A neuropsychological-genetic profile of atypical cri du chat syndrome: implications for prognosis

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Abstract

Cri du chat syndrome is associated with a deletion on the short arm of chromosome 5. The main diagnostic feature is a high pitched, cat-like cry which has recently been localised to 5p15.3 and is separate from the remaining clinical features of the syndrome, which have been localised to 5p15.2. The present study describes a family of four who have a deletion slightly distal (5p15.3) to the critical region. Detailed neuropsychological evaluations indicated a similar pattern of cognitive performance to that reported for subjects with typical CDCS but with only minimal intellectual impairment. In addition, in this family the 5p deletion is transmitted in an autosomal dominant fashion, contrasting with most cases of CDCS, which are either de novo or occur as an unbalanced product of a balanced translocation in a normal parent. This study confirms the importance of differentiating between 5p deletions that coincide with the typical cri du chat phenotype which includes severe to profound learning disability and deletions that only delete the distal critical region that coincides with a milder degree of cognitive impairment and a much improved prognosis.

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Cri du chat syndrome (CDCS) is a relatively rare chromosome disorder that affects approximately 1 in 40 000-50 000 live births. The syndrome is known to result from a variable terminal deletion of the short arm of chromosome 5 and represents one of the most common deletion syndromes in humans.[1] Recent molecular studies[2 3] have pinpointed the critical region to a small region within 5p15.2. Subjects with deletions in this region present with the characteristic high pitched, "cat-like" cry, from which the syndrome derives it name,[4] and have a striking facial appearance which appears to change with age. In childhood, the face is round with hypertelorism, a broad nasal bridge, and low set ears, whereas in adolescence the length of the face increases to become long and slender.[1] Other features such as respiratory and cardiac problems have also been frequently cited.[5] The cognitive and behavioural phenotype includes severe learning disability, slow psychomotor development, failure to thrive, hyperacusis, and a receptive-expressive language discrepancy.[6–10] The importance of the critical region to the manifestation of typical CDCS has been further highlighted by the results of recent studies that have described subjects with 5p deletions outside the critical region and who do not present with the severity of clinical characteristics described above.[2 3 11 12] These findings indicate that deletions of different segments of 5p may result in distinct behavioural-cognitive phenotypes.

The present study examines a rare family of four (father and three offspring) all of whom have a del(5p) karyotype. Each offspring was diagnosed at birth with the cri du chat syndrome because of an unusual cry and low birth weight. However, their karyotypes all showed a deletion slightly distal (5p15.3) to the critical region (5p15.2). Chromosomal analysis of the children's parents showed that their father also carried the same deletion. Detailed neuropsychological evaluations indicated a similar pattern of cognitive performance to that reported for patients with typical CDCS but with considerably milder intellectual impairments. In addition, in this family the 5p deletion is transmitted in an autosomal dominant fashion, contrasting with most cases of CDCS, which are either de novo or occur as an unbalanced product of a balanced translocation in a normal parent.

Methods

The father is aged 39½ years (right handed) and has no history of any developmental delay (remained in education until 16 years) and no facial dysmorphism, although he is reported as having had an unusual cry as an infant. The oldest sib (sib 1) is aged 13 years 9 months (right handed), the second sib (sib 2) is aged 10 years 8 months (right handed), and the youngest sib (sib 3) is aged 6 years 7 months (right handed). All sibs presented with the cat-like cry and slight facial dysmorphism in infancy. Failure to thrive and mild psychomotor development were also reported in sibs 2 and 3 but not in the oldest child. Two of the sibs (1 and 3) attend mainstream school and sib 2 attends a school for children with mild-moderate learning disabilities. At the time of testing neither the father nor the sibs required the use of hearing aids and none reported any early middle ear problems that may have affected their earlier speech and language development.

Agreement for publication of photographs could not be obtained.

Materials

Conventional G banded chromosome analysis was undertaken on cultured blood samples. These studies showed the presence of a termi-

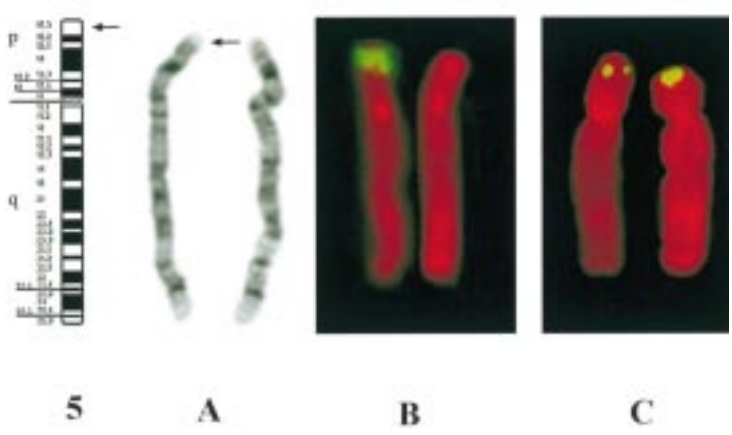

Figure 1 Ideogram of chromosome 5 with deletion breakpoint arrowed and partial karyotypes, (A) G banded, (B) FISH with telomeric probes pcp5, (C) FISH with cri du chat critical region probe D5S23. The deleted chromosome is on the right hand side of each pair.

nal deletion of the distal short arm of one chromosome 5 (p15.3-pter) in all family members (fig 1). Fluorescence in situ hybridisation (FISH) studies with a chromosome 5 telomeric region painting probe (Biovation probe SPBP5) confirmed the deletion of 5p15.3. Further FISH studies with the cri du chat critical region D5S23 locus specific probe (Oncor) which maps to p15.2 showed the presence of signals on both chromosome 5 homologues in all family members. The deletion breakpoint was therefore localised to proximal p15.3.

COGNITIVE MEASURES

Level of cognitive functioning

This was measured by the Wechsler Intelligence Scale for Children-Revised (WISC-III)[13] and the Wechsler Adult Intelligence Scale (WAIS-R).[14] This battery of tasks comprises two scales, a verbal scale and a performance scale. On the verbal scale, subtests measure a number of abilities related to general knowledge (Information), verbal reasoning (Similarities), mental arithmetic, vocabulary skill (oral definition of words), verbal short term memory (Digit Span), and verbal comprehension. On the performance scale, subtests measure abilities related to perceptual analyses (Picture Completion), manual sequencing of blocks to form a story (Picture Arrangement), visuoconstruction skill (Object Assembly, Block Design, and Coding), visuospatial skill (Symbol Search), and visuomotor skill (Mazes).

Language skills

Receptive and expressive language abilities were assessed using the following measures. Comprehension of vocabulary was measured by the British Picture Vocabulary Scales (BPVS)[15] and has an age range of 2.0 to 19.0 years. The subject is presented with an array of four pictures and must indicate which one represents the word spoken by the experimenter, for example, "ball". Arrays of increasing difficulty are presented until the child reaches a ceiling. The BPVS allows the calculation of a vocabulary age.

Comprehension of grammar was measured by the Test of the Reception of Grammar (TROG)[16] which assesses the understanding of selected aspects of grammar in children aged 4 to 13 years plus, using a picture pointing response format that eliminates the need for expressive language ability. Each subject is presented with an array of four pictures and has to indicate which one represents the sentence spoken by the examiner, for example, "he is sitting on the table" as opposed to the grammatical distracter "she is sitting on the table". This test is concerned with understanding parts of speech, simple and complex sentences, pronouns, word inflections, relative clauses, and embedding. The TROG also allows the calculation of an age equivalent score.

Expressive vocabulary was measured using the One Word Expressive Language Scale (EOWPVT).[17] There are two versions of this task. The first is designed for children aged 2-12 years and the second for use with older children aged 12-16 years. In both versions the child is presented with a series of black and white pictures and must verbally name the object in each picture. Items of increasing difficulty are presented until the child reaches a ceiling. The EOWPVT yields an age equivalent score, deviation IQs, and centile ranks.

Articulation

This was measured by the Goldman-Fristoe Test of Articulation (GFTA),[18] which assesses spontaneous production of all except one of the English consonant sounds as well as 11 consonant blends. The total score is 68.

Reading skills

These were assessed using the Wechsler Objective Reading Dimensions (WORD).[19] This comprises three sections: Basic Reading, Reading Comprehension, and Spelling. Each section allows for the calculation of an age equivalent score.

Results

Table 1 summarises scores across the measures of IQ, language, articulation, and reading skills.

INTELLECTUAL LEVEL

Father

Full scale IQ on the WAIS-R was 95 which falls within the average range of ability (IQs of 90-109) with both verbal IQ and performance IQ also within the average range (verbal 93, performance 100). Examination of the individual subtests indicate that on the verbal scale performance was best on the Digit Span task and the Similarities task and worse on the Vocabulary task. On the performance scale, performance was best on the Picture Completion task and Object Assembly task and worse on the Digit Symbol task.

Sibs

Full scale IQs on the WISC-III were as follows. The oldest sib (sib 1) was 92 which falls within the average range of ability with performance IQ also within the average range (PIQ 101) but

Table 1 Summary of scores across the measures of verbal and performance intelligence, receptive and expressive language, articulation and basic reading, comprehension and spelling

Measures	*Sib 1 (13.9 y)*	*Sib 2 (10.8 y)*	*Sib 3 (6.7 y)*
Intellectual level			
Verbal IQ	86	70	99
Performance IQ	92	75	113
Full Scale IQ	101	70	105
Language skills			
(Age equivalent score in years and months)			
Receptive			
BPVS	12.6	8.9	6.4
TROG	11.0>	8.0	6.0
Expressive			
EOWPVT	8.0	5.0	3.4
Articulation			
(Centile score)			
GFTA	<50th	<50th	<50th
Reading skills			
(Age equivalent in years and months)			
Basic reading	16.0	8.0	6.4
Reading comprehension	9.9	<6.0	<6.0
Spelling	12.6	7.6	<6.0

verbal IQ within the low average range (VIQ 86). The difference between the two scores was significant at the 0.05 level of significance. Sib 2 was 70 which falls within the low range of ability with performance IQ (PIQ 75) and verbal IQ (VIQ 70) also within the low range. Sib 3 was 105 which falls within the average range with performance IQ also within the average range (PIQ 113) and verbal IQ within the average range (VIQ 99). The difference between the two scores was significant at the 0.05 level of significance. Examination of the individual subtests indicate that on the verbal scale all three sibs performed best on the Digit Span task, irrespective of IQ, and worse on the verbal comprehension and vocabulary tasks. On the performance scale, both sib 1 and sib 3 performed best on the Picture Completion task while sib 2 performed best on the Object Assembly task. Interestingly, all three performed worse on the Digit Symbol task.

LANGUAGE AND ARTICULATION SKILLS

All three sibs had age equivalent estimates within one to two years of their chronological ages on the measures of receptive language (BPVS and TROG). In contrast, all age equivalent estimates on the measure of expressive language (EOWPVT) fell three to five years below their chronological age (table 1). In addition, misarticulations were common, with all sibs falling within or below the 50th centile for their age range. When errors occurred they included sound substitutions and distortion of vowels and consonants.

READING AND SPELLING SKILLS

On a measure of basic reading, sibs 2 and 3 both had age equivalent estimates within two years of their chronological age. The oldest sib, however, produced an age equivalent score three years above chronological age. In contrast, on a measure of reading comprehension, sib 1 performed four years below chronological age, while sibs 2 and 3 both fell below floor level (<6.0 years) on this measure. Performance was also reduced on a measure of spelling ability with age equivalent estimates one to three years below their chronological ages (table 1).

Discussion

The present study assessed the pattern of cognitive functioning in a family of four (a father and three children) initially diagnosed with cri du chat syndrome. Subsequent FISH analysis showed that the deletion breakpoint was localised to 5p15.3 and did not include the critical region. The main clinical characteristic that had led to diagnosis had been the presence of a cat-like cry at birth. Additional clinical features had included failure to thrive, slow psychomotor development, and slight facial dysmorphism in the sibs, although the father himself had no dysmorphic facial features. In terms of their neuropsychological profile, however, the present study found no evidence to indicate severe levels of intellectual impairment, but it did indicate a pattern of cognitive strengths and weaknesses that were similar to, but more subtle in characterisation, than those displayed by patients with typical CDCS (5p15.2).

Of potential significance is the finding that the father and all three sibs appear to have strengths in non-verbal skills, particularly those requiring manipulation of spatial designs, but weaknesses in verbal skills, such as those requiring comprehension and expression of verbal information. Closer examination of verbal skills in the sibs showed a pattern of reduced expressive language and articulation skills compared to receptive language skills. Interestingly, an expressive-receptive discrepancy has also been reported in children with typical CDCS but to a much greater degree of severity.[9] In addition, reading skills were significantly impaired in all but one of the sibs (sib 1) who displayed enhanced basic reading skills compared to reading comprehension and spelling skills. In contrast, sibs 2 and 3 both performed at floor level on almost all of the reading and spelling tasks.

These findings are important for two main reasons. Firstly, they confirm the results of previous genetic studies of distinct phenotypic features associated with deletions of different segments of distal 5p.[2 3 11] Secondly, they provide a detailed neuropsychological profile of subjects with a deletion of 5p15.3 in whom there is minimal intellectual impairment, but who display a specific verbal-performance discrepancy in the direction of reduced verbal skills, and in particular delayed expressive language skills. Recent evidence from two molecular studies has also indicated that deletions of 5p15.3 may result in specific speech delay with no major intellectual impairment,[2 20] although authors from both studies relied almost exclusively upon IQ data. Taken together, these recent findings indicate the possibility of anomalous cerebral lateralisation underlying cognitive functioning in subjects with a 5p15.3 deletion. It may be that abnormal gene expression within this region has influenced early brain development, specifically area(s) associated with phonological processing. Indeed, Church *et al*[2] have identified a candidate gene (DAT1[21]) located in 5p15.3 which encodes a type 1 dopamine transporter. Further molecular work is clearly needed to define deletions relative to the actual genes and to understand

the role of variable gene expression in the resulting phenotype.

In conclusion, the present study clearly indicates the importance of accurately differentiating between 5p deletions that result in a typical cri du chat syndrome phenotype and the severity of cognitive impairment that is associated with it and deletions that result in a milder cri du chat phenotype and much better prognosis.

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