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REVIEW PAPER

Genetic insights into the functional elements of language

Adam Szalontai · Katalin Csiszar

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Abstract Language disorders cover a wide range of conditions with heterologous and overlapping phenotypes and complex etiologies harboring both genetic and environmental influences. Genetic approaches including the identification of genes linked to speech and language phenotypes and the characterization of normal and aberrant functions of these genes have, in recent years, unraveled complex details of molecular and cognitive mechanisms and provided valuable insight into the biological foundations of language. Consistent with this approach, we have reviewed the functional aspects of allelic variants of genes which are currently known to be either causally associated with disorders of speech and language or impact upon the spectrum of normal language ability. We have also reviewed candidate genes associated with heritable speech and language disorders. In addition, we have evaluated language phenotypes and associated genetic components in developmental syndromes that, together with a spectrum of altered language abilities, manifest various phenotypes and offer details of multifactorial determinants of language function. Data from this review have revealed a predominance of regulatory networks involved in the control of differentiation and functioning of neurons, neuronal tracks and connections among brain structures associated with both cognitive and language faculties. Our findings, furthermore, have highlighted several multifactorial determinants in overlapping speech and language phenotypes. Collectively this analysis has revealed an interconnected developmental network and a close association of the language faculty with cognitive functions, a finding that has the potential to provide insight into linguistic hypotheses defining in particular, the contribution of genetic elements to and the modular nature of the language faculty.

Introduction

In recent years, interdisciplinary efforts incorporating converging results from clinical studies, brain imaging, neurophysiology, cell and developmental biology, and animal models have provided increasingly deeper insight into the mechanistic basis of many of the unique features of human language. Furthermore, advances in the genetic (Newbury and Monaco 2010; Bacon and Rappold 2012; Kang and Drayna 2012; Peterson and Pennington 2012) and genomic analyses (Lambert et al. 2011; Zhang et al. 2011; Konopka et al. 2012) of speech and language disorders have identified specific molecular, cellular, neuronal, and cognitive elements associated with language phenotypes. While these disorders cover a wide range of conditions with heterologous and overlapping phenotypes and complex etiologies harboring both genetic and environmental influences, several genes with prominent roles in language development and ability have recently been identified (Bacon and Rappold 2012).

The exact language-related mechanisms for most of these genes and their encoded gene products remain to be fully characterized, there has been, however, considerable recent advance in understanding the associated pathological processes through which additional mechanistic details of language-related functions have also been revealed. Polygenic disorders that involve various phenotypes,

A. Szalontai
Theoretical Linguistics Program, Eotvos Lorand University, Budapest, Hungary

K. Csiszar (✉)
John A. Burns School of Medicine, University of Hawaii, 1960 East West Road, Biomed T415, Honolulu, HI 96822, USA
e-mail: kcsiszar@aol.com

including a spectrum of altered language abilities, present a complex picture that is more challenging to interpret (Brock 2007; Pennington and Bishop 2009; D'Souza and Karmiloff-Smith 2011; Levy and Eilam 2012). However, some characteristics of language impairment in complex syndromes have been identified and offer valuable insight into the multifactorial determinants of language ability.

In this review, we have summarized the most recent results from studies directed at both single genes with established functional associations to speech and language ability, and genetic determinants of heritable speech and language disorders including childhood apraxia of speech (CAS), specific language impairment (SLI), stuttering, dyslexia, and speech and sound disorder (SSD). We have also reviewed other heritable syndromes in which language and speech phenotypes are dominant, but not exclusive pathologies.

From this comparative analysis several regulatory networks, signaling pathways, and structural elements have emerged that are specifically associated with speech and language ability. We have evaluated the significance of multifactorial determinants in overlapping speech and language phenotypes, and discussed the interactions of language and cognition that have been revealed through the analysis of impaired developmental pathways. Finally, we have also discussed these genetic findings in the context of theoretical linguistics, particularly with regard to hypotheses describing the contribution of genetic elements to, and the modular nature of the language faculty.

Genetic elements and language phenotypes

A multitude of human genome sequence variants have emerged recently that are either functionally linked to or associated with phenotypes characterized principally as language ability. Such sequence variants are either present as allelic variants within the coding sequence of known genes and/or sequence variants in non-coding genetic elements. A similar range of sequence variants have also been shown to be associated with more complex phenotypes in which language impairment is only a part of the phenotypic spectrum of these clinical conditions.

In this review, we have attempted to provide novel insights into the biological mechanisms that contribute to human language ability. In this specific context therefore, we have sought to describe genomic sequence variants—established as being associated with a language phenotype—within three comparative categories of increasing complexity with respect to both genotype and phenotype.

The first of these categories encompass allelic variants of genes known to be functionally associated with language ability. A second more complex comparison includes a review of genetic determinants (both coding and non-coding sequence variants) that are associated with overlapping phenotypes in several heritable speech and language disorders. The third category is the most complex—an analysis of language phenotypes and associated genes within pleiotropic clinical conditions, of which language impairment is only a part of the phenotype. These three categories are not impermeable and we have structured this review in this manner to facilitate some clarity in an analysis that embraces the different fields of linguistics and genetics.

Through the very nature of this analysis, we do not intend this manuscript to be a comprehensive review of all known or likely candidate genotypes. Nor is it our intention to review all known or likely phenotypic conditions in which language is or may be a phenotypic component. And when appropriate, we have endeavored to indicate throughout the forthcoming text, when and why we have limited our discussion to and of particular disorders.

Genes functionally associated with language ability

FOXP2 in developmental speech and language ability

FOXP2 is a member of the Forkhead box (FOX) transcription factor family (FOXP1-4) and is a conserved DNA binding transcription regulator. Heterozygous mutations of the *FOXP2* gene were among the first gene mutations proven to cause a disorder with speech development and language deficits. Since *FOXP2* was linked to language ability in a family with developmental verbal dyspraxia including lack of control of orofacial muscles and deficient production of fluent speech affecting both expressive and receptive language (Lai et al. 2000, 2001), the role of *FOXP2* in speech and language acquisition has been extensively studied. In addition to large chromosomal deletions involving the *FOXP2* gene that resulted in language features (Rice et al. 2006; Tomblin et al. 2009) linkage to language ability of various mutated FOXP2 alleles including missense (Lai et al. 2001), non-sense mutations (MacDermot et al. 2005), and translocation breakpoints (Lai et al. 2000; Feuk et al. 2006; Shriberg et al. 2006) were confirmed in various populations. The most prominent and consistent feature of the *FOXP2*-linked disorder is speech and language impairments with a core phenotype of difficulty in the learning and production of coordinated sequences of orofacial movements that affects the production of fluent speech (Vargha-Khadem et al. 2005; Bacon and Rappold 2012; Watkins 2011). *FOXP2* was also shown to affect various cognitive functions (Watkins et al. 2002). *FOXP2* expression is developmentally regulated in brain regions including the motor

cortex, striatum, and cerebellum responsible for fine motor control. FOXP2 in turns regulates the expression of numerous target neural genes and is central in regulatory networks with relevance to speech and language functions (Vernes et al. 2007; Graham and Fisher 2013). FOXP2 impacts neurite outgrowth in primary neurons, modulates neuronal network formation, and modifies neural plasticity in cortico-basal ganglia circuits with a concomitant and pleiotropic impact on sensory-guided motor learning of articulation patterns (Spiteri et al. 2007; Vernes et al. 2011; Fisher and Scharff 2009; Newbury et al. 2009), functions that have been supported by extensive animal model study data (Enard 2009; Schulz et al. 2010; Gaub et al. 2010; Clovis et al. 2012; Kurt et al. 2012).

*FOXP*1 in language developmental delay and deficit

Among the *FOXP* family members, *FOXP1* (with closest homology to *FOXP2*) has been also implicated in human cognitive disorders that involve language phenotypes. Deletion of *FOXP1* together with three other genes at the 3p13 locus was noted in a patient with developmental delays and speech and language deficits (Pariani et al. 2009). A verbal dyspraxia patient was also identified with *FOXP1* gene coding changes (Vernes et al. 2009). A *FOXP1* deletion was identified in a patient with Chiari I malformation (cerebellar tonsil abnormality) and epileptiform discharges with motor development and speech delays (Carr et al. 2010). A large-scale study of learning disability cases identified deletions of the *FOXP1* gene in three unrelated patients with neurodevelopmental deficiencies and severely affected speech and language (Horn et al. 2011). In a case with de novo *FOXP1* intragenic deletion, the phenotypic spectrum that included intellectual disability (ID) and severe language impairment suggested that FOXP1 may have a more global impact on brain development than FOXP2 (Hamdan et al. 2010). Analysis of six known cases, all heterozygous for *FOXP1* mutations, identified developmental delay, retarded motor development, mild to moderate intellectual disability, behavioral problems, and speech and language deficits with more affected expressive language (Horn et al. 2011). A rare 3p14.1 de novo microdeletion affecting the entire coding region of the *FOXP1* gene in an adult patient with a phenotype of autism, severe speech delay, and deficient motor coordination further demonstrated a role for *FOXP1* haploinsufficency in neurological and language deficits (Palumbo et al. 2012). In areas of the developing brain, FOXP1 expression overlaps with FOXP*2* (Teramitsu et al. 2004), forms heterodimers with FOXP2, and acts as a transcriptional regulator in common developmental and neurodevelopmental pathways (Li et al. 2004). Rare mutations of *FOXP1* and *CNTNAP2* were noted to converge on shared functional pathway demonstrated in an autistic case (O'Roak et al. 2011). While aberrant FOXP2 and FOXP1 functions manifest in an overlapping expressive language phenotype, there are also distinct cognitive and language features that support both shared and distinct neurodevelopmental roles (Bacon and Rappold 2012). FOXP2 functional deficiencies affect both expressive and receptive language with a core feature of abnormal articulation due to impairment of orofacial movements required for normal speech. Altered FOXP1 more significantly contributes to a spectrum of neurodevelopmental disorders resulting in cognitive phenotypes that include speech and language (Pariani et al. 2009; Horn et al. 2011; Talkowski et al. 2012; Palumbo et al. 2012) and that appear to more specifically affect expressive language (Hamdan et al. 2010; Horn 2012). As deficiently functioning *FOXP1* alleles identified so far consistently associate with global cognitive impairments, altered language features in these patients were proposed to be linked to altered cognitive functions (Bacon and Rappold 2012).

FOXG1 and the FOXG1 syndrome

Submicroscopic deletions in chromosome 14q12 involving the *FOXG1* gene and intragenic *FOXG1* mutations have been identified in patients with features overlapping classic congenital Rett syndrome. An extensive clinical analysis of a panel of patients with *FOXG1* mutations identified distinctive complex features including mild postnatal growth development, microcephaly, mental retardation, and absent language (Kortum et al. 2011). Brain imaging revealed simple gyral pattern, reduced white matter volume in the frontal lobes, corpus callosum hypogenesis, and variable mild frontal pachgyria, features that correlated with impaired language capacity. In subjects with microduplication involving *FOXG1* and also *PRKD1* with developmental delay and epilepsy, cognitive impairment, and severe speech delay, increased *FOXG1* dosage was proposed to be responsible for some of the neurodevelopmental phenotypes (Brunetti-Pierri et al. 2011). In two cases of congenital Rett syndrome with an inability to acquire speech sounds, *FOXG1* mutations (without *MECP2* involvement) were identified as contributing to hypoplasia of the corpus callosum and frontal lobe (Takahashi et al. 2012). A study of seven patients, two with de novo *FOXG1* point mutations and five with 14q12 deletions, suggested that among features of the core FOXG1 syndrome phenotype (postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum dysgenesis) dyskinesia and corpus callosum dysgenesis were not always present (Allou et al. 2012). Lack of sufficient detail for syndromal spectrum was attributed to an *MECP2*-negative patient population

($n = 12$) presenting with features of the FOXG1 syndrome, however, with no mutations within FOXG1 (Pratt et al. 2013). In atypical Rett syndrome including severe intellectual impairment, developmental delay, postnatal microcephaly and hypotonia, 14q12 deletions were identified that affected *PRKD1* but not the *FOXG1* gene (Guerrini and Parrini 2012). However, in spite of a spared *FOXG1*, expression levels of *FOXG1* were decreased and the phenotypic overlap of these cases with *FOXG1*-mutated Rett syndrome variants was attributed to misregulated *FOXG1* expression (Ellaway et al. 2012). Supporting the involvement of misregulated *FOXG1* in severe Rett-like syndrome, a long-range active transcriptional regulatory element of the *FOXG1* gene was identified in patients that carried 14q12 deletions (that did not affect *FOXG1*) but with phenotypes reminiscent of *FOXG1*-mutated subjects (Allou et al. 2012).

NRXN1 and impaired language ability

Mutations within the gene for neurexin-1 (*NRXN1*) have been implicated in a variety of conditions including autism and schizophrenia. Language delays were also observed in a meta-analysis that evaluated the spectrum of phenotypes associated with *NRXN1* mutations (Ching et al. 2010). Among these cases, 12 exonic deletions were identified that affected the coding region of the *NRXN1* gene and resulted in functionally altered NRXN1 protein. The phenotypes of individuals with these *NRXN1* gene deletions proved variable and included in addition to language delays, autism spectrum disorder and mental retardation. A subsequent analysis of the clinical spectrum associated with defects or heterozygous variants of *NRXN1* confirmed mild or, in the majority of cases, severe intellectual disability, absent or impaired language ability, and normal or only mildly delayed motor development (Gregor et al. 2011). NRXN1, a neuronal cell adhesion protein, is known to have a role in synaptic differentiation. Thus, deficient NRXN1-associated impaired excitatory synaptic differentiation (de Wit et al. 2009) may contribute to the phenotype including cognitive impairment (Zweier 2012). The closely related *NRX2* gene was also found in association with severe language developmental delay. Mutated forms of the NRXN1 and NRX2 proteins failed to bind the established post-synaptic binding partners leucine-rich repeat transmembrane protein (LRRTM2) and neuroligin 2 (NLG2) that in interactions with neurexins influence cross-talk between post- and pre-synaptic sites, both of which are required for synaptic development and effective signal transmission between neurons (Gauthier et al. 2011; Varley et al. 2011). Gene alterations (copy number variations and deleterious heterozygous mutations) within synaptic organizing proteins have been reported in association with common pathogenic mechanisms in neurodevelopmental disorders affecting cognition and behavior including speech and language delay, autism spectrum disorders (ASD), intellectual disability/mental retardation, and schizophrenia (Grayton et al. 2012; Gregor et al. 2011).

CNTNAP2 in language development and performance

Multiple studies involving distinct clinical populations implicate the contactin-associated protein-like 2 gene (*CNTNAP2*) in aspects of language development and performance. *CNTNAP2* is in the same pathway as FOXP2 that directly binds to intron 1 of the *CNTNAP2* gene and regulates its expression (Peñagarikano and Geschwind 2012). It is a neuronal cell adhesion protein that shows a gradient with a frontal cortical enrichment within the developing human brain, consistent with a role in patterning circuits that serve higher cognition and language. In a case study with a complex set of speech and language difficulties including stuttering, a 10-Mb chromosome 7q33-35 deletion was identified disrupting several genes including *CNTNAP2* (Petrin et al. 2010). Among three individuals with a chromosome rearrangement (ins(7;13)(q32q34;q32)) two had language delay, minor facial dysmorphism, and neuropsychiatric disorders including mental retardation and epilepsy (Sehested et al. 2010). Comparison of the clinical and cytogenetic findings of a case with a 12.2-Mb deletion within 7q34–q36.2 including *CNTNAP2*, and previously reported cases confirmed *CNTNAP2* haploinsuffiency and further suggested a role for CNTNAP2 in language delay and/or autism spectrum disorder. More specifically, common allelic variants within exons 13–15 of the *CNTNAP2* gene were found to influence early language acquisition as part of the normal variation in the general population and increase susceptibility to SLI or autism when occurring together with other risk factors (Whitehouse et al. 2011). Heterozygous *CNTNAP2* gene defects have been reported, in addition to severely impaired speech development, to be associated with variably delayed motor development, and intellectual disability (Gregor et al. 2011; Zweier 2012). In SLI *CNTNAP2* polymorphisms were in significant quantitative association with nonword repetition (a heritable behavioral marker of this disorder, Vernes et al. 2008) and for SLI-related risk variants, altered brain activity was detected during language processing in normal carriers (Whalley et al. 2011). Nonword association was demonstrated for a *CNTNAP2* SNP in developmental dyslexia together with a *FOXP2* SNP (Peter et al. 2011). *CNTNAP2* was also identified as an autism susceptibility gene (Alarcon et al. 2008) that, however, was not confirmed in an ethnically different cohort (Toma et al. 2012). Another common variant (rs7794745, AA vs AT/TT) proved to contribute to

sentence processing (Kos et al. 2012) and while syntactic manipulation revealed neurocognitive processing differences between the genotype groups, there was no processing difference with respect to semantic manipulation. Allelic variants AA and T carriers also had brain activation differences in imaging analyses (Whalley et al. 2011). In an artificial syntax learning paradigm the AA group demonstrated larger activation in the left inferior frontal cortex, and the behavioral results showed that T carriers acquired structural knowledge in a more efficient way (Folia et al. 2011). Thus, the effects of *CNTNAP2* allelic variants extend between various neurodevelopmental disorders and contribute to variations in the normal population (Graham and Fisher 2013).

CYP19A1 a candidate in reading, speech and language

The *CYP19A1* gene on chromosome 15q21.2 (within a locus linked to speech and language disorders) encodes an aromatase of the cytochrome P450 superfamily with multiple functions including conversion of androgens into estrogens, control of differentiation of specific brain areas, and sexual differentiation of the brain. Allelic variants were found associated with dyslexia and changes in quantitative measures of language and speech such as reading, vocabulary, phonological processing, and oral motor skills. *CYP19A1* expression in human brain correlates with the expression of dyslexia susceptibility genes *DYX1C1* and *ROBO1* suggesting a regulatory role that is further supported by increased cortical neuronal density and cortical heteroplasia noted in aromatase deficient mice, features that were also noted in *Robo1* null mice and in human brain specimens from dyslexic subjects (Anthoni et al. 2012).

CMIP and *ATP2C2* in phonological short-term memory

Chromosome 16q has been known to have significant linkage to nonword repetition, a measure of phonological short-term memory commonly impaired in SLI. In a high-density screen of 16q in language-impaired subjects (a family-based and a population cohort), associations were detected for two candidate genes within the SLI1 genomic region, that show highly significant and consistent linkage to nonword repetition, the c-maf-inducing protein gene (*CMIP*) and calcium-transporting ATPase type2C member2 (*ATP2C2*). In modeling experiments, each of these loci proved to exert independent effects upon nonword repetition ability, and thus may independently act to modulate phonological short-term memory (Newbury et al. 2009; Li and Bartlett 2012). In a meta-analysis, *CMIP* was also found in association with hearing threshold (Girotto et al. 2011), and in a case study, CMIP haploinsufficiency was shown to be in association with ASD and developmental delay (Van der Aa et al. 2012). In addition, association of *CMIP* with reading-related traits points to potential overlapping genetic etiologies between language impairment and dyslexia (Scerri et al. 2011). CMIP is a cytoskeletal adaptor in interactions with several proteins (FilaminA, RelA, PI3 kinases) and is involved in multiple pathways during synaptic formation and neuronal migration. ATP2C2 is known to regulate cellular calcium and manganese levels, both essential in neuronal processes (Newbury and Monaco 2010).

PCDH11 and language capacity

The protocadherin genes, *PCDH11X/Y*, are located on both the X and Y chromosomes in Homo sapiens, while in other hominid species only the X chromosome gene carries a *PCDH11* gene. The evolutionary consequence of the duplicative translocation of a 3.5-Mb region including the *PCDH11* gene from the ancestral X chromosome to the Y chromosome and subsequent sequence modifications are hypothesized to include sexual dimorphism of cerebral asymmetry/lateralization, a dimension which is a determinant of human ability to handle symbols, and a hominid specific capacity for language (Crow 2002; Williams et al. 2006). Confirming this theory, a case study of a male child with loss of both of the X and Y chromosome copies of *PCDH11* reported a significant non-syndromic speech delay characterized by grammatically reduced sentences of a few words without ASD or major dysmorphic or abnormal congenital features (Speevak and Farrell 2011). *PCDH11X* and *PCDH11Y* belong to the cadherin superfamily, members of which play significant roles in cell–cell adhesion, signaling, and cellular diversity and are highly expressed in the brain at all developmental stages including the fetal neocortex, ganglionic eminences, cerebellum, and inferior olive and in the adult brain, the cerebral cortex, hippocampus, and cerebellum (Priddle and Crow 2012).

Genetic elements in heritable language disorders

Childhood apraxia of speech

Childhood apraxia of speech (or developmental verbal dyspraxia) is a rare, severe and persistent speech disorder defined by the association of inconsistent error production on both consonants and vowels across repeated production of syllables and words, lengthened and impaired coarticulatory transitions between sounds and syllables, and inappropriate prosody (ASHA 2007). In a multigenerational pedigree ('KE'), in half of the members, *FOXP2* mutations have been identified that co-segregated with CAS,

oromotor apraxia and low scores on nonword repetition tasks (reviewed in Raca et al. 2012). In a study aimed at identifying novel candidate genes for CAS, a total of 16 copy-number variations were identified on 10 chromosomes with potential consequences in speech and language development. Several subjects demonstrated copy-number variations in two or three genomic regions, one a simultaneous occurrence of a heterozygous *FOXP2* mutation with chromosome 2 copy-number variation, and one a 16p11.2 microdeletion and copy-number variations on chromosomes 13 and 14 suggesting the involvement of heterogenous genomic pathways in this disorder (Laffin et al. 2012). The 16.p11.2 microdeletion (typically 550 kB) syndrome phenotype, in addition to neurodevelopmental features and mild intellectual disability, also includes speech–language impairment as the most common clinical deficit (Shinawi et al. 2010; Raca et al. 2012). In two well-characterized persistent CAS patients, chromosome 16.p11.2 microdeletions were identified in the same approximate region as in other CAS cases that collectively led to the conclusion that 16.p11.2 deletions present higher attributable risk for CAS than the more rare *FOXP2* mutations. Causal pathway associations were also proposed among 16.p11.2 deletions and CAS, epilepsy, and autism (Raca et al. 2012). In a study directed at rare subtelomeric 12p13.33 deletions known to be associated with intellectual disability and speech delay, 9 new microdeletion cases were identified with speech delay as the first unique symptom that fulfilled CAS criteria together with a neurobehavioral phenotype. The smallest common deleted region contains the *ELKS/ERC1* gene as a CAS candidate with synaptic function within neuromuscular junctions. Additional genes affected by the microdeletion, such as the brain expressed *CACNA1C*, may also contribute to the variability of the phenotype that ranges from healthy carriers to mild or severely affected patients (Thevenon et al. 2013).

Specific language impairment

Specific language impairment (SLI) is an inherited disorder of language acquisition despite adequate intelligence and opportunity and in the absence of any explanatory medical condition. SLI is a heterogeneous disorder that includes speech disorders with no obvious motoric etiology, deficits of expressive language (grammar, syntax, semantics), and impairments in expressive linguistic abilities (Rice 2012). In SLI, allelic variants of *ATP2C2* and *CMIP* associated with performance on a task of phonological short-term memory highlighted the importance of memory processes in language acquisition (Newbury et al. 2009). In addition, linkage was found to the SLI region on chromosome 16 and to chromosomes 1 (DYX8), 3 (DYX5), 6 (DYX2, *KIAA0319*), 7 (*FOXP2*), and 15 (DYX1) (Rice 2012). In SLI subjects, *FOXP2* showed association with reading, language and articulation, and *KIAA0319* with measures of speech, language and reading, further supporting the etiological relationship between speech and language disorders and dyslexia (Rice 2012). Alleles of the regulatory *CNTNAP2* are associated with quantitative measures of nonword repetition tasks, that in turn is associated with SLI, and are known to increase susceptibility to SLI (Whitehouse et al. 2011) and to be involved in early language acquisition (Rice 2012). The *CNTNAP2* genomic region is also in association with language delay in autism, thus the FOXP2-CNTNAP2 pathway may provide a mechanistic link between clinically distinct syndromes (Vernes et al. 2008). *KIAA0319*, in addition to its role in neuronal migration (Peschansky et al. 2010), was also proposed to participate in epigenetic regulation, a mechanism with a yet unknown significance in SLI (Rice 2012). As only few coding mutations have been reported to account for the influence of these genes in SLI or related disorders, alterations in their regulatory regions have been hypothesized to be involved. Building on these findings, a model with disrupted epigenetic regulation and growth signaling has been proposed for SLI. The model predicts that through aberrant cellular level timing, neocortical functioning may be affected in a developmental age-related fashion during phases of language acquisition (Rice 2012).

Stuttering

Stuttering is a disorder of speech fluency characterized by interruptions in speech flow and involuntary repetitions and elongation of syllables (reviewed in Newbury and Monaco 2010). Multiple genome-wide linkage and association studies for persistent familial stuttering and meta-analyses have provided only modest linkage to various chromosomes with only partial locus replications across studies that may be due to locus or allelic heterogeneity, low penetrance, or common occurrence of phenocopies. Consanguineous family studies provided more definite evidence for linkage to chromosome 12.q23.3 a consistent region (STUT2) (Riaz et al. 2005). Sequence analysis of 45 genes within STUT2 identified coding mutations in the GlcNAc-1-phosphotransferase alpha/beta subunits (*GNPTAB*) gene (Riaz et al. 2005; Kang et al. 2010). Mutations of the functionally related *GNPTG* gene encoding a subunit that in combination with the product of *GNPTAB* forms the functional GlcNAc-1-phosphotransferase enzyme, were also confirmed in stuttering subjects (Kang et al. 2010). Functional alterations of persistent stuttering-associated mutations were confirmed in another functionally related gene, the phosphodiester α-GlcNAcase (*NAGPA*) (Lee et al. 2011). Proteins encoded by *GNPTAB, GNPTG* and

NAGPA are components of the lysosomal enzyme-targeting pathway. Severe mutations (different from those in stuttering subjects) that abolish the GNPTAB protein are known to cause fatal lysosomal storage disease mucolipidosis II; mutations that reduce GNPTAB activity result in mucolipidosis III_A; and mutations of the *GNPTG* gene in mucolipidosis III_C. Mucolipidosis II patients have severe speech deficits and in a case of mucolipidosis III, a subject was reported with stuttering and unclear speech. Stuttering has been noted in other lysosomal storage disorders including Tay–Sachs disease, Salla disease and sialuria further supporting a major role for intracellular lysosomal functions in stuttering (Kang and Drayna 2012).

Developmental dyslexia

The neurodevelopmental disorder dyslexia consists of a specific learning disability involving impaired pseudoword reading, spelling, phonological and orthographic coding, rapid automatic naming, executive functions inhibition, and rapid automatic switching. Dyslexia is associated with anatomical and functional aberrations including white matter disruption in the left hemisphere perisylvian region, and under-activation of the left hemisphere temporoparietal region resulting in deficient phonological processing, and also under-activation of the left hemisphere occipitotemporal region involved in word recognition (Peterson and Pennington 2012). The dyslexia phenotype is associated with multiple genes together with the strong involvement of environmental factors. At nine risk loci (DYX1-9) linked to dyslexia, six candidate genes have been identified: *DYX1C1* (DYX1, 15q21), *DCDC2* and *KIAA0319* (DYX2, 6p21), *C2orf3* and *MRPL19* (DYX3, 2p12–p15), and *ROBO1* (DYX5, 3p12–q12). Of these *DYXC1C1*, *DCDC2, KIAAA*, and *ROBO1* are in co-regulatory networks and influence neuronal migration and axon guidance (Peterson and Pennington 2012). Additional candidate genes identified include *CMIP* that has also been shown to be involved in SLI (Scerri et al. 2011), *MC5R*, *DYM*, and *NEDD4L* (18p11.2–q12.20) (Scerri et al. 2010), and *DGKI* (within a 0.3-Mb region of 7q33) (Matsson et al. 2011). *DYX1C1*, identified in a Finnish cohort (Taipale et al. 2003) and confirmed in other populations (Bates et al. 2010; Paracchini et al. 2011), was found to directly affect the development of reading ability (Zhang et al. 2011). The DYX1C1 protein modulates estrogen receptor signaling and expression of genes involved in neuronal migration (*RELN*), and also associates with cytoskeletal proteins (Tammimies et al. 2012). In dyslexic individuals with the same weakly expressed *ROBO1* haplotype, impaired interaural interaction varied with ROBO1 expression in a dose-dependent manner (Lamminmaki et al. 2012) and a *ROBO1* risk-haplotype was linked to impaired hemispheric connectivity in auditory pathways (Simpson et al. 2000; Lamminmaki et al. 2012). *DCDC2* with a role in microtubule polymerization influenced reading ability and was linked to memory impairment (Marino et al. 2012). In a study aimed to determine if dyslexia candidate genes affect specific or broad cognitive traits, association was detected between reading skills and *KIAA0319*, *DCDC2*, and *CMIP*. *DCDC2* was specifically associated with dyslexia, while variants of *CMIP* and *KIAA0319* were associated with reading skill across the normal ability range (Scerri et al. 2011). Allelic variants of *DYX1C1*, *DCDC2*, and *KIAA0319* also demonstrated significant association with white matter volume in the left temporo-parieteal region containing pathways that connect the middle temporal gyrus with the inferior parietal lobe suggesting a mechanism that underlies variability in reading ability in normal and impaired readers (Darki et al. 2012). In neuroimaging studies, *KIAA0319* risk alleles were linked to asymmetry in functional activation of the superior temporal sulcus and revealed an activation pattern different from *FOXP2*-associated activation in the left frontal cortex (Pinel et al. 2012).

Speech and sound disorder

Speech and sound disorder is a relatively common childhood disorder that affects the ability to produce and properly use speech sounds and include deficits in articulation, a range of phonological tasks, and/or cognitive representation of language (Newbury and Monaco 2010). The disorder is heterogeneous depending on the severity, cause, speech errors, and involvement of other aspects of the linguistic system. Various subtypes have been proposed based on error types or underlying etiology, but a universal classification system is lacking (Waring and Knight 2013). A subgroup of SSD has motor impairment (Peter 2012), while the majority of cases have primarily affected phonological development. SSD overlaps with language impairment and reading disability at diagnostic, cognitive, and etiological levels that similarly vary with subtype (Pennington and Bishop 2009; Lewis et al. 2011). The conversational speech normalizes at later ages, but residual differences remain and can be identified in adults with a history of SSD. In adolescents with childhood history of SSD, involvement of speech production-related processes was supported by fMRI analysis that detected right lateralized hypoactivation in the inferior frontal gyrus, suggesting a deficit in the phonological processing loop that supports phonological memory, and also hypoactivation in the middle temporal gyrus that may indicate a deficit in speech perception (Tkach et al. 2011). Various studies provided evidence for genetic factors (Peter et al. 2012) and in SSD families, linkage has been identified between

phonological memory and decoding traits and chromosome 3 (DYX5), and also chromosomes 1 (DYX8), 6 (DYX2), and 15 (DYX1), a locus that was subsequently liked to quantitative measures of oral motor control, articulation, and phonological short-term memory (Newbury and Monaco 2010). In a genome-wide linkage study of familiar SSD subtype with deficit in motor sequencing, linkage analysis revealed a newly emerging region at 8q24, identified 6p21 that overlaps with the dyslexia candidate DYX2 locus implied in rapid alternating naming (rapid sequencing of alternative targets in both), 7q32 that is also implicated in dyslexia, and 7q36 adjacent to the *CNTNAP2* region (Peter et al. 2012). Candidate genes *ELP4* and *PAX6* were also identified to contribute to SSD and Rolandic epilepsy (Pal et al. 2010). A study evaluating the contribution of *FOXP2* identified a predominance of a T allele (5′ of the ATG initiator codon) and multiple cases with a triplet deletion within exon 5 in SSD subjects (Zhao et al. 2010).

Language phenotype-associated genes in complex syndromes

In complex syndromes language impairment often occurs in the context of severe intellectual disability, overall developmental delay, and multiple pathologies affecting various organs. Currently only in a few of these syndromes has the affected language faculty been characterized in detail. As more information emerges on impaired language mechanisms within these clinical phenotypes and their linkage to specific genetic deficiencies is established, novel insights may be gained into determinants of cognitive and language abilities and their interactions.

Autism spectrum disorders

Autism spectrum disorders are a complex group of neuropsychiatric conditions involving deficiencies in social communication, mental flexibility, and poor language skills (Tomblin et al. 2009). Recent progress in identifying ASD mechanisms and candidate genes supported the involvement of multiple brain regions, including the frontal lobes, anterior temporal lobes, caudate, and cerebellum (Abrahams and Geschwind 2010). Modeling studies identified abnormal synaptic pruning as a possible mechanism and the probable basis for behavioral regression unique to autism and predicted shared gene variants between autism and language impairment (Thomas et al. 2010). Analysis of gene expression patterns in the prefrontal cortex where excess neuron numbers and cortical overgrowth are pronounced in the majority of autism cases provided evidence for dysregulation in pathways governing cell number, cortical patterning, and differentiation in developing autistic prefrontal cortex. Adult autistic prefrontal cortex, however, showed dysregulation of signaling and repair pathways suggesting age-dependent gene expression changes and distinct pathological processes (Chow et al. 2012). ASD and SLI co-occur at higher than chance levels, suggesting a scenario for a shared etiology (Tomblin 2011). Language impairment in comorbid (ASD + SLI) cases may be a consequence of ASD risk factors, and different from those seen in SLI. Molecular genetic studies, however, have confirmed a common risk genotype for ASD and SLI (Bishop 2010). In addition to evidence of linkage of the FOXP family of transcription factors (including *FOXP1*, *FOXP2*, and *FOXP4* alleles) to the ASD phenotype (Bowers and Konopka 2012), a number of other candidate genes have also emerged. The neuroligin genes occur on both the X and Y chromosomes and the encoded neuroligin proteins are involved in the same synaptic networks as neurexins (NRXN) with common *NRXN* variants known to affect risk for both SLI and autism. Promoter-linked insertion or deletion polymorphisms of the serotonin-transporter gene (*SLC64A*) have also been implicated in ASD in family-based association studies. Of these, maternally inherited copies of a short allele of *SLC64A* (deletion polymorphism, the *5-HTTLPR* risk variant) result in a more impaired overall level of language ability (Kistner-Griffin et al. 2010). A phenotypic spectrum associated with duplication of chromosome Xp11.22–p11.23 involving over 50 genes was reported to include both ASD and SLI. Within this chromosome region, a WNT signaling pathway member, *TBL1X*, was confirmed to be associated with ADS risk in males (Chung et al. 2011). Converging evidence supports that both common and rare variants of the *CNTNAP2* gene also confer risk for ASD and ASD-related conditions such as language delay or developmental language disorders. However, the influence of these allelic variants on CNTNAP2 functions remains unclear (Peñagarikano and Geschwind 2012). Recently, two chromosome 7q31-36 genes, *WNT2* and *EN2*, were suggested to act together during language development in ASD (Lin et al. 2012) and linkage of aberrant WNT pathway activation and dendrite growth to autism risk was also confirmed (Kalkman 2012). Loss of function mutation within the *SHANK* genes encoding proteins important for formation and stabilization of synapses have been also identified in ASD subjects (Uchino and Waga 2013). In a case with severe ID and language impairment, a triple translocation and a breakpoint at 11q13.3 were demonstrated to disrupt the *SHANK2* gene. The translocation also resulted in copy-number variations involving duplication of two synaptic genes *CHRNA7* and *GPRIN2*. Co-occurrence of a *SHANK2* mutation and *CHRNA7* duplication in

two other ASD cases suggested convergence of these genes in common synaptic pathway (Chilian et al. 2013).

Epilepsy

Recent genetic studies have identified molecular pathways that appear common to epilepsy and language impairment and provided insight into the neural basis of language impairment in children with new-onset epilepsy where recurrent seizures contribute to cognitive and behavioral deterioration. Rearrangements within chromosome 16p11.2 affecting 27 genes commonly result in speech or language delays and a high percentage of concomitant seizures (Shinawi et al. 2010). Analysis of a series of overlapping deletions within 16p13.2–p13.3 associated with delayed speech, seizures, and intellectual disability identified the *GRIN2A* gene as a candidate for this disorder (Reutlinger et al. 2010). The *GRIN2B* and *GRIN2A* genes encode *N*-methyl-D-aspartate (NMDA) receptor subunits NR2B and NR2A that mediate excitatory neurotransmission and that were found mutated in individuals with mental retardation and epilepsy (Endele et al. 2010). Duplications of chromosome 14q11.2–q13.1 that manifest with a Rett syndrome-like phenotype including developmental delay, severe speech delay, and developmental epilepsy include the *FOXG1*, *C14ORF23*, and *PRKD1* genes. Of these, *FOXG1* with an important role in the developing brain was proposed to be the main functional candidate (Brunetti-Pierri et al. 2011). Developmental epilepsy patients with a novel 2q23.1 microdeletion syndrome resulting in haploinsufficiency of the *MBD5* gene demonstrate Angelman syndrome-like features (mental retardation, seizures, microcephaly, and coarse facies) and also repetitive behavior and minimal speech. Individuals with larger deletions at this locus that involves the adjacent *ECP2* gene have a broader clinical phenotype (Williams et al. 2010). Of these genes *MBD5* proved to be the single causal gene for intellectual disability, epilepsy, and ASD (Talkowski et al. 2011, 2012). MBD5 and the Rett syndrome-associated MEPC2 proteins are members of the methyl-CpG-binding domain family with gene regulatory functions in cell division, growth, and differentiation, while EPC2 is a member of the polycomb protein family involved in heterochromatin formation (van Bon et al. 2010) a function reflected in a broad spectrum of clinical phenotypes of affected individuals. Mutation of the *DYRK1A* gene has been recently reported to cause absent or delayed language together with epilepsy, microcephaly, and intellectual disability consistent with the role of DYRK1A in signaling pathways controlling brain growth and size through neuronal proliferation and neurogenesis (Courcet et al. 2012). Heterozygous allelic variants of the *CNTNAP2* and *NRXN1* genes are associated with developmental language disorder, autism, mental retardation, schizophrenia, and epilepsy. Aberrant expression of the FOXP2 target gene sushi-repeat (*SRPX2*) was noted to results in seizures and developmental verbal dyspraxia (Pal et al. 2010). In Rolandic epilepsy (RE), the 11.13 locus containing *ELP4* and *PAX6*, was found pleiotropic (one gene allele affecting multiple phenotypes) in the development of both the centrotemporal spike EEG signature of RE and SSD (Pal et al. 2010; Addis et al. 2012) while reading disability was influenced by the 1q42 and in some populations by the 7q21 loci (Strug et al. 2012).

Chromosome 4p-syndrome and advanced language structure deficiencies

Analysis of quantitative and qualitative data in a large cross-cultural study of communication and expressive language manifestations of subjects with chromosome 4p-syndrome (the largest deletion includes the 4p16.3 band and contiguous gene regions) including Wolf–Hirschhorn syndrome, Pitt–Rogers–Danks syndrome, Proximal 4p Deletion syndrome, and complex chromosomal rearrangements associated with 4p, demonstrated a heterogeneous population with a complex phenotypic and cognitive-behavioral profile (Fisch et al. 2012) including dysmorphic facial features, organ defects, seizures, and cognitive impairment (Coppola et al. 2013). Individuals with a 4p-related condition demonstrate limited overall communication and expressive language skills or do not develop productive speech and language. A relatively small cohort of the study population, however, was noted to have productive expressive skills and advanced language structures and broadened the spectrum of expressive language skills associated with chromosome 4p-syndrome with the largest 4p deletion resulting in the most severely affected expressive language phenotype (Marshall 2010). Loss of the Wolf–Hirschhorn syndrome candidate 1-like 1 gene (*WHSC1L1/MMSET*) that codes for a chromatin organizing histone methyltransferase and also shown to have a role in DNA damage response, has been considered to be responsible for the core phenotype of the disease (Pei et al. 2013). Within the Wolf–Hirschhorn critical regions 1 and 2 (WHSCR1-2), seven genes, *FAM193A*, *ADD1*, *NOP14*, *GRK4*, *MFSD10*, *SH3BP2*, and *TNIP2*, may be deleted and the deletion may also include regulatory sequences that can affect the expression of additional genes within a defined temporal and spatial developmental window (Hannes et al. 2012).

6p25 and speech and language disorder

Deletions of 6p25 as a recognized clinically identifiable syndrome are characterized by intellectual disability,

language impairment, hearing deficit, and among others, craniofacial and central nervous system anomalies. In two dizygotic twins with the smallest deletion of 0.9 kb so far identified, dysmorphic features and brain alterations were reported including focal increase of the right perifrontal subarachnoid space and mild anomaly of the gyral pattern resulting in borderline-mild intellectual disability, speech and language difficulties, and behavioral problems. Among the genes mapped to the deleted region, *LYRM4* is known to be down-regulated in the cerebellar cortex of schizophrenia patients (Bozza et al. 2012). Chromosome 6p25 deletions in six reported cases included the *FOXC1* gene, the haploinsufficiency of which was suggested to be the major contributing factor to the phenotype of these patients with ocular and cerebellar abnormalities (Delahaye et al. 2012). *FOXC1* was also deleted in a patient, together with several other genes resulting in malformations and severe language impairment (Anderlid et al. 2003). FOXC1, a Forkhead-box transcription factor family member, plays a critical role in the tangential migration of cortical interneurons along the cortical marginal zone that is the primary mode of migration of neurons translocating into the cerebral cortex from subpallial domains (Zarbalis et al. 2012).

Candidate language-associated genes in Williams syndrome

Williams syndrome (WS) is an autosomal dominant disorder characterized by cardiovascular disease, endocrine and growth abnormalities, failure to thrive in infancy, distinctive facial features, mild mental retardation, and cognitive and personality characteristics. The symptoms also include attention deficit disorder, anxiety, and a specific speech and language profile. Patients are often reported to demonstrate near-normal expressive language despite the presence of significant intellectual and nonverbal impairments. As individuals with WS have a strong drive to interact and are extremely sociable in spite of their limited comprehension of basic social norms their language use might be uniquely related to excessive social drive (Fishman et al. 2011) and in turn to altered gene networks with dysregulation of neuropeptides (Jarvinen et al. 2013). Detailed analysis of the WS patients' language revealed relative strengths in concrete vocabulary, verbal short-term memory, and grammatical abilities that were at the level expected for a general normal intellect, but considerable weakness in relational/conceptual language and pragmatics (Mervis and John 2010; Mervis and Velleman 2011; Carney et al. 2013). Oral narratives in WS also differed from typically developing subjects, mainly due to a significant increase in the frequency of disfluencies in terms of hesitations, repetitions, and pauses, that may represent significant markers of language problems for these patients (Rossi et al. 2011). In lexico-semantic tasks including semantic and phonological fluency, WS subjects do not differ from controls, disproving the earlier hypothesis that they may have a peculiar semantic system (Garayzabal and Cuetos 2010). In definition tasks at younger ages, WS patients' performance level was similar to typically developing individuals, however, their ability to define words fell away from predicted normal levels at older ages, as more sophisticated definitions were expected and indicated less lexical-semantic knowledge than expected based on the level of receptive vocabulary (Purser et al. 2011). In metaphorical language comprehensions, WS subjects were also found to access different, less abstract knowledge (Thomas et al. 2010). Individuals with WS also display an unusual sensitivity to noise, and alterations in sensitivity to input that may modify their language development (Elsabbagh et al. 2011). The disorder is caused by the contiguous deletion of 25 genes on chromosome 7q11.23 that occurs in over 99 % of individuals with Williams syndrome. Among the affected genes there are several functional candidates that may contribute to the associated cognitive and language features, specifically transcriptional regulators *GTF2IRD1* and its adjacent paralogue *GTF2I* (Vandeweyer et al. 2012) that were shown in a mouse model of WS to affect motor dysfunction and altered vocalization (Howard et al. 2012). In larger deletion cases encompassing the *GTF2IRD2* gene, a higher-level role in executive functioning (spatial functioning, social reasoning, and cognitive flexibility) was identified for this transcription factor (Porter et al. 2012).

Speech impairment in HDR syndrome (10p15.3)

Chromosome 10p terminal deletions have been associated with DiGeorge syndrome phenotype, and within the same genomic region haploinsufficiency of the *GATA3* transcription factor gene is known to cause hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome. HDR subjects have moderate-to-severe sensorineural hearing loss with shifted speech reception thresholds and disturbed speech recognition in noise (van Looij et al. 2006). Genetic and clinical analysis of four patients revealed mental retardation and speech impairment and two patients with similar dysmorphic features exhibited autistic behavior. A combination of these 6 and the review of 10 previously published cases with similar 10p deletions and molecular and cytogenetic mapping data suggested that partial deletions of chromosome 10p14–p15 represent a syndrome with a distinct and more severe phenotype than previously assumed, including severe mental retardation, language impairment, and autistic behavior. While deletion of 4.3 Mb within 10p14 is associated with autism, a critical region involved in speech impairment was defined within a

1.6-Mb region of 10p15.3 (Lindstrand et al. 2012). In 19 unrelated individuals with submicroscopic deletions involving 10p15.3 the clinical phenotype included, in addition to speech delay and language disorder, cognitive, behavioral and developmental differences, motor delay, craniofacial and brain anomalies, and seizures. Within 10p15.3 the little known *ZMYND11* and *DIP2C* genes were most commonly deleted and their haploinsufficiency may contribute to the clinical features (DeScipio et al. 2012).

10q22–q23 deletions and duplications associated with speech developmental delay

Rearrangements within 10q22–q23 result in speech developmental delay, macrocephaly, facial dysmorphism, and cerebellar abnormalities with broad phenotypic spectrum. Reciprocal deletions within this region were reported to lead to speech and language delays. Among the affected genes, three language function-related genes, Neuregulin 3 (*NRG*) involved in signaling in cell proliferation, migration, and survival, Bone morphogenetic protein 1 (*BMPR1*) a developmental regulator, and Glutamate receptor delta 1 (*GRID1*) a key player in synaptic plasticity, have been identified (van Bon et al. 2011). Linkage studies have also implicated 10q22–q23 as a schizophrenia susceptibility locus in several (Chen et al. 2009), but not all (Pasaje et al. 2011), populations. Association studies carried out in schizophrenic patients suggested that *NRG3* may be modulating early attentional processes for perceptual sensitivity (Morar et al. 2011).

12p12.1 in language delay and 12p13.31–q14.3 in deficient auditory duration discrimination

Haploinsufficiency of the *SOX5* gene (12p12.1) that encodes a transcriptional regulator with a dosage-sensitive role in cell fate determination during embryonic development and the development of the nervous system, consistently, results in prominent speech delay, intellectual disability, dysmorphic features, and aberrant behavior (Lamb et al. 2012). In a study of a three-generation family with a simple segregation of language impairment, a locus for auditory processing (the major functional deficit) mapped to 12p13.31–q14.3 (Addis et al. 2010). Affected members presented with communication impairments, performed poorly on a non-word repetition task, and showed late discrimination negativity in their brain activation patterns for syllable duration measured by event-related brain potentials. Together with psychoacoustic data that demonstrated deficiencies in auditory duration discrimination, the results indicated increased processing demands in discriminating syllables of different duration that may form the cognitive basis for language impairment in affected subjects. Subsequent genome-wide linkage analysis identified a haplotype with several candidate genes that reached the maximum possible logarithm of odds ratio (LOD) score and fully co-segregated with language impairment, consistent with an autosomal dominant, fully penetrant mode of inheritance (Addis et al. 2010).

Prader-Willi/Angelman syndrome: language delay associated with 15q11.2

Microdeletions and microduplications within the region 15q11.2 cause either Prader-Willi or Angelman syndrome depending on the parent of origin. The deletions are flanked by either proximal BP1 or BP2 breakpoints and a distal BP3 breakpoint. The larger deletions (BP1–BP3) both in Prader-Willi and Angelman patients result in a more severe phenotype. Within the BP1–BP2 region there are four evolutionarily conserved genes that are not imprinted: spastic paraplegia-associated *(NIPA1)*, the magnesium transporter *NIPA2*, *CYFIP1* the encoded protein of which interacts with FMRP in synaptosomal complexes, and a member of the cytoskeletal tubulin complex, *TUBGCP5*. Alterations within these four genes impact, to a varying degree, behavioral and neurological functions and show associations with speech and motor delays, seizures, behavioral problems, and autism. In a large cohort study of subjects with BP1–BP2 deletions or duplications, the majority demonstrated behavioral or neurological problems and particularly prevalent speech delays that were universally observed in both the deletion and duplication subjects. The deletion subjects more frequently had intellectual disability than the duplication subjects that presented with overall milder phenotypes (Burnside et al. 2011). Children with Angelman syndrome have a distinct developmental and behavioral profile; their cognitive skills are stronger than their language and motor skills, and their receptive language skills are stronger than their expressive language skills (Gentile et al. 2010). In a study aimed to determine the basis for severe language development delay in Angelman patients, impairment of white matter integrity was observed. While white matter alteration appeared throughout the brain, only those in temporal white matter pathways were found associated with deficient language and cognition (Peters et al. 2011). In addition, morphological changes were present in the fiber bundles both in the right and left arcuate fasciculus that connect the language comprehension region of the temporal lobe with the speech-generating region of the frontal lobe and are involved in language and cognitive functions. Some of these changes were attributed to developmental deficiencies in axon guidance due to loss of the *UBE3A* gene that resides within the affected genomic region and is a strong functional candidate (Wilson et al. 2011). The UBE3A

protein is expressed in neurons of the hypocampus, cerebellum, and cortex, it is involved in the ubiquitin proteosome and has a role in regulating, through degradation, levels of axon guidance molecules, and thus contributes to proper formation of tracts (Sartori et al. 2008).

Chromosome 17p11.2: Potocki–Lupski syndrome

Potocki–Lupski syndrome is a result of microduplication of low-copy repeat sequences within chromosome 17p11.2. In addition to diminished speech ability and severe expressive language impairment (Ercan-Sencicek et al. 2012), Potocki–Lupski syndrome patients suffer from cognitive deficits, dysmorphic features, hypotonia, feeding difficulties, developmental delay, and behavioral abnormalities including autism spectrum disorder, anxiety, and inattention (Yusupov et al. 2011). Syndromes associated with microdeletion and microduplication have long been known to display specific neurobehavioral traits. However, there are only a few dosage sensitive genes that are affected by these rearrangements. Smith–Magenis syndrome is characterized by reciprocal microdeletions, while in Potocki–Lupski syndrome microduplications occur within chromosome 17p11.2. The dosage sensitive gene within this region (deduced to be 1.3 Mb with 18 genes) responsible for most phenotypes has been identified as the retinoic acid induced 1 gene (*RAI1*). In a recent case with mild intellectual disabilities and language developmental delay, the shortest (0.25 Mb) microduplication was identified that included *RAI1* (Lee et al. 2012). The RAI1 protein has transcription factor activity, it is highly expressed in neurons, has a likely role in modulating aspects of neuron function and differentiation (Carmona-Mora et al. 2012), and is involved in neurobehavioral phenotypes (Carmona-Mora and Walz 2010).

22q11.2 deletion syndrome

Subjects with 22q11.2 hemizygous microdeletion show, in addition to a spectrum of phenotypic anomalies, delayed or absent speech (Cusmano-Ozog et al. 2007), a wide range of variations in their intellectual ability (Michaelovsky et al. 2012; Wu et al. 2013), and in aspects of memory and hearing (Persson et al. 2012). Deficits in visual-spatial abilities and visual-object long- and short-term memory were also noted in individuals without intellectual disability. In lexical comprehension tests 22q11.2 syndrome subjects (children and adolescents) demonstrated significantly lower scores on receptive tasks than unaffected controls, while there was no difference in their expressive task scores. They also scored significantly lower for receptive and expressive morphosyntax while categorical task and phonological task analyses revealed preserved abilities for categorical and phonological fluency (Vicari et al. 2011). In adults, high prevalence of speech and hearing problems proved to be part of the phenotype (Persson et al. 2012). 22q11.2 syndrome is a contiguous (typically 3 Mb) deletion that affects over 40 genes including *SNAP29* that has been implicated in cerebral dysgenesis (McDonald-McGinn et al. 2013). A 0.8-Mb microdupication at 22q11.2 in a subject with motor delays and language impairment affected 14 genes including *CRKL*, *ZNF74*, *PIK4CA*, *SNAP29*, and *PCQAP* known to contribute to aspects of the phenotype (Pebrel-Richard et al. 2012).

22q13.3 deletion-associated language developmental delay

Chromosome 22q13.3 deletion syndrome (Phelan–McDermid syndrome) is a contiguous gene disorder due to deletions of the distal chromosome 22 arm that results in significant language development delay, mental retardation, hypotonia, and autistic features (Phelan and McDermid 2012). Haploinsufficiency of the *SHANK3* gene proved to be the major cause of the neurological symptoms in this deletion syndrome. In a study of a large cohort of Japanese autistic patients that manifested 22q13.3 syndrome features, a series of *SHANK3* gene alterations were identified that included a 6 amino acid deletion in the SH3 domain, a missense variant within the PDZ protein domain, and insertion or deletion of a 10 base pair GC sequence 9 base pairs downstream from exon 11 (Waga et al. 2011). SHANK3 is a multidomain scaffolding protein enriched in excitatory synapses with important roles in the formation, maturation, and maintenance of synapses in the developing brain (Uchino and Waga 2013).

Language impairment in Noonan syndrome

Noonan syndrome (NS) is a rare genetic alteration in which diagnosed children have normal intelligence, but a small percentage of NS patients have intellectual disabilities. In a case study of a Caucasian girl with Noonan syndrome, in addition to various systemic problems, mild mental delay and language disturbances were reported (Ierardo et al. 2010). In a more comprehensive study, frequent language impairments were found in patients that were also associated with higher risk for reading and spelling difficulties. Language ability significantly correlated with nonverbal cognition, hearing ability, articulation, motor dexterity, and phonological memory. Results collectively indicated that variations in language skills were related to cognitive, perceptual, and motor factors rather than due to specific aspects of language selectively affected in this syndrome (Pierpont et al. 2010). Most cases of Noonan syndrome are

attributed to mutations in one of three genes, *PTPN11*, *SOS1*, or *RAF1*. *PTPN11* gene (12q24.1) mutations account for approximately 50 %, *SOS1* gene (2p22–p21) mutations for 10–15 %, and *RAF1* gene (3p25) mutations for 5–10 % of all Noonan syndrome cases. In addition, about 2 % of NS patients have mutations in the *KRAS* gene (12p12.1) with a usually more severe or atypical form of the disorder. Noonan syndrome has been also linked to mutations in the *BRAF* (7q34), *NRAS* (1p13.2), or *MAP2K1* (15q21) genes (Tartaglia et al. 2010), encoding components of central signaling pathways in cellular differentiation, migration, and development. The mutated variants of these signaling components are known to have an overall increased activity and such a gain of function may result in the disruption of regulatory systems. However, no clear distinctions in phenotype–phenotype correlations have been yet established for these diverse, potentially causative pathways.

Rett syndrome: *MECP2* and language regression

Rett syndrome is a neurodevelopmental disorder that affects predominantly females and manifests in early childhood following an apparently normal psychomotor development during the first 6–18 months. Key features of typical Rett syndrome include developmental stagnation, gait abnormalities, loss of purposeful hand movements, autistic features, a high frequency of seizures, and regression or loss of expressive language (Neul et al. 2010). The most commonly identified relatively milder atypical form of Rett syndrome is characterized by regained language following regression. The regained language, however, is not completely normal (Marschik et al. 2013) and many subjects have speech perseveration and pronoun reversal (reviewed in Neul 2010). In Rett cases with some preserved speech and language abilities, analysis of early speech–language development revealed evidence for early onset abnormal speech–language functions with intermittent normal and abnormal verbal features including two types of vocalizations (normal sequences and atypical inhalatory, pressed or high pitched), limited phonological and lexical complexity and restricted compositional variability (Maricic et al. 2012).

While a congenital variant of Rett syndrome with severe mental retardation and absent speech–language has been shown to be associated with mutations in the *FOXG1* gene (Allou et al. 2012), the majority of patients (over 90 % of typical Rett syndrome and 50–70 % of atypical cases) carry loss-of-function mutated versions of the X inactivation-subject Methyl-CpG-binding protein 2 (*MECP2*) gene (Guerrini and Parrini 2012). About 5 % of Rett syndrome cases, however, do not have *MECP2* mutations and functional alterations of the MECP2 protein have also been identified in subjects who do not have features of Rett syndrome but do exhibit other neurodevelopmental conditions (Neul 2010). Diminished expression of MECP2 resulting in phenotypic overlap with Rett syndrome was also reported in disorders related to the transcription factor MEF2C (5q14.3) and was attributed to a shared pathway (Zweier and Rauch 2012). Duplications of *MECP2* primarily affect males and cause distinct neurodevelopmental features indicating a sensitivity of the nervous system to MECP2 dosage that is further supported by more severe phenotypes in triplication cases. These features include X-linked mental retardation, moderate to severe intellectual disability, autistic features, shortened life span, and partial or complete loss of acquired highest-level language skills (Ramocki et al. 2009). Developmental regression timing analysis identified regression in language skills (in 8 of 17 patients) and in other subjects (7/17), regression in other skill areas that coincided with seizure onset and autism diagnosis with later skill loss onset than either in Rett syndrome or ASD (Peters et al. 2013). Impairments in cortical sensory processing in Rett syndrome, as in ASD (with a predominance of reduced MECP2), are thought to contribute to higher-order phenotypic deficits and are reflected in auditory-evoked potentials and fields including increased latency of cortically sourced components that are associated with language and developmental delay in autism. While ascribing similar mechanisms of idiopathic ASD to Rett syndrome has been controversial, in a mouse model of Rett syndrome (heterozygous MECP2 deficiency) specific latency differences and select gamma and beta band abnormalities associated with ASD have been recapitulated, suggesting common cortical pathomechanisms for Rett syndrome and ASD (Liao et al. 2012).

MECP2 contains a methyl-CpG binding domain (MBD) and is part of a family of nuclear proteins. MECP2 can repress transcription from methylated gene promoters and, among its diverse epigenetic functions, also affect terminal neuronal differentiation in the developing brain (Marschik et al. 2013). MECP2 levels are regulated by microRNA together with levels of proteins of the MECP2-interacting co-repressor complexes including HDAC4 and TBL1X (Han et al. 2013). Aberrant MECP2 functions may lead to abnormal brain development through maladjustment of neuronal gene expression to synaptic signals during the critical period of early neuronal differentiation and synaptic maturation (Kaufmann et al. 2005). More recently, MECP2-associated neurological defects in Rett syndrome have been proposed to arise from a disruption of homeostatic plasticity (Blackman et al. 2012). Additional mouse model studies confirmed aberrant maturation and maintenance of synapses and circuits in multiple brain systems in MECP2 deficiency and concluded that some of the deficits arose from alterations in signaling pathways including

PI3K/Akt (reviewed in Castro et al. 2013). While there is also evidence for a role for MECP2 in developmental neocortex plasticity (Blackman et al. 2012), mechanistic relationships between MEPC2 functions and language skills and/or regression have yet to be established.

Language profile in Fragile X syndrome

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability, and the most common single gene disorder associated with autism with well-documented language impairments. The syndrome is caused by an expanded CGG repeat (>200 repeats) in the 5′UTR part of the Fragile X Mental Retardation Gene (*FMR1*) resulting in deficiency or absence of FMR1, an RNA-binding protein that regulates the translation of genes important in synaptic development (Wang et al. 2012). In addition to established effects of FMR1 on dendritic maturation and axonal growth, in X premutation allele carriers, lower connectivity was detected between hippocampal and frontal regions that likely affect recall and functional memory (Wang et al. 2012). Mutated forms for many of the FMR1-regulated genes have also been linked to ASD (Tassone et al. 2012) that may explain the high comorbidity between FXS and ASD. Deficient FMR1 protein function is also known to result in dysregulated neurotransmitter systems including the metabotropic glutamate receptor 1/5 (mGlu1/5) and GABA pathways (Paluszkiewicz et al. 2011). Although individual differences are large, most subjects with FXS display weaknesses across all language and literacy domains. Expressive, receptive, and pragmatic language abilities as well as literacy skills are similar to those of younger, normally developing peers, although there are areas in which impairments exceed developmental-level expectations including higher occurrence of repetitions (Finestack et al. 2009). FXS boys with and without autism spectrum disorder on measures of verb (VM) and noun (NM) morphosyntax scored lower on both compared to typically developing boys of similar mental ages. Part of the morphosyntactic impairment in FXS appeared attributable to cognitive, environmental, and speech factors. However, patients with FXS performed at levels lower than expected from differences in these extra-linguistic factors alone, across both the verb and the noun domains (Estigarribia et al. 2012). Genetic variation at the *FMR1* locus also correlated with pragmatic language and theory of mind both in autism and FXS subjects suggesting an overlap in the social and language phenotypes and a molecular genetic basis to these phenotypic profiles (Losh et al. 2012).

Klinefelter syndrome and XXX and XYY trisomies

Klinefelter syndrome results from the presence of an extra copy of the X chromosome (47, XXY) and its variants from additional copies of the X chromosome. Klinefelter language and communication problems have close similarities with the manifestation of SLI and features of ASD. Similar language and communication problems characterize the XYY trisomies. The neuroligin genes that occur on both X and Y chromosomes encode neuroligin proteins that are involved in the same synaptic networks as neurexins (NRXN) with common NRXN allelic variants affecting risks for SLI and autism. In Klinefelter syndrome, increased (triple) dose for neuroligin is predicted to have detrimental consequences, particularly in cases where this occurs in conjunction with disease-risk variants of the neurexin genes (Bishop and Scerif 2011). In addition, the potential effect of increased copy numbers for the *PCDH11X* and *PCDH11Y* genes, for which lack of activity was reported to cause significant speech delay and limited word use, may contribute to the language phenotype in Klinefelter syndrome patients (Speevak and Farrell 2011). The developing brain is highly sensitive to the organizing effects of steroids of gonadal origin including processes of neurogenesis, migration, dendritic growth, and synaptic patterning that have a significant impact on behavioral phenotypes and impairments in the domains of speech and language consistent with the reduced androgen production characteristic of the syndrome (McCarthy 2013).

Discussion

The preceding analysis of heritable disorders involving impaired speech and language phenotypes reveals a complex spectrum of clinical symptoms. It is also apparent that the genes and chromosomal loci known to be associated with many of these phenotypes are functionally diverse. In order to compare some of these details, we have summarized these phenotypic and genotypic characteristics in Table 1. A number of observations can be made from these data and we have selected the following areas for detailed discussion:

Regulatory networks and language ability

The significance of reorganizational processes, the predominance of regulatory networks, and a critical role for regulatory determinants involved in language ability during brain development are further supported by a recent study of genetic networks in the developing cerebral cortex. These networks include fast-evolving non-coding sequences that harbor human-specific changes with possible divergence in their repertoires for transcription factor binding sites. The noted enrichment of FOXP2 targets through this process confirmed a key organizing role for FOXP2 in language development (Lambert et al. 2011).

Table 1 Genes associated with heritable speech and language disorders

Gene symbol and chromosome location	Normal or aberrant CNS structural and functional associations	Associated language and cognitive features
FOXP2 (7q31)	Development of the motor cortex, striatum, cerebellum, and orofacial muscles (Spiteri et al. 2007; Vernes et al. 2007, 2011; Newbury et al. 2010)	Verbal dyspraxia or childhood apraxia of speech (CAS) (Lai et al. 2000; MacDermot et al. 2005; Feuk et al. 2006; Vargha-Khadem et al. 2005; Laffin et al. 2012), sensory guided auditory–motor learning of articulation patterns (Watkins et al. 2002), generation and sequencing of speech sounds, expressive and receptive language ability (Bacon and Rappold 2012), mild CI (Watkins et al. 2002), ASD (Bowers and Konopka 2012)
FOXP1 (3p13)	Regulation of neurodevelopmental pathways (Li et al. 2004)	Retarded speech and language development, cognitive phenotypes (Pariani et al. 2009; Horn 2012; Horn et al. 2011; Hamdan et al. 2010; Talkowski et al. 2012; Palumbo et al. 2012), specific effect on expressive language, ID (Hamdan et al. 2010), limited expressive vocabulary (Horn 2012), verbal dyspraxia, ASD (Bowers and Konopka 2012)
FOXG1 (14q12)	Simple gyral pattern, reduced white matter volume in frontal lobes, corpus callosum, and frontal lobe hypogenesis (Kortum et al. 2011; Takahashi et al. 2012)	Absent language, MR (Kortum et al. 2011), impaired language capacity, language delay in Rett syndrome (Takahashi et al. 2012), and Rett syndrome-like phenotypes (Allou et al. 2012; Guerrini and Parrini 2012)
FOXC1 (6p25)	Anterior eye chamber and cerebellar abnormalities (Delahaye et al. 2012), migration of cortical neurons into the cerebral cortex (Zarbalis et al. 2012)	Severe speech and language deficits, hearing deficit, ID in 6p25 deletion syndrome (Bozza et al. 2012; Delahaye et al. 2012)
NRXN1 NRX2 (2p16.3)	Excitatory synaptic differentiation (de Wit et al. 2009), synaptic development and effective signal transmission between neurons (Gauthier et al. 2011; Varley et al. 2011)	Severe language delay with affected cognition (Ching et al. 2010), ASD, SLI (Bowers and Konopka 2012), severe ID (Gregor et al. 2011)
CNTNAP2 (7q35)	Role in patterning circuits that serve higher cognition and language (Peñagarikano and Geschwind 2012), activation pattern in the left inferior frontal cortex and acquisition efficiency of structural knowledge (Folia et al. 2011)	Early language acquisition and performance involving expressive and receptive abilities, nonword repetition ability in SLI (Vernes et al. 2008), dyslexia (Peter et al. 2011), suttering (Petrin et al. 2010), developmental language delay in ASD (Peñagarikano and Geschwind 2012), sentence processing (Kos et al. 2012), syntactic processing (Whalley et al. 2011), allele effects extend between various neurodevelopmental disorders and variations in the normal population (Graham and Fisher 2013), severe ID (Gregor et al. 2011)
CYP19A1 (15q21.2)	Sexual differentiation of the brain (Anthoni et al. 2012)	Quantitative measures of language and speech, reading, vocabulary, phonological processing, oral motor skills, dyslexia susceptibility
CMIP (16q23)	C-Maf inducing protein	Phonological short-term memory, nonword repetition ability, SLI (Newbury et al. 2009; Li and Bartlett 2012), dyslexia, reading skills across the normal ability range (Scerri et al. 2011), hearing threshold (Girotto et al. 2011), ADS and developmental delay (Van Der Aa et al. 2012)
ATP2C2 (16q24.1)	Ca-transporting ATPase	Phonological short-term memory, nonword repetition ability, SLI (Newbury et al. 2009; Li and Bartlett 2012)
PCDH11X (Xq21.3) *PCDH11Y* (Yp)	Cerebral asymmetry and lateralization (Crow 2002, 2010; Williams et al. 2006)	Ability to handle symbols, deficiency linked to severe language delay, limited word use, Klinefelter syndrome-associated language phenotype (Speevak and Farrell 2011)

Table 1 continued

Gene symbol and chromosome location	Normal or aberrant CNS structural and functional associations	Associated language and cognitive features
GNTPAB GNTG NAGPA (12q23.3)	Cell metabolism, lysosomal enzyme-targeting pathway (Riaz et al. 2005; Kang and Drayna 2012)	Repetition, prolongation, or cessation of sound in stuttering (Kang and Drayna 2012)
ROBO1 (3p12)	Axon guidance, midline crossing of major nerve tracts (Simpson et al. 2000)	Dyslexia (Lamminmaki et al. 2012)
DYX1C1 (15q21.3)	Neuronal migration (Tammimies et al. 2012), white matter volume in the left temporo-parietal region (Darki et al. 2012)	Deficits in development of reading ability in dyslexia (Taipale et al. 2003; Bates et al. 2010; Paracchini et al. 2011; Zhang et al. 2012)
DCDC2 (6p21.3)	Association with white matter volume in the left temporo-parietal region (Darki et al. 2012)	Reading and memory impairments in dyslexia (Marino et al. 2012; Scerri et al. 2011)
DGK (7q33)		Linkage to dyslexia (Matsson et al. 2011)
KIAA0319 (6p22.3)	Association with white matter volume in the left temporo-parietal region (Darki et al. 2012), asymmetry in functional activation in temporal sulcus (Pinel et al. 2012)	Reading skills across the normal ability range (Scerri et al. 2011), developmental language and reading disorders (Pinel et al. 2012)
SLC64A (17q11) *5-HTTLPR* risk variant	Serotonin transporter	ASD, maternally inherited copies linked to more impaired overall level of language, ID (Kistner-Griffin et al. 2010)
WNT2, EN2 (7q31-36)	Aberrant WNT activation and dendrite growth in ASD (Kalkman 2012)	In ASD act in concert to influence language development (Lin et al. 2012)
GRIN2A (16p13.2–p13.3)	Excitatory neurotransmission (Endele et al. 2010)	Language delay in epilepsy, memory and learning, ID (Reutlinger et al. 2010)
MBD5 (2q23.1)	Transcriptional regulator	Minimal speech, seizures, repetitive behavior, ID (Williams et al. 2010), developmental epilepsy, ASD (Talkowski et al. 2011)
EPC2 (2q23.1)	Heterochromatin formation (van Bon et al. 2010)	Developmental epilepsy with affected language, ID (Williams et al. 2010)
DYRK1A (21q22)	Brain growth, development, and size (Courcet et al. 2012)	Impaired learning, delayed or absent language, ID, epilepsy (Courcet et al. 2012)
SRPX2 (Xq21.33-23)	Development of speech and language centers in the brain	Seizures and developmental verbal dyspraxia, MR (Pal 2011).
GTF2IRD1 GTF2I (7q11.23)	Transcriptional regulators (Vandeweyer et al. 2012; Howard et al. 2012)	Williams syndrome-specific cognitive and language profile, weakness in relational/conceptual language and pragmatics (Mervis and John 2010; Mervis and Velleman 2011), hesitations, repetitions and pauses (Rossi et al. 2011), reduced lexical-semantic knowledge (Purser et al. 2011) and metaphorical language comprehension (Thomas et al. 2010)
GATA3 (10p15)	Transcriptional regulator in cell differentiation	Sensorineural hearing loss, shifted speech reception threshold, disturbed speech recognition (van Looij et al. 2006), language impairment and autistic behavior in HDR syndrome (Lindstrand et al. 2012)
NRG3, BMPR1 GRID1 (10q22-23)		Speech and language developmental delays (van Bon et al. 2011)
SOX5 (12p12)	Development of the nervous system (Lamb et al. 2012)	Prominent speech delay, ID (Lamb et al. 2012), impaired nonword repetition ability and communication, deficient auditory duration discrimination involving other 12p12 gene deletions (Addis et al. 2010)
NIPA1 NIPA2 CYFIP1 TUBGCP5 (15q11.2)	Deficiency in white matter tracts connecting temporal lobe language comprehension region with frontal lobe speech-generating region (Peters et al. 2011)	Severe speech and motor delays, absent speech in Prader-Willi/Angelman syndrome, ID (Burnside et al. 2011)
UBE3A (15q11.2)	Regulation of axon guidance and proper formation of tracts (Sartori et al. 2008)	Functional candidate gene for severe speech and motor retardation and ID in Angelman syndrome (Sartori et al. 2008; Peters et al. 2011)

Table 1 continued

Gene symbol and chromosome location	Normal or aberrant CNS structural and functional associations	Associated language and cognitive features
RAI1 (17p11.2)	Neuronal differentiation (Carmona-Mora et al. 2012)	Severe expressive language impairment in Potocki–Lupski syndrome (Ercan-Sencicek et al. 2012; Yusupov et al. 2011) with neurobehavioral phenotypes (Carmona-Mora and Walz 2010)
SHANK3 (22q13.3)	Formation and functioning of synapses in developing brain (Uchino and Waga 2013)	Significant language development delay, MR in 22q13.3 (Phelan–McDermid) syndrome (Phelan and McDermid 2012; Waga et al. 2011)
PTPN11 (12q24) *SOS1* (2p21) *RAF1* (3p25)		Variations in language ability in correlation with nonverbal cognition, hearing ability, articulation, motor dexterity, and phonological memory (Pierpont et al. 2010), language delay in Noonan syndrome, ID (Ierardo et al. 2010)
BRAF (7q34) *NRAS* (1p13.2) *MAP2K1* (15q21)	Gain of function leading to perturbation of central signaling pathways	Language delay (Pierpont et al. 2010) linked to Noonan syndrome (Tartaglia et al. 2010)
MECP2 (Xq28)	Regulation of gene expression in response to synaptic signals during neuronal differentiation (Kaufmann et al. 2005), maturation of synapses and multiple brain circuits (Castro et al. 2013), homeostatic plasticity in the neocortex (Blackman et al. 2012)	Rett syndrome and associated language regression in typical and in some of the atypical cases (Guerrini and Parrini, 2012), early-onset abnormal speech-language functions with intermittent normal and abnormal verbal features including two types of vocalizations, limited phonological and lexical complexity, restricted compositional variability (Maricic et al. 2012), and impaired cortical sensory processing in Rett syndrome and ASD (Liao et al. 2012).
FMR1 (15q11-13)	Deficient connectivity between frontal and hypocampal regions affecting recall and functional memory (Wang et al. 2012)	Weaknesses across all language and literacy domains, high occurrence of repetitions (Finestack et al. 2009), morphosyntactic impairment (Estigarribia et al. 2012), linked to ASD (Tassone et al. 2012)

CI cognitive impairment, *ID* intellectual disability, *MR* mental retardation

A polymorphism study of the *FOXP2* locus that identified haplotypes within potential regulatory elements further supported such mechanisms (Ptak et al. 2009). One such example is the human-specific substitution in intron 8 of *FOXP2* that affects the binding site for transcription factor POU3F2 and that is likely to alter *FOXP2* expression (Maricic et al. 2012; Graham and Fisher 2013). Evolutionary studies of human-specific genes expressed in the brain confirmed that recently evolved genes are more likely to be expressed during early brain development and within newly evolved brain regions such as the neocortex (Zhang et al. 2011). Indeed, human brain-specific transcriptional networks proved to have a predominance of genes differentially expressed in the human frontal lobe and a significant increase in transcriptional complexity within the frontal lobe. Gene co-expression signatures related to neuronal processes identified enrichment of neuronal morphological processes and genes co-expressed with *FOXP2*. In the neocortex, an increased connectivity was noted for genes involved in neuronal process formation and structures that underlie neuronal functional activity and plasticity (Konopka et al. 2012), further supporting the view that phenotypic novelty resulted from reorganizational processes rather than individual gene functions.

A language-related consequence of cerebral regulatory and structural reorganization is reflected in the control of human vocalization. While other mammals lack such a connection, recent studies established that motor areas of the human neocortex are directly connected to brainstem motor neurons involved in laryngeal control (Fitch 2010).

Transcriptional regulatory patterns associated with language development

Among the language-associated genes, a prominent representation of transcriptional regulatory networks determine neuronal gene expression with broad downstream effects on neuronal function and impact on the development of the motor cortex, striatum, and cerebellum, and patterning circuits that serve higher cognition. Members of the Forkhead-box family (FOXP2, FOXP1, FOXG1, and FOXC1) (Fisher and Scharff 2009; Newbury and Monaco 2010; Newbury et al. 2010; Vernes et al. 2011) and their targets CNTNAP2 (Peñagarikano and Geschwind 2012)

and SRPX2 (Pal 2011) play a central role in this network. The critical role of transcriptional regulation of neuronal migration during development is also highlighted by DYX1C1 (Tammimies et al. 2012; Zhang et al. 2012) and further supported by functions of KIAA0319 (Darki et al. 2012; Scerri et al. 2011). Transcriptional regulation of cell fate and differentiation also significantly contribute to cognitive and language functions as indicated by the involvement of MBD5 (Talkowski et al. 2011), GTF21RD2 and GTF21 (Howard et al. 2012; Vandeweyer et al. 2012), GATA3 (Lindstrand et al. 2012), SOX5 (Lamb et al. 2012), WNT2 and EN2 (Kalkman 2012), and RAI1 (Carmona-Mora et al. 2012).

Signaling pathways in neurodevelopment and language

Regulatory signaling mechanisms related to language functions include DYRK1A (Courcet et al. 2012) and NRG3 (van Bon et al. 2011) in cell proliferation, survival, or apoptosis, PCDH11X/Y in cellular diversity (Crow 2002), the PTPN11/SOS1/RAF1 signaling pathway in cellular differentiation (Pierpont et al. 2010), BRAF/NRAS/MAP2K1 signaling (Tartaglia et al. 2010), and G-protein coupled signaling in neuronal maturation (SHANK3) (Uchino and Waga 2013). Aberrant signaling through these mechanisms has broad and severe neurodevelopmental consequences (microcephaly, epilepsy, schizophrenia, cerebral asymmetry, Noonan syndrome) and includes intellectual disabilities with absent language, severe language delay, semantic dementia, limited word use, or dyslexia. Estrogen signaling, including an element of estrogen biosynthesis (CYP19A1) (Anthoni et al. 2012) and a modulator of estrogen receptor signaling (DYX1C1), have both been associated with a more narrow phenotype in dyslexia (affected vocabulary, phonological processing, oral motor skills, reading, and spelling) (Paracchini et al. 2011; Zhang et al. 2012).

Genetic insight into structural elements of language

Genetic data-derived insight into major brain structures involved in language functions points to the importance of neural plasticity in cortico-basal ganglia circuits and developmental processes of the motor cortex, striatum, and cerebellum (FOXP2) (Spiteri et al. 2007, Vernes et al. 2007, 2011; Newbury et al. 2010), the gyral pattern and white matter volume in the fontal cortex (Kortum et al. 2011), and the centrally involved corpus callosum (FOXG1) (Paul 2011), proper neuron migration into the cerebral cortex (FOXC1) (Zarbalis et al. 2012), patterning of circuits in the frontal cortex that serve higher cognition (CNTNAP2) (Peñagarikano et al. 2011, Folia et al. 2011), white matter volume in the left temporo-parietal region and connecting tracks between the middle temporal gyrus and the inferior parietal lobe (DYX1C1, DCDC2, KIAA0319) (Darki et al. 2012; Pinel et al. 2012), sexual differentiation of the brain (CYP19A1) (Anthoni et al. 2012), dimorphism in cerebral asymmetry and lateralization as a requisite for symbol handling ability (PCDH11X, Y) (Crow 2002, 2010; Williams et al. 2006), midline crossing of major nerve tracts (ROBO1) (Simpson et al. 2000), white matter tracts connecting language comprehension region in the temporal lobe with speech-generating region of the frontal lobe (NIPA1, NIPA2, CYF1P1, TUBGCP5) (Peters et al. 2011), and connectivity between frontal and hypocampal regions affecting recall and working memory (FMR1) (Wang et al. 2012).

The significant contribution of synaptic networks to cognitive functions and language development and ability is emphasized by deficient FMR1-mediated regulation of genes involved in synaptic development that results in a dysregulated neurotransmitter system, delayed language, affected expressive morphosyntax, and mental retardation in Fragile X-syndrome (Wang et al. 2012; Estigarribia et al. 2012). Failure of the synaptic organizers (NRXN1, NRX2, and NLD2) to bind their post-synaptic partners leads to impaired excitatory synaptic differentiation, severe language delay, SLI, and affected cognition in ASD (Gauthier et al. 2011; Varley et al. 2011). Aberrant transport and recycling of serotonin (SLC64A) are linked to an impaired overall level of language in autism (Kistner-Griffin et al. 2010). Excitatory neurotransmission deficiency (GRIN2A, B) is involved in impaired memory and learning ability and language delay in epilepsy (Endele et al. 2010; Reutlinger et al. 2010). Alterations in glutamate receptor channel-mediated fast excitatory synaptic transmission and synaptic plasticity (GRID1) are implicated in language delay in schizophrenia (van Bon et al. 2011), and the lack of proper connections between neurotransmitter receptors and signaling (SHANK3) in language delay in 22q13.3 syndrome (Waga et al. 2011).

Multifactorial determinants and overlapping speech and language phenotypes

There is strong evidence that the neuronal architecture of the language faculty is shaped by genetically determined elements, both in language disorders and in normal variations in syntactic and semantic processing abilities (Kos et al. 2012). However, none of these genes can be assigned exclusively to language. In the case of FOXP2, for example, functions determined by numerous downstream target genes, many of which act outside the central nervous system, are unrelated to language and include expression in various epithelia (Yang et al. 2010), or involvement in N-cadherin-mediated neuroepithelial organization and

progenitor cell maintenance (Rousso et al. 2012). FOXP1 also has a general role in cell growth and differentiation and its aberrant expression contributes to the development of lymphoma, hepatocellular carcinoma, and breast cancer (Katoh et al. 2012), while *CNTNAP2* is involved in exfoliative glaucoma (Shimizu et al. 2012). In addition, the involvement of complex regulatory processes, multiple molecular mechanisms, and various structural and functional elements involved in language ability do not support the existence of a previously proposed gene, or a set of genes, specific for language (Gopnik 1990; Pinker 1999). Similarly, our genetic analysis did not provide obvious support for language-related genes, to be categorized as genes either exclusively involved in linguistic impairments, and/or genes involved in general cognitive impairments with and without affected language (Benítez-Burraco 2009, 2012; Longa 2009).

Genetic mechanisms underlying susceptibility to common neurodevelopmental and speech and language disorders involve interactions between allelic or copy number variants in various genes and environmental factors (Newbury and Monaco 2010; Addis et al. 2012). In examples, such as CAS, SLI, and dyslexia, deficiencies in multiple mechanisms converge into a distinct phenotype (multiple gene alleles-one clinical condition scenario). Conversely, risk loci confer risk across diagnostic boundaries (Talkowski et al. 2012), one gene may have pleiotropic effect such as genes for upstream regulators (*FOXP2*, *CNTNAP2*, *FOXP1*), genes involved in neuronal migration (*KIAA0319*), or in converging synaptic pathways (*NRXN1*, *SHANK2*, *CHRNA7*), that may influence multiple traits (one gene or allele-multiple phenotypes scenario). The allelic variants of these genes extend between various neurodevelopmental disorders affecting features of cognition, behavior, and language (Grayton et al. 2012; Gregor et al. 2011), and also contribute to variations in the normal population (Bishop 2010; Scerri et al. 2011; Graham and Fisher 2013). Dissecting these overall phenotypes into clinical traits or endophenotypes, together with more refined genetic analyses, may uncover the mechanistic bases for these conditions. Yet single causal mutations are unlikely in such complex genetic disorders (Addis et al. 2012).

The considerable phenotypic overlap among speech and language disorders includes diagnostic, cognitive, and etiological considerations. For example, SSD shares the greatest etiological overlap with dyslexia (Newbury and Monaco 2010). SSD, SLI, and dyslexia overlap in diagnosis, cognition, and etiology, all three disorders lack sharp dividing lines between impairment and normality and fit with the continuous liability threshold model that assumes a continuous liability distribution of multifactorial causes (genetic and/or environmental) for a disorder (Pennington and Bishop 2009).

Language and cognition: impaired developmental pathways

Some of the heritable neurodevelopmental disorders have been proposed to be conditions in which general cognitive abilities may be intact and only language is affected (such as SLI), or in which selective functional modules are impaired while others, such as language, appear normally functioning (such as Williams syndrome). Such interpretations are often viewed as evidence for either modular preservation of language or for atypical constraints on cognitive development (Brock 2007). On closer examination, however, these disorders not only have deficits in a particular functional domain, but also manifest wide-spread phenotypic changes. In SLI, generally considered as a single affected function within an otherwise normally functioning brain with intact cognition, children proved to have lower performance IQ (Botting 2005), an overall increased radiate white matter that influenced their intrahemispheric and corticocortical connections (Herbert et al. 2004), and asymmetry in their language-association cortex (De Fosse et al. 2004). In addition, the independent contributions of multiple genes and multiple gene loci (Newbury et al. 2009; Rice 2012) and the involvement of multiple pathomechanisms, some of these overlapping with dyslexia (Rice 2012), do not favor a single affected module explanation for SLI. A developmental model argues for an even higher order of complexity, that in SLI patients, lower level deficits in overall brain functions may also affect language at critical developmental stages, and furthermore, as language emerges from multiple abilities (attention sharing, speech pattern detection, phonetic and phonemic discriminations, speech processing speed), a lower level deficit in any of these attributes could contribute to the SLI language phenotype (D'Souza and Karmiloff-Smith 2011).

Williams syndrome with selective deficits in certain cognitive elements, but relatively preserved facial recognition and language, has been considered both as evidence for modular preservation of a language system with functionally distinct intact and impaired modules, and as evidence for atypical constraints of cognitive development (Brock 2007). Consistent evidence for a lack of a preserved language module and specific spatial language deficits in Williams syndrome, that mirror deficits in nonverbal spatial cognition, however, support an atypical early language acquisition (Brock 2007). The Williams language profile has also been linked to two transcriptional regulators (*GTF21RD1* and *GTF21*) (Vandeweyer et al. 2012) of which *GTF2IRD2* has a higher-level role in executive functioning (Porter et al. 2012). Extensive developmental studies have additionally revealed that of the 28 genes deleted within the critical Williams region, functional deficiencies of the 22 brain-expressed genes profoundly

affect brain development and result in atypical brain biochemistry with depressed energy metabolism and synaptic activity, aberrant neuronal density and layering, brain size and morphology, and regional and functional connectivity. Language phenotype features in Williams syndrome patients, therefore, are not indications for selectively spared domains, but rather emerge as products of neural and cognitive processes that are different from those in typically developing individuals (reviewed in (Karmiloff-Smith 2012).

Comparison of cognitive developmental trajectories and adaptive behavior in Williams and Fragile X (*FMR1*) syndrome subjects further supports atypically developing gene–brain–behavior pathways that were also specific for these genetic disorders (Fisch et al. 2012). In neurodevelopmental syndromes, age of language onset and pace of acquisition depart significantly from normal. In considering the centrality of genetic timing and the network properties of cognition, these developmental timing disruptions have been proposed not as simply delays, rather indicators of deviant and abnormal developmental schedules with deleterious phenotypic consequences (Levy and Eilam 2012).

One may argue that during atypical development with closely interacting intact and impaired functional elements, different brain structures and cognitive functions may emerge creating the potential to generate a systematically different language. A recent study addressing this hypothesis (Musolino and Landau 2012), however, has shown that subjects with Williams syndrome performed according to the same abstract principles when tested with syntactic and semantic phenomena (scope, c-command, and an understanding of De Morgan's law of propositional logic) as controls, suggesting that the knowledge of language was of the same nature in patients and control subjects. From a linguistic point of view, language development in Williams syndrome may be considered as resulting from the unimpaired working of a functional language competence or module. From a biological viewpoint, lack of a different language system does not exclude atypical developmental pathways to language that, actually, has multiple deficiencies in these subjects (Levy and Eilam 2012) and attests to the dynamic and robust nature (Jackendoff 2011) of the language acquisition process (Brock 2007).

Genetic networks and the language faculty

The nature and extent of the influence of gene function on the human faculty of language are critical constituents to the central assumptions of competing linguistic theories. One of the most influential of these theories (Chomsky 1995, 2005, 2010) has assumed an innate language faculty with strong connections to and a defining influence of neural circuitry shaped by gene functions. A single genetic event [commonly interpreted as a single mutation scenario (Jackendoff 2011)] that rewired the human brain has been proposed to create an abstract cognitive mechanism responsible for the development of language (Chomsky 2010). While it is unlikely that a single genetic change resulted in the development of language ability, a predominance of language-associated regulatory networks (Lambert et al. 2011; Ptak et al. 2009; Graham and Fisher 2013), significantly increased transcriptional complexity within the frontal lobe, and increased connectivity in the neocortex for genes that determine neuronal activity and plasticity (Konopka et al. 2012) favor the view that phenotypic novelty of both cognitive and language faculties resulted from reorganizational processes due to relatively few initial genetic events.

Within this framework a modular organization of cognitive functions was also assumed in which language constitutes its own module (Hauser et al. 2002). Earlier views of modularity (Newport 2011), largely based on functional features of adult brain structures, predicted a normal brain with specified modules and an atypical brain with a combination of intact and impaired modules. Developmental studies of heritable syndromes with altered gene functions affecting brain development from the outset challenge the existence of genetically determined, independently functioning and minimally interconnected cognitive or language modules (Karmiloff-Smith 2009). Our extensive review of heritable speech and language disorders and selected syndromes with affected language similarly revealed dynamic developmental processes and multidirectional interactions of genes, cellular mechanisms, brain structures, cognition, and language resulting in a functional organization that does not attest, from a biological standpoint, to a modular conceptualization of language. This evidence, however, does not rule out the postulation of a module from a linguistic stance formulated as a virtual functional module (Griffits 2007), or as more recently defined an idiosyncratic cognitive capacity, entity, or ability (Benítez-Burraco 2012) and conceptualized by a distinction between linguistic and biological perspectives.

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