromosomal aberration was first reported by Ladda et al. (1974) who identified a t(8p+;11q−) in a 3-year-old patient with bilateral aniridia and Wilms' tumor diagnosed at 19 months. Computer analysis of optical microscope scanning profiles of chromosomes 8 and 11 revealed an interstitial deletion of 8p. Francke et al. (1977) and Riccardi et al. (1978) demonstrated a short interstitial deletion of 11p in another patient with aniridia and Wilms' tumor. Simultaneously Andersen et al. (1978a, b) reported a deletion of 11p in a patient with aniridia and gonadoblastoma, but without Wilms' tumor. Some 10 patients have now been reported with aniridia, Wilms' tumor, and/or gonadoblastoma. They are reviewed by Francke et al. (1979) and the relevant clinical and cytogenetic data are summarized in Table 1. Two instances are now known of familial transmission due to a parental rearrangement (Hittner et al. 1979; Yunis and Ramsay 1980). The patient first studied by Ladda et al. (1974) was reexamined by Francke et al. (1979) and shown to have indeed an interstitial deletion of 11p. The shortest deletion common to all patients is band 11p13.

Several gene loci have been precisely localized on 11p: LDHA on p12.3→p12.8, HBB (the Hb cluster) on p1205→p1208, and SA11-1 and 3 (cell surface antigens) on p13→pter, ACP2 on p11→p12 (Human Gene Mapping 5 1979). More recently Wieacker et al. (1980) assigned the catalase (CAT) locus to 11p by cellular hybridization.

We here report a 20-month-old male patient with severe mental and growth retardation, aniridia and glaucoma, ambiguous external and internal genitalia, and gonadoblastoma, with no evidence of Wilms' tumor. Chromosome analysis showed a deletion of 11p13 and enzymatic activity determination allowed the regional assignment of the CAT gene to 11p13.

Case Report

The patient, born in Algeria on June 28, 1978, was considered as a male. His parents are Algerians and consanguineous (probably at the fifth degree). The mother is healthy and was 26 years old. The father was 34 years old. He suffers from epilepsy. The propositus has two brothers and two sisters. One of the brothers has unilateral cryptorchidism.

Birth weight was 2,500 g; length at birth and head circumference are unknown. Bilateral congenital glaucoma was diagnosed at two months. Delayed psychomotor development and growth retardation were noted in early infancy. The patient was transfered to Paris at 20 months of age for treatment of his glaucoma.

At this time growth retardation was evident: length: 69.5 cm (−4 SD); weight: 6,650 g (−4 SD); head circumference: 42 cm (−5 SD); bone age: eight months. Psychomotor development was much delayed and corresponded to that of a 6-month-old infant. Blindness was complete with clinically evident, bilateral glaucoma and opaque cornea. Hearing was normal, as well as tonus and reflexes. There was no striking dysmorphism (Fig. 1). Penile hypospadias was present. The penis was 30 mm long with a very moderate chordee. the scrotum was flat, normally striated, and empty. No gonad could be palpated. Karyotype analysis was requested because of this sexual anomaly.

It was then decided to operate on the glaucoma because of the severe discomfort it seemed to cause to the patient even through it was beyond effective cure. When trabeculectomia was performed bilateral

Offprint requests to: J. de Grouchy

0340-6717/81/0057/0300/$01.40

Table 1. Relevant data from ten patients reported in the literature and the present case

Patient	Chromosomal rearrangement	Mental retardation	Height (percentile)	Eyes	Sex chromosomes	Genitalia	Tumor	Other
1	(8;11)(p21.2;q14.4) del(11)(p1407p1304) parents normal	+	50th	Aniridia, glaucoma, cataracts, megacornea	XY	Slightly ventral orifice of urethra	Unilateral nephroblastoma at 19 months	Partial malrotation of right kidney
2	del(11)(p1400p11.3) parents not studied	+	10th	Aniridia, glaucoma, cataracts, ptosis	XY	Coronal hypospadias, no palpable testis, small scrotum	None at 12 years	Obstructive uropathy
3	del(11)(p15.1p1208) parents normal	+	25th	Aniridia, glaucoma, cataracts, nystagmus, strabismus, ptosis	XY	Microphallus, perineal hypospadias, unilateral cryptorchidia, anterior urethral diverticulum	Nephroblastoma unilateral (left) at 42 months	Female sex of rearing
4	del(11)(p15.1p1305) parents not studied	+	25th	Aniridia, ptosis	XY	Ambiguous genitalia, no mullerian derivative gonads present, hypospadias 3rd degree	None at $8\frac{1}{4}$ years	
5	del(11)(p13p11) parents normal	+	?	Aniridia, glaucoma, cataracts, nystagmus	XX	Female external genitals, small gonadal streaks	Benign gonadoblastoma autopsy: 21 months	Mild coloboma of the nares, micrognathia low-set ears, central hearing impairment, abnormally rotated left kidney
6	del(11)(p1300p15.1) parents normal	+	?	Aniridia, glaucoma, cataracts	XX		Bilateral nephroblastoma at 36 and 49 months	
7	Identical twin of patient 6	+	?	Aniridia, glaucoma, cataracts, exotropia	XX		None at 7 years	Malrotation left kidney
8	del(11)(p11.3p14) mother's karyotype: ins(11)(q22p11.3p14)	+	3rd	Aniridia, glaucoma, cataracts, corneal clouding, esotropia, mild ptosis	XX	Normal female	None at 10 months	
9	del(11)(p13p14.1) mother's karyotype: ins(2;11) (q32;p13p14.1)	+	5th	Aniridia, cataracts, nystagmus, ptosis	XY	Bilateral undescended testes	Bilateral nephroblastoma at 15 and 36 months	Microcephaly, half-brother and aunt both with aniridia Wilm's tumor had died
10	inv(7)(q21.2q3100) del(11)(p1305p1405) parents normal	±	50th	Aniridia, glaucoma, corneal clouding, nystagmus	XY	Ambiguous genitalia, micropenis, hypospadias, normal testicular biopsies, small scrotum	None at $3^{10}/_{12}$ months	
11	t(4;7;15) (q21.2;p14;q26) del(11)(p13p14) parents normal	+	3rd	Aniridia, glaucoma, corneal clouding	XY	Hypospadias, severe gonadal dysgenesis, presence of Mullerian derivatives	Bilateral gonadoblastoma, surgery at 23 months	Catalase deficiency

Patient 1. Ladda et al. 1974; Francke et al. 1979
Patient 2. Smith et al. 1977 (patient AC); Francke et al. 1977 (patient C); Riccardi et al. 1978 (patient 1)
Patient 3. Smith et al. 1977 (patient LM); Francke et al. 1977 (patient B); Riccardi et al. 1978 (patient 2)
Patient 4. Riccardi et al. 1978 (patient 3); Francke et al. 1977 (patient A)
Patient 5. Andersen et al. 1978 a, b; Warburg et al. 1980
Patients 6 and 7. Twins. Cotlier et al. 1978; Francke et al. 1978; Maurer et al. 1979; addendum in Riccardi et al. 1978; Riccardi et al. to be published
Patient 8. Hittner et al. 1980
Patient 9. Yunis and Ramsay 1980
Patient 10. Riccardi et al. to be published (case 1)
Patient 11. Present report; Junien et al. 1980 (patient 1)

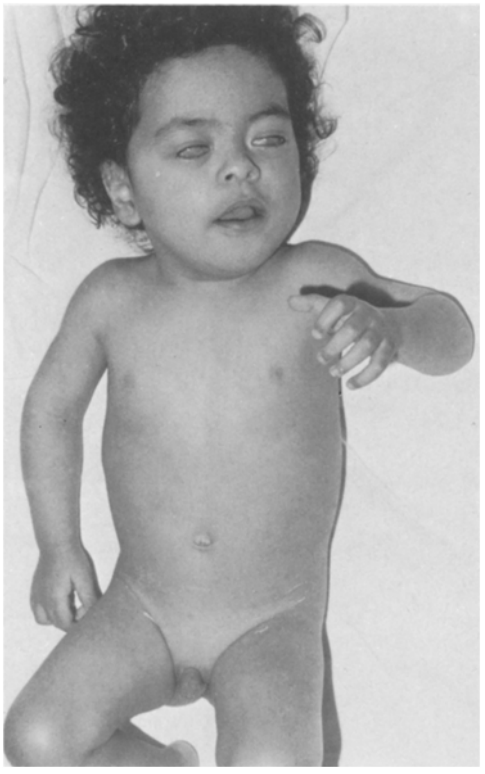


Fig. 1. Photography of the patient at 22 months

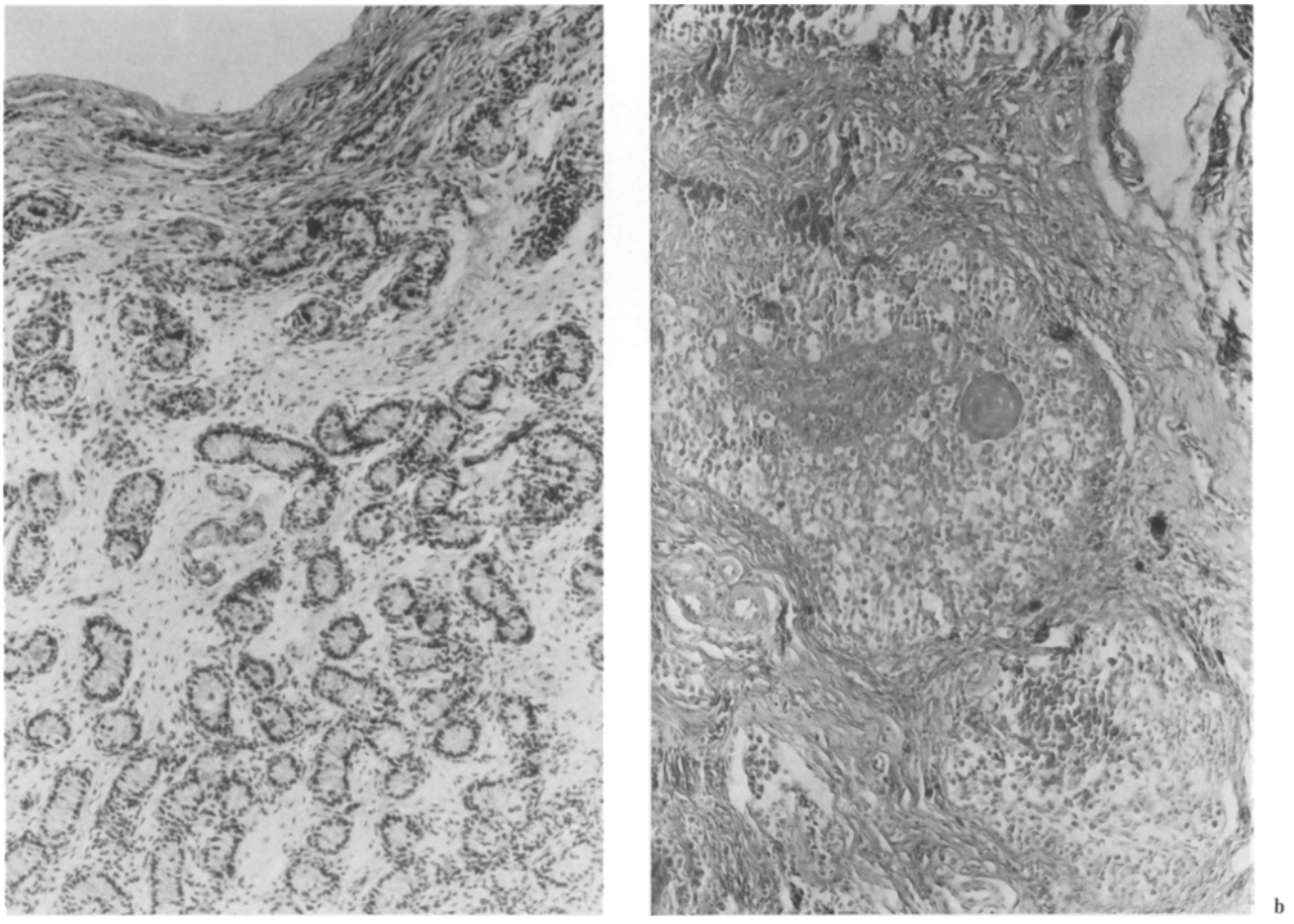
aniridia was discovered. The discovery of an interstitial deletion of 11p in association with aniridia prompted further investigations in order to detect a latent nephroblastoma (Wilms' tumor) or gonadoblastoma.

Ultrasound scan revealed normal sized kidneys. Intravenous pyelogram showed normal morphology and function of the kidneys and excretory cavities. Suprapubic cystography and mictional urethrography showed bilateral vesicoureteral reflux without urinary complication, and no urogenital sinus.

Stimulation tests of pituitary function gave normal results: under luteinizing hormone releasing hormone (LHRH), plasma follicle-stimulating hormone (FSH) levels rose from 0.8 to 7.4 mU/ml and luteinizing hormone (LH) levels from 0.5 to 0.8 mU/ml. Testicular function was also normal, as shown by human chorionic gonadotropin (HCG) stimulation: plasma testosterone rose from an undetectable level to 2.3 ng/ml (after three intra-muscular injections of 1,500 U every other day).

Operation for bilateral cryptorchidism was undertaken initially by a horizontal inguinal incision and was rapidly transformed in laparotomy because of the discovery of ambiguous internal genitalia. This revealed a vagina of normal size and situation and a uterus apparently complete and in continuation with two ducts having the consistancy of Fallopian tubes. On the left, this tube did not develop tubal folds. On the right, a pavillion and normal plicae were present. The gonads appeared as long, thick, yellow streaks located at the posterior side of the tubes. On the right side there was a vas deferens ending in the vaginal cul-de-sac and with no evident connection with the right gonad. Total resection of the internal genitalia was decided. The vagina was sutured as low as possible, very near the supposed urethrovaginal fistula.

Histologic examination confirmed the presence of uterus and vagina. The upper genital tract was ambiguous with Müllerian and Wolffian structures. Both gonads contained seminiferous tubules which occasionally appeared dysgenetic (Fig. 2a), and areas of typical gonadoblastoma (Fig. 2b).



a b

Fig. 2. a Dysgenetic testicular tissue: seminiferous tubules, devoid of germinal elements, are embedded in abundant connective tissue, arranged in whorls, as in rudimentary gonadal streaks. Azan ×350. **b** Typical gonadoblastoma: nests of germ cells with large nuclei contain rounded hyaline bodies. Azan ×350. (Microphotographs: Dr. Nathalie Josso)

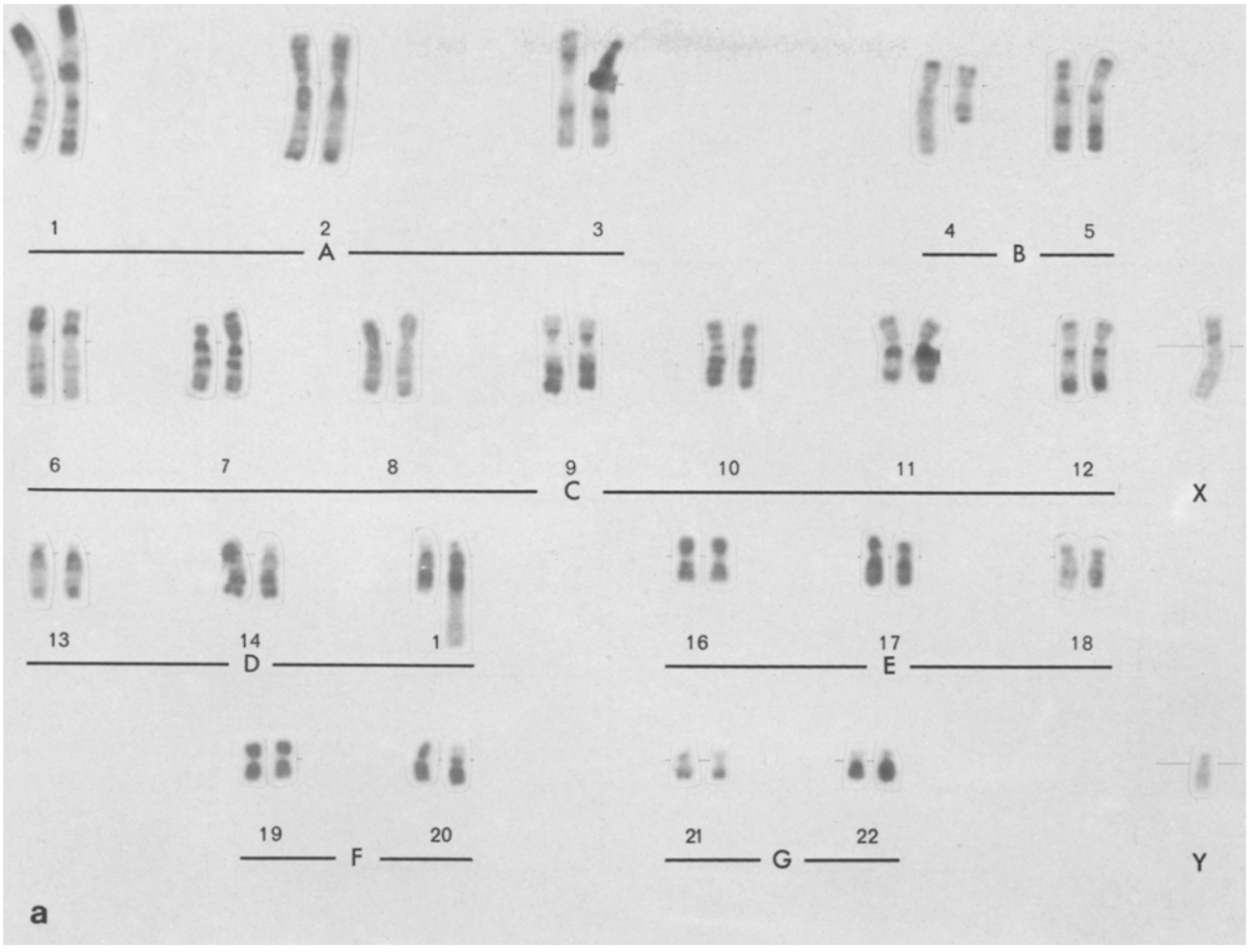


Fig. 3a and b. Karyotype of the patient showing the complex t(4;7;15) (q212;p14;q26) as well as the del(11)(p13p14). **a** R-banding; **b** G-banding

Laboratory Investigations

Hematologic investigations showed microcytosis which could not be related to abnormal hemoglobin synthesis (see below), and hyposideremia which could rapidly be cured by iron therapy. X-rays showed, as well as the delayed bone age, moderate osteoporosis. Phosphocalcic metabolism was normal. No endocrine or digestive disorder could be found to explain the severe growth retardation. Otherwise, all usual blood and urinary tests gave results within normal limits.

Cytogenetic Investigations

The patient's karyotype was established after applying RHG-, RBA-, GTG-banding to cultured lymphocytes and fibroblasts. Blood cells metaphases were also obtained after addition of mitomycin to the culture medium (final concentration 0.15 μg/ml) 20 h before harvesting, in order to obtain a higher degree of banding resolution.

A three-chromosome translocation was identified (Fig. 3): t(4;7;15) (q212;p14;q26). The 4qter fragment was translocated onto the 15 and 7p14pter onto the 4q remaining segment. This series of probably circulary translocations was considered balanced. In addition, an interstitial deletion was detected in 11p and limited to band 11p13. The breakpoints seemed to be at the proximal margins of p13 and p14 (Fig. 4). The complete karyotype formula was therefore: 46,XY, t(4;7;11)(q212;p14;q26),del(11)(p13p14). Both parents had normal karyotypes.

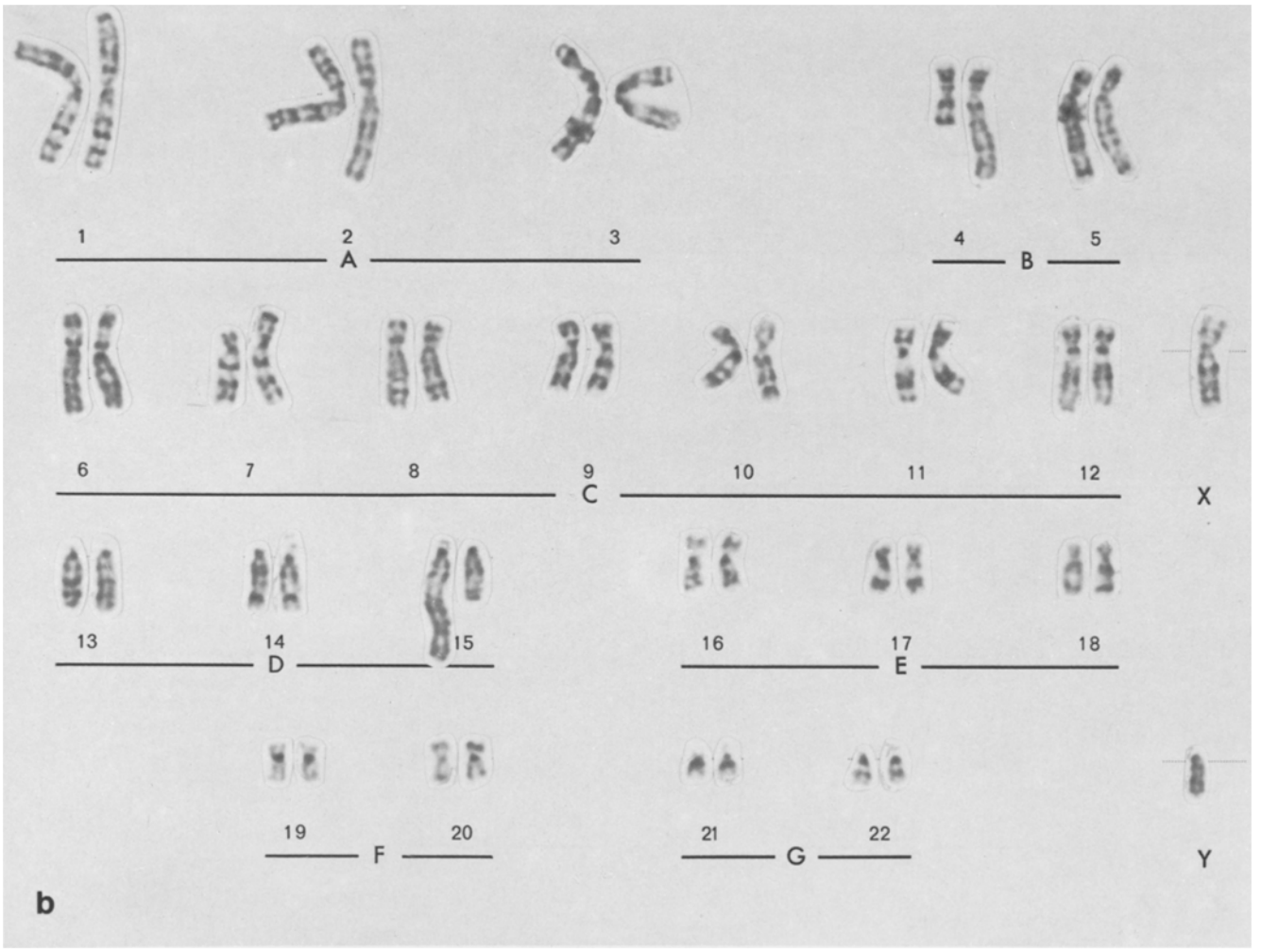
Sister chromatid exchanges were analysed in the patient's lymphocytes and fibroblasts. Their frequency was normal. In 29 blood cells it varied from 0 to 13 with a mean of seven exchanges per cell. In 17 fibroblasts the variation was from 6 to 19, with a mean of 10 exchanges per cell.

Genetic Markers

The blood group phenotypes of the patient and his parents failed to show any abnormal transmission. Several genetic markers, known to be assigned to chromosome 11 and more specifically to 11p, were investigated. There was no evidence for a thalassemia-like syndrome. HbA was 93%, HbF: 4%, and HbA2: 2.9%. Although HbF was elevated, HbA2 and globular values were normal. Lactate dehydrogenase A (LDHA) activity was normal. Catalase activity was found significantly decreased in the patient's red and white blood cells (Junien et al. 1980).

Discussion

Our patient was first referred to us because of bilateral glaucoma with corneal opacity, and it was only at surgery that aniridia was discovered. The association of aniridia, mental retardation, ambiguous genitalia, and del(11p) then initiated a search for nephroblastoma and gonadoblastoma. Wilms' tumor was not detected but laparotomy, which was performed to find the gonads, revealed male pseudohermaphroditism with Müllerian structures—a vagina, a uterus, and Fallopian tubes—as well as streak gonads. Total resection of the internal genitalia



was decided and histopathology disclosed the presence of dysgenetic testes and bilateral gonadoblastoma.

Only one other patient with identified del(11p) is known to have had gonadoblastoma (patient 5 in Table 1). Her chromosomal sex was XX and her external genitalia were female but streak gonads were found at autopsy. It is therefore essential to evaluate the state of the gonads, in males as well as in females, the discovery of dysgenetic gonads commanding gonadectomy.

Wilms' tumor was found in four out of eleven patients. The tumor was uni- or bilateral. The age of first diagnosis varied from 15 to 42 months. The observation of Wilms' tumor developing in only one of identical twins (patients 6 and 7), demonstrates the postzygotic nature of the tumor and that the chromosomal deletion is only a predisposing factor for carcinogenesis. Exactly the same lesion of the genome may or may not lead to a tumoral process. In other words, the existence or not of Wilms' tumor does not imply different rearrangements within the visible 11p deletion.

Most patients had various facial dysmorphisms but it seems impossible to single out evocative features. Mental retardation and ambiguous genitalia in the male are constant but less specific and of various degrees. Aniridia remains the most important element of the syndrome and is always associated with other eye anomalies—glaucoma, cataracts, nystagmus, ptosis, strabismus, corneal clouding—which result in partial or complete blindness.

When considering the chromosomal rearrangements, the size of the deleted segment varies, the breakpoints on 11p being located between p11.3 and p15.1. As shown by Francke et al. (1979) the smallest region of overlapping is the distal half of band 11p13. In two cases out of eleven the deletion was due to a balanced parental rearrangement. Karyotyping of the parents is therefore required to prevent familial recurrence. It is also noteworthy that in three de novo cases other structural rearrangements were also present. Their significance is far from clear. They may indicate chromosome instability in the gametes.

Increased sister chromatid exchanges have been demonstrated in fibroblasts from a patient with del 13q14-retinoblastoma (Turleau et al. 1980). Our patient had a normal rate of exchanges in fibroblasts as well as in leukocytes. This could reflect an important basic difference between both syndromes.

The 11p13 band is neighbored by important gene loci. Among those that are more easily investigated are LDHA, ACP2, HBB, and CAT (Fig. 5). Patients 3, 4, 10, and 11 had normal values for LDHA activity. Patients 2 and 8 had a decreased activity. These results are consistent with the assignment of the LDHA gene to p1203→p1208 (Francke et al. 1977). The Hb cluster (HBB) is closely linked to LDHA in p1205→

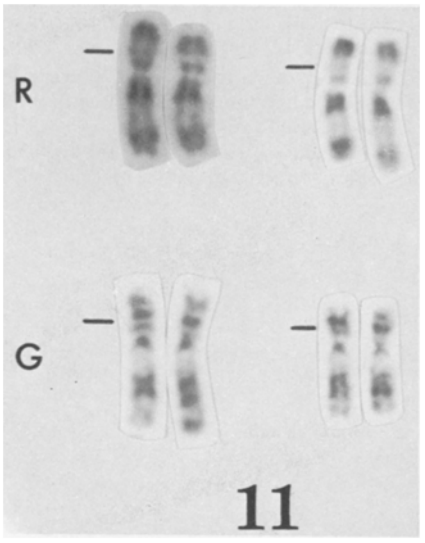


Fig. 4. Chromosomes 11 showing the del(11)(p13p14) in R- and G-banding

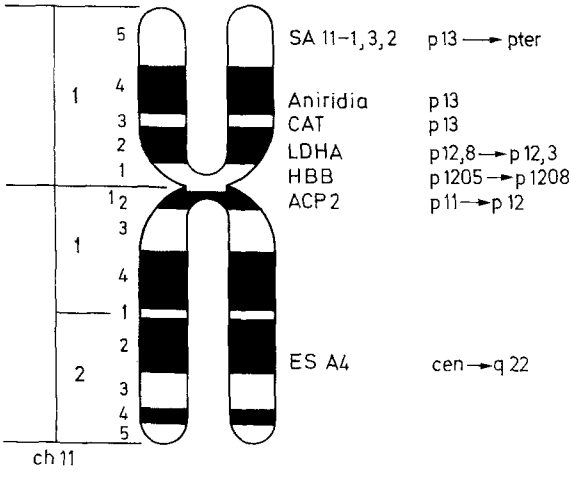


Fig. 5. Gene mapping of chromosome 11 showing the gene assignments discussed in the text

p1208, nearer to the centromere. Results obtained by Francke et al. (1977) and the present case report are consistent with this assignment.

Concerning the CAT locus, its assignment to 11p was recently suggested by Wieacker et al. (1980) who had used somatic cell hybridization and showed cosegregation with LDHA. The enzymatic activity of CAT was studied in our patient as well as in two other patients, one being trisomic for 11p13 and the other trisomic for 11p except band 11p13 (Junien et al. 1980). Results were entirely compatible with the regional assignment of CAT to 11p13. If this assignment is confirmed in other patients, assay of CAT activity will become an important complementary laboratory investigation in patients with aniridia. It is indeed conceivable that the deletion may be too small to be microscopically detectable but still involve the CAT locus.

The association of del 11p, aniridia, mental retardation, ambiguous genitalia, and a high risk for developing nephroblastoma or gonadoblastoma is remarkable by many aspects which have been discussed here. Still another remarkable aspect is the recent discovery that the gene locus for dominant aniridia is localized on 2p in close linkage with the ACP1 locus, while the ACP2 locus is localized on 11cen→p12, near 11p13. This obviously brings to mind hypotheses on evolution by gene duplications (Ferrell et al. 1980).

As mentioned above, the aniridia complex has many points in common with the del13q14-retinoblastoma association. A further point of similarly could well be the eventual discovery that the gene for dominant retinoblastoma is not localized on chromosome 13, but elsewhere and why not in association with an esterase gene, closely linked to 13q14, for instance the gene for esterase A4 on the long arm of chromosome 11?

Acknowledgments. The authors are grateful to Dr. Dominique Labie (Institut de Pathologie Moléculaire, Paris) for studies of the patient's hemoglobin, and to Françoise Chavin-Colin and Marie-Odile Cabánis for their valuable technical assistance.

Dr. Catherine Turleau is Chargé de Recherche and Dr. J. de Grouchy Directeur de Recherche at the C.N.R.S.

References

Andersen SR, Geertinger P, Larsen HW, Mikkelsen M, Parving A, Vestermark S, Warburg M (1978a) p11 deletion syndrome. Aniridia, urogenital malformation and imbecility. Ugeskr Laeger 140:2112

Andersen SR, Geertinger P, Larsen HW, Mikkelsen M, Parving A, Vestermark S, Warburg M (1978b) Aniridia, cataract and gonadoblastoma in a mentally retarded girl with deletion of chromosome 11. Ophthalmologica 176:171–177

Brusa P, Torricelli C (1953) Nefroblastoma di Wilms ed affezioni renali congenite nella casistica dell'IIPAI di Milano. Minerva Pediatr 5: 457–463

Cotlier E, Rose M, Moel SA (1978) Aniridia, cataracts and Wilms tumor in monozygous twins. Am J Ophthalmol 86:129–132

Ferrel RE, Chakravarti A, Mintz Hittner H, Riccardi VM (1980) Autosomal dominant aniridia: probable linkage to acid phosphatase-1 locus on chromosome 2. Proc Natl Acad Sci USA 77:1580–1582

Francke U, George DL, Brown MG, Riccardi VM (1977) Gene dosage effect: intraband mapping of the LDHA locus using cells from four individuals with different interstitial deletions of 11p. Cytogenet Cell Genet 19:197–207

Francke U, Holmes LB, Riccardi VM (1979) Aniridia-Wilms' tumor association: evidence for specific deletion of 11p13. Cytogenet Cell Genet 24:185–192

François J, Coucke D, Coppieters R (1979) Aniridia-Wilms' tumor syndrome. Ophthalmologia 174:35–39

Hittner HM, Riccardi VM, Francke U (1979) Aniridia due to chromosome 11 deletion. Ophthalmologica 86:1173–1183

Human Gene Mapping 5 (1979) Edinburgh Conference 1979. Cytogenet Cell Genet 25:1–236

Junien C, Turleau C, Grouchy J de, Said R, Rethoré MO, Baccichetti C, Dufier JL (1980) Regional assignment of catalase (CAT) gene to band 11p13. Association with the aniridia-Wilms' tumor-gonadoblastoma (WAGR) complex. Ann Génét (Paris) 23:165–168

Ladda R, Atkins L, Littlefield J, Neurath P, Marimuthu KM (1974) Computer-assisted analysis of chromosomal abnormalities: detection of a deletion in aniridia/Wilms' tumor syndrome. Science 185: 784–787

Maurer HS, Pendergrass TW, Borges W, Honig GR (1979) The role of genetic factors in the etiology of Wilms' tumor. Two pairs of monozygous twins with congenital abnormalities (Aniridia; hemi-hypertrophy) and discordance for Wilms' tumor. Cancer 43:295–208

McKusick VA (1975) Mendelian inheritance in man. Catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes. Fourth edition. Johns Hopkins University Press, Baltimore and London, p 837

Miller RW, Fraumeni JF, Manning MD (1964) Association of Wilms' tumor with aniridia, hemihypertrophy and other congenital malformations. N Engl J Med 270:922–927

Riccardi VM, Sujansky E, Smith AC, Francke U (1978) Chromosomal imbalance in the aniridia-Wilms tumor association: 11p interstitial deletion. Pediatrics 61:604–610

Riccardi VM, Hittner HM, Francke U, Yunis JJ, Ledbetter D, Borges W (to be published) The aniridia-Wilms' tumor associtation: the critical role of chromosome band 11p13. Cancer Genet Cytogenet

Smith ACM, Sujansky E, Riccardi VM (1977) Aniridia, mental retardation and genital abnormality in two patients with 46,XY,11p–. New Syndromes, Birth Defects 13:257

Turleau C, Cabanis MO, Grouchy J de (1980) Augmentation des échanges de chromatides dans les fibroblastes d'un enfant atteint de del(13) rétinoblastome. Ann Génét (Paris) 23:169–170

Warburg M, Mikkelsen M, Andersen SR, Geertinger P, Larsen HW, Vestermark S, Parving A (1980) Aniridia and interstitial deletion of the short arm of chromosome 11. Metab Ped Ophthal 4:97–101

Wieacker P, Mueller CR, Mayerova A, Grzeschik KH, Ropers HH (1980) Assignment of the gene coding for human catalase to the short arm of chromosome 11. Ann Génét (Paris) 23:73–77

Yunis JJ, Ramsay NKC (1980) Familial occurrence of the aniridia-Wilms' tumor syndrome with deletion 11p13–14.1. J Pediatr 96: 1027–1030

Received November 24, 1980

Note Added in Proof

We have studied another patient with aniridia, nephroblastoma, mental and growth retardation, and found a deletion of approximately half of band 11p13. This patient had a very low catalase activity, thus confirming the assignment of the cat gene to 11p13.