Impact of Chromosome 4p- Syndrome on Communication and Expressive Language Skills: A Preliminary Investigation

Althea T. Marshall
Southern Connecticut State University, New Haven

Chromosome 4p- syndrome, a presumed rare autosomal disorder (Chen, 2009), results from the deletion of multiple tandem genes from a variably sized portion of the shorter arm (p) of chromosome 4. Chromosome 4p- syndrome occurs in 1 in 50,000 births, with a 2:1 Female:Male sex predilection (Lurie, Lazjuk, Ussova, Presman, & Gurevich, 1980). Seventy-five percent to 90% of 4p- cases result from de novo (i.e., spontaneous) errors of preferential paternal origin (Lurie et al., 1980). An ethnic predilection does not exist (Chen, 2009), and there are no notable gender differences relative to cognitive–behavioral skills (Fisch, Battaglia, Parrini, Youngblom, & Simensen, 2008). There are at least 500 known cases of 4p- syndrome in children under 10 years of age in the United States (J. Carey, personal communication, October 9, 2003) and an unknown number internationally. Battaglia, Carey, and Wright (2001) stated that the prevalence of 4p conditions is difficult to establish accurately due to misdiagnosis of 4p- with other syndromes and the fact that only 58% of the cases are detected by standard cytogenetic techniques; subclinical individuals with normal cytogenetic results and 4p microdeletions are rarely identified. Maas et al. (2008) hypothesized that the incidence of 4p- syndrome is more consistent with that of Angelman syndrome—approximately 1 in 20,000 births.

Chromosome 4 is one of the largest and gene dense of the 24 chromosome pairs in the cells of the human body (Saccone, De Sario, Della Valle, & Bernardi, 1992). Even the smallest disruption in the integrity of the genes on this chromosome has a deleterious effect on an individual’s genome. Although Wolf, Reinwein, Porsch, Schröter, and Baitsch (1965) and Hirschhorn, Cooper, and Firschein (1965) described the essential phenotype associated with Wolf-Hirschhorn syndrome (WHS), Pitt-Rogers-Danks syndrome (PRDS), Proximal 4p Deletion syndrome, and complex chromosomal rearrangements associated with 4p-.

**ABSTRACT:** Purpose: The purpose of this investigation was to examine the impact of Chromosome 4p- syndrome on the communication and expressive language phenotype of a large cross-cultural population of children, adolescents, and adults.

Method: A large-scale survey study was conducted and a descriptive research design was used to analyze quantitative and qualitative data regarding the communication and expressive language manifestations of 200 children, youth, and adults from 16 countries and Puerto Rico who had been diagnosed with 4p conditions, including Wolf-Hirschhorn syndrome (WHS), Pitt-Rogers-Danks syndrome (PRDS), Proximal 4p Deletion syndrome, and complex chromosomal rearrangements associated with 4p-.

Results: Individuals with Chromosome 4p- syndrome represent a heterogeneous population with complex phenotypic profiles. The majority of the participants exhibited communication and expressive language skills below the 36-month developmental functioning level. A relatively small cohort of the study population exhibited advanced expressive language skills, a finding not reported in the professional literature.

Conclusion: Results broaden the spectrum of expressive language skills associated with Chromosome 4p- syndrome and highlight the communication potential of a subset of individuals with 4p abnormalities for development of advanced language structures. It is hypothesized that the largest 4p deletion, which includes the 4p16.3 band and contiguous gene regions, results in the most severely affected expressive language phenotype.

**KEY WORDS:** language, developmental disabilities, genetics
4p defects in 1965, modern genetics has yet to systematically describe the impact of 4p chromosome abnormalities on linguistic development in the human species. Hence, the primary aim of this large-scale international survey study was to provide a wide-angle perspective regarding the severity and scope of communication and expressive language impairments associated with 4p- syndrome. The study also sought to expand the spectrum of communication and expressive language abilities associated with 4p genomic defects by broadly highlighting the relatively advanced communication and productive expressive language skills of a small subset of individuals with 4p- syndrome. Third, the study aimed to determine whether the preliminary data supported formulation of a hypothesis that the most significantly compromised communication and expressive language behavior exhibited by study participants was associated with the largest 4p deletion, which includes the 4p16.3 gene region on the tip (i.e. telomere) of the distal short arm of chromosome 4 (Figure 1).

**Chromosome 4p- Variants and Genotype–Phenotype Correlations**

There is a spectrum of heterogeneous clinical anomalies associated with chromosomal deletion on the short arm (p) of chromosome 4. Although the 4p16.3 gene region is most noted for Huntington’s chorea (HC) when mutated, it is also responsible for Wolf-Hirschhorn syndrome (WHS) when deleted (Anca et al., 2004; Battaglia, Carey, & Wright, 2006). Figure 2 portrays an individual who has been diagnosed with WHS, one of the major chromosome 4p- variants resulting from a microdeletion of the end (i.e. telomere) of chromosome 4p. The 4p16.3 band also contains the DFNA 6 gene, which has been linked to nonsyndromic autosomal dominant hearing loss (Chen, 2009; Lesperance et al., 1995). Geneticists conjecture that Pitt-Rogers-Danks syndrome (PRDS) overlaps the critical gene region associated with a diagnosis of WHS (Battaglia et al., 2001; Wright, Clemens, Quarrell, & Altherr, 1998). Proximal 4p Deletion syndrome (Battaglia et al., 2001) is a 4p- variant that results from deletion of several adjacent genes in the central region proximal to WHS and PRDS (Fryns et al., 1989). The fourth primary 4p- subgenotype involves less frequent complex chromosome rearrangements that occur in 12% of diagnosed individuals (Battaglia & Guerrini, 2005). It is not unusual for an individual with a 4p deletion to also be diagnosed with additional genetic material from another chromosome region (i.e., duplication) on the short arm of chromosome 4 (South, Whitby, Battaglia, Carey, & Brothman, 2008; Zollino et al., 2004).

Delineation of a definitive phenotype associated with the distinct chromosome 4p- genotypes is compromised by heterogeneity of patient manifestations that have not been studied systematically (Fisch et al., 2008). The available research is controversial and continues to be debated in the medical literature, most especially with regard to whether specific clinical manifestations are dependent on the location of the 4p gene defect or the size of the affected genetic material (Battaglia et al., 2001; Bergemann, Cole, & Hirschhorn, 2005; Fisch et al., 2008; Maas et al., 2008; Rauch et al., 2001; Schlickum et al., 2004; Stec et al., 1998; Takeno et al., 2004; Van Borsel, De Grande, Van Buggenhout, & Frynes, 2004; Wieczorek et al., 1998; Zollino et al., 2000; Zollino et al., 2003; Zollino et al., 2004). Geneticists hypothesize that individuals with the largest 4p deletions, which include the critical 4p16.3 band and contiguous gene regions, demonstrate the most severely compromised neurobehavioral outcomes (Maas et al., 2008; Zollino et al., 2008). Substantial variation in clinical manifestations, however, is reported to be associated with all 4p conditions as well as within each distinct 4p- subgenotype. A definitive relationship between genotype and phenotypic manifestations in the 4p- population, therefore, has not been confirmed.

**Communication and Expressive Language Phenotype of 4p- Syndrome**

Table 1 delineates the communication disorders-related domains that are variably compromised by salient chromosome 4p- clinical features. Although there is considerable data-based information regarding the variable clinical expression of the 4p- variants, cohesive data are lacking to determine if there is any syndrome-specific communication, language, and/or speech behavior exhibited by a large
number of individuals with 4p chromosomal abnormalities or if communication and expressive language behavior varies based on the size and location of specific 4p deletions or complex chromosome rearrangements. There is virtually no definitive source in the extant medical or professional literature regarding the communication and language developmental expectations of the 4p- population or the distinct clinical entities within the larger 4p- cohort. References in the literature to the natural course of communication development in the 4p- population are cursory and are primarily based on anecdotal descriptions from a small number of survey respondents or clinical case observations. The reported information suggests that individuals who have been diagnosed with 4p- related conditions typically do not develop productive speech and language, and that most probands demonstrate absent or limited overall communication and expressive language skills (Battaglia & Carey, 1999; Battaglia et al., 2006; Chen, 2009; Estabrooks et al., 1995; O’Brien & Yule, 1995; Petit, Schmit, Van den Berghe, & Fryns, 1996; Shprintzen, 1997; Stengel-Rutkowski, Warkotsch, Schimanek, & Stene, 1984; Tschernigg, Petek, Wagner, & Kroisel, 2002; Van Borsel et al., 2004; Battaglia et al., 2001) and Sabbadini, Bombardi, Carlesimo, Rosato, and Pierro (2002) reported that the small percentage of individuals with 4p anomalies who do acquire verbal language reach only a minimally functional communicative level and that, in most cases, expressive language is limited to “gutteral or disyllabic sounds that were occasionally modulated in a communicative way” (Battaglia et al., 2001, p. 85). There is extremely limited anecdotal evidence in the recent medical and professional literature indicating that a small cohort with 4p conditions do, indeed, develop productive expressive language skills in a typical trajectory (Battaglia, Filippi, & Carey, 2008; Brady, May, & Fernhoff, 2005; Maas et al., 2008; Marshall, 2007; Shprintzen, 2000; Van Borsel et al., 2004; Van Buggenhout et al., 2004; Zollino et al., 2008). The dearth of empirically based information suggests, however, that caregivers, clinical scientists, and human service providers, including genetic counselors, are not updated relative to how the genetic origins of 4p conditions variably affect communication and expressive language behavior in this population and the potential for a cohort of individuals with 4p conditions to develop competent expressive language skills. Indeed, parents and other care providers from the international 4p- community report that inadequate communication and expressive language developmental guidance may prevent individuals with 4p- abnormalities from maximizing their cognitive–linguistic potential and fully participating in the social circle of life.

METHOD

Participants

This survey study involved 200 participants from 16 countries and the commonwealth of Puerto Rico. The study participants were
The participants were stratified into subgroups by age, gender, and geography but were not grouped by race or ethnicity. A range of ethnicities, however, was represented in the substantial data set, including 152 White (76%), 31 (15.5%) Hispanic or Latino, 5 (2.5%) Asian, 1 (.5%) Native Hawaiian, and 11 (5.5%) African American participants. Participants were sociodemographically heterogeneous and ranged in age from 1 year to 47 years (M = 8.9; SD = 7.7). Health status of the participants was variable and was dependent on comorbid factors. Data were collected regarding 70 males (35%) and 130 females (65%). Of the 200 participants, 182 (91%, 116 females and 66 males) were under the age of 21, and 18 (9%, 14 females and 4 males) were between the ages of 21 and 47. Among the participants’ primary language were the romance languages, French, Italian, and Spanish; the West Germanic languages; American English with dialectical diversity; Dutch; Korean; Portuguese; and German. Ninety-nine percent of the participants were monolingual; 2% were bilingual in English and Spanish.

Recruitment, sampling, and data collection. Three hundred and twenty-five surveys were distributed to the U.S. 4p- Support Network. Sampling was based solely on the respondents’ affiliation with the 4p- support group without consideration to stratification by the participants’ socioeconomic status, age, gender, or ability level. In order to preserve confidentiality of the participants, the envelopes were addressed and mailed to each support network member in the United States and international affiliates in Canada, Mexico, and Puerto Rico by the president of the 4p- Support Network and not the author. The single criterion for potential participants’ inclusion in the study was a diagnosis of a chromosome 4p abnormality. There were no exclusionary conditions relative to age, gender, ethnicity, race, or geography for participation in the study. The single exclusionary criterion was diagnosis of an intellectual impairment associated with a genetic etiology other than the 4p abnormality.

The author requested that the parents or care providers of persons with 4p- syndrome from countries with English as the primary language complete the survey questionnaire and mark items on the Receptive–Expressive Emergent Language Scale—2 (REEL–2; Bzoeh & League, 1991) and the MacArthur Communicative Development Inventories (CDI; Fenson et al., 1993) that characterized the communicative behavior of the study participants. As language samples are acknowledged to be useful to analyze the complexity of morphosyntactic production in individuals with intellectual disabilities (Condouris, Meyer, & Tager-Flusberg, 2003), the author also requested the respondents to provide a sample of the participants’ verbal language that was elicited during open-ended conversation with the respondent or other interlocuter in the examples section D of the CDI Words and Sentences inventory. Although materials, discourse contexts, or setting were not specified, the respondents were encouraged to use “interviewing” (Hadley, 1998) and a variety of materials, such as photos, toys, games, movies, books, and topics of interest (e.g., school, family, friends, pets) to stimulate conversational reciprocity and elicit decontextualized personal narratives if appropriate. The author also obtained three communication samples during clinical observation (real time, audio, or DVD) of the participants or follow-up telephone interviews with 1 participant.

Measures were taken to ensure the confidentiality of participants as the 165 (51%) completed surveys were received by assigning a number to each respondent and a corresponding number or code on the returned completed surveys.

Additional anecdotal data regarding the participants’ cognitive (e.g., symbolic play) development, receptive language, speech motor/feeding, and academic skills were obtained from letters and e-mail correspondence between study respondents and the author. These data, photos, and developmental records were coded, organized into patterns, and stored for future qualitative analysis.

Due to interest from the international community to clarify the 4p- communication phenotype and for the purpose of providing a cross-cultural description of individuals with 4p- syndrome across a wide geographic spectrum with different primary languages, 32 additional survey questionnaires were sent to the Australian and German 4p- Support Networks. The English questionnaire was then translated into German by a bilingual member of the German 4p- Support Network and was posted on the Internet (http://www.wolfhirschhorn.de/buch/ Fragebogen%20Althea.doc). The response rate to this survey was 53%, or 17 surveys. Further networking via e-mail with individuals participating on the international 4p- listservs yielded a small number of respondents (n = 18) from Africa, England, France, Republic of Korea, Brazil, Spain, Italy, Denmark, Sweden, Scotland, and Belgium, bringing the total number of surveys received to 200. Questionnaires received in languages other than English (n = 23) were translated into English before coding data.

Instruments

A questionnaire/survey was developed to obtain demographic, medical history, and professional services data from the parents/guardians of children, youth, and adults who had been diagnosed with a 4p condition. The validity of parent-reported developmental gains and expressive language behavior is well documented in the professional literature (Hauerwas & Stone, 2000). Valid parental reporting in linguistically diverse and special populations is also documented (Dinnebeil & Rule, 1994; Thordardottir & Weismer, 1996). Fenson et al. (1994) and Saudino et al. (1998) further confirmed that parent-reported expressive language is significantly correlated with formal objective measures of language production.

The majority of the survey questions were designed to ascertain the parent or care provider’s perception of the communication, receptive–expressive language, sensory, oral–motor, swallowing, feeding, and nonlinguistic cognitive behavior (i.e., play) of the target population. Questions were culled from converging evidence in the existing medical and professional literature regarding cognitive, communication, sensory development, and related disorders.

In order to determine age-equivalent receptive–expressive language scores for individuals with 4p conditions with limited communication and expressive language skills, the REEL–2 and the CDI were included as part of the survey to be completed by parents or care providers of English-speaking participants. In order to ensure that nonverbal participants using alternative and augmentative communication (AAC) were adequately represented, the investigator adapted both CDI inventories by adding an AAC column for respondents to indicate that the participants’ primary communication modality was use of an aided or unaided AAC system.
Rescorla and Alley (2001) affirmed the reliability and validity of parent surveys that include a vocabulary checklist such as the CDI, an instrument that is also considered to be effective for older, developmentally delayed individuals than the measure was initially intended for (Cox, Dale, & Resnick, 2000). Moreover, content, criterion-related, and construct validity has been demonstrated for the CDI as a measure of vocabulary and grammar in typically developing children and children with developmental disabilities in English-speaking countries (Dale, Bates, Resnick, & Morisset, 1989; Fenson et al., 1994; Miller, Sedney, & Miolo, 1995; Yoder, Warren, & Biggar, 1997). Reliability, internal consistency, and concurrent validity, as measured by correlations with tester-administered measures, have also been demonstrated for the REEL–2 (Bzoch & League, 1991).

**Data Coding and Analyses**

In addition to questionnaire translations, the raw data compilation process included examination and manual recording of individual survey responses. In preparation for entering the data obtained from respondents who completed the REEL–2 checklists, a quantitative index of receptive and expressive language was computed for each survey participant by dividing the obtained age score by the chronological age and multiplying by 100. Receptive and expressive language quotients (LQs) were then assigned the following language impairment severity levels ranging from within normal limits to profoundly delayed for participants whose expressive language functioning level was consistent with a developmental age ≤ 36 months: within normal limits (70–100), mild language delay (52–69), moderate language delay (36–51), severe language delay (20–35), and profound language delay (< 20). The CDI yielded data relative to the participants’ total productive vocabulary, level of lexical diversity, utterance length, and use of morphosyntactic structures. Although the CDI data were broadly interpreted for the present study, they were primarily collected for summarization in a subsequent paper.

Expressive language impairment levels were also calculated for a small subset of English-speaking individuals (n = 7) whose most advanced expressive behavior was > the 36-month developmental language level and who provided sufficient expressive language information for linguistic analysis. All language transcripts were orthographically transcribed by the author, a licensed and certified speech-language pathologist (SLP), into computer text files using notations employed by Simmons-Mackie, Damico, and Damico (1999) or were transcribed using Version 6.1 of the Systematic Analysis of Language Transcripts (SALT) computer language analysis system (Miller & Chapman, 2000). The samples were then analyzed for diversity of word classes; morphosyntax based on the SALT data; number, length, and proportion of terminable-units (T-units) with embedded dependent clauses as defined by Hunt (1977); and complex sentence development using a procedure described by Paul (1981). The macrostructure and microstructure of the oral and/or written personal narratives were examined for number of words and ideas, complexity and clarity of semantic content, integrated focus, and cohesive adequacy (Applebee, 1978; McCabe & Rollins, 1994; Paul, Hernandez, Taylor, & Johnson, 1996). Impairment levels were determined by the author following qualitative analysis of the aforementioned conversational and narrative language sample transcripts based on a synthesis of semantic, morphosyntactic, and linguistic pragmatic developmental expectations (Dore, 1978; Paul, 1981, 2007; Retherford, 2000; Westby, 1980); school record review; standardized test results; and a written language sample for 1 study participant. Criteria adapted from the Functional Communication Profile—Revised (FCP–R; Kleiman, 2003) were used to assign communication and expressive language impairment severity levels to the 7 individuals who evidenced productive language use. The following language impairment severity levels were designated for the 4 adult participants, 18 years or older: within normal limits, mild (skills consistent with the 9- to 13-year level), moderate (5- to 9-year level), severe (2- to 5-year level), and profound (0- to 2-year level). The following language impairment severity levels were designated for the 3 participants younger than 18 years of age: mild (up to 1 year delayed), moderate (1–2 years delayed), severe (2–3 years delayed), and profound (>3 years delayed).

**Reliability**

Three licensed SLPs certified by the American Speech-Language-Hearing Association independently verified transcription and coding of the language transcripts and conversational and narrative language analyses, as well as the author’s assignment of severity level for the 7 participants whose expressive symbolic language level exceeded the 3-year developmental level. The independent raters were provided with each participant’s chronological age and instructions for using the language impairment severity rating criteria. The author requested that the independent raters use the criteria to assign a language impairment severity level based on review of the language transcripts and any supporting documentation (e.g., school work samples). Interrater agreement for transcription accuracy, analysis, and severity level assignment was 100%.

**RESULTS**

**Communication and Expressive Language Level**

The author broadly categorized the 200 participants’ reported communication and expressive language behaviors into stages based on a normative developmental model (Paul, 2007). The major characteristics associated with each developmental level are summarized in Table 2. Of the 200 respondents who completed the REEL–2 or provided a representative expressive language sample, 46% of the participants demonstrated communication skills at the preintentional level, 21% demonstrated communication skills commensurate with the prelinguistic intentional level, 20% demonstrated communication skills at the single-symbol level, 9.5% demonstrated communication skills at the two- to three-symbol (i.e., verbal words, gestures, or icons) expressive language level, and 3.5% evidenced expressive language skills > the 3-year developmental level.

**Participants’ Communication Mode: Symbolic Language Users**

Of the participants with symbolic language use, 34% (n = 79) primarily used an AAC system to symbolically express communicative intent. Of these, 44 (56%) used single iconic gestures or approximated manual signs (symbol sequencing) to communicate;
Table 2. Study participants’ (N = 200) most advanced level of communication and expressive language behavior.

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of participants</th>
<th>%</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
<th>Key expressive communicative behaviorsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presymbolic, preintentional, and prelinguistic</td>
<td>93</td>
<td>46</td>
<td>7.6</td>
<td>7.7</td>
<td>1–38</td>
<td>Gazing; smiling; reflexive crying; vegetative sounds; “raspberries”; clicks; coos; high-pitched squeals; vocalization of lax vowels /a/, /e/, and /o/ and velar stops /k/ and /g/</td>
</tr>
<tr>
<td>Prelinguistic, intentional, and social communication</td>
<td>41</td>
<td>21</td>
<td>7.6</td>
<td>5.7</td>
<td>1–21</td>
<td>Canonical babbling; variegated babbling; turn-taking gestural routines (e.g., “peek-a-boo,” “pat-a-cake”); paralinguistic behavior (e.g., facial expressions, body orientation); contact gestures (e.g., raising arms to be picked up, holding objects up); distal gestures (e.g., head nod to indicate “no,” referential pointing with index finger)</td>
</tr>
<tr>
<td>Aided or unaided linguistic</td>
<td>40</td>
<td>20</td>
<td>9.8</td>
<td>5.7</td>
<td>2–26</td>
<td>Referential single symbols (verbal words or iconic gestures) or holophrases; general and specific norms, action words, modifiers, and demonstratives; diverse semantic roles and pragmatic functions</td>
</tr>
<tr>
<td>single-symbol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aided or unaided two-symbol</td>
<td>4</td>
<td>2</td>
<td>9.0</td>
<td>8.2</td>
<td>3–21</td>
<td>“Telegraphic sentences”; two-symbol semantic relations incorporating determiners, adjectives, demonstratives, locatives/prepositions, negatives, quantifiers, relational words, catenatives wanna and gonna, and bound morphemes</td>
</tr>
<tr>
<td>semantic relations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aided or unaided three-symbol</td>
<td>15</td>
<td>7.5%</td>
<td>13.9</td>
<td>11.1</td>
<td>4–47</td>
<td>Context-bound and/or decontextualized declarative statements containing grammatical morphology, rule-governed noun and verb phrases and negatives; questions</td>
</tr>
<tr>
<td>sentences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaided simple and complex</td>
<td>7</td>
<td>3.5%</td>
<td>17.9</td>
<td>10.3</td>
<td>6–36</td>
<td>Multiple utterances per speaking turn; decontextualized complex constructions containing negatives, declaratives, imperatives, interrogatives, past tense voice, passive transformations, nominal clauses, relative clauses, subordinate adverbial/object clauses, temporal/causal relationships, and cohesive ties</td>
</tr>
<tr>
<td>sentences during conversation and in oral/written personal narratives and poetry</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*aBehavior evidenced by 1 participant; bBehavior demonstrated by some but not all participants.

9 (11%) used no-tech picture systems to communicate, including visual symbols, iconic picture boards, picture books, and the Picture Exchange Communication System (PECS; Bondy & Frost, 1998); 13 (17%) used voice output communication aids that require use of a distal point or full hand to indicate communicative intent; and 13 (17%) used touch screen computer inputs such as a mouse or track ball that control an enlarged on-screen cursor to point and click or standard computers with adapted keyboards to communicate.

### Conversational Discourse Skills

The expressive language of a small cohort of the most advanced expressive language users (n = 7) reflected a broad array of sophisticated social discourse skills during reciprocal conversation, including use of dialogue during role playing; polite forms; topic initiation and topic maintenance via topic-initiating and topic-continuing questions; contingent statements/queries to share experiences; conversational repair/revision strategies; and clarification requests. The 7 participants used sentential complements to express emotional state and to empathically comment on the thoughts and feelings of others using mental state verbs (e.g., I think, I know), reflecting their ability to represent “theory of mind” (Hale & Tager-Flusberg, 2003). In addition to perspective taking, conversational samples revealed the participants’ appreciation of humor and the use of ellipsis and other cohesive devices to sequentially link events and to describe temporal, cause–effect, or interpersonal relationships. Conversational acts (Dore, 1978) included requests, descriptions, statements, and acknowledgments. Other performatives included the competent use of verbal language to convey and exchange information during dyadic interaction; tell jokes; tease; discuss personal preferences (e.g., music, food); creatively problem solve during representational play and curriculum-relevant activities (i.e., games, science-based activities); predict solutions; and anticipate future events.

### Oral Reading and Written Language Expression

Of the 200 participants, 15 (7.5%) reportedly identified the alphabet letter names and 8 (4%) read high-frequency sight words. One adult participant, identified with Proximal 4p- syndrome, reportedly possessed reading skills consistent with at least the fourth-grade reading level, sufficient for her successful employment. Nine (4.5%) participants reportedly wrote letters to form meaningful words. The aforementioned participant with proximal 4p deletions provided authentic written samples of letters and sequentially and temporally organized personal narratives, prose, and reflective, thematically linked poetry (end rhyme), incorporating lexical diversity and multicausal grammatical structures, character description, imagery, figurative language, point of view, reference to emotional state, and expression of identity.
Emergent Age of Highest Expressive Language Use

Respondents provided sufficient information regarding the age that 25 of the 66 symbolic language users initiated use of aided or unaided single symbols, two-symbol combinations, three-symbol phrases, and sentences or complex sentences. Variously slow developmental progression was associated with the acquisition of single symbols (ages 1–12), two-symbol combinations (2–10 years), three-symbol combinations (3–14 years), and complex sentences (3–8 years). Although the most advanced participants acquired single symbol use by 6 years of age, progression from two-symbol combinations to consolidation of simple and complex sentence structures could not be predicted.

Severity of Expressive Language Delay

Sufficient information was provided by 90% (n = 180) of the 200 respondents to determine the severity of the participants’ expressive language delay based on a comparative analysis of their chronological age with language quotients derived from results of their REEL–2 or qualitative analysis of their oral and written language transcripts. Table 3 shows that the majority of participants evidenced severe and profound expressive language delays. Based on a morphosyntactic analysis of transcribed discourse-level communication and authentic written language samples provided by one 36-year-old female participant with proximal 4p deletions (4p13 and 4p15.2) who received intensive special education services through junior high school and resource room services during high school, her oral communication and verbal expressive language skills were assessed to be broadly within normal limits for her chronological age. Although the majority of the participants demonstrated developmental progression in expressive language behavior with advanced age, the severity of the participants’ expressive language delay increased with chronological age for 99% of the cohort. Slow rate of expressive language development and advancing age, therefore, appeared to contribute to widening the developmental gap.

Phenotypic Effects and Gender, Country of Origin, and Primary Language

Variation in communication and expressive language phenotypic effects based on gender was not identified. This finding is consistent with an earlier research conclusion (Fisch et al., 2008) that there were no gender differences in the cognitive–behavioral manifestations in a cohort of individuals with 4p- conditions.

Table 3. Number and percentage of participants (n = 180) assigned to each of five severity levels by language age.

<table>
<thead>
<tr>
<th>Severity level</th>
<th>≤ 3 years</th>
<th>&gt; 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 48 (27%)</td>
<td>n = 132 (73%)</td>
</tr>
<tr>
<td>Within normal limits</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mild delay</td>
<td>3 (6.2%)</td>
<td>5 (3.8%)</td>
</tr>
<tr>
<td>Moderate delay</td>
<td>9 (18.8%)</td>
<td>10 (7.6%)</td>
</tr>
<tr>
<td>Severe delay</td>
<td>28 (58.3%)</td>
<td>10 (7.6%)</td>
</tr>
<tr>
<td>Profound delay</td>
<td>8 (16.7%)</td>
<td>106 (80.3%)</td>
</tr>
</tbody>
</table>

The present data also did not reveal any geographic or primary language influences on the spectrum of communication and expressive language phenotypes represented in the study.

Preliminary Genotype–Expressive Language Phenotype Observations

The 83 participants (41.5%) with a documented diagnosis of one of the four primary chromosome 4 variants represented in the study provided sufficient information (Table 4) regarding both genotype and expressive communicative behavior for preliminary genotype–phenotype observation. Geneticists (Bergemann et al., 2005; Maas et al., 2008; Zollino et al., 2003) concur that such observations should be cautiously interpreted, however, as the data are compromised by unavailable definitive genomic information for individuals who were not assessed with the recently available whole genome analysis technology and the markedly variable expression of multiple genes as they interplay with specific motor, language, cognitive, developmental, and unknown or not yet understood genetic processes in all individuals with 4p- syndrome. Although the descriptive data did not reveal any definitive genome–phenotype patterns in the current study, broadly interpreted data suggest that all participants with the documented largest deletions, covering and flanking the 4p16.3 (WHS) critical region, exhibited the most profound communication and expressive language impairments. Conversely, the data did not suggest that the expressive language behavior of all individuals with smaller deletions restricted to the gene-dense 4p16.3 (WHS) region were less severely affected than those individuals exhibiting deletions proximal to the 4p16.3 (WHS) with or without associated complex 4p chromosomal arrangements.

DISCUSSION

The present study of the communication and language phenotypic features of individuals with 4p conditions across cultural–linguistic boundaries is the largest ever attempted and addresses the stated research goal to describe the language disorder profile associated with individuals with WHS and related 4p- conditions (Battaglia & Carey, 2008). Before this investigation, little was known about the course and sequence of the communication and expressive language behavior exhibited by a diverse group of individuals with 4p abnormalities. The central study aims were to increase the specificity of the communication and expressive language phenotype of individuals with 4p conditions and expand the descriptive epidemiology of this complex disorder by highlighting the communicative potential of a subset of the participant pool. The study also sought to formulate a preliminary hypothesis regarding genotype and expressive language manifestations in individuals with 4p genomic defects as a basis for future empirical study.

Analyses of the preliminary study findings suggest that individuals with 4p conditions constitute a large, heterogeneous clinical population with complex communication and expressive language phenotypic profiles. The majority of the participants exhibited significantly compromised communication and expressive language skills below the 36-month developmental functioning level. Whereas Battaglia and Carey (2008) reported mild intellectual disabilities for 10% of the individuals they studied with 4p conditions,
moderate intellectual disabilities for 25%, and severe intellectual disabilities for 65%, results of the current study suggest that the majority of individuals with 4p conditions exhibit more significant impairments in communication and expressive language domains. This preliminary finding is in agreement with a prior description of a cohort of older individuals who exhibited a relatively mild 4p- physical phenotype yet were diagnosed with moderate to profound expressive language impairments (Van Buggenhout et al., 2004). Although nonlinguistic social–pragmatic communication behavior was an area of relative strength for the participant population, the majority exhibited profound expressive language delays. Marked variability, however, was noted in the range of the participants’ expressive language behaviors, with a contrastively small 4p- cohort demonstrating the potential to develop advanced language production and functional reading skills. One participant demonstrated written language skills sufficient for writing letters, personal narratives, and poetry. The topography of communicative acts that were exhibited across the 4p- participant pool included natural, contact, and distal gestures; graphic symbol selection; manual signs; and simple or complex verbal and written language expression.

Preliminary findings do not reveal quantifiable strands of variation in response patterns based on participants’ gender, country of origin, or primary language, nor do they predict longitudinal changes in language production skills. For those participants who developed productive language, the trajectory was generally consistent with typical developmental language patterns exhibited by unaffected children and shares common characteristics of all individuals with developmental disabilities. Rate of expressive language growth for the majority of the aided or unaided communicators, however, was not linear in that study respondents reported a typically slow acquisition of expressive behavior followed by atypical, protracted plateaus before evidence of further expressive language development through adolescence. One participant, for example, acquired single-symbol use at 2 years of age but did not acquire two-symbol combinations until age 10 and three-symbol phrases or sentences until age 14. Another participant acquired single-symbol use at age 6 and began formulating simple sentences at age 13. A “critical period” for expressive language development in the 4p- population was not supported.

Although the majority of the productive expressive language users initiated expressive symbol use during the first 6 years of life, 1 participant did not acquire single-symbol use until age 12. One participant, who consolidated use of complex sentences at age 8, did not initiate single-symbol use until age 6. The expressive behavior plateau levels of all participants who acquired symbol use were variable. Although most school-age participants diagnosed with a 4p chromosomal abnormality reportedly increased their communication and expressive language skills in response to speech-language therapy services, the developmental lags in expressive language development widened for the majority of the 4p- population with advancing age. Slow and variable expressive language skills continued to develop through adolescence for a cohort of individuals with 4p conditions, suggesting that language intervention should continue during the teenage years dependent on pertinent factors such as cognitive status and receptive language level.

Although the preliminary study findings do not significantly contribute to clarifying the debate regarding the correlation between deletion location, size, and phenotypic expression in individuals with 4p abnormalities, the limited data are in agreement with an earlier hypothesis (Bergemann et al., 2005; Wieczorek et al., 2000; Zollino et al., 2000; Zollino et al., 2003; Zollino et al., 2008) that the largest contiguous 4p deletions, which include the 4p16.3 (WHS) gene region, are associated with the most severely compromised behavioral phenotypes. Conversely, the preliminary findings do not confirm the suggestion (Chen, 2009; Van Borsel et al., 2004; Zollini et al., 2003) that individuals with deletions restricted to the 4p16.3 (WHS) region exhibit comparatively milder phenotypic effects than do those individuals exhibiting deletions proximal to the 4p16.3 (WHS) region with or without associated complex chromosomal rearrangements. Although the overall study findings are consistent with earlier research (Fisch et al., 2008) that failed to identify a definitive relationship between 4p deletion size and cognitive–behavioral abilities, the present study data do support the premise that the phenotypic expression of 4p genomic defects can be classified into two broadly defined categories—a severe or profound “classical” phenotype and a comparatively “mild” phenotype (Meloni, Shepard, Battaglia, Wright, & Carey, 2000; Zollino et al., 2003).

**Clinical Implications**

The study data are clinically relevant for SLPs and audiologists who play a significant role in assessing communication, language,

<table>
<thead>
<tr>
<th>4p segment affected</th>
<th>Precanonical vocalizations</th>
<th>Canonical babbling</th>
<th>Variegated babbling/jargon</th>
<th>Single symbol</th>
<th>Two-symbol combinations</th>
<th>Three-symbol sentences</th>
<th>Complex sentences</th>
</tr>
</thead>
<tbody>
<tr>
<td>4p16.3 only (WHS)</td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td>#</td>
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<tr>
<td>4p proximal deletions (not including 4p16.3)</td>
<td>#</td>
<td>%</td>
<td>#</td>
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<td>%</td>
<td>#</td>
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<tr>
<td>4p- and other complex chromosome rearrangements</td>
<td>#</td>
<td>%</td>
<td>#</td>
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<td>#</td>
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<tr>
<td>Large 4p deletions (4p15.1 to terminal end including 4p16.3)</td>
<td>#</td>
<td>%</td>
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*Mosaicism, ring chromosome 4, and gene duplications in addition to gene deletions.*

**Table 4.** Spectrum of most advanced expressive language levels associated with main 4p- genome classifications (n = 83).
swallowing, feeding, and hearing; providing guidance to family members and other human service providers regarding prognoses; and prescribing intervention recommendations to facilitate optimal developmental gains. Although the majority of the study participants evidenced a profound expressive language delay, the highly competent communication exhibited by a small cohort highlights the communication and expressive language potential of some individuals with a 4p condition. Results suggest that clear boundaries do not exist regarding the communication skills of this population and that the abilities of individuals with 4p- syndrome should not be underestimated. The most salient “take-home” message is that heterogeneous communication and expressive language skills should be therapeutically addressed with the expectation that differentiated assessment and intervention will further facilitate communication and expressive language competence in all individuals with 4p- syndrome and significant developmental progression in a cohort with 4p abnormalities.

**Study Limitations**

Methodological flaws temper the study conclusions and, therefore, the data presented should be interpreted cautiously. First, data are descriptive in nature and, in most cases, are based on unsubstantiated caregiver report. Second, formal genetic data are lacking for a large percentage of the participant pool. Cytogenetically detected 4p deletions were not defined for a majority of the oldest participants, who were broadly diagnosed with conventional genetic testing before the advent of whole genome study technology. This genotype information is particularly germane to formulating hypotheses regarding the impact of genotypic variation on phenotypic expression in the 4p- population. Furthermore, only 2 of the participants diagnosed with WHS were studied with the recently available whole genome analysis technology. These analyses revealed a previously undiagnosed duplication from another chromosome region on the 4p arm in addition to a 4p deletion for both participants, supporting the contention that the genotypes of a subset of individuals with 4p- syndrome could potentially be modified based on results of sophisticated whole genome testing (Zollino et al., 2003) by revealing microdeletions or chromosome rearrangements. As the reported genotypes for the study participants may well be incomplete, any preliminary hypotheses regarding genotype–phenotype correlations should be considered conjecture until all participants’ genomes are definitively delineated with state-of-the-art genomic analysis techniques.

Third, the analytic model used for the present study did not examine the major sources of variance beyond genotype, including individual care provider style, sensitivity, responsibility, and education level; psychological characteristics; family interaction and child care customs; cultural setting; socioeconomic factors; heterogeneity of participants’ educational programs; learning styles; speech-language therapy history and its effect; maturation effect; diet; toxins; and other societal or social components. The causal influence of nongenetic factors, including age initiated, duration, longitudinal effects, and form of speech-language intervention (i.e., treatment effect), on shifting the individual participant’s developmental trajectory was not determined. The impact of comorbid medical conditions (e.g., severe seizures, stroke, hypotonia, conductive and/or sensorineural hearing loss, feeding difficulties in infancy) and medication use, including seizure medicines, on modifying the individual participant’s clinical phenotype was also not determined.

Fourth, as study participants were recruited through 4p- support networks, individuals diagnosed with 4p- syndrome who are older or who evidence the most advanced expressive language behavior may be underrepresented in the current study due to lack of affiliation with a 4p- support group or an incomplete or erroneous diagnosis.

A final methodological issue concerns the use of the CDI and the REEL–2. Although most appropriate for use with the younger participants, their valid use was compromised as age increased, particularly for those older participants who developed productive expressive language. Also, the CDI, REEL–2, or survey questions did not address the participants’ rate of communication development. Some respondents, for example, reported only occasional use of words, modified signs, and other forms of AAC as the primary expressive communication modalities; other respondents reported participants’ frequent expressive language use.

**Future Research Direction**

The current study elucidates and expands on the existing behavioral phenotype associated with chromosome 4p abnormalities and contributes to clarifying functional understanding of how 4p gene deletions and related complex rearrangements variably affect human communication behavior. It is anticipated that the study findings will contribute to future clinical and cytogenetic research designed to further describe the variable communication and expressive language phenotype of people with 4p genomic defects and how these abnormalities influence the course of language development through the life span. Further extrapolation of information from the current unique, multidimensional population database should also lead to hypotheses regarding the degree to which cognitive impairment, dysphagia, feeding disorders, sensorineural hearing loss, and other neuromotor deficits compromise the optimum development of communication and expressive language development in the 4p- population. Additional data collection and correlation analyses should further elucidate the relationship between expressive syntax development and receptive language skills, specifically with regard to whether expressive language skills are less developed than would be expected based on receptive language age. Further research should also discern the contribution of comorbid complex motor speech impairments to delayed expressive language development in the 4p- population. It is expected that this information will ultimately contribute to determining if a distinct communication and expressive language profile is associated with 4p- syndrome.

The fields of behavioral genomics and human neurogenetics offer the promise that, as specific genes that influence human behavior are identified and brain structure and function are further analyzed, geneticists will accurately delineate the genetic differences that contribute to phenotypic heterogeneity and long-term developmental change in individuals with 4p- syndrome. It is projected, therefore, that the present study data will contribute to the existing genomic database in order to facilitate researchers’ exploration of the genotype variables that influence the course of communication and expressive language development in individuals with 4p conditions. Such research will potentially clarify predictable clinical issues and provide data-based prognostic information for future communication and expressive language function. This knowledge is important to determining the evidence-based assessment, intervention, and counseling “best practice”
recommendations to support optimum communication and language development in individuals with chromosome 4p abnormalities.

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Contact author: Althea T. Marshall, Southern Connecticut State University, Department of Communication Disorders, Davis Hall Room 012 L 501, Crescent Street, New Haven, CT 06515.
E-mail: marshalla1@southernct.edu.