The Genetic Bases of Speech Sound Disorders: Evidence From Spoken and Written Language

THEORETICAL/REVIEW ARTICLE

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The purpose of this article is to review recent findings suggesting a genetic susceptibility for speech sound disorders (SSD), the most prevalent communication disorder in early childhood. The importance of genetic studies of SSD and the hypothetical underpinnings of these genetic findings are reviewed, as well as genetic associations of SSD with other language and reading disabilities. The authors propose that many genes contribute to SSD. They further hypothesize that some genes contribute to SSD disorders alone, whereas other genes influence both SSD and other written and spoken language disorders. The authors postulate that underlying common cognitive traits, or endophenotypes, are responsible for shared genetic influences of spoken and written language. They review findings from their genetic linkage study and from the literature to illustrate recent developments in this area. Finally, they discuss challenges for identifying genetic influence on SSD and propose a conceptual framework for study of the genetic basis of SSD.

KEY WORDS: genetics, reading disorders, speech sound disorders, language disorders

Speech sound disorders (SSD), defined as a significant delay in the acquisition of articulate speech sounds, have an estimated prevalence of 3.8% in 6-year-old children, with higher rates in younger children (Shriberg, Tomblin, & McSweeny, 1999). More than half of these children encounter later academic difficulties in language, reading, and spelling (Aram & Hall, 1990; Bishop & Adams, 1990; Felsenfeld, McGue, & Broen, 1995; Menyuk et al., 1991; Nathan, Stackhouse, Goulandris, & Snowling, 2004; Shriberg & Kwiatkowski, 1988). The residual effects of a preschool SSD may be life long, yet for the majority of individuals the etiological basis of the disorder is unknown. Recent studies supporting a genetic component to SSD hold promise in furthering our understanding of causal mechanisms.

The significance of identifying underlying genetic factors for SSD is fourfold. First, from a clinical perspective, identification of genetic factors underlying SSD may result in improved diagnosis and early identification of those at risk, allowing for environmental intervention at a young age (Fisher & DeFries, 2002). Second, from a basic science perspective, identifying these factors may lead to the discovery of key genetic pathways (i.e., functional studies of the proteins coded for by specific genes and the resulting metabolic, structural, signaling, transcription regulation, or other cellular pathways), thus bridging the gap between genetics and the neurobiological bases of these disorders (Fisher & DeFries, 2002;

Fisher, Lai, & Monaco, 2003). Third, from a nosology perspective, examining and identifying common genetic factors associated with SSD, language impairment (LI), and reading disorders (RD) may assist in the development of meaningful diagnostic categories based on shared underlying deficits, such as impaired phonological representations (Raitano, Pennington, Tunick, Boada, & Shriberg, 2004; Tunick & Pennington, 2002). Finally, from an evolutionary viewpoint, genetic studies of speech and language disorders may provide insight into the evolution of the human capacity for speech and language (Fisher, 2005; Fisher et al., 2003).

The goals of this article are to present evidence for genetic transmission of SSD, to review results from recent genetic findings of SSD, and to discuss possible shared genetic etiologies for SSD, LI, and RD. First, findings from genetic studies of SSD will be presented, exemplifying various genetic methodologies. Research on genetics of LI and RD will be reviewed, and genetic overlap with SSD discussed. Finally, findings will be summarized and future directions discussed. See the Appendix for definition of common genetic terms.

Genetic Studies of SSD

Prevalence and Comorbidity

The prevalence of SSD in 6-year-old children was reported by Shriberg et al. (1999) as 3.8%, with rates of 4.5% for boys and 3.1% for girls. Rates for younger children are much higher, with some studies reporting rates of 15.6% in 3-year-old children (Campbell et al., 2003; Shriberg et al., 1999). The percentage of children with SSD who also have LI has been estimated at 6%–21% for children with receptive language disorders, and 38% to 62% for children with expressive language disorders (Shriberg & Austin, 1998). Thus, comorbid expressive disorder is two to three times more common in SSD than comorbid receptive disorder. A recent study by Blood, Ridenour, Qualls, and Hammer (2003) suggested that SSD may also be significantly comorbid with stuttering. These investigators surveyed speech-language pathologists who work with children who stutter. Information was provided for 2,628 children. The speech-language pathologists reported that 33.5% of the children had comorbid articulation disorders and 12.7% had comorbid phonology disorders.

Familial Aggregation Studies

The study of the genetic bases of spoken and written language began with behavioral genetic methods that utilized statistical techniques for determining familial aggregation of traits, and then progressed to more sophisticated molecular genetic methods. Early studies of SSD, LI, and RD sought to establish that the disorder clustered in some families (Pennington, 1997). These familial aggregation studies demonstrated that the prevalence of a disorder within a family of a proband (the index case from whom other family members are identified) was greater than the prevalence of the disorder in the population as a whole.

Several studies have specifically focused on children with SSD. An early study by Morley (1967) reported a history of SSD in first-degree relatives in 6 out of 12 families in which the proband child had apraxia of speech. Studies of the familial aggregation of SSD have reported a higher percentage of family members affected by speech and language disorders in families of children with SSD than in control families (Felsenfeld et al., 1995; Lewis, Ekelman, & Aram, 1989). Approximately 26% of nuclear family members and 13.6% of extended family members were affected in a cohort of children with SSD, as described by Lewis (1992). Brothers showed higher affection rates (40.9%) than sisters (19.4%), with mothers (18.2%) and fathers (18.3%) almost equally affected. A subsequent segregation analysis supported familial transmission of SSD but was unable to distinguish between major gene and multifactorial transmission models (Lewis, Cox, & Byard, 1993).

Twin Studies

Family studies cannot separate genetic influences from effects of shared or nonshared environmental factors. Family aggregation studies of SSD were followed by twin studies that examined the concordance for the disorder in monozygotic (MZ) twins and dizygotic (DZ) twins. If concordance rates are higher for MZ than DZ twins, a genetic component to the disorder is implied as MZ twins are identical genetically whereas DZ twins share on average 50% of segregating genes.

An early twin study of articulation skills was conducted by Matheny and Bruggemann (1973). They studied 101 same-sex twins, 22 opposite-sex twins, and 94 siblings between the ages of 3 and 8 years. The Templin–Darley Screening Test of Articulation was administered to each child. The following correlations between twins were found: .84 for identical boys, .56 for fraternal boys, .90 for identical girls, and .83 for fraternal girls. These differences in the MZ–DZ correlations suggested a strong genetic influence on articulation for at least the boys.

Bishop, North, and Donlan (1995) examined 63 MZ and 27 DZ twin pairs, some of whom had isolated SSD and some of whom had a combination of an SSD and receptive and/or expressive LI. They found higher concordance for MZ (boys = .92; girls = 1.0) than DZ (boys = .62; girls = .56) twins, but were not able to examine subtype differences in concordance rates because of small sample size.

A twin study that examined twin pairs for SSD has also reported significantly higher concordance rates for SSD in MZ (.95) than in DZ (.22) twins (Lewis & Thompson, 1992). Another twin study conducted by Bishop (2002) demonstrated high rates of heritability for SSD (h^2 = 0.97) and common genetic influences for motor impairment and SSD (h^2 = 0.71). However, twin studies using contemporary speech analysis procedures have not been carried out to examine MZ–DZ twin pair differences in type of speech sound error, phonological processing abilities, other comorbid disorders, or developmental trajectories for speech sound development. Such studies may be more informative than investigations of concordance rates for the binary trait of SSD.

Molecular Genetic Studies

Although familial clustering or aggregation studies can establish that a trait or disease clusters in families, the explanation for the excess clustering can only be established after testing specific hypotheses, whether a trait is genetic or environmental. Molecular genetic studies, which examine the DNA of individual family members, seek to identify regions of a chromosome that harbor potential genes that influence susceptibility for SSD. Genes and environment together confer susceptibility to the development of a disorder (Gottesman & Gould, 2003). That is, a specific variant (allele) of a gene in combination with the environment may predispose an individual to SSD. Genes direct the synthesis of proteins that may in turn influence neural development, maturation, or functioning, thus affecting cognitive processes associated with speech and language. For example, recently two genes have been associated with dyslexia: the *ROBO1* gene (Hannula-Jouppi et al., 2005) and the *DCDC2* gene (Schumacher et al., 2005). Both of these genes influence axonal and neural migration. The alleles of these genes that disrupt neural development may predispose an individual to RD.

Common research designs in molecular genetic studies of spoken and written language include linkage, association, and mutation analyses. Linkage analysis evaluates how markers (pieces of DNA that can be assayed at the molecular level and followed through families) and phenotypes based on family data are jointly inherited at various locations in the genome. Some recent reviews of linkage methods are described in Fisher and DeFries (2002) and Schaid, Olson, Gauderman, and Elston (2003). The phenotype may be binary, as in the presence or absence of disease, or continuous; the genes influencing the latter are referred to as *quantitative trait loci* (QTLs). Linkage designs use coinheritance of the trait in many family members, examining both affected and unaffected individuals, along with their corresponding DNA to localize a gene (or genes) to a general area on a specific chromosome. Initially, this area is often broad in width and additional studies (called "fine mapping") need to be conducted to home in on the actual gene, as a segment of a chromosome can house many hundreds of genes. Linkage studies can be limited to a portion of a chromosome, an entire chromosome, or the entire genome that consists of 22 autosomes and the sex chromosomes.

In contrast to linkage studies, association studies use information on shared ancestral inheritance going back more than a few generations; both case-control (without families) and family-based designs are possible. This design more directly tests if the variant under examination is the causative variant or is in very close proximity to the actual causative variant. The major difference between linkage and association is that linkage seeks to localize the potential genes to millions of base pairs of DNA, whereas association studies seek to localize the genetic signal to thousands of base pairs. Where linkage analysis assesses the coinheritance of trait and marker *loci within families,* association analysis evaluates the nonindependence of specific trait and marker *alleles across families* or unrelated individuals. Association studies are usually done when candidate genes are known. Linkage studies are performed when there is no a priori hypothesis regarding the location of candidate genes. Association studies examine a smaller region of the chromosome than do linkage studies. Another limitation of association studies may be problems with population stratification. Both linkage and association analyses may interrogate specific chromosomal regions or genes, or may search the entire genome without a priori assumptions about disease pathobiology. This latter approach is referred to as a *genome scan.* Studies may then be undertaken to identify the responsible gene(s).

Few studies have examined the genetic basis of speech problems. Molecular genetic studies of SLI and dyslexia have typically failed to distinguish individuals with comorbid SSD from those with only SLI or dyslexia. Table 1 provides a summary of molecular genetic studies of SSD, LI, and RD and the linkages associated with these disorders. As evident in this summary, some measures such as nonword repetition tasks have been used in studies of each of the three disorders, suggesting overlap among the disorders. Although the genetic basis of SSD has received little research attention, candidate chromosome regions for this disorder are suggested by studies of LI and RD. As reviewed next, several collaborative research groups have recently begun to focus on the molecular basis of SSD.

Investigations of the KE family provide an excellent example of research that progressed from familial aggregation studies to molecular genetic studies and ultimately to neurological studies and a mouse model. Hurst, Baraitser, Auger, Graham, and Norell (1990) described an unusual

Table 1. Summary of linkage studies of dyslexia, SLI, and SSD phenotypes.

Chromosome	Region (markers)	Authors	Sample size	Phenotypes showing linkage	Measures showing linkage
1	1p34-36	Rabin et al., 1993	9 families	Dyslexia	
	1p (D1S253–D1S436) (D1S199–D1S478)	Grigorenko et al., 2001	8 families	Phonemic awareness, phonological decoding, rapid naming, single-word reading, and vocabulary	Wechsler and Peabody Tests
	1p34-p36	Tzenova et al., 2004	100 families	Spelling, phonological coding	Woodcock Reading Mastery Tests; Wide-Range Achievement Test
2	2p12-16 (D2S337–D2S286)	Francks et al., 2002	119 families	Dyslexia	Colorado Learning Disability Test Battery
	2p15-16	Fagerheim et al., 1999	1 large extended family	Dyslexia	
	2p11 (DYX3)	Kaminen et al., 2003	11 families	Dyslexia	Finnish Reading and Spelling Tests
	2p11 (D2S2216)	Peyrard-Janvid et al., 2004	11 families	Dyslexia	Finnish Reading and Spelling Tests
3	3p12-13	Nopola-Hemmi et al., 2001	1 large extended family	Phonological awareness, rapid naming, and dyslexia	Finnish Reading and Writing Test; Neuropsychological Test Battery
	(D3S2465, D3S3716, and D3S1595)	Stein et al., 2004	77 families	Phonological memory, single-word decoding	Multisyllabic Word Repetition; Nonsense Word Repetition; and Woodcock Reading Mastery Tests
6	6p21.3 (D6S105)	Cardon et al., 1994, 1995	19 extended families, 46 twin pairs	Reading disability	Peabody Individual Achievement Test; Wechsler Intelligence Scale for Children
	6p22.3-21.3 (D6S109–D6S306)	Grigorenko et al., 1997	6 extended families	Phoneme awareness, phonological decoding, rapid naming, and single-word reading	Woodcock Johnson Psychoeducational Battery—III; Peabody Picture Vocabulary Test; and Wide-Range Achievement Test
	6p21.3 (D6S464–D6S273)	Grigorenko et al., 2000	8 extended families	Single-word reading, vocabulary, and spelling	Woodcock Johnson Psychoeducational Battery—III; Peabody Picture Vocabulary Test; and Wide-Range Achievement Test
	6p23-p21 (D6276-D6S105)	Gayan et al., 1999	79 families (126 sib pairs)	Phoneme awareness, phonological decoding, and orthographic choice	Wechsler Intelligence Scale for Children; PIAT; Olson's Experimental Measures
	6p21.3 (D6276, D6S105)	Fisher et al., 1999	82 nuclear families	Phonological decoding, orthographic coding	
	6q11.2-q12 (D6S254, D6S965, D6S280, and D6S251)	Petryshen et al., 2001	96 families	Phonological awareness phonological coding, and spelling	Woodcock Johnson Psychoeducational Battery—III; Rapid Auditory Naming Task; and WRAT
	6p21.3	Smith et al., 1991	19 extended families	Dyslexia	
	6p21.3-22 (D6S461)	Kaplan et al., 2002	104 families	Reading language, orthographic choice	Wechsler Intelligence Scale for Children; PIAT orthographic choice; homonym choice; phoneme transposition; and phoneme deletion

(Continued on the following page)

Table 1 *Continued.* **Summary of linkage studies of dyslexia, SLI, and SSD phenotypes.**

Chromosome	Region (markers)	Authors	Sample size	Phenotypes showing linkage	Measures showing linkage
	6P21.3 (D6S1597–D6S1571)	Deffenbacher et al., 2004	349 families	Phoneme awareness, phonological decoding, single-word reading, and orthographic coding	Colorado Learning Disability Test Battery
7	7q31	Fisher et al., 1998		Sequential articulation	
13	13q21 (D13S800)	Bartlett et al., 2002	5 families	Reading discrepancy score	Test of Language Development—Primary:3; Wechsler Intelligence Scale for Children; and Woodcock Reading Mastery Tests
15	cen 15	Smith et al., 1983	9 families	Dyslexia	
	cen 15	Bisgaard et al., 1987	5 families	Dyslexia	
	15q15-15qter	Smith et al., 1990	19 families	Dyslexia	
	ynz90; ju201	Fulker et al., 1991	19 families		
	15q21 (D15S143)	Grigorenko et al., 1997	6 families	Single-word reading	Woodcock Reading Mastery Tests
	15q	Rabin et al., 1993	9 families	Dyslexia	
	15q21 (D15S132, (D15S143)	Schulte-Korne et al., 1997	7 families	Dyslexia	
	15q15.1-15.3 (D15S994)	Morris et al., 2000	178 families	Reading disability	Wechsler Intelligence Scale for Children; Neale Analysis of Reading Abilities
	15q (GATA50C03-D15S143)	Chapman et al., 2004	111 families	Single-word reading	Woodcock Reading Mastery Tests
16	D16S515–D16S520	The SLI Consortium, 2002, 2004	98 families	Nonword repetition reading, comprehension spelling	Clinical Evaluation of Language Fundamentals; Wechsler Intelligence Scale for Children; and Nonword Repetition Test
18	18p11.2 (D18S53)	Fisher et al., 2002	84 nuclear families	Single-word reading, phonological processing, and orthographic processing	Spelling; spoonerisms; phoneme transposition/deletion; nonword reading; and real-word reading
18	18p11.2 (18S53)	Fisher et al., 2002	89 families from United Kingdom, 119 families from United States	Single-word reading, phonological and orthographic processing	Spelling; spoonerisms; phoneme transposition/deletion; nonword reading; and real-word reading
19	D19S220–D19S418	The SLI Consortium, 2002, 2004	98 families	Expressive language	Clinical Evaluation of Language Fundamentals—Preschool
21		Fisher et al., 2002	119 families		

Note. In some cases, participants were not directly tested; rather, the phenotype was determined based on clinical diagnosis. In other cases, the test was not reported in the article—most of these were not English-speaking.

three-generation family in which half of the members presented with a severe SSD. Investigation also revealed an oral facial dyspraxia and a wide range of expressive and receptive linguistic deficits in both written and spoken language in affected family members (Vargha-Khadem et al., 1998; Watkins et al., 2002). Pedigree analysis revealed that the inheritance pattern in the KE family was compatible with a single autosomal dominant locus. Fisher, Vargha-Khadem, Watkins, Monaco, and Pembrey (1998) completed a genome-wide linkage study with family

members and identified a region on chromosome 7 that appeared to cosegregate with SSD and language disorder. They further localized the gene locus for affected family members' orofacial apraxia and associated speech-language disorders (designated as *SPCH1*) to a region at 7q31, and finally identified the causative gene as a brain-expressed transcription factor called *FOXP2*. Individuals who carried the mutant *FOXP2* allele presented a variety of deficits, including poor speech, as well as impairments in IQ, receptive and expressive language, reading, and writing. Neuroimaging studies indicated that the affected family members have bilateral morphological abnormalities, including low levels of gray matter density in caudate nucleus, inferior frontal gyrus, precentral gyrus, temporal pole, and cerebellum. High levels of gray matter density in the posterior superior temporal gyrus, angular gyrus, and putamen were also observed (Belton, Salmond, Watkins, Vargha-Khadem, & Gadian, 2003; Watkins et al., 2002). A functional magnetic resonance imaging study of the KE family showed underactivation of Broca's area and other related areas in affected family members compared with unaffected family members (Liegeois et al., 2003). These findings suggest that the *FOXP2* gene has pleiotropic effects on multiple aspects of brain development, accounting for the cooccurrence of SSD, LI, and RD.

A next step was to develop a mouse model for the *FOXP2* gene. The advantage of using mouse models is that they can be genetically manipulated and that the mouse genome is well known. However, a limitation when using a mouse model is that a phenotype representing higher brain functions, such as speech and language, may not be observed (Inoue & Lupski, 2003). The *FOXP2* gene is expressed in both mouse and human tissues, including the brain and the lungs (Kaestner et al., 1993; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). Recently, a mouse model for the *FOXP2* gene was developed (Shu et al., 2005). Mice with disruption in the *FOXP2* gene demonstrated abnormal vocalization related to social communication. Disruption of both copies of the *FOXP2* gene resulted in severe motor impairment and cerebellar abnormalities—and possibly a shorter life span.

Several families have been identified with other variants of the *FOXP2* gene (one with a translocation), thus indicating that the *FOXP2* gene may be responsible for SSD in other families as well as in the KE family. A recent report found that 1 child out of 49 children who were studied with reported childhood apraxia of speech had different heterozygous coding changes in the *FOXP2* gene. In addition, this child's mother and sibling also exhibited the coding changes, and one of these changes was a nonsense mutation (see the Appendix for definition) that resulted in a truncated protein product (MacDermot et al., 2005). The rarity of this mutation suggests that although the *FOXP2* gene may account for the SSD in a few isolated families, such mutations do not contribute significantly to the attributable risk for SSD in the population as a whole. Locus-specific attributable risk is the rate of SSD in a population that can be attributed to a specific genetic factor. In the search for genetic bases for SSD, we are seeking to identify genes that have high rates of attributable risk, so that the findings may be generalizable to a larger group. However, in defense of *FOXP2* as an important gene in SSD, extensive characterization of this gene at a molecular level has not been conducted in many populations to determine if subtle effects can be detected. The findings are currently limited to a few reports and need further investigation.

A recent study by Smith, Pennington, Boada, and Shriberg (2005) examined 111 probands with SSD and 76 siblings. Smith et al. hypothesized that SSD and RD overlap in cognitive manifestations and etiology. They examined linkage of SSD to loci on chromosomes 1, 6, and 15 that have well-documented associations with RD. Measures used included the Goldman–Fristoe Test of Articulation, normalized Percentage of Consonants Correct—Revised, a composite measure of phonological awareness, and a nonword repetition task. Results showed that linkage to chromosome 1 (1p36) did not reach significance for any of the traits, although linkage approached significance for Goldman–Fristoe Test of Articulation. It, however, did link significantly to a region on chromosome 6 (6p22). Both the Goldman–Fristoe Test and the nonword repetition task linked significantly to a region on chromosome 15 (15p21). Although the possibility of separate genes for SSD and RD in these regions cannot be ruled out, it is more likely that RD and SSD share genes in these regions that may influence neurological functions. See Table 1 for a summary of molecular genetic findings.

Generalist Genes Versus Specific Gene

Two different approaches have been taken in studies of spoken and written language. One approach is to consider genes unique to a specific disorder (such as LI, RD, or SSD), and the other approach is to search for generalist genes that are thought to influence cognitive processes that underlie multiple disorders. Historically, developmental disorders such as LI, RD, and SSD were viewed as distinct disorders each with a unique set of genetic influences. Thus, researchers sought to establish the genetic basis of each disorder separately. Recent findings, however, suggest pleiotropy, or effects of a single locus/gene on multiple language/learning disorders including LI, RD, and SSD (Stein et al., 2004). Using behavioral data, Pennington and colleagues have investigated the relation between literacy and SSD (Pennington & Lefly, 2001; Raitano et al., 2004; Tunick & Pennington, 2002). They have suggested that RD and SSD may both be due to problems in the development of phonological

representations, thus explaining the high comorbidity of these disorders and supporting the genetic hypothesis of pleiotropy. Plomin and Kovas (2005) have referred to genes with broad rather than specific effects as *generalist* genes, and have proposed that such genes contribute to multiple forms of learning disabilities. However, the division of genes into specific genes and generalist genes may be somewhat artificial. It is likely that there is a continuous range of genetic effects on traits from the very broad to the specific.

Behaviorally defined clinical phenotypes are postulated to result from core cognitive deficits or *endophenotypes,* which in turn have a specific genetic etiology (Bishop & Snowling, 2004; Castellanos & Tannock, 2002; Fisher & DeFries, 2002; Pennington, 1999). Gottesman and Shields (1972) introduced the concept of endophenotypes for psychiatric disorders, adapting it from John and Lewis (1966) who studied insect evolution. Endophenotypes are objectively measurable biophysiologic, neuroanatomical, cognitive, or neuropsychological parameters that are closely associated with a specific behavioral trait and are useful in detecting genetic influences on the behavioral phenotype (Gottesman & Gould, 2003; Inoue & Lupski, 2003). Presumably, endophenotypes are facets of a clinical phenotype, and therefore are simpler than the clinical phenotype and more directly related to the underlying genetic basis for the disorder (Gottesman & Gould, 2003). The endophenotype is hypothesized to involve fewer genes than the clinical phenotype, simplifying the genetic analysis (Gottesman & Gould, 2003). For example, phoneme awareness is a useful endophenotype for RD as well as SSD. Although the clinical phenotypes of RD and SSD involve multiple cognitive processes, phoneme awareness has been associated with several chromosome regions. All of these endophenotypes are also susceptible to interaction with environmental factors. As the phenotypes for each disorder are identified, core deficits common to these disorders may be identified. Next we review what is currently known about genetic influences on LI and RD.

Genetic Studies of LI

Prevalence and Comorbidity

The prevalence of LI at kindergarten has been reported at 8% for boys and 6% for girls, with an overall rate of 7.4% (Tomblin et al., 1997). SSD are often comorbid with LI. Shriberg et al.(1999) reported rates of comorbidity between speech delay and LI in children with persistent speech delay of 11%–15% at 6 years of age, with considerably higher rates of 40%–60% reported for preschool children (Shriberg & Austin, 1998). High rates of comorbidity of LI with RD have also been reported. Bishop (2001) examined domains of receptive and expressive language and articulation. She reported rates of comorbidity of LI and RD for 29% of children with impairment in a single domain, 72% for children with two domains impaired, and 88% for children with impairment in all three domains. Flax et al. (2003) found that 68% of LI probands also met the criteria for RD.

Familial Aggregation

Familial aggregation for LI is well documented. Specifically, 23%–40% of first-degree family members of probands with LI are affected with these same disorders (Felsenfeld et al., 1995; Gopnik & Crago, 1991; Lahey & Edwards, 1995; Lewis, 1992; Spitz, Tallal, Flax, & Benasich, 1997; Tallal, Ross, & Curtiss, 1989; Tomblin, 1989). Several studies have examined familial aggregation of expressive language disorders of which phonology disorders or SSD are a subset. Whitehurst et al. (1991) failed to find significant familial aggregation for disorders in 62 children with expressive language delay. However, these negative findings may reflect the fact that family history data were collected by questionnaires through the mail and not by interviews. Furthermore, although children received the Templin–Darley Test of Articulation on follow-up visits, no attempt was made to distinguish children with SSD alone and SSD with other LI. Tomblin examined the family histories of 97 children with LI but also did not differentiate SSD from other LIs. Neils and Aram (1986) examined family histories of 74 children with LI, finding that articulation problems were the most common speech-language disorder reported in these families. Lahey and Edwards, who classified children with mixed expressive/receptive language delay, expressive language delay only, or mild delay, found that children with expressive language delay alone had higher familiar aggregation of LI than children with mixed expressive/receptive language delay.

Twin Studies

As evidence for genetic influences in LI, twin study researchers have consistently found a higher concordance rate for LI in MZ than in DZ twin pairs (Bishop, North, & Donlan, 1996; Lewis & Thompson, 1992; Tomblin & Buckwalter, 1998). Concordance typically ranges from .70–.86 for MZ pairs and .38–.46 for DZ pairs. The heritability of LI has been estimated at 45% using the DeFries–Fulker method (Tomblin & Buckwalter, 1998). More severe forms of LI are more heritable. Employing the DeFries–Fulker extremes analysis, the heritability of LI ranged from .38–76, depending on the severity (Viding, Spinath, Price, Dale, & Plomin, 2004).

In a large twin study conducted in the United Kingdom, the Twins Early Development Study (TEDS), researchers examined 3,000 twin pairs (Dale et al., 1998).

The heritability of vocabulary skills at 2 years of age was greater for children who scored in the lowest 5% of the sample than for the remainder of the sample. Heritability was estimated at .73 for the lower 5% of the sample compared with .25 for the entire sample. Environmental influences were estimated at .18 for the LI group compared with .69 for the entire sample. Findings from TEDS at 4 years of age showed that the heritability of a general language measure increased as a function of severity from .38 to .76, again indicating stronger genetic influence at the lower end of the spectrum of language ability (Viding et al., 2004). A study of twins with normal language abilities at 4 years showed that genetic influences on language overlapped significantly with genetic influences on nonverbal skills (correlation = .63; Colledge et al., 2002). Kovas et al. (2005) found that grammar, comprehension, vocabulary, verbal fluency, verbal memory, phonological awareness, articulation, and nonword repetition at 4½ years of age were moderately influenced by additive genetic effects.

Consistent with findings reviewed previously, an adoption study by Felsenfeld and Plomin (1997) demonstrated that a positive family history for speech-language disorders in the biological parents better predicted the affection status of the child than the family history of the adoptive parents. Unfortunately, most previous studies of genetic influence on LI have included children with both SSD and LI in their samples and have failed to assess articulation skills, precluding analysis of genetic influences on SSD.

Molecular Genetic Studies

Several investigators have recently conducted genome scans for specific language impairment (SLI; Bartlett et al., 2004; The SLI Consortium, 2002, 2004). As reviewed earlier, the *FOXP2* region on 7q31 was of particular interest. Newbury et al. (2002) failed to find evidence for a locus at 7q31 for SLl in the genome-wide scan. Examining all the known exons of the *FOXP2* gene of 43 probands with SLI, these investigators discovered a coding variant in one individual, but it did not segregate with SLI.

Recently, O'Brien, Zhang, Nishimura, Tomblin, and Murray (2003) examined DNA samples from 96 probands with SLI by sequencing exon 14 of *FOXP2*. No mutations were found in exon 14 of *FOXP2,* but a strong association was found to a marker within the CFTR gene and another marker on 7q31, D7S3052, both of which are adjacent to *FOXP2*. However, the two markers showing association with SLI are on opposite sides of the *FOXP2* gene and are likely to be too far apart to represent a single gene effect.

Another study of SLI found significant linkage to a chromosome region on 13q21 in both a Canadian sample and a U.S. sample (Bartlett et al., 2004). The families in this study were identified on the basis of having a minimum of two family members with SLI. Although linkage was found for a reading phenotype, linkage for the LI phenotype was weak. The weak linkage finding may be due to the comorbidity of LI and RD, suggesting a possible common genetic etiology. Another study by Fisher et al. (2002) reported weak linkage findings for families with dyslexia to 13q22, a region adjacent to 13q21. Because in older individuals a reading phenotype is easier to identify than a language phenotype, the linkage results may reflect the sensitivity of the tests to active or prior reading versus language involvement (Fisher et al., 2003).

The SLI Consortium (2002, 2004) examined 98 nuclear families ($N = 473$ individuals) in which the proband child was diagnosed with SLI. This study used a QTL mapping strategy for measures of receptive and expressive language and for nonword repetition. Significant linkage was found at 16q24 for nonword repetition and at 19q13 for the expressive language measure (The SLI Consortium, 2002, 2004). The endophenotype of nonword repetition appears to be useful in the dissection of the genetic underpinnings of LI, RD, and SSD. Bishop et al. (1996) found nonword repetition to be heritable in a twin study of LI, and suggested that this may be a useful behavioral marker in genetic studies of LI. Interestingly, significant linkage for quantitative traits was not found at the *FOXP2* region on 7q31 or at other chromosome regions associated with RD, possibly reflecting the limited number of quantitative phenotypes (Clinical Evaluation of Language Fundamentals, Test of Language Development, and nonword repetition) used in the SLI Consortium Study. Greater overlap of LI and RD may have been identified if a wider array of endophenotypes had been assessed. See Table 1 for a summary of genetic findings.

Genetic Studies of Reading Disorders

Prevalence and Comorbidity

The prevalence rate of RD in the population is estimated at 5% in school-age children (Francks, MacPhie, & Monaco, 2002), with a recurrence risk for siblings of probands of approximately 40%. SSD are often comorbid with reading disorders. In a sample of children at high risk for RD, 28% were referred to speech therapy compared with 12.5% of children at low risk for RD (Pennington & Lefly, 2001). Follow-up studies of children with preschool SSD have found later academic difficulties in 50%–75% of their samples (Aram & Hall, 1990; Bishop & Adams, 1990; King, Jones, & Laskey, 1982; Lewis et al., 1989; Nathan et al., 2004; Shriberg & Kwiatkowski, 1988). Our follow-up study of children

with preschool SSD found that 18% of children with SSD alone and 75% of children with both SSD and comorbid language disorders had reading problems in middle elementary school (Lewis, Freebairn, Hansen, & Taylor, 2002). Only a few studies have followed children with SSD and language disorders beyond elementary school (Lewis, O'Donnell, Freebairn, & Taylor, 2002; Weiner, 1974). The findings of these studies indicate that written language deficits and academic difficulties persist into adolescence and beyond. Related studies by Pennington and colleagues (Pennington & Lefly, 2001; Raitano et al., 2004) also suggest that early developmental problems in spoken language predict the later emergence of dyslexia in high-risk families.

The comorbidity of early developmental problems in spoken language and the later emergence of dyslexia may be explained by the shared and unshared processes for speech sound and written language processing (Bishop & Snowling, 2004; Caplan, 1992, 1994; Carrow-Woolfolk & Lynch, 1982; Catts & Kamhi, 1986; Ellis, 1984). The analysis of speech and written text may rely on phonological representations for converting phonetic speech units or written graphemes to phonemes (Harm & Seidenberg, 1999). Phonological memory and phonological analysis are key aspects of this conversion process, with meaning attached to the utterance or text through core cognitive and linguistic processes. However, some processes contributing to speech production and writing may be more modality specific, involving the selection and retrieval of a template for the intended word, assembly and sequencing of phonetic units or graphemes, and execution of the motor program. Genetic and environmental factors influence such endophenotypes and, in turn, affect both SSD and spoken and written language disabilities. A genetic or environmental factor that weakens phonological processing skills, for example, will have adverse consequences for both speech sound and written language output.

Familial Aggregation Studies

Many early studies documented that dyslexia aggregates within families (Decker & DeFries, 1980; DeFries, Singer, Foch, & Lewitter, 1978; Finucci, 1978; Gilger, Pennington, & DeFries, 1991; Hallgren, 1950; Smith, Pennington, Kimberly, & Ing, 1990). Past research also demonstrated familial aggregation of reading-related skills such as phonological short-term memory, phonological decoding, and spelling (Raskind, Hsu, Berninger, Thompson, & Wijsman, 2000). The most extensive study to date, the Colorado Family Reading Study (Decker & DeFries, 1980), demonstrated genetic heterogeneity in the transmission of dyslexia (DeFries & Gillis, 1991; Pennington, 1991).

Twin Studies

Twin studies and adoption studies have supported a genetic component of dyslexia, with estimated heritability ranging from .30 to .72 (Bakwin, 1973; Cardon et al., 1994; DeFries, Fulker, & LaBuda, 1987; Francks et al., 2002). Heritability estimates for reading-related skills are .67 for orthographic matching, .32–.49 for single-word recognition, .55 for phonological awareness, and .44 for rapid naming (Gayan & Olson, 2001; Grigorenko et al., 2001). Gayan and Olson (2001, 2003), who examined heritabilities for word recognition, orthographic coding, phonological decoding, and phoneme awareness, provided evidence for common genetic etiologies for deficits in these skills. Their results also suggested independent genetic etiologies for orthographic coding and phonological decoding. These findings support both process-specific genes and generalist genes.

Molecular Genetic Studies

The genetic mechanism of dyslexia is complex. Regions associated with this disorder have been identified on chromosome 1 (Rabin et al., 1993), chromosome 2 (Fagerheim et al., 1999; Francks et al., 2002; Kaminen et al., 2003; Peyrard-Janvid et al., 2004), chromosome 3 (Nopola-Hemmi et al., 2001), chromosome 6 (Cardon et al., 1994, 1995; Fisher et al., 1999; Gayan et al., 1999; Grigorenko, Wood, Meyer, & Pauls, 2000; Petryshen, Kaplan, Hughes, Tzenova, & Field, 2002), chromosome 15 (Grigorenko et al., 1997; Smith, Kimberling, Pennington, & Lubs, 1983), and chromosome 18 (Fisher et al., 2002). The 6p22.3–6p21.3, a region on chromosome 6, has been linked to several dyslexia-related cognitive processes, including phonological memory, phonological awareness, speed of naming, short-term verbal memory, single-word reading, spelling, and vocabulary (Fisher et al., 1999; Gayan et al., 1999). Some of these cognitive phenotypes may also cooccur with SSD. Table 1 provides a summary of these linkage findings.

Nine regions (DYX1–DYX9) have been implicated in dyslexia as listed by the Human Genome Nomenclature Committee. Recently, the first candidate genes have been reported for dyslexia including the *EKN1* gene (*DYX1C1*) on chromosome 15 (15q21; Taipale et al., 2003; K. G. Wiig et al., 2004), *ROBO1* on chromosome 3 (Hannula-Jouppi et al., 2005), and a 77-kb region of chromosome 6 (6p22.2) encompassing several candidate genes (Cope, Harold, et al., 2005; Francks et al., 2004). However, several recent studies have failed to support the *DYX1C1* candidate gene on 15q21 (Cope, Hill, et al., 2005; Marino et al., 2005; Scerri et al., 2004). A candidate gene for dyslexia on chromosome 3, *DYX5,* called *ROBO1* has been linked to dyslexia in one large family and to speech sound disorder in a subset of small families (Hannula-Jouppi et al., 2005). The

ROBO1 gene is an axon guidance receptor gene. Several candidate genes on chromosome 6p22.2 have also been implicated in dyslexia. A recent report identified *DCDC2* on chromosome 6 as a possible gene for dyslexia (Schumacher et al., 2005). Interest in the gene is heightened by the involvement of this gene in cortical neural migration and maturation (Schumacher et al., 2005). Another gene, *KIAA0319,* also on chromosome 6 with the gene product expressed in the brain, was also identified as a susceptibility gene for dyslexia (Cope, Harold, et al., 2005).

Our Linkage Analyses of SSD

A linkage study carried out by our research group (Stein et al., 2004) also supports genetic overlap of SSD and RD. Our linkage study focused on children with SSD and used QTL linkage methods to link characteristics of these disorders to chromosome regions previously associated with RD. The participants in these studies were 674 individuals from 151 families ascertained through a proband with a moderate-to-severe SSD (see Table 2). Proband children were enrolled in speech-language therapy and referred from the clinical caseloads of speech-language pathologists in Northeastern Ohio. Children were required to have (a) normal hearing as demonstrated by passing a pure-tone hearing screening; (b) normal intelligence as defined by a prorated Performance IQ of at least 80 on the Wechsler Preschool and Primary Scale of Intelligence—Revised (Wechsler, 1989) or Wechsler Intelligence Scale for Children (3rd ed.; Wechsler, 1991); (c) normal peripheral speech mechanism as documented by a *z* score within one standard deviation unit from the reference data on the Total Structure subscale of the Oral and Speech Motor Control Protocol (Robbins & Klee, 1987); (d) speech sound production deficits in single words as sampled in the Goldman–Fristoe Test of Articulation (Goldman & Fristoe, 1986) and the Khan–Lewis Phonological Analysis test (Khan & Lewis, 1986); and (e) speech sound errors in conversational speech as defined by an intelligibility rating of <90%, at least 4 of 10 phonological processes (error types), and failure to produce at least 2 of 10 distinctive speech sound features.

Table 2. Summary of participants.

Characteristic	*n*
No. of families	151
Participants	698
Males	399
Fathers	155
Brothers	244
Females	299
Mothers	145
Sisters	154

We also tested siblings of proband children. Criteria for the affection status for SSD in siblings were the same as those applied to the proband. Parents and older siblings whose ages fell outside the normed age range on the Goldman–Fristoe Test of Articulation were categorized following the procedures described by Lewis and Freebairn (1993). Parents were interviewed and phenotyped based on self-report of a disorder or enrollment in speech-language therapy, reading intervention, or special class placement as a child. A subset of parents were directly tested on challenging articulation measures such as the Multisyllabic Word Repetition Task, the Nonsense Word Repetition Task, and the Pig Latin Task (Lewis, Freebairn, & Taylor, 2000). Findings indicated 75% agreement between sibling affection status for SSD as determined by historical report and affection status based on direct testing, and 74% agreement between parent affection status as defined by these two methods. An extensive test battery of standardized speech sound, receptive and expressive language, reading decoding and comprehension, spelling, and phonological processing measures were administered to all probands and their siblings. Although the test battery varied with the age of the participants, the measures assessed comparable skills across age groups (see Table 3 for specific measures). In addition, histories of children's speech, language, and academic problems were ascertained via parent interview.

To examine the genetic basis of SSD traits, we selected a region on chromosome 3 for linkage analysis. The rationale for examining this region was previous research showing RD and hypothesized pleiotropy of SSD with RD. We are in the process of examining additional chromosome regions on 1, 7, 6, and 15. However, we present results from only chromosome 3 here to illustrate a genetic linkage for SSD. SSD traits were measured in this study using two factor scores based on the measures in Table 3: an articulation/phonology factor and a language factor. We observed that the locus on chromosome 3 was linked to both factors. We then examined individual measures for linkage. Measures of phonologic coding/decoding (i.e., Rapid Automatized Naming Task and Nonsense Word Repetition Task demonstrated the strongest linkage. Corresponding tests for single-word decoding (i.e., Word ID and Word Attack) also demonstrated linkage (see Table 4), as did a test of oral motor skills—the Fletcher Time-By-Count Test (Fletcher, 1978). Many of these traits were significantly correlated, further suggesting that they have a common influence.

The findings in this study indicate that the traits in common with SSD and RD are influenced by a QTL on chromosome 3 (cf. Stein et al., 2004). These results, thus, are consistent with those of Smith et al. (2005), suggesting that SSD and RD share some common genetic

Table 3. Measure administered to participants.

Articulation Measures
Goldman–Fristoe Test of Articulation (Goldman & Fristoe, 1986)[a,b]
Khan–Lewis Phonological Analysis (Khan & Lewis, 1986)[a]
Conversational speech sample analysis (Shriberg et al., 1997)[a,b]
Oral-Motor Measures
Oral and Speech Motor Control Protocol (Robbins & Klee, 1982)[a]
Fletcher Time-by-Count Test (Fletcher, 1978)[b]
Phonological Processing Measures
Segmentation Task (Kamhi & Catts, 1986)[a]
Multisyllabic Word Repetition (Catts, 1986)[a,b]
Nonsense Word Repetition (Kamhi & Catts, 1986)[a,b]
Rapid Automatized Naming—Colors (Denkla & Rudel, 1976)[a,b]
Elision Task (Torgesson, personal communication)[b]
Language Measures
Clinical Evaluation of Language Fundamentals—Preschool (Wiig et al., 1992)[a]
Test of Language Development—Primary:3 (Newcomer & Hammill, 1997)[a,b]
Clinical Evaluation of Language Fundamentals (3rd ed.; Semel et al., 1995)[b]
Peabody Picture Vocabulary Test (3rd ed.; Dunn & Dunn, 1997)[a,b]
Expressive One Word Picture Vocabulary Test (Gardener, 1990)[a,b]
Written Language
Woodcock Reading Mastery Tests—Revised (Woodcock, 1987 Word ID and Word Attack)[b]
Wechsler Individual Achievement Test (Reading Comprehension score; Wechsler, 1992)[b]
Test of Written Spelling (3rd ed.; Larsen & Hammill, 1994)[b]
Test of Written Language (2nd ed.; Hammill & Larsen, 1988)[b]
Nonverbal Intelligence
Wechsler Preschool and Primary Scale of Intelligence—Revised (Wechsler, 1989)[a,b]
Wechsler Intelligence Scale for Children (3rd ed.; Wechsler, 1991)[b]
Genetic
Family history questionnaire (Lewis & Freebairn, 1993)[a,b]
DNA sample[a,b]

[a]Preschool test battery. [b]School-age test battery.

basis. Although the genome-wide scan by the SLI Consortium failed to find linkage for LI to chromosome 3, this negative finding may reflect study differences in ascertainment methods, measures of quantitative traits, or both. Additionally, we focused on deficits in phonologic coding and decoding, the traits that linked most strongly to the locus on chromosome 3. The SLI Consortium, in contrast, focused on children with LI, many of whom may not have had phonologic coding/decoding deficits. Future studies, with better specified phenotypes and a broader array of measures, are needed to determine if LI also links to this region on chromosome 3. Association studies of specific genes, such as those identified in studies of dyslexia on chromosomes 3 and 6, need to be conducted.

Table 4. Summary of measures showing linkage to chromosome 3.

Genomic region	Marker	Measure	*p*
3p12	D3S2465	NSW	8×10^{-5}
3p12	D3S2465	MSW	.000642
3q12	D3S3655	SEP	.0293
3q12	D3S1752	TWST	.00014

Note. NSW = nonsense word repetition; MSW = multisyllabic word repetition; SEP = speech error phrases; TWST = Test of Written Spelling total score.

Thus far, the molecular genetic studies of SSD lag behind those of dyslexia. With the convergence of the linkage signals on chromosomes 1, 3, 6, and 15 for these two cognitive linguistic traits, it should now be possible to interrogate specific candidate genes for dyslexia (e.g., *ROBO1, DCDC2,* and *EKN1*) as candidate genes for SSD.

Summary of Literature and Implications for Genetic Mapping of SSD

The previously mentioned studies indicate that SSDs are etiologically complex disorders. Because the phenotype of SSD is heterogeneous and changes with development, the search for genetic influences will be challenging. We consider some of these challenges, propose a conceptual framework for genetic studies of SSD, and suggest future research directions.

Challenges for Elucidating Genetic Influences on SSD

The challenges of research in this area relate to the complex nature of genetic influences and to inadequacies in our current level of knowledge as detailed below:

1. *It is likely that SSDs have more than a single etiology.* An individual's susceptibility for SSD may be due to a single gene effect such as in the case of the disorder observed in the KE family or to multiple underlying genetic and environmental etiologies. Our study of chromosome 3 (Stein et al., 2004), and the investigation by Smith et al. (2005) of chromosomes 1, 6, and 15, provide evidence for multiple genetic influences on SSD. These findings suggest that multiple genes will contribute to population risk for SSD.
2. *Similar phenotypes may have different underlying etiologies.* Similar SSD phenotypes in families may not be the result of the same combination of genetic or environmental factors. A model by Bishop and Snowling (2004) proposes four levels of causality: genes, neurobiology, cognition, and behavior. Children with the same behavioral impairment may present

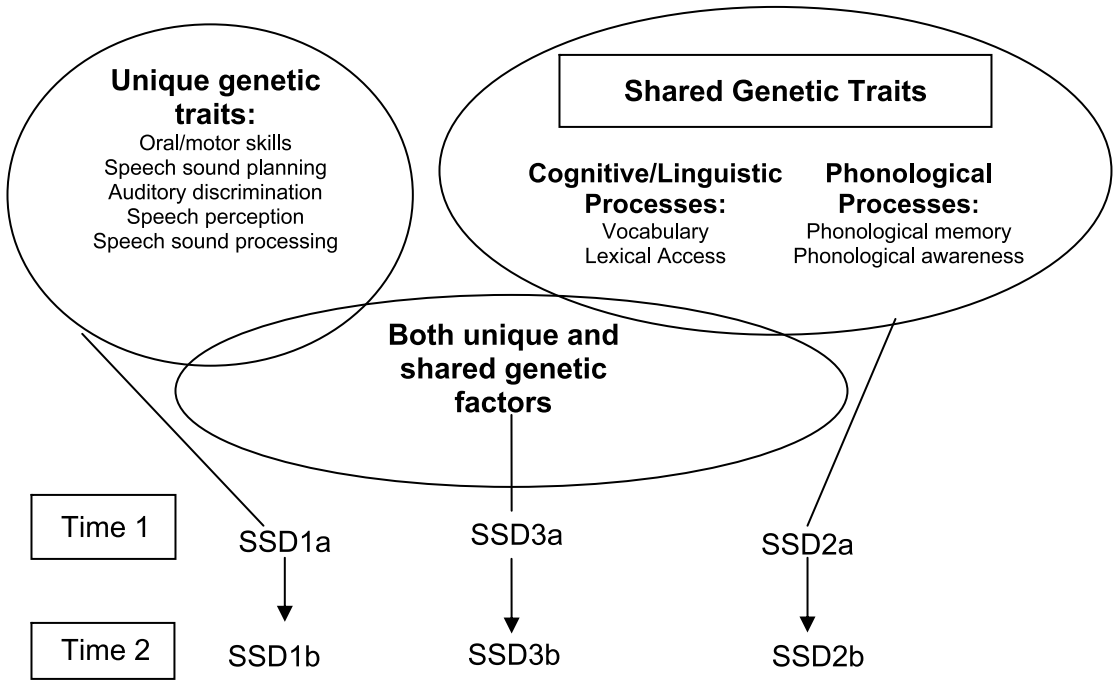
with different cognitive impairments. Conversely, children with similar cognitive impairments may present with different behaviors, depending on the environment and other abilities. A single cognitive marker or endophenotype, therefore, may not be sufficient to identify homogeneous groups of children (Bishop & Snowling, 2004).

3. *Similar genotypes may give rise to different phenotypes.* The same genetic mutation may have different effects in different individuals because of interactions with other genes or the environment. This may explain the interindividual variability in the deficits that is observed within a single family. For example, the proband may have an isolated SSD, while his sibling may have SSD accompanied by additional language problems, and his parent an RD.
4. *There is not a direct pathway from genes to the phenotypes.* Genes do not lead directly to phenotypes. Instead, genetic, cellular, anatomical, and environmental conditions interact to produce an SSD phenotype (Inoue & Lupski, 2003). Furthermore, genes may influence speech sound production indirectly through hypothesized cognitive constructs or endophenotypes (Gottesman & Gould, 2003). Endophenotypes may themselves be heteromorphous (i.e., having different forms at different periods of the life cycle). A given endophenotype may be controlled by more than one gene, thus leading to potential genetic heterogeneity in trait susceptibility. Conversely, a single gene may contribute to multiple cognitive abilities because the process is under common genetic and neural control (Stein et al., 2004).
5. *Environmental effects on SSD are not well specified.* Risk (or susceptibility) genes interact with environmental risk factors, as well as protective factors, to determine an individual's risk for SSD. Some risk factors for speech delay that have been studied include gender, low maternal education, low socioeconomic status, and prolonged otitis media with effusion (Campbell et al., 2003; Shriberg et al., 2005). Environmental effects include biological, social, educational, and emotional factors. Environmental effects include the shared family environment as well as the environment that is unique to an individual family member. Studies of environmental factors are needed to identify important influences on SSD and to understand the interaction of genes and environment.
6. *Developmental changes in the phenotype.* Phenotypic changes in SSD with development mandate a need to use different measures and definitional criteria at different ages. Assessment of older siblings and parents who no longer present with an overt SSD is difficult and may require measures such as a Pig Latin task or repetition of tongue twisters to tap the underlying endophenotype. However, the association of such measures to those employed with younger family members is largely undocumented, making it difficult to know if deficits detected at later ages are residual forms of the same disorder or symptoms of a different disorder. Further research is needed, for example, to determine if SSD in early childhood can evolve into a phonological deficit and accompanying RD (Pennington, 2003). Indirect or distal causal pathways are also responsible (Jackson & Coltheart, 2001). For example, a child may present with an early SSD and later with spelling difficulty. The early SSD and the current spelling difficulty may both be due to deficits in the acquisition, storage, and retrieval of accurate phonological representations, all of which may be coded for by the same gene. Alternatively, difficulty with speech sound production itself may negatively impact the phonological representations necessary to generate correct word spellings, evidencing a less direct causal pathway.
7. *Subtypes of SSD are not well described and comorbid conditions are not well understood.* Genetic research has revealed that SSD are heterogeneous, with subtypes that differ in expression, comorbidities, and developmental course. Research has failed to lead to a consensus regarding SSD subtypes and the etiological factors associated with them. Although SSD are frequently comorbid with other language-learning disorders, the basis of this comorbidity is poorly understood. It is unclear, for example, if SSD increases a child's vulnerability to language-learning problems or if these disorders reflect common genetic influences, environmental influences, or both. Several models have been proposed to describe relations between SSD, LI, and RD. Speech processing models, such as the one described by Stackhouse and Wells (1997), propose underlying phonological and semantic representations that impact spoken and written language. Disturbances in these representations may lead to comorbid disorders. Findings from linkage studies are consistent with such models. Evidence for linkage of SSD to regions previously identified in linkage studies of LI and RD supports Pennington's (2003) observation that cognitive/linguistic endophenotypes underlie both SSD and RD (Pennington, 2003), as well as Plomin and Kovas's (2005) proposal for generalist genes that impact multiple types of developmental disabilities.

Conceptual Framework for SSD

Figure 1 illustrates a proposed conceptual framework of genetic influences on SSD that is based on the genetic studies reviewed earlier. Genetic studies of SSD suggest possible etiologies for SSD and provide information

Figure 1. Unique and shared genetic influences may contribute to SSD (speech sound disorders). This figure depicts multiple hypothesized subtypes of SSD resulting from unique genetic influences, shared genetic influences, and a combination of both unique and shared influences (SSD1a, SSD2a, and SSD3a). The phenotype of SSD changes with development as depicted by Time 2 (SSD1b, SSD2b, and SSD3b).



on the phenotypic expressions of these disorders. The emergence of SSD in childhood may reflect genetic influences that affect processes unique to SSD, as well as those that affect processes common to spoken and written language. Skills unique to SSD include deficits in articulation, oral motor ability, and motor planning, as well as some aspects of auditory perception and auditory discrimination. Skills potentially affecting both SSD and spoken and written language include the ability to form, maintain, and manipulate phonological representations. As shown in Figure 1, SSD may result from genes influencing unique or shared processes. We acknowledge that some genes may have both specific and general effects and that most likely these effects fall on a continuum. These differing genetic influences may account for distinct subtypes of SSD (indicated in the figure by the Time 1 outcomes SSD1a, SSD2a, and SSD3a). The framework also recognizes that outcomes may change with age, as depicted in the figure by the Time 2 outcomes SSD1b, SSD2b, and SSD3b.

Implications for Future Research

The studies reviewed in this article provide a point of departure for future studies of genetic influences on SSD. The findings from these studies indicate directions to pursue in the search for genetic influences on SSD across the genome. Specifically, the results suggest ways to limit the search to smaller segments of particular chromosomes. Future studies will attempt to identify genes in these regions and describe their influence on neurodevelopment and ultimate expression as SSD. The research on RD has already identified nine possible candidate chromosome regions. A genome scan may also be useful in locating genes that make unique contributions to SSD, but that are unrelated to SLI or RD. Genome scans are conducted when there is no a priori hypothesis regarding where the gene is located. Subsequent genetic studies can then narrow the gene search.

Multivariate linkage analysis will also be useful in advancing knowledge of the genetic relation of multiple traits. Multivariate methods analyze several traits simultaneously. Specifically, these methods examine the covariance between traits to parse the effects of a genetic locus on each trait, which will thus enable us to dissect these pleiotropic effects more finely. These methods are easily extended for the analysis of longitudinal data, thus helping us understand how SSD predisposes to RD. To date, few groups have done true multivariate linkage analysis. Studies of Marlow et al. (2003) and Gayan et al. (2005), both of which examined RD, illustrate the benefits of this approach. These studies found pleiotropic effects that would not have been evident in more conventional univariate analyses.

The identification of genes associated with SSD will inform us about the core phenotypic features of SSD, ultimately helping with early accurate diagnosis. Genetic studies allow us to construct and test models of spoken and written language that highlight common underlying processes. Such models will assist us in understanding the interrelationships among SSD, LI, and RD, and allow us to develop more effective clinical interventions appropriate for subgroups and at a particular stage of development.

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Appendix. Glossary of terms.

Allele	A variant at a gene.
Association	The strength of the cooccurrence of allele and pheonotype in sets of individuals; association in this context is defined for genetic studies.
Attributable risk	A measure of public health impact of an exposure or characteristic (such as a gene); it is the rate of disease occurrence ("risk") in a group that is exposed to a particular factor that can be attributed to the exposure to it.
Candidate gene	A gene whose function is thought to influence a neurobiological process, cognitive ability, or diagnostic susceptibility.
Concordance	Presence of a particular condition in two family members.
Dizygotic	Fraternal twins: Twins resulting from two separate eggs being fertilized by two separate sperms.
Endophenotype	Measureable components of a disorder that genes may impact, but it is more proximal to the gene than a direct clinical measure.
Exons	The sequences in a gene that make up the code for the mature protein.
Genome scan	Examination of hundreds (or thousands) of markers throughout the genome for linkage or association.
Genotype	The combination of alleles at a locus present in each individual.
Heritability	The proportion of variation in the phenotype in the population that is due to genetic factors.
Linkage	The degree to which a marker is in close enough proximity to the causative mutation to segregate with the trait of interest within a family.
Locus (plural, loci)	A site of a specific gene or marker on a chromosome.
LOD (logs of the odds score)	A statistical term that indicates whether two loci are linked or unlinked. Linkage mapping involves comparing two likelihoods. The LOD score is the logarithm of the likelihood ratio: If it exceeds a given threshold, the null hypothesis can be rejected.
Major gene effect	A single gene contributes substantially to the variance in a trait.
Marker	Naturally occurring variants in the DNA sequence that can be used to track the inheritance pattern of a particular chromosomal location in families or individuals.
Model free linkage	A linkage analysis that does not assume a priori a specific genetic transmission model such as recessive or dominant.
Monozygotic	Identical twins: Twins that develop from a single fertilized egg cell through its division into two genetically identical parts.
Nonsense mutation	A mutation that results in a truncated protein. A nonsense mutation occurs when a base pair changes and codes for a "stop" codon, so the protein sequence is cut short.
Oligogenic	A few different genes working together to contribute to a particular phenotype.
Phenotype	Cognition, behavior, anatomy, physiology, and so forth that results from the genotype and the environment.
Pleiotropy	Multiple phenotypes that are influenced by one gene or locus.
Polygenic	A trait influenced by many genes, each with such small effect that it cannot be easily identified using standard genetic methods.
Proband	The index case from whom other family members are identified.
Transcription	The synthesis of an RNA molecule (message) from DNA in the cell nucleus.