ROBERTSONIAN TRANSLOCATIONS AND ABNORMAL PHENOTYPES

GROUPE DE
CYTOGÉNÉTICIENS FRANÇAIS
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The present study is a continuation of the French collaborative study on inversions in man (Groupe de Cytogénéticiens Français. Annales de Génétique, 1986, vol. 29, n° 3, pp. 127-215). It is devoted to Robertsonian translocations observed in association with abnormal phenotypes. The data were collected by French laboratories having participated in the inversions study. Their identifications are the same and are given in the appendix. Not all of the laboratories involved in the previous investigation had relevant data pertaining to the present one. We are most grateful to the doctor Simone Gilgenkrantz who collected the data from the laboratories and prepared the manuscript.

GROUPE DE CYTOGÉNÉTICIENS FRANÇAIS. Coord. Simone GILGENKRANTZ. — Robertsonian translocations and abnormal phenotypes.
Ann Génét, 1989, **32,** n° 1, 5-9.

SUMMARY : The Groupe de Cytogénéticiens Français collected 32 cases of Robertsonian translocations with an abnormal phenotype of which 21 t(13q;14q)'s. Nineteen were inherited, four had had occurred de novo ; and nine were of unknow origin. The 21 t(13q; 14q)'s were grouped according to the phenotype. Some suggested partial 13 trisomy (hexadactyly ; eye defect), others partial 13 monosomy (facial dysmorphism ; thumb anomalies). Three de novo t(15;15)'s with Prader-Willi syndrome show that non identifiable partial monosomies may be associated with the occurence of Robertsonian translocations. The mechanism leading to the fusion of acrocentrics are discussed.

KEY-WORD : Robertsonian translocation.

GROUPE DE CYTOGÉNÉTICIENS FRANÇAIS. Coord. Simone GILGENKRANTZ. — Translocations robertsoniennes et phénotypes anormaux. *(En Anglais).*
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RÉSUMÉ : Le Groupe de Cytogénéticiens Français a rassemblé 32 cas de translocation robertsonienne avec phénotype anormal, dont 21 t(13q14q). Dix-neuf cas étaient hérités, quatre de novo, et 9 d'origine inconnue. Les 21 cas de t(13q14q) ont été regroupés selon la symptomatologie. Quelques cas étaient évocateurs d'une trisomie 13 partielle (hexadactylie, atteinte oculaire), quelques autres d'une monosomie 13 partielle (dysmorphie faciale, anomalies des pouces). L'existence de trois cas de t(15;15) de novo, avec syndrome de Prader-Willi, démontre qu'une monosomie partielle non décelable cytogénétiquement peut accompagner la survenue d'une translocation robertsonienne. Enfin, les mécanismes aboutissant à la fusion de chromosomes acrocentriques sont analysés.

MOT-CLÉ : Translocation robertsonienne.

INTRODUCTION

Robertsonian translocations may be observed in patients with abnormal phenotypes, as are apparently balanced reciprocal translocations. They are not rare in the general population. There is, however, an obvious bias of ascertainment favoring the discovery of a Robertsonian translocation in a subject with an abnormal phenotype, since many requests for karyotyping are done because of phenotypic abnormalities. The association may be fortuitous, but this relationship between apparently balanced Robertsonian translocations and abnormal phenotypes deserves further clarification.

We decided to classify Robertsonian translocations according to the chromosome pairs involved, distinguishing between *de novo* and transmitted ones. In cases of *de novo* translocations, we tried to find out whether the clinical symptomatology could be related to a submicroscopic deletion. Finally, in familial cases, we tried to analyse the mode of transmission and the possibility of secondary duplications or deficiencies arising at meiosis, and leading to phenotypic abnormalities in subsequent generations.

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MATERIAL

This study was carried out on 32 phenotypically abnormal patients carrier of a Robertsonian translocation. While bearing in mind that there are many possible sources of error in such a multicenter study, it was estimated that these 32 cases correspond to 3.5 % of all the Robertsonian translocations detected in the participating Centers, from a total of 144,070 karyotypes. The pairs involved and the inherited or *de novo* nature of the disorder were as follows in table I.

TABLE I

t	Number	Origin of translocation			
		Paternal	Maternal	*De novo*	Unknown
13q14q	21	7	7		7
15q22q	3	1	2		
14q21q	2	1			1
Dq15q	6	1		4	1

t(13q14q) and abnormal phenotype

Twenty-one « de novo » or familial t(13q14q)'s associated with an abnormal phenotype were found. In some families, several phenotypically abnormal patients carrying the translocation were detected, thus giving altogether more than 21 abnormal subjects. The clinical findings were as follows :

Neonatal period

Urogenital abnormalities in a fetus, detected by ultrasonography : megaloureter, persistence of a cloaca with abnormalities of the genital region and confirmed by necropsy. BR1.

Dysmorphic syndrome and dwarfism in a premature 34-week baby. Death of the baby occurred at seven days. Diastrophic dwarfism was suggested. The translocation was of paternal origin. R02.

Encephalocele with facial dysmorphism in a newborn (no other information).

Isolated mental deficiency

In one child of a sibship of five of which two had translocations transmitted by the father and grandfather. Fifteen subjects were studied. Nine other translocation carriers were normal. Recurrent miscarriages were noticed in the couples with the translocation. DI1.

Urogenital abnormalities

Unilateral renal agenesis in a mentally retarded girl.

Agenesis of the left testicle and oligospermia (the origin of the translocation is unknown). TR1.

Hypogonadism, hypospadias, and mental retardation in a 13-year-old boy. The mother had the translocation. T01.

Hemiuterus and absence of the left Fallopian tube in an otherwise normal girl (the origin of the translocation in unknown). TO1.

Male pseudohermaphroditism with partial insensitivity to testosterone in one patient. Two sisters and the father were carriers but phenotypically normal. PA7.

Dysmorphic syndromes

Three generations of one family were studied : the mother, who carried the translocation and was of small stature, but otherwise normal. Five of her six children had the translocation : they were phenotypically normal except for one mentally retarded girl, who was small and had had delayed onset of puberty ; another daughter had two children with facial dysmorphism, abnormal hands, and psychomotor retardation. NA1.

Two generations in one family : a boy with postaxial hexadactylism, amblyopia, and obesity, suggesting Laurence-Moon-Biedl syndrome. His sister, a normal carrier, had a son with a symptomatology much alike his uncle's. NA1.

A 1-year-old child with bilateral hexadactylism, dysmorphia with hypotelorism, ventricular septal defect, and growth retardation. The mother carrier was phenotypically normal. TO1

An 8-year-old girl with a triangular face, retrognathia, a high-arched palate, and psychomotor and growth retardation. The mother carrier was phenotypically normal. TO1.

A woman with epilepsy, small stature, mental retardation, and facial dysmorphism (the origin of the translocation is unknown). DI1.

A girl with facial dysmorphism, psychomotor retardation, cardiopathy, and talipes equinovarus (maternal origin). VE1.

A boy with facial dysmorphism and cardiopathy (the origin of the translocation is unknown). TO1.

A girl with facial dysmorphism, growth retardation, and incurved femurs (parents not karyotyped). PA15.

A girl with microcephaly and profound mental retardation (the origin of the translocation was maternal). In the three generations studied, the other translocation carriers were normal. PA7.

t(15q22q)

Three cases with an abnormal phenotype :

A boy with dysmaturity, imperforate anus, syndactylism, and slight dysmorphism. The translocation was of maternal origin. Three other subjects in the family were phenotypically normal carriers. PA7.

Eleven translocation carriers were detected in 3 generations of a family with 11 subjects who had the translocation. Recurrent abortions were observed, and one boy had facial dysmorphism, mental retardation, and a bilateral simian crease. PA7.

A dysmature boy with perceptive deafness, polyuria with Bartter's syndrome, and growth retardation (−5 SD) (the translocation was of maternal origin). CH1.

t(14q21q)

Two cases with hematological disorders :

Chronic myelogenous leukemia (CML) in a 27-year-old female (with Ph1). TO1.

Polycythemia in a 60-year-old man who had transmitted the translocation to two daughters. NN1.

t(Dq15q)

Six cases :

t (13q15q) with amenorrhea and obesity (1 case). TO1.

t (14q15q) with microcephaly and growth retardation (1 case). NA1.

t (14q15q) with mental retardation (1 case). SE1.

t (15q15q) : three cases, with a phenotype of Prader-Willi syndrome.

One of these (Emberger et al., 1977), a girl, born in 1974, with facial dysmorphism, hypotonia leading to obesity, and mental retardation. MO1.

The second, a girl who presented with a typical picture of Prader-Willi syndrome. High resolution banding showed a t(15;15)(p11.1;q12), thus revealing the loss of the q11 region of one of the two chromosomes 15. CH1.

The third was in a 7-month-old girl with severe hypotonia, retarded psychomotor development, and acromicria. Although she was not actually obese (weight 8 500 g), the clinical picture was compatible with Prader-Willi syndrome in the preobese phase. BO2.

In all three cases the translocation was *de novo*. Whether this fusion of two homologous chromosomes was of paternal or maternal origin is not known.

DISCUSSION

In recent years the practice of prenatal diagnosis has shown that apparently balanced chromosomal alterations can accompany abnormal phenotypes. It thus becomes difficult to decide what to do during pregnancy if it is a *de novo* abnormality (Evans et al., 1978). Techniques of molecular biology have shown in several cases that an apparently balanced karyotype, even after high-resolution banding, can involve duplication or deletion in coding regions. Previously, statistical studies had shown that the frequency of the association of mental retardation and congenital malformations (MR/MCA) is higher in carriers of apparently balanced rearrangements than in the general population (Jacobs et al., 1974 ; Nielsen and Rasmussen, 1976 ; Evans et al., 1978 ; Fryns et al., 1986, 1988 ; Aurias et al., 1978).

In our collaborative study, it was not possible to make a valid statistical comparison of the frequency of the association MR/MCA in subjects with Robertsonian translocations and its frequency in the general population. The 3.5 % level of abnormal phenotypes in subjects carrying a Robertsonian translocation, which is much higher than in the general population, raises nonetheless the question of whether there is a causal relationship. In a United Nations report (1982), based on 67,014 newborns, the incidence of Robertsonian translocations was about 0.1 % and t(DqDq)'s were almost three times more frequent than t(DqGq)'s. In our study, t(DqDq)'s were about 6 times more frequent than t(DqGq)'s. We therefore decided to analyse the phenotypes according to the chromosome pairs involved in the translocations and try to find out if duplications or deficiencies of certain juxtacentromeric regions might be responsible for the observed clinical signs.

Among the t(13q14q)'s we found two main phenotypes :

— the first comprised small stature, moderate mental retardation, facial dysmorphism, abnormalities of the fingers, and hypogonadism. Hypoplasia with camptodactyly and proximal implantation of the thumbs suggested partial monosomy 13. The facial dysmorphism in one case was similar to that described recently in an interstitial 13q14 deletion (Pankau et al., 1987) ;

— the second phenoytpe, observed in two families, comprised bilateral hexadactyly and an ocular disorder (hypertelorism in one case, amblyopia in both patients in the other family), all of which suggested partial trisomy 13.

Unfortunately we do not have a complete iconography for the 9 cases reported here of t(13q14q) with MR/MCA. In most of our cases, the translocation was inherited.

In both instances of t(14q21q)'s there were hematological disorders. Chronic myeloid leukemia (CML) in a patient with t(14q21q) is not unusual ; other cases have been reported (Becher et al., 1985 ; Engel et al., 1965 ; Kohno and Sanberg, 1978 ; Velasquez et al., 1976). In a recent publication (Becher et al., 1987), CML in a Ph1 positive patient was associated with a Robertsonian translocation (called t(15q22q) in the title, but actually a t(14q22q), judging from the figures). In all cases, a chromosome 14 was involved.

Among the t(15q15q)'s three cases of Prader-Willi syndrome demonstrate the possible association of a « Robertsonian » translocation and a juxtacentromeric deletion. The frequency of Prader-Willi syndrome in conjunction with translocations has been studied recently (Prader-Willi Conference, 1987). In all three of our cases, there was fusion of two homologous chromosomes. This type of Robertsonian translocation always occurs *de novo*. It presumably occurs when a gamete (perhaps the oocyte) carrying two fused homologous chromosomes encounters a

gamete that has lost one chromosome of this same pair (Creau-Goldberg et al., 1987 ; Kirkels et al., 1980). The mechanisms of formation of disomic gametes at meiosis are either isochromosome formation or centromeric fusion. When there is a deletion, only the second hypothesis is sustainable, with loss of one centromere and a small segment of the long arm for one of the two chromosomes 15 involved in the translocation.

When attempting to explain Robertsonian translocations with an abnormal phenotype, we must take into account mechanisms that can occur during the fusion of two acrocentric chromosomes. If the alteration arose *de novo,* it would involve monocentric chromosomes with loss of a centromere and of nucleolar organizing regions (NORs). If the alteration was inherited from a parent with a normal phenotype, one must assume that a secondary rearrangement occurred at meiosis at the centromeric regions.

Cytogenetic analysis has been carried out in man, during meiosis, in particular during pachytene (Kohno and Sanberg, 1978). Even if both centromeres are retained, as happens in many Robertsonian translocations (Mattei et al., 1979), the NORs have disappeared (Hurley and Pathak, 1977 ; Gosden et al., 1978, 1979 ; Zankl and Hahmann, 1978 ; Brasch and Smith, 1979 ; Mikkelsen et al., 1980). The breakpoints are thus on the short arms, in the DNA satellite region. In the association with the homologous chromosomes bearing a NOR, images of bivalents can be in cis or in trans ; the images seen are almost always in cis (Luciani et al., 1984), and would permit alternate segregation, thus with no risk of nondisjunction, which has been confirmed by family studies (Dutrillaux and Lejeune, 1970 ; Evans et al., 1978 ; Boue, 1979). No heterosynapsis was shown ; however, only a few meioses were studied. Cytogenetic analysis has not been done in human female meioses. It is not certain that the mechanism is the same, because of the importance in male meiosis of the sex vesicle, which is not present in female meiosis. In the cases in which the abnormal phenotype appeared in a child from a t(13q14q) family, its origin was always maternal (in all of 8 cases). However, this observation is not statistically significant.

At maternal meiosis exchanges can take place with unequal crossing-over in regions of homologous DNA sequences, producing duplications or deficiencies.

For all cases of Robertsonian translocations with an abnormal phenotype, it would therefore be useful to carry out high resolution banding, C-banding, and DAPI, and to use specific and polymorphic probes to look for finer changes in the DNA than can be studied with the standard cytogenetic techniques.

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LIST OF CYTOGENETICS LABORATORIES IN FRANCE

— Classification by towns

— Codes give an indication of the town by 2 letters, and an identification of the laboratories by numbers. These codes are used for references in the analysis of chromosomal abnormalities (tables I to XXII).

— AMIENS :
Centre de Gynécologie Obstétrique. Cytogénétique : *AM1*

— BESANÇON :
CHU St-Jacques. Cytogénétique : *BE1*

— BORDEAUX :
Hôp. Haut-Lévêque. Pessac. Hématologie : *BO1*
Maternité Hôp. Pellegrin. Cytogénétique : *BO2*

— BREST :
Fac. Médecine et CHU. Cytogénétique : *BR1*

— CAEN :
CHU Côte-de-Nacre : *CA1*
CHRU Clémenceau. Néonatalogie : *CA2*

— CHAMBERY :
CH Lab Cytogénétique : *CH1*

— CLERMONT-FERRAND :
Hôtel-Dieu. Cytogénétique et Fac. Médecine. Histo-Embryo-Cytogénétique : *CF1*

— DIJON :
Fac. Médecine. Cytogénétique : *DI1*

— GRENOBLE :
Hôp. Sablons. Cytogénétique et Biol. Reprod. : *GR1*
Fac. Médecine. La Tronche. Cytogénétique et Biol Reprod. : *GR2*

— LE HAVRE :
CHG Anatomo-Pathologie. Cytogénétique : *LH1*

— LILLE :
Biologie Médicale : *LI1*
Hôp. Calmette. Cytogénétique : *LI2*
CH St-Philibert : *LI3*

— LIMOGES :
Fac. Médecine. Cytologie et Cytogénétique : *LM1*

— LYON :
Hôp. E. Herriot. Hématologie. Cytogénétique : *LY1*
Fac. Médecine Nord. Histo-Embryo-Cytogénétique : *LY2*

— MARSEILLE :
Fac. Médecine. Génétique : *MA1*
Fac. Médecine Nord. Embryo-Cytogénétique : *MA2*
U242 INSERM. Hôp. Timone. Génétique Médicale : *MA3*

— MONTPELLIER :
Centre Transfusion : *MO1*

— MULHOUSE :
Centre Hospitalier : *MU1*

— NANCY :
Centre Transfusion Sanguine : *NA1*

— NANTES :
Hôtel-Dieu, Cytologie Cytogénétique et Fac. Médecine, Histo-Embryo-Cytogénétique : *NN1*
Maternité CHR, Lab Diagnostic Anténatal Cytogénétique : *NN2*

— NICE :
Fac. Médecine. Pathol. Cellulaire et Génétique : *NI1*

— NÎMES :
Fac. Médecine. Cytologie Clinique et Cytogénétique : *NM1*

— ORLÉANS :
Hôp. de La Source. Cytogénétique : *OR1*

— PARIS :
CHU Bichat. Histo-Embryo-Cytogénétique : *PA1*
CHU Broussais. Hôtel-Dieu. Histo-Embryo-Cytogénétique : *PA2*
CHU Cochin-Port-Royal. Histo-Embryo-Cytogénétique : *PA3*
Hôp. St-Vincent-de-Paul. Cytogénétique : *PA4*
CHU Lariboisière-St-Louis. Centre Hayem. Cytogénétique : *PA5*
Hôp. F. Widal. Histo-Embryo-Cytogénétique : *PA6*
CHU Necker-Enfants Malades. U 173 INSERM : *PA7*
CHU Necker-Enfants Malades. Cytogénétique : *PA8*
CHU Paris-Ouest. Hôp. Ambroise-Paré. Cytogénétique : *PA9*
CEBIOP. U 73 INSERM. Château de Longchamp : *PA10*
CHU Pitié-Salpêtrière. Cytogénétique : *PA11*
CHU St-Antoine. Embryo-Cytogénétique : *PA12*
Institut Curie. UA 620 CNRS : *PA13*
Hôp. Val-de-Grâce : *PA14*

— PARIS-Banlieue :
CHU Bicêtre. Histo-Embryo-Cytogénétique : *PA15*
CHU Bobigny. Histo-Embryo-Cytogénétique : *PA16*
CHU Créteil. Fac. Médecine. Cytogénétique : *PA17*
CEN Fontenay-aux-Roses. Génétique Expérimentale : *PA18*
Gif-sur-Yvette. Biologie et Génétique Evolutive : *PA19*
Gif-sur-Yvette. CNRS. GPDP : *PA20*
Jouy-en-Josas. INRA-CNRZ : *PA21*
Villejuif. INSERM U 253 : *PA22*
Versailles. Inst. Hématologie. Cytogénétique : *PA27*

— POITIERS :
Hôtel-Dieu. Histologie : *PO1*
Fac. Médecine. Histologie : *PO2*
CHU La Miletrie. Hématologie-Cytogénétique : *PO3*
CH Guingamp. Biologie : *PO4*

— RENNES :
CHU. Fac. Médecine. Histo-Embryo-Cytogénétique : *RE1*

— ROUEN :
CRTRS Génétique Humaine : *RO1*
Hôp. Charles-Nicolle. Anatomo-Pathol-Cytogénétique : *RO2*

— SAINT-ETIENNE :
CHU. Cytogénétique : *SE1*

— STRASBOURG :
Fac. Médecine. Histo-Embryo-Cytogénétique : *ST1*
Hospices Civils. Inst. Puériculture : *ST2*

— TOULOUSE :
CHU Purpan. CRTS : *TO1*

— TOURS :
CHR Bretonneau. Unité Génétique : *TR1*

— VERSAILLES :
Institut Hématologie-Cytogénétique : *VE1*