Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia

K. E. Watkins, N. F. Dronkers and F. Vargha-Khadem

1Developmental Cognitive Neuroscience Unit, Institute of Child Health, University College London Medical School, London, UK and 2Center for Aphasia and Related Disorders, VA Northern California Health Care Center, Martinez, California, USA

Correspondence to: Kate Watkins, Cognitive Neuroscience Unit, Montreal Neurological Institute, 3801 University Street, Montreal, QC, Canada H3A 2B4
E-mail: kwatkins@bic.mni.mcgill.ca

Summary
Genetic speech and language disorders provide the opportunity to investigate the biological bases of language and its development. Critical to these investigations are the definition of behavioural phenotypes and an understanding of their interaction with epigenetic factors. Here, we report our investigations of the KE family, half the members of which are affected by a severe disorder of speech and language, which is transmitted as an autosomal-dominant monogenic trait. The cognitive manifestations of this disorder were investigated using a number of linguistic and non-linguistic tests. The aims of these investigations were to establish the existence of a ‘core’ deficit, or behavioural phenotype, and to explain how such a deficit during development might give rise to the range of other impairments demonstrated by affected family members. The affected family members were compared both with the unaffected members and with a group of adult patients with aphasia resulting from a stroke. The score on a test of repetition of non-words with complex articulation patterns successfully discriminated the affected and unaffected family members. The affected family members and the patients with aphasia had remarkably similar profiles of impairment on the tests administered. Premorbidly, however, the patients with aphasia had enjoyed a normal course of cognitive development and language experience. This benefit was reflected on a number of tests in which the patients with aphasia performed significantly better than the affected family members and, in the case of some tests, at normal levels. We suggest that, in the affected family members, the verbal and non-verbal deficits arise from a common impairment in the ability to sequence movement or in procedural learning. Alternatively, the articulation deficit, which itself might give rise to a host of other language deficits, is separate from a more general verbal and non-verbal developmental delay.

Keywords: developmental disorders; language impairment; aphasia; behavioural phenotypes; genetics

Abbreviations: ANOVA = analysis of variance; DF = linear function; DFA = discriminant function analysis; PIQ = performance intelligence quotient; SLI = specific language impairment; TROG = Test for Reception of Grammar; VIQ = verbal intelligence quotient; WAIS-R = revised Wechsler adult intelligence scale; WISC-R = Wechsler Intelligence Scale for Children–revised; WISC-III = Wechsler Intelligence Scale for Children, third edition; WPPSI = Wechsler Preschool and Primary Scales of Intelligence

Introduction
Developmental disorders of speech and language occur in ~7% of children (Tomblin et al., 1997) in the absence of causal factors such as mental retardation, deafness, neurological deficits or social deprivation. Pedigree analyses and twin studies provide evidence for a genetic aetiology in many of these disorders (Tallal et al., 1991; Lewis, 1992; Bishop et al., 1996), and their investigation may provide insights into the biological bases of language, its evolution and its development. The definition of behavioural phenotypes is of critical importance to the investigation of these disorders, particularly in view of their developmental nature. Also, the effects of an impairment presenting during childhood on the development of other aspects of behaviour and cognition needs to be considered.

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Here, we describe our investigations of a large family with a genetic disorder of speech and language, known as the KE family (see Fig. 1). Half of the members of the first three generations are affected by a disorder of speech and language that renders them sometimes agrammatical and often unintelligible. The disorder is developmental, manifesting itself early in childhood in the first attempts at speech and persisting throughout adulthood. Speech appears effortful and word endings often are unclear. Word order also frequently is compromised. Nearly all members of the family live in the same neighbourhood and socialize together regularly. Most of the affected and unaffected family members are employed in the service sector (e.g. fast-food restaurants, cleaning services, public transport). Of the affected members, the majority left the education system at age 16 years, typically ceasing speech therapy from that time. Despite their difficulties in communication, however, they remain sociable, amicable and persevering in their efforts to be understood.

The classification for affected and unaffected status in each family member is based on the assessment of speech and language function. There is total agreement as to this classification among researchers, the family members themselves, and clinicians and teachers, who have known the family over a number of years. The disorder is transmitted as an autosomal-dominant monogenic trait (Hurst et al., 1990). A genetic linkage study mapped the disorder in the KE family to a locus designated \textit{SPCH1}, a 5.6 centimorgan interval in 7q31 (Fisher et al., 1998). More recently, a point mutation has been identified in the affected family members, which alters an invariant amino acid residue in the DNA-binding domain of a forkhead/winged helix transcription factor, encoded by the gene \textit{FOXP2} (Lai et al., 2001). These genetic analyses further corroborate the behavioural classification and can be used as an independent index of affected or unaffected status.

In the first report of the KE family, Hurst et al. (1990) described the affected members as suffering from a ‘severe form of developmental verbal apraxia’. Since that initial report, however, the nature of this disorder has been a subject of considerable debate. Gopnik and colleagues (Gopnik, 1990; Gopnik and Crago, 1991; Gopnik and Goad, 1997) focused on the linguistic impairments of the affected individuals; in particular, their deficit in the use of inflectional morphosyntactic rules (e.g. changing word endings to mark tense or number), which has been described as selective. However, the first and subsequent reports of the KE family (Hurst et al., 1990; Vargha-Khadem et al., 1995; Alcock et al., 2000) indicated that the disorder is not selective to inflectional morphology, but rather affects the processing and expression of phonology and syntax, as well as non-linguistic oral praxis. In addition, affected family members have significantly lower non-verbal intelligence quotients (performance intelligence quotients; PIQs) compared with the unaffected family members. All of these studies agree that the affected family members are impaired on tests of morpho-syntax, but the relationship between this impairment and deficits in other language and cognitive domains is unclear.

This study attempts to address this issue by providing a comprehensive description of the behavioural and cognitive deficits that constitute the phenotype shown by the affected members of the KE family, and by comparing their performance on a series of cognitive tasks with that of a group of patients with aphasia due to left hemisphere stroke. The latter comparison makes it possible to examine the differential effects on cognition of a language disorder that is acquired after normal development and one that is present throughout

\begin{figure}
\centering
\includegraphics[width=\textwidth]{ke-family-pedigree.png}
\caption{Pedigree of the KE family. Filled shapes = affected members; open shapes = unaffected members; circles = females; squares = males; / = deceased. Note: the affected female family member in the first generation, who contributed to the data presented here, is now deceased.}
\end{figure}
development. It is likely that both developmental disorders and acquired disorders of language have advantages and disadvantages for cognition. The advantages of a developmental disorder over an acquired one are that there is presumably maximal brain plasticity and capacity for reorganization and compensation. In contrast, an acquired disorder could have advantages over a developmental one because of the pre-morbid period of normal development and normal use of language and other cognitive functions. It is likely that behaviours and strategies learnt during a period of normal development influence the recovery process after an acquired lesion.

Although some aspects of the phenotype in the KE family have been reported previously (Vargha-Khadem et al., 1995), the data presented here are more complete with respect to both the comparison with the group of adult patients with aphasia and the type and extent of statistical analyses performed.

**Methods**

**Subjects**

Thirteen affected and 12 unaffected members of the KE family were assessed. The affected group consisted of one member of the first generation, three members of the second generation and nine members of the third generation (age range = 9–75 years, mean 25.3 years). The unaffected group consisted of 12 members of the third generation (age range = 9–27 years, mean 17.1 years). Eleven patients with expressive aphasia resulting from left hemisphere stroke were also investigated. Details of these patients are given in Table 1.

This research was approved by the Ethics Committee of Great Ormond Street Hospital for Children NHS Trust and the Institute of Child Health and the Research and Development Committee at the VA Northern California Health Care System; subjects gave informed consent.

**Tests and procedures**

**Intelligence tests**

The performance (non-verbal) scale of the age-appropriate Wechsler Intelligence Scale [WISC-III (Wechsler Intelligence Scale for Children, third edition; Wechsler et al., 1992); WAIS-R (Wechsler Adult Intelligence Scale—revised; Wechsler, 1986); WISC-R (Wechsler Intelligence Scale for Children—revised); or WPPSI (Wechsler Preschool and Primary Scales of Intelligence)] was administered to all subjects. The members of the KE family also completed the verbal scale of these tests.

**Receptive language tests**

Receptive vocabulary (lexical decision). Subjects heard 30 words and 30 non-words (selected from those used in the
Table 2  Intelligence testing: group means and standard deviations

<table>
<thead>
<tr>
<th>Test</th>
<th>Unaffected</th>
<th>Affected</th>
<th>Aphasic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIQ*</td>
<td>98.3 (14.6)</td>
<td>83.2 (10.6)</td>
<td>105.7 (19.7)</td>
</tr>
<tr>
<td>Picture completion</td>
<td>9.4 (1.8)</td>
<td>8.0 (2.4)</td>
<td>11.3 (3.1)</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>8.1 (2.8)</td>
<td>6.0 (2.4)</td>
<td>12.4 (4.4)</td>
</tr>
<tr>
<td>Block design</td>
<td>9.7 (3.4)</td>
<td>9.1 (2.7)</td>
<td>11.3 (3.3)</td>
</tr>
<tr>
<td>Object assembly</td>
<td>9.7 (3.1)</td>
<td>8.5 (2.1)</td>
<td>10.7 (3.7)</td>
</tr>
<tr>
<td>Coding</td>
<td>11.0 (2.6)</td>
<td>5.4 (2.0)</td>
<td>7.8 (2.7)</td>
</tr>
<tr>
<td>VIQ</td>
<td>91.5 (8.9)</td>
<td>74.1 (8.8)</td>
<td>–</td>
</tr>
<tr>
<td>Information</td>
<td>7.8 (1.8)</td>
<td>5.9 (1.8)</td>
<td>–</td>
</tr>
<tr>
<td>Similarities</td>
<td>9.4 (2.6)</td>
<td>5.9 (2.4)</td>
<td>–</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>9.1 (2.2)</td>
<td>5.7 (1.7)</td>
<td>–</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>7.4 (0.8)</td>
<td>5.0 (1.8)</td>
<td>–</td>
</tr>
<tr>
<td>Digit span</td>
<td>9.5 (2.9)</td>
<td>6.3 (2.4)</td>
<td>–</td>
</tr>
</tbody>
</table>

Significantly impaired scores relative to the other group(s) are highlighted in bold. *Standard score = mean ± SD = 100 ± 15; all subtest scores = mean ± SD = 10 ± 3. †Significantly impaired score relative to the aphasic group only.

word and non-word repetition test; Gathercole and Baddeley, 1989) and were asked to indicate whether each was a real word or a nonsense word.

Receptive grammar. The Test for Reception of Grammar (TROG; Bishop, 1982) was administered. The number correct out of 80 was recorded, as well as the score for 16 sentences specifically examining comprehension of embedded relative clauses.

Expressive language tests

Word and non-word repetition. Subjects heard a list of 40 words and one of 40 non-words (Gathercole and Baddeley, 1989) and were required to repeat each item. The words ranged from two to five syllables in length and the non-words from one to four syllables. Half of the words and non-words contained only single consonants (e.g. killer, rubid), thus requiring simple articulatory output; the other half contained consonant clusters (e.g. thimble, hampent) requiring more complex articulation.

Naming. Subjects were required to name 36 line drawings (Oldfield and Wingfield, 1965). Average response latencies were calculated for the items correctly named.

Verbal fluency. Subjects generated as many words as possible in 2 min that belonged to either a phonemic category (two categories: words beginning with the letter ‘F’ or ‘M’) or a semantic category (two categories: fruits or animals). Similarly, subjects were given 5 min to write as many words as they could that began with the letter S.

Inflectional and derivational morphological production. Word and non-word versions of a test of morphological production were administered (Vargha-Khadem et al., 1991).

Subjects were shown a picture and required to complete a pair of sentences. The first sentence contained a word that could be modified to complete the second sentence (e.g. ‘Look at how small these elephants are. This one over here must be the . . . ?’ [smallest]). In the non-word version, novel creatures and non-words were used (e.g. ‘This creature is snoozing. We call him a . . . ?’ [snoozzer]). Half of the items required a derivational morpheme (i.e. a morpheme that alters the meaning of the word, sometimes changing its grammatical class; e.g. ‘This boy has lots of spots [noun]. He is very spotty [adjective]’) and half required an inflectional morpheme (i.e. a morpheme that indicates change in tense or number; e.g. ‘This boy loves to ski. He says nothing is as much fun as skiing.’).

Past tense production. Twenty sentence pairs (K. E. Patterson, personal communication) were read to each subject. The first sentence of each pair was in the present (habitual) tense, and the subject was required to complete the second sentence in the past tense. Half of the sentences required construction of regular past tense (e.g. walk—walked) and half required an irregular past tense form (e.g. teach—taught).

Non-word reading and spelling. Subjects read 30 monosyllabic pronounceable non-words. Another 30 monosyllabic non-words were read to the subject for written spelling.

Praxis

Limb. Limb praxis was assessed using a rating scale for 15 simple movements of the arms (e.g. combing hair; making a circle in the air; demonstrating the use of a key). Each movement was rated on a scale from zero to three points: zero for no movement or an incorrect movement, one point for an attempt at the correct movement but poor execution, two points for a correct movement with minor problems in execution and three points for a correct execution of the movement required.

Orofacial. The same rating scale was used to assess performance of movements of the oral and facial musculature (e.g. making the noise of a dog; clicking the tongue; singing; biting the bottom lip; closing the left eye) and sequences of movements (e.g. blowing up the cheeks, then licking the lips, then smacking the lips). If the movement was not executed perfectly following the verbal command, it was demonstrated and the imitation of the movement was scored according to the rating scale from zero to three as described above.

Statistical analysis

Separate one-way analyses of variance (ANOVA) s were run for each test, comparing the scores of the three groups: affected family members, unaffected family members and aphasic controls. Post hoc comparisons were made using Tukey’s honestly-significant-difference ranges test with a significance level of $P < 0.05$. Homogeneity of variance was assessed, and if there was a significant difference in the variance of the groups then non-parametric analyses were performed. Mixed between-within design multivariate ANOVAs with within-subject factors were also conducted.
Discriminant function analyses (DFAs) were run to explore which variables, or combination of variables, best discriminated the affected family members from the unaffected family members and from the aphasic controls. Stepwise DFAs were used allowing statistical criteria to determine the order of entry of variables into the analysis.

## Results

### Analyses of variance

#### Intelligence tests

There was a significant difference among the PIQs of the three groups \(F(2,33) = 6.95, P = 0.003\). The affected group had a significantly lower mean PIQ than the unaffected and aphasic groups, which did not differ from each other (see Table 2). There were significant differences among the three groups for three of the subtests of the performance scale: picture completion \(F(2,33) = 5.19, P = 0.011\); the aphasic group had a significantly higher mean score than both the affected and the unaffected group; picture arrangement \(F(2,22) = 7.14, P = 0.004\); the aphasic group had a significantly higher mean score than both the affected and the unaffected groups; and coding \(F(2,29) = 13.63, P < 0.001\); the unaffected group had a significantly higher mean score than both the affected and the aphasic groups. In summary, the affected group have lower mean scores than the other two groups for all the non-verbal subtests, but the only significant impairment relative to the unaffected group was on the coding subtest. The aphasic group was also significantly impaired relative to the unaffected group on the coding subtest. This might have been expected because some patients had little or no use of the dominant hand as a result of their stroke. The aphasic group had a significantly higher mean score on the picture arrangement subtest compared with the affected and the unaffected groups. This difference may be due to variations in educational backgrounds among the groups or to the test used. Members of the aphasic group were given the WAIS-R version of this test, whereas some members of the other two groups were given the WISC-III version of this test, whereas some members of the other two groups were given the WISC-III version.

In the KE family, five affected family members have undergone repeated assessments of intelligence (see Table 3). These longitudinal data show a large drop in PIQ for three of the five, consistent with the idea that a disorder of speech and language may adversely affect the development of intelligence or of the skills required to maintain a given level of intelligence as the individual matures. The two cases that did not show a decline in PIQ obtained low scores on the first test administration.

Compared with the unaffected group, the affected group also had significantly lower mean verbal intelligence quotient (VIQ) \((t = 4.91, P < 0.001)\) and mean scores for the verbal subtests (see Table 2): information \((t = 2.65, P = 0.014)\); similarities \((t = 3.24, P = 0.004)\); arithmetic \((t = 4.29, P < 0.001)\); vocabulary \((t = 4.09, P = 0.001)\); and digit span \((t = 3.01, P = 0.006)\).
Receptive language tests

Receptive vocabulary (lexical decision). There was a significant difference among the three groups for the scores on the lexical decision test \(F(2,31) = 10.64, P < 0.001\); the affected group was significantly impaired relative to the other two groups, which did not differ; see Table 4. Thus, the affected group had restricted lexical knowledge as a result of their developmental disorder, whereas the aphasic group, whose members had acquired their lexical knowledge prior to their stroke, was unimpaired on this test.

Receptive grammar. The unaffected group had a significantly higher mean score for the 80 items of the TROG (see Table 4) than the affected group \((Z = 2.26, P = 0.024)\) and the aphasic group \((Z = 3.18, P = 0.002)\) as well as for the items of the TROG that assess embedded relative clauses \(F(2,29) = 6.59, P = 0.004\). Thus, both the affected and aphasic groups are impaired at receptive grammar despite the fact that their disorders present with predominantly expressive language impairment. The receptive impairment is related not just to morphosyntax but also to syntax at the word-order level.

Expressive language tests

Word repetition. For the analyses of the word repetition test, there were two within-subject factors, the number of syllables (levels: 2–5) and articulation difficulty (levels: simple and complex), and the between-subject factor of group (three groups). There were significant main effects of group \(F(2,30) = 25.82, P < 0.001\); the unaffected group had a significantly higher mean score than the affected and aphasic groups, and the aphasic group had a significantly higher mean score than the affected group, number of syllables \(F(3,90) = 29.85, P < 0.001\); scores decreased as number of syllables increased, and articulation difficulty \(F(1,30) = 24.55, P < 0.001\); scores for simple articulation were significantly higher than for complex. There was also a significant interaction between group and number of syllables \(F(6,90) = 4.90, P < 0.001\). This was due to impaired performances by the aphasic group, relative to the unaffected group, at three and four syllables, and by the affected group, relative to the aphasic group, at three and five syllables (see Fig. 2A and B).
In summary, the affected family members were impaired at repetition of words of both simple and complex articulation relative to the unaffected and the aphasic groups. Also, the effect of increased number of syllables was significantly more pronounced in the affected group than in the other two groups. The aphasic group was also impaired at word repetition compared with the unaffected group \( t = 3.64, P = 0.001 \) and the effect of increased number of syllables was more significant in the aphasic group than in the unaffected group.

**Non-word repetition.** The factors in the non-word repetition test were the same as those for word repetition except that the number of syllables ranged from one to four. There were significant main effects of group \( F(2,31) = 35.08, P < 0.001 \); the unaffected group had a significantly higher mean score than the affected and aphasic groups, which did not differ, number of syllables \( F(3,93) = 67.52, P < 0.001 \); as for word repetition and articulation difficulty \( F(1,31) = 57.20, P < 0.001 \); as for word repetition. There were also significant interactions between group and number of syllables \( F(6,93) = 4.46, P = 0.001 \), between group and articulation difficulty \( F(2,31) = 8.97, P = 0.001 \) and between number of syllables and articulation difficulty \( F(3,93) = 8.04, P < 0.001 \).

In summary, the affected and aphasic groups were significantly and equally impaired in repetition of non-words relative to the unaffected group. These effects were significantly more pronounced for non-words requiring complex articulation compared with those requiring simple articulation (see Fig. 2C and D). Similarly, these group effects increased in significance with increasing numbers of syllables.

Comparison of word and non-word repetition indicates that the aphasic group showed significantly better repetition of words than non-words, whereas the affected group was equally impaired at both. This is presumably because, pre-morbidly, the aphasic patients had learnt and used the articulation patterns of the words in the word repetition test.

**Naming.** The unaffected group had significantly higher accuracy scores on the naming test than the affected group \( Z = 2.26, P = 0.024 \) and the aphasic group \( Z = 2.41, P = 0.016 \), the scores of which did not differ significantly from each other. The unaffected group had significantly shorter response latencies for correctly named words than the aphasic group \( Z = 2.39, P = 0.001 \), but the affected group did not differ significantly from either of the other two groups on this variable (for the group means, see Table 4). In summary, the affected and aphasic groups were both impaired at naming to confrontation, but were not significantly different from each other. However, the aphasic group alone was impaired in the time taken to produce a response.

**Verbal fluency.** The verbal oral fluency data were analysed using a mixed between–within design ANOVA, with two within-subject factors, lexicality (levels: words and non-words) and type of morphology (types: inflectional and derivational), and one between-subject factor of group. There were significant main effects of group \( F(2,30) = 36.68, P < 0.001 \); significantly higher scores for the unaffected group compared with both the affected and aphasic groups, who did not differ; see Fig. 4), lexicality \( F(1,30) = 231.20, P < 0.001 \); significantly higher scores for words than non-words and type of morphology \( F(1,30) = 7.63, P = 0.010 \); significantly higher scores for inflectional than for derivational morphology. There was also a significant interaction between group and lexicality \( F(2,30) = 9.15, P = 0.001 \); the group effect was more pronounced for the non-words than for the words.

**Past tense production.** The data for the past tense production test were analysed using a mixed between–within design ANOVA, with two within-subject factors, lexicality (levels: words and non-words) and type of morphology (types: inflectional and derivational), and one between-subject factor of group. There were significant main effects of group \( F(2,29) = 32.86, P < 0.001 \); both the affected and aphasic groups were impaired relative to the unaffected group, but the aphasic group also had significantly lower scores than the affected group; see Fig. 3). The effect of fluency type was not significant nor was the interaction between group and fluency type. For written fluency test scores, there was a significant group difference \( F(2,25) = 19.81, P < 0.001 \), due to significantly lower scores of the aphasic group compared with the affected and unaffected groups and of the affected compared with the unaffected group (see Fig. 3). Thus, the affected group was impaired at generating lexical items under semantic and phonemic (both oral and written) conditions, but the aphasic group was impaired even further on the same tests.

**Inflectional and derivational morphology.** The data for the word and non-word versions of morphological production were analysed using a mixed between–within design ANOVA, with two within-subject factors, lexicality (levels: words and non-words) and type of morphology (types: inflectional and derivational), and one between-subject factor of group. There were significant main effects of group \( F(2,30) = 36.68, P < 0.001 \); significantly higher scores for the unaffected group compared with both the affected and aphasic groups, who did not differ; see Fig. 4), lexicality \( F(1,30) = 231.20, P < 0.001 \); significantly higher scores for words than non-words and type of morphology \( F(1,30) = 7.63, P = 0.010 \); significantly higher scores for inflectional than for derivational morphology. There was also a significant interaction between group and lexicality \( F(2,30) = 9.15, P = 0.001 \); the group effect was more pronounced for the non-words than for the words. 

![Fig. 3 Verbal fluency tests. Bars = group means; error bars = standard error of the mean; white = unaffected; black = affected; grey = aphasic. *Significantly greater than aphasic group; **Significantly greater than both affected and aphasic groups. Note: the time limit was 2 min for the semantic and phonemic fluency conditions and 5 min for written fluency.](image)
ANOVA with a within-subject factor of verb type (types: regular and irregular) and a between-subject factor of group. There was a significant main effect of group \( F(2,31) = 8.75, P = 0.001 \); the unaffected group had significantly higher scores than the affected and aphasic groups, who did not differ; see Fig. 5], but not of verb type, and the interaction was not significant. Thus, the affected and aphasic groups were significantly impaired at past tense production for both regular and irregular verbs relative to the unaffected group. Non-word reading and spelling. The unaffected group had significantly higher scores on the non-word reading test than the affected group \( Z = 3.56, P < 0.001 \) and the aphasic group \( Z = 3.07, P = 0.002 \). The affected and aphasic groups did not differ significantly. Similarly, for the non-word spelling test, there was a significant difference among the three groups \( F(2,22) = 11.55, P < 0.001 \); the unaffected group had significantly higher scores than the other two groups, who did not differ; see Table 4]. These differences reveal that reading and spelling non-words are severely impaired in both the affected and the aphasic groups.

Praxis
Limb. There were no significant group differences on the test of limb praxis (see Table 4 for the group means).
Orofacial. For orofacial praxis, the unaffected group had significantly higher scores than the affected group \( Z = 3.64, P < 0.001 \) and the aphasic group \( Z = 3.76, P < 0.001 \). The affected and the aphasic groups were not significantly different from each other (see Table 4 for the group means).

It should be noted that the praxis scales are rating scales and, because it was not possible for the rater to be blind to the group status of the subject, this may have influenced the scoring.

Discriminant function analysis
Affected versus unaffected family members
The previous analyses revealed that, compared with the unaffected group, the affected group was significantly impaired on the following tests: PIQ, coding subtest, VIQ and all verbal subtests, lexical decision, TROG, word and non-word repetition (both simple and complex articulation), object naming, phonemic, semantic and written fluency, word and non-word morphological production, past tense production, non-word reading and spelling, and orofacial praxis. A DFA was performed with the goal of finding a linear function (DF) of independent variables that would yield the largest possible ratio of the between-groups variance to the total variance in an ANOVA.
Based on the results described above, the following variables were selected for the DFA: PIQ, VIQ, lexical decision, TROG (score out of 80), complex and simple non-word repetition (separately), naming accuracy, verbal fluency (combined score for phonemic and semantic categories), word and non-word morphological production (combined inflectional and derivational scores), past tense production and orofacial praxis. As VIQ was entered, the verbal subtests were not. Also, because there were missing data for the coding subtest, word repetition, written fluency, non-word reading and non-word spelling tests, those variables were not entered. Finally, because there had been no significant group interactions with the type of morphology in the morphological production test, and type of fluency in the verbal fluency tests, the scores for these conditions within the tests were combined, thereby reducing the number of variables selected. Data for 11 affected and nine unaffected family members were entered into the DFA.

The variable of complex non-word repetition was entered in the first step of the analysis. It accounted for 100% of the variance and was statistically significant ($\chi^2 = 30.81, P < 0.001$). The analysis was terminated, as none of the other variables survived a statistical test for entry into the analysis (see Table 5). Thus, the affected family members can be best discriminated from the unaffected members by their performance on a test of repetition of non-words with complex articulation patterns.

### Affected family members versus patients with aphasia

The previous analyses also revealed that the aphasic group was significantly impaired relative to the affected group on the three verbal fluency tests only, namely phonemic, semantic and written fluency. In contrast, the affected group was significantly impaired relative to the aphasic group on the following tests: PIQ, picture completion subtest, picture arrangement subtest, lexical decision and word repetition. A DFA was performed for the affected and aphasic groups like that described above for the affected and the unaffected groups.

Based on the previous results, the following variables were selected for the DFA: PIQ, picture completion subtest, lexical decision, word repetition and verbal fluency score (combined score for phonemic and semantic categories). The data for the picture arrangement subtest were not included because of missing data. Also, the scores for phonemic and semantic categories were combined because there was no significant group interaction with the type of fluency on the verbal fluency tests. Data for 12 affected family members and 10 aphasic controls were entered into the DFA.

The variable of verbal fluency was entered in the first step of the analysis, followed by lexical decision in step two. These two variables accounted for 100% of the variance and were statistically significant ($\chi^2 = 28.99, P < 0.001$; see Table 6). The analysis terminated with no further steps. Thus, the affected family members can be best discriminated from the aphasic patients by their performance on two tests, namely verbal fluency and lexical decision.

### Discussion

**Identifying a ‘core’ deficit in the affected family members**

The results reported in this study reveal that the affected family members, as a group, were impaired on almost every test administered. This is in accord with the previous report by Vargha-Khadem et al. (1995). However, the results of the DFA, comparing affected and unaffected family members, demonstrated that performance on a test of repetition for non-words containing complex articulation patterns could alone successfully discriminate the two groups from each other. It is a good candidate, therefore, for a behavioural phenotype of this disorder. Several studies have shown that children with specific language impairment (SLI) have difficulty in repeating non-words (Kamhi and Catts, 1986; Kamhi et al., 1988; Lewis et al., 1989). Another study examined twins, at least one of whom was diagnosed with SLI, and concluded that performance on a non-word repetition test was a good phenotypic marker for SLI even in adolescents whose apparent language deficits had resolved (Bishop et al., 1996).

Below we discuss the range of deficits seen in the affected members of the KE family and how they might be related to each other and to the underlying neuropathology. Before this discussion, however, it is worth raising several notes of caution. First, the number of statistical comparisons presented here is considerable, as is the number of significant differences among these groups. The possibility is raised, therefore, that some of these differences are false positives. Examination of the group means and variances suggests, however, that these differences are large and, therefore, likely to be genuine.
Secondly, the purpose of the DFA was to identify variables that might be considered as phenotypic markers for the disorder seen in the KE family. The number of subjects entered into such analysis, however, was limited by those available for testing. The results of these exploratory analyses should be interpreted as suggestive rather than conclusive, until receiving corroboration from other studies of similarly impaired populations. Finally, although we draw comparisons between the affected members of the KE family and children with SLI, our subjects do not meet diagnostic criteria for SLI in view of their deficit on PIQ (see Table 2). Also, the presence of an articulation disorder persisting into adulthood, as seen in the KE family, is not typical of children with SLI. Several studies have identified clinical markers for SLI, however, and some of these might have relevance for the impairments seen in the KE family: non-word repetition impairment (Bishop et al., 1996); impaired phonological working memory (Gathercole and Baddeley, 1990); and protracted use of the optional infinitive (Rice and Wexler, 1996; Rice et al., 1998). These are discussed where relevant.

What is the deficit in non-word repetition?
Gathercole and Baddeley, who devised the test used in our study, suggest that impairment in non-word repetition is related to a specific deficit in the storage of phonological information in working memory. In their study (Gathercole and Baddeley, 1990), a group of children with SLI were impaired at recalling lists of words and at repeating non-words. These deficits were thought to be unrelated to articulation, however, because the children with SLI did not show a differential effect of complex versus simple articulation on non-word repetition, nor were they impaired in a test of articulation rate. Bishop et al. (1996), however, reported a non-word repetition impairment in a much larger group of children with SLI and found that even when those with poor or atypical articulation were excluded, the children with SLI showed significantly greater impairment on non-words with complex articulation than on those with simple articulation. It is worth considering, therefore, that the deficits seen in these individuals and other populations with SLI on tests such as those used here may be due to deficits not in phonological working memory per se, but rather in sequential articulation of phonological units.

Impaired morphosyntax in the affected family members
The results of the analyses reported in this study confirm that the affected family members have a deficit in the use of morphosyntax, consistent with previous reports on this family by Gopnik and colleagues (Gopnik, 1990; Gopnik and Crago, 1991; Gopnik and Goad, 1997). Such deficits are similar to those seen in children with SLI and ascribed by Rice and colleagues (Rice and Wexler, 1996; Rice et al., 1998) to an extended period of use of the optional infinitive. The affected family members (some of whom have reached adulthood) were significantly impaired relative to the unaffected members on a test of inflectional and derivational morphological production. Even more specifically, this deficit was demonstrated on a test of past tense production. Contrary to the previous reports, however, the affected family members were impaired at production of irregular as well as regular past tense. Since irregular past tense production is not rule based, but relies upon lexical knowledge, this deficit is unrelated to morphosyntactic rule use. Furthermore, the analyses reported here also demonstrate deficits in the affected family members on many other linguistic tests. The claim that this family has a specific deficit in morphosyntactic rule use is therefore untenable. Even so, the relationships between the articulation deficit, the deficit in morphosyntax and the other deficits require explanation.

One possibility is that the deviant articulation results in poor phonology, rendering morphological production difficult. This explanation is supported by the findings of Fee (1995) who reported phonological abnormalities in the speech of affected family members (see also Vargha-Khadem et al., 1995). It is worth noting that in her study, Fee excluded the data for two affected family members because they were unintelligible. In the study by Fee (1995), final word consonants were either devoiced (e.g. ‘d’ pronounced as ‘t’) or deleted, and consonant clusters were reduced. Such productions are crucial for accurate expression of morphological markers, particularly in past tense productions where the distinguishing morpheme occurs at the end of the word.
Praxic impairments in the affected family members

Impairments were found in the affected and aphasic groups on a test of orofacial praxis but not on a test of limb praxis. A genetic abnormality that affects brain mechanisms responsible for articulation of speech sounds via the orofacial apparatus or frank neurological damage of the same system is unlikely to be so selective as to leave other components of the orofacial system unaffected (Mateer and Kimura, 1977; Kimura and Watson, 1989). Speech is probably the most sophisticated and complex product of the orofacial system, requiring highly organized coordination of movements. Even so, impairments in less sophisticated orofacial movements, which do not involve speech but require either simultaneous or sequential movements, have been documented in the group of affected family members (Alcock et al., 2000). These findings led Vargha-Khadem et al. (1995) to suggest that the articulatory impairment in the affected family members was due to an underlying oral dyspraxia. This is a reasonable suggestion, which is discussed below with reference to the other impairments documented in the affected family members.

Impaired non-verbal intelligence in the affected family members

The mean PIQ of the affected family members was significantly lower than that of the other two groups, indicating that their difficulties extend from speech and language to the non-verbal domain (see Table 2). Furthermore, three of the five affected family members who underwent repeated intelligence tests showed a significant decline in PIQ (see Table 3). This is consistent with data from longitudinal studies of children with SLI (Tallal et al., 1991) who show decreases in PIQ over a period of 4-5 years. Non-verbal cognitive development may appear normal at younger ages until it plateaus in early adolescence (or even earlier), after which an apparent decline is witnessed.

Examination of the non-verbal subtest scores indicates that the affected family members were impaired relative to the unaffected group on the coding subtest only. This subtest requires the association of a series of symbols with a set of digits. The symbols must be copied beneath the digits, which are presented in a random order. This is a timed test, which is aided by rapid learning of the associations between the symbols and the digits.

If we consider this coding deficit together with the articulation impairment and the oral dyspraxia, the possibility is raised that these three share an underlying deficit, such as a sequencing impairment or a deficit in learning of associations. Such impairment might produce deficits on a number of tasks, both verbal and non-verbal. We cannot rule out the possibility, however, that the genetic abnormality in the KE family produces a general, but mild developmental delay affecting both verbal and non-verbal abilities, as well as a more specific verbal impairment that arises from the articulation deficit.

Similarities between the affected family members and patients with aphasia

In comparison with the unaffected family members in whom speech and language abilities are unimpaired, the affected family members and the patients with aphasia demonstrated a range of impairments on nearly all of the verbal tests administered. The patterns of impairment in the affected family members and in the patients with aphasia were remarkably similar. This is not surprising given the presence of dysarthria or apraxia of speech or both in most of the patients with aphasia. They were equally impaired in receptive grammar, non-word repetition, particularly for non-words requiring complex articulation, object naming, production of inflectional and derivational morphology, both regular and irregular past tense production, non-word reading and spelling, and orofacial praxis. The patients with aphasia all had unilateral lesions of the opercular region in the left hemisphere, extending in some cases to subcortical structures. MRIs of the brains of the KE family members, however, revealed no focal brain pathology, a finding consistent with reports in other developmental disorders, such as autism, SLI and Williams syndrome. Morphometric analyses of these images, however, have demonstrated abnormalities in the affected family members bilaterally, affecting the caudate nucleus and motor- and speech-related cortical regions (see Watkins et al., 2002). The underlying pathology in the affected members of the KE family, therefore, is covert and less focal than that seen in the patients with aphasia, yet results in remarkably similar deficits in speech and language.

Differences between the affected family members and the aphasic patients

Despite the similarities, the comparison of the affected and aphasic groups also revealed the differential effects of a developmental versus an acquired speech and language impairment. For example, the affected group had significantly higher scores than the aphasic group on the tests of verbal fluency. The principal locus for a deficit in verbal fluency in brain-damaged adults appears to be the left orbitofrontal cortex (Milner, 1964). Patients with lesions to the face area of the motor strip (posterior to Broca’s area), however, are often even more impaired in verbal fluency than those with orbitofrontal lesions (Milner, 1964; Kolb and Whishaw, 1990). Many of the aphasic patients had lesions to the insular cortex and dorsolateral prefrontal cortex, and it is likely that these lesions encroach upon the face area of primary motor cortex.

The aphasic group was found to have significantly higher scores than the affected group on PIQ, picture completion and
picture arrangement subtests, lexical decision and word repetition. With the exception of the scores for the word repetition test, the scores were not significantly lower than those for the unaffected group, whose performance was normal. Thus, it appears that a developmental speech and language disorder could have detrimental effects on various components of non-verbal intelligence, as well as on lexical development and familiarity with the articulation patterns of common words.

The results of the DFA support these conclusions. The verbal fluency score best discriminated between the performances of these two groups, followed by the lexical decision score. The latter appeared to share a significant amount of the variance with the other variables, namely PIQ, picture completion and word repetition, suggesting that these variables are related to a common underlying factor. We propose that the common factor is previous normal language development and use and that its absence has detrimental effects on both linguistic and non-linguistic function.

**Relating the impairments in the affected family members to each other and to the underlying neuropathology**

The articulation problem in the affected members of the KE family is the most obvious feature of the behavioural phenotype, and performance on a test of non-word repetition with complex articulation alone successfully discriminated affected from unaffected family members. We have argued that this articulation deficit renders production of morphological suffixes difficult, accounting for the deficit in morphosyntax previously described. The deficit in articulation could lead not only to impaired phonological representation, but also to impoverished language representation more generally. Impaired phonological analysis, resulting from poor subvocal rehearsal of incoming speech, could interfere with the ability to draw analogies between words with articulation patterns in common and, particularly in a developmental context, to learn implicitly the rules of syntax (Ullman, 2001). These conclusions are supported by the similarities between the affected family members and the patients with aphasia. Despite the overt and focal pathology underlying the impairments in the latter compared with the covert and diffuse pathology seen in the affected family members, these two groups shared deficits across the many language areas assessed. They differed, however, on non-verbal tests, such that the affected family members had a greater non-verbal impairment than the patients with aphasia. This raises at least two possibilities for an explanation of the core deficit in the affected family members: the verbal and non-verbal impairments are due to a mild but general developmental delay and the articulation deficit arises separately, or the underlying pathology that results in the articulation impairment also affects the development of non-verbal abilities, such as those assessed by the coding subtest and oral praxis.

Interestingly, the scores of affected members of the KE family on these three tests (repetition of non-words with complex articulation, coding and oral praxis) were found to correlate with the size of the caudate nuclei in a study of brain morphometry (see Watkins *et al.*, 2002). The relationships between performance and caudate nucleus size were not straightforward, and the causality of the relationship has yet to be determined. Nevertheless, these correlations raise the possibility that the gene product interferes with the normal development of the caudate nucleus (and possibly other components of the motor system) and that this in turn impairs procedural learning. Such a deficit could affect acquisition of various motor skills and behavioural rules (Salmon and Butters, 1995; Knowlton *et al.*, 1996). In the affected members of the KE family, such a deficit might manifest itself most obviously in impaired articulation but also in a plethora of verbal and non-verbal deficits.

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