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SHORT COMMUNICATION

Quality of life in Turner syndrome is related to chromosomal constitution: implications for genetic counselling and management

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Issues of self-appraisal, friendships and academic attainments are uniquely salient for all adolescents. For girls with Turner syndrome, social problems and learning difficulties often become more serious at this time, yet may be unacknowledged by those responsible for paediatric care because their focus is on growth and sexual maturation. Data on the social and educational adjustment of 110 45,X (monosomic) females aged between 6 and 25 years is presented. Detailed information on the patients' precise karyotype was used to demonstrate systematic differences in adjustment between those whose single X chromosome was maternally derived and those in whom it was paternal. Implications for educational support and parental guidance are discussed. □ *Educational attainments, karyotype, non-verbal intelligence, quality of life, social adjustment, Turner syndrome, verbal intelligence*

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Introduction

Turner syndrome is a chromosomal disorder in which all, or a substantial part, of one X chromosome is missing due to non-disjunction, or chromosome loss during gametogenesis or early cleavage of the zygote. The condition is associated with a range of psychosocial difficulties, primarily involving immaturity and problems with social relationships, although intelligence is usually entirely normal for verbal skills (1–4). Studies of older individuals have found that impairment in the ability to make and sustain friendships, apparent during adolescence, often continues into adult life (4). Apart from those with a small ring-X chromosome, which has been associated with mental retardation (5), Turner syndrome is thought not to be characterized by a diminished overall level of verbal intelligence. There is considerable variability in the cognitive and behavioural phenotype, which has received little attention to date. Most authors who have considered the relevance of the great variability in karyotype to phenotypic variation have confined their remarks to the differences between mosaicism and monosomy, although there are recent exceptions (6).

The aim of this study was to test the hypothesis that phenotypic variability in social, educational and behavioural adjustment in childhood could be related to systematic differences in the parental origin of the single X chromosome that is found in about 50% of patients with Turner syndrome. In about 70% of girls with monosomic (45,X) Turner syndrome, the single X chromosome is maternal in origin ($45,X^m$); in the remainder, it is paternal in origin ($45,X^p$) (7).

Patients and methods

Patients were drawn from throughout the UK, including Northern Ireland, and from Southern Ireland. The sociodemographic distribution of the sample closely reflected that of the general population. The present report is confined to 110 females with Turner syndrome, aged between 6 and 25 years, as this is the age range in which issues of social adjustment and quality of life are particularly pertinent. Screening of all patients on our Turner syndrome database was conducted by postal questionnaires using a set of instruments (8–10) that were completed by parents, teachers and patients (aged 11 years and over). Parents were asked to complete the Child Behaviour Checklist (CBCL), 1991 Revision (8), which is a standardized assessment procedure for obtaining parents' ratings on a broad range of clinically relevant problem behaviours in children. Teachers were asked to respond to a structured questionnaire about educational

attainments as well as providing a Teacher Report Form (9). Patients aged between 11 and 18 years were asked to complete the Youth Self Report (YSR) (10). Standard scores (T scores) are reported for the attention problems, social problems, thought problems, delinquency and aggression syndrome subscales, as these were the areas of greatest difficulty for patients in the sample. Although CBCLs were completed for everyone in this sample who was in the appropriate age group, there are nine missing YSRs. Usually these were not completed because the girl in question did not have sufficient ability to understand the questions, and their parents decided not to ask them to do so. In addition, there are 27 missing teacher reports.

We rekaryotyped all subjects (11) and determined the parental origin of the normal X chromosome by comparing proband and parental DNA polymorphisms located on distal Xp, in a region that was deleted in both 45,X and 46,XXp patients. There were 79 females with a single maternal X chromosome and 31 with a single paternal X chromosome. In an additional 3 cases we were unable to determine the parental origin.

Parents were asked to record their child's current height and weight from the last clinic attendance. Data refer to values obtained at a wide range of different ages; height and body mass index (BMI) were therefore standardized for age and are expressed in SDS, in terms of the current UK standards (12–13). Overall, 78% were being treated with growth hormone and 91% of patients over the age of 12 years were receiving oestrogen replacement therapy. All were healthy; two girls with significant neurological disease unrelated to Turner syndrome were excluded. From a combination of personal examination (using a structured schedule), review of clinic records and parental report, we compiled two indices of stigmata that are associated with Turner syndrome. The first (visible stigmata) comprised physical features that would be evident to others, such as the patient's peers. The total was simply a sum of 17 such features (scored 0/1) including webbed neck, strabismus, short fingers, low-set ears, etc. The second comprised stigmata that would not be obvious to an observer (invisible stigmata), such as diabetes, coarctation of the aorta, and hypertension. A simple summed score was compiled of oral-motor dysfunction (sucking, chewing and swallowing competence) in infancy, a time when feeding difficulties in Turner syndrome are common (14). A quantitative score of the child's gross motor and fine motor skills was also compiled on the basis of the parental report.

Neuropsychological testing was conducted blind to the parental origin of the normal X chromosome using standard test procedures to give estimates of verbal and non-verbal (performance) IQ (15–16). Parents have not been informed of the parental origin of their daughter's X chromosome, a decision that was made after extensive discussions with paediatricians, clinical geneticists, parent groups and others concerned with the welfare of these individuals.

Results

There was no significant difference in age between the two groups at the time of their original examination or assessment (Table 1). The mean values of height for age were similar in both subcategories of Turner syndrome based on the results of karyotyping. However, the 45,X^m group were significantly lighter than those with a paternal X chromosome, and they had a lower BMI. This was not due simply to the influence of a small number of very deviant subjects, as can be seen from the identical standard deviations. Verbal IQ was significantly lower in those with a maternal as compared to those with a paternal X chromosome, although the non-verbal IQs were virtually identical. Consequently, the mean discrepancy between the two IQ scores differed substantially. If social class was controlled in an analysis of covariance, the verbal IQ differences were no longer

Table 1. Characteristics of monosomic (45,X) girls aged 6–25 years with Turner syndrome, by parental origin of normal X chromosome.

	Karyotype					Karyotype			
	45, X^m (n = 67)		45, X^p (n = 26)			45, X^m (n = 79)		45, X^p (n = 31)	
	Mean	SD	Mean	SD		Mean	SD	Mean	SD
Height SDS	−2.13	1.4	−2.11	1.6	Age at examination (years)	12.02	6.6	12.41	5.4
Weight SDS	−0.99[a]	1.2	−0.21[b]	1.0	Visible stigmata (maximum 17)	7.9	3.8	7.0	3.8
BMI SDS	0.27[c]	1.3	0.97[d]	1.3	Invisible stigmata (maximum 10)	1.9	1.1	1.9	1.7
Verbal IQ	95.1[e]	17.8	104.1[f]	17.7	Infantile oral-motor dysfunction				
Performance IQ	80.1	17.8	78.9	15.5	(maximum 3)	1.29[g]	1.14	0.77[h]	1.14
Verbal–performance					Motor skill deficit (maximum 12)	2.93[g]	2.7	1.67[h]	2.1
discrepancy	14.5[e]	15.4	25.2[f]	19.5					
Full-scale IQ < 70									
(n [%])	10 (19)		2 (8)						

SD, standard deviation. a < b, p = 0.01; e < f, p = 0.02; c < d, p = 0.04; g > h, p = 0.01.

statistically significant. However, social class (entered as a binary dummy variable) was not associated with the verbal–performance discrepancy, and this retained a degree of discrimination in the analysis of covariance (df1, F = 3.3, $p < 0.08$). Patients with a maternal X chromosome were more likely to have had significant oral-motor dysfunction during infancy, and to have poorer gross and fine motor coordination at the time of the study than 45,X^p subjects. They were not distinguished by the number or the type of visible or invisible stigmata of Turner syndrome.

The screening survey of parents and teachers showed that the proportion of girls of school age who had received a statement of special educational needs, indicating academic failure, was considerably higher for both monosomic populations than the general population, for whom the figure is only 2% (Table 2). Monosomic girls with a maternal X chromosome seemed to have more severe problems, requiring extra help at school, in several subjects. In contrast, those with a single paternal X chromosome were functioning relatively well.

In terms of the parent-rated CBCL, the 45,X^m subjects had mean scores on the attention problems, thought problems, and aggression subscales that were significantly higher than those in the 45,X^p sample (Table 3). When individual items within the subscale 'thought problems' were considered, the two items most frequently endorsed by parents were both associated with obsessive–compulsive symptomatology. The proportions were very similar in the two subsamples. 'Can't get her mind off certain thoughts; obsessions' was endorsed for 24/56 45,X^m patients (43%) and for 13/29 45,X^p patients (45%). The comparable figure in the general population of girls of equivalent age is about 25% (8). The item 'repeats certain acts over and over; compulsions' was endorsed for 14/56 45,X^m patients (25%) and for 5/29 of the 45,X^p sample (17%). The figure for the general population is < 10%.

Table 2. Educational attainments of girls with Turner syndrome aged 5–16 years.

	45,X^m (n = 59)	45,X^p (n = 21)	Significance
Mainstream school[a]			
n/total[c]	55/59	21/21	
% within karyotype	93.2	100	NS
Extra help[b]			
n/total[c]	20/39	2/15	
% within karyotype	51.3	13.3	$\chi^2 = 4.99$, $p < 0.03$
Special school[d]			
n/total[c]	4/59	0/21	
% within karyotype	6.7		NS
Statement of special educational needs[a]			
n/total[c]	17/59	5/21	
% within karyotype	28.8	23.8	NS
Specific learning difficulties[e]			
Maths			
n/total[c]	6/41	1/15	
% within karyotype	14.6	6.7	NS
Science			
n/total[c]	5/38	1/15	
% within karyotype	13.2	6.7	NS
English			
n/total[c]	5/41	2/15	
% within karyotype	12.2	13.3	NS
Physical education			
n/total[c]	7/23	0/8	
% within karyotype	30.4	0	NS

[a] Proportion is given for those aged 5–16 years at follow-up.
[b] Proportions are those for whom teacher reports were available, receiving additional classroom assistance in mainstream school because of specific learning difficulties. Value is within each karyotype.
[c] Total is number of subjects for whom teacher information was available.
[d] Mainly schools for moderate or severe learning difficulties.
[e] Defined as falling far below grade level in subject.
NS, not significant.

Table 3. Behaviour rating scale standard (T) scores for monosomic 45,X^m compared with monosomic 45,X^p Turner syndrome.

Karyotype	*n*	Attention problems	Social problems	Thought problems	Delinquency	Aggression
Parent-rated CBCL (4–18 years)						
45,X^m	66	63.4 ± 12.3[a]	63.6 ± 11.5	58.7 ± 9.4[c]	54.1 ± 6.8	56.8 ± 10.0[e]
45,X^p	26	58.4 ± 8.8[b]	60.7 ± 11.0	55.6 ± 6.5[d]	52.0 ± 3.8	52.3 ± 4.4[f]
Teacher-rated TRF (6–16 years)						
45,X^m	37	55.8 ± 6.2	58.2 ± 7.2[g]	53.8 ± 7.4[g]	51.6 ± 3.9	54.3 ± 4.8
45,X^p	14	53.9 ± 7.7	53.9 ± 5.4[h]	50.6 ± 2.1[h]	51.3 ± 3.5	52.9 ± 4.5
Self-report YSR (11–18 years)						
45,X^m	29	58.6 ± 10.9	61.6 ± 11.6[e]	52.8 ± 5.3[g]	53.0 ± 4.9	54.7 ± 7.5[g]
45,X^p	15	54.5 ± 6.4	53.7 ± 6.0[f]	50.2 ± 0.5[h]	51.8 ± 3.5	51.0 ± 2.1[h]

CBCL, Child Behaviour Checklist; TRF, Teacher Report Form; YSR, Youth Self Report. a > b, $p = 0.03$; e > f, $p = 0.004$; c > d, $p = 0.07$; g > h, $p = 0.02$.

Teachers also rated the girls with the single maternal X chromosome as having more social problems than those with a 45,X^p genotype, as well as more thought problems (endorsing the same items as parents, indicating obsessive–compulsive symptomatology). A very similar picture was seen in the ratings made by girls aged 11–18 years who completed the YSR. The social problems endorsed by teachers and by the girls themselves were concerned primarily with not getting along with other children, behavioural immaturity, and preferring the company of younger children.

Conclusions

We have undertaken a cytogenetic, molecular, phenotypic, behaviour and cognitive study of girls with Turner syndrome, and found evidence that an imprinted X-linked locus influences social–cognitive skills and behaviour (17–18). Our original publication presented data on social adjustment according to the findings from a questionnaire that was designed with the aim of identifying social–cognitive deficits. This paper supplements and extends those original findings with an enlarged sample of subjects, and a more detailed account of social adjustment and educational attainments. The main message from the research is clear: there are psychological differences within the monosomic Turner syndrome population that are not related to differences in their physical phenotype.

Our findings beg the question: what genetic influences are responsible for the cognitive and behavioural impairments associated with the adjustment differences in both groups? If we could understand these better, we would possibly be able to devise interventions to improve the quality of life of girls with Turner syndrome. Nevertheless, we can conclude with some confidence that educational progress and social success differ systematically in patients with Turner syndrome, depending on their chromosomal constitution. These findings have implications for parental guidance and information at the time of diagnosis, for the provision of remedial education, and potentially for genetic counselling.

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References

1. Rovet JF, Ireland L. The behavioural phenotype in children with Turner syndrome. Pediatr Psychol 1994;19:779–90
2. McCauley E, Kay T, Ito J, Trader R. The Turner syndrome: cognitive deficits, affective discrimination and behaviour problems. Child Dev 1987;58:464–73
3. McCauley E, Ross JL, Kushner H, Cutler G. Self-esteem and behaviour in girls with Turner syndrome. Dev Behav Ped 1995;16:82–8
4. Downey J, Elkin EJ, Erhardt AA, Meyer-Bahlburg M, Bell J, Morishima A. Cognitive ability and everyday functioning in women with Turner syndrome. J Learn Dis 1991;24:32–9
5. Collins AL, Lockwell AE, Jacobs PA, Dennis NR. A comparison of the clinical and cytogenetic findings in 9 patients with a ring (X) cell line and 16 45,X patients. J Med Genet 1994;31:528–33
6. Ross JL, Kushner H, Zinn AR. Discriminant analysis of the Ullrich–Turner syndrome neurocognitive profile. Am J Med Genet 1997;72:275–80
7. Jacobs PA, Betts PR, Cockwell AE, Crolla JA, Mackenzie MJ, Robinson DO, et al. A cytogenetic and molecular reappraisal of a series of patients with Turner's syndrome. Ann Hum Genet 1990;54:209–23
8. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, VT: Department of Psychiatry, University of Vermont, 1991
9. Achenbach TM. Manual for the Teacher's Report Form and 1991 Profile. Burlington, VT: Department of Psychiatry, University of Vermont, 1991
10. Achenbach TM. Manual for the Youth Self-Report Form and 1991 Profile. Burlington, VT: Department of Psychiatry, University of Vermont, 1991
11. Jacobs PA, Dalton P, James R, Mosse K, Power M, Robinson D, et al. Turner syndrome: a cytogenetic and molecular study. Ann Hum Genet 1997;61:471–83
12. Freeman JV, Cole TJ, Chin S, Jones PRM, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 1995;73:17–24
13. Boyce L, Cole T. Castlemead Growth Program, Welwyn Garden City: Castlemead Publications, 1993
14. Mathisen B, Reilly S, Skuse D. Oral-motor dysfunction and feeding disorders in infants with the Turner syndrome. Dev Med Child Neurol 1992;34:141–9
15. Wechsler D. The Wechsler Intelligence Scale for Children – manual. New York: Psychological Corporation, 1992
16. Wechsler D. Wechsler Adult Intelligence Scale – revised. New York: Psychological Corporation, 1986
17. Skuse D, Bishop D, Elgar K, Morris E. Phenotype–karyotype relationships in Turner syndrome. In: Stabler B, Bercu B, editors. Therapeutic outcome of endocrine disorders: efficacy, innovation and quality of life. New York: Springer-Verlag, 1998 (in press)
18. Skuse DH, James RS, Bishop DVM, Coppins B, Dalton P, Aamodt-Leeper G, et al. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. Nature 1997;387:705–8