Published in final edited form as:

Curr Opin Neurol. 2009 April ; 22(2): 126–130. doi:10.1097/WCO.0b013e3283292414.

At the height of fashion: what genetics can teach us about neurodevelopmental disabilities

Elena L. Grigorenko^{a,b}

^aYale University, New Haven, Connecticut, USA

^bMoscow State University, Moscow, Russia

Abstract

Purpose of review—The last decade has generated much interest in the genetics of developmental disorders. This interest, in part, is focused on two issues: the specificity/generality and the type/frequency of the genetic mechanisms involved.

Recent findings—First, it appears that studies are more fruitful and their results more replicable, broadly speaking, when they conceptualize disorders not holistically, as categorical units, but componentially, through various quantitative processes. Second, there have been several successful investigations of severe impairments in a number of isolated families with higher than typical frequencies of developmental disorders. Yet, it has been difficult to generalize the genetic mechanisms involved in these rare cases to the general population.

Summary—Current findings suggest the involvement of multiple genetic mechanisms in the manifestations of childhood-onset conditions. It is possible that each ‘facet’ (or component) of a disorder is controlled by a semi-independent set of genes. Numerous components appear to be deficient in more than one disorder, possibly explaining comorbidity. The genetic foundation of developmental disorders may be formed not by isolated genes, but rather by a combination of genes and the pathways that these genes regulate. These accumulating findings have direct implications for designing both diagnostic and treatment approaches to childhood-onset disorders.

Keywords

developmental disorders; general and specific; genetic mechanisms; rare and common

Introduction

The last decade of research in molecular genetics and genomics narrowed the field’s gaze on a new interest – the etiology of disorders with an onset in childhood (hereafter, neurodevelopmental disabilities or developmental disorders). Prior to the late 1990s, the overwhelming majority of publications on the etiology of neurological and psychiatric disorders focused primarily on disorders with an onset in adulthood (e.g., schizophrenia, dementia, various muscular degeneration disorders). However, a number of discoveries in the field of developmental disorders have changed the landscape of the work, such that studies of

Correspondence to Elena L. Grigorenko, Child Study Center, Yale University, 230 South Frontage Road, New Haven, CT 06519-1124, USA Tel: +1 203 737 2316; fax: +1 203 785 3002; elena.grigorenko@yale.edu .

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

early onset disorders are now as fashionable – as engaging, numerous, and influential – as studies of late-onset conditions. Recently, the field has enjoyed the spotlight due to a number of high-profile publications [1•–4•].

In this brief review, I attempt to comment on two rather central issues currently being examined in the genetic cause of developmental disorders: [1•] the specificity and generality of the genetic mechanisms involved in these disorders, and [2•] studies of common and rare genetic variants as strategies to elucidate these mechanisms. The first issue, at least partially, relates to questions of correlated symptoms within a disorder and comorbidities across different disorders. The second issue relates to questions of the homogeneity and heterogeneity of developmental disorders and, correspondingly, the generalizability of findings. Commenting on these issues, I will sample from a number of childhood-onset disorders, such as autism spectrum disorders (ASDs), disorders of spoken and written language (DSWL), and attention-deficit hyperactivity disorder (ADHD).

General or specific?

When typical development is considered, generally everything in cognition (or rather, all of its components) correlates to a certain degree; the same is true of indicators of spoken and written language functioning. A review of the psychological processes referred to as ‘deficient’ in DSWL [i.e., speech and sound disorder (SSD), specific language impairment (SLI), and developmental dyslexia] generates a relatively limited list of components that are repeatedly featured in these disorders. These processes include but are not limited to phonology, orthography, morphology, and semantics. For example, specific psychological functions such as phonological representation (i.e., a type of cognitive processing, manifested, for example, in phonological memory and captured by nonword repetition tasks) appear to be deficient in all of these disorders. Thus, questions have arisen about whether these are different disorders or variable manifestations of the same disorder, and whether these disorders have distinct or fully or partially overlapping psychological architectures. In the context of this review, the most interesting issue is whether studies of the genetic bases of these disorders and their components can clarify their behavioral and psychological framework. Three issues bear mentioning.

First, there is a substantial literature indicating componential overlap among various developmental disorders and hypothesizing that some genetic regions harbor genes that contribute to multiple disorders that share these components. Specifically, researchers have considered phenotypic and genetic overlaps between SLI and ASDs, SSD and developmental dyslexia, and ADHD and developmental dyslexia. Here, I present only select examples to illustrate the logical underpinning of this approach. The first example pertains to the comparison of holistic diagnoses, such as SLI and ASDs, which share atypicality of language development, although in very different manifestations. It has been noted in the literature that when certain language-related aspects of the autism phenotype are considered (e.g., delay in the development of phrase speech, language impairment in parents of probands, or using a quantitative trait of language functioning), the same chromosomal regions (2q, 7q, and 13q) appear to be linked to both disorders in different samples [5,6]. The second example pertains to the so-called componential processes of developmental disorders. Specifically, both patients with SSD and developmental dyslexia demonstrate deficits on tasks related to phonological processing (e.g., nonword repetition and nonword decoding). When these phenotypes are considered in a sample of probands with SSD and their relatives, four previously identified susceptibility regions for developmental dyslexia (3p12–q13, 6p22, 15q21, and 1p36) also demonstrate linkage with SSD [7,8], indicating multiple, or pleiotropic, influences of the same genes on multiple phenotypes. The third example pertains to cross-referenced phenotypes – for example, reading performance in a sample of ADHD probands and their family members

and performance on attention tasks in a sample of developmental dyslexia probands and their family members. When these strategies are implemented, there is also evidence of overlap in genetic susceptibility regions (e.g., 6p21–22 [9]). Fourth, there is an intriguing tendency for a number of genetic regions to crop up in investigations of different phenotypes. A relevant illustration is region 7q31–35, reported by a number of research groups to harbor genes for various forms of speech and language disorders and to be associated with mental retardation and autism [10]. Fifth, there are many other case examples where a chromosomal abnormality (e.g., deletion, addition, or relocation of chromosomal material) results in a number of psychological challenges, including mental retardation and language delay (e.g., 7q11, 15q11–13 [11,12]). To summarize, when different language-related phenotypes are considered within distinct developmental disorders, evidence suggests that particular regions of the human genome appear to be linked to these phenotypes no matter how the disorder is defined or through which disorders a given sample was ascertained. This notion deviates from the traditional expectation of finding specific genes for specific disorders and formulates the idea that genes might contribute to specific processes, leading to the manifestation of the corresponding phenotypic traits, which then may be shared by different disorders. Thus, the same genes may contribute to different disorders due to the overlap between these disorders' componential structures (psychological processes).

The second issue to consider comes from studies of developmental dyslexia. Today, there are six interesting candidate genes for developmental dyslexia and reading-related processes (a 15q (the number signifies the chromosome number, q signifies the long arm and p the short arm; for example, 15q is the long arm of chromosome 15) gene *DYX1C1*, two 6p genes, *KIAA0319* and *DCDC2*, a 3p gene *ROBO1*, and two 2p genes, *MRPL2* and *C2orf3* [13]), all of which are active candidates, but none of which have been either fully accepted or rejected as such. The consensus is that any association of all or some of these six genes with developmental dyslexia is probably of small magnitude. Yet, despite an inconsistent pattern of replications and nonreplications of these genes' involvement with developmental dyslexia, one remarkable feature of these genes is a certain degree of commonality, at least in broad strokes, in their functions. Four of the six genes (*DYX1C1*, *KIAA0319*, *DCDC2*, and *ROBO1*) appear to be involved in early stages of brain development. Correspondingly, it is unlikely that these genes are reading-specific; however, there are not much data on the other behavioral phenotypes these genes might be involved with (there is a published report on the lack of association between *DYX1C1* and ASDs). To summarize, developmental dyslexia-associated candidate genes appear to be involved, at least to a minor degree, with the formation of the anatomical foundation for higher cognitive functions such as reading (and possibly others).

Third, it is important to recognize the huge degree of variability in both linkage and association studies with regard to what particular phenotypes are considered [14]. Genetic studies of developmental dyslexia have benefited tremendously from cognitive models of reading and reading difficulties. These models are complex: They reference multiple psychological processes and consider dynamics of development and learning in the establishment of the brain-based systems and representations supporting reading. Not surprisingly, the pattern of results emerging from behavior-genetic and molecular-genetic studies of these models is also complex. Different componential processes show different estimates of heritability [15]. And, when considered as phenotypes in linkage and association studies, they do not show identical or even similar patterns of results. The accumulation of literature in the field of developmental disorders indicates that these observations are true not only for developmental dyslexia but also for other DSWL [16•], autism [17•], and ADHD [18•]. Although poorly understood at this point, this pattern of results cannot be explained by the existence of 'generalist' genes [19]. Although it is appealing to assume the existence of main genetic effects for holistic disorders, results of quantitative and molecular-genetic studies of psychological components of these

disorders do not permit us to default to parsimonious models of major main effects. Results repeatedly suggest both overlapping (i.e., underlying comorbidities) and unique (i.e., generating specificities) genetic influences on componential phenotypes.

Rare or common?

Another set of interesting and controversial observations arising from recent research on developmental disorders pertains to studies of rare families with a clear Mendelian transmission pattern of the affected status. The advantage of working with these families is that they, unlike studies of mixed samples from the general population, often result in the identification of the gene whose functional disruption is associated with the phenotype of interest. The disadvantage of such studies is that their generalizability to common related disorders in the general population has been rather limited. Thus, the field currently struggles with this tension between precision vs. generalizability.

A case that illustrates such tension is that of the transmission of a developmental disorder of speech and language in a large, three-generation pedigree of Pakistani origin from the United Kingdom (referred to as KE). Approximately 50% of the members of this family suffer from a severe complex disorder that distorts speech, language, and cognitive functioning, and is passed through the generations in a simple Mendelian pattern of dominant transmission (i.e., the disorder is present in each generation at a particular rate). Since the presentation of the family in the literature in the early 1990s [20], many subsequent steps have been undertaken to track the behavioral manifestation of the disorder [21], its brain correlates [22], and its genetic causes [23].

This family's phenotype is complex, with deficiencies manifesting as verbal dyspraxia (i.e., speech articulation problems) and difficulties in receptive and expressive vocabulary, morphology, and syntax. Also of note is that, in the KE family, difficulties penetrate all types of linguistic processing (i.e., oral and written language) in aspects of both reception and production. Finally, when compared with the unaffected individuals in the pedigree as a group, affected individuals are characterized by lower nonverbal IQ. However, the cognitive difficulties do not co-segregate 'true' with speech and language difficulties. Moreover, a number of deficits (e.g., cognitive deficits) are observed among unaffected individuals. This might suggest that two independent disorders are manifesting themselves in this family. Yet, there appears to be a single phenotype that best differentiates affected from unaffected individuals – individual performance on a nonword repetition task, which is a measure of phonological representation [21].

Given the dominant pattern of transmission of this complex disorder in the KE family, researchers expected that the disorder was controlled by a single major gene [24]. Through multiple steps of genetic analyses, researchers identified a probable single gene located on chromosome 7q31. Bioinformatics revealed that the gene encoded a DNA-binding motif, a three-dimensional structural element or fold within the DNA sequence – which also appears in a variety of other molecules – in the so-called forkhead/winged-helix domain [25]. Correspondingly, the gene was named *FOXP2* (forkhead box P2). This family of genes codes for proteins that specifically bind to promoter or enhancer regions of the DNA and thereby controls the transcription of other genes. When the gene was sequenced in a member of the KE family, a mutation divulging a G-to-A (histidine to arginine) nucleotide change in exon 14 of *FOXP2* was discovered. This mutation was not found in any individual of the 364 screened control individuals who had no disorders of speech and/or language, but it co-segregated perfectly with the affected status in the KE family and, thus, was recognized as the cause of the disorder being transmitted in this family [23]. Subsequent investigations of other patients with similar phenotypes revealed additional mutations in *FOXP2* that caused deficiencies in

four of these patients [26]. It was hypothesized that, like other transcription factors, the *FOXP2* protein might be important in embryogenesis, especially at the stage of brain development [24]. However, the specifics of this causal chain have yet to be determined [27,28].

The identification of *FOXP2* as a causal gene for the complex form of speech and language disorder in the KE family and four additional cases generated significant and enthusiastic interest in this gene. A number of researchers began to investigate genetic associations between *FOXP2* and different types of developmental disorders of speech and language. These investigations unfolded to include more common cases of speech and language impairments [29–31] and ASDs [29,32]. The results of these investigations have been mixed. A recent report, however, gives a hint as to why this might be the case: there is now evidence [4••] that *FOXP2* influences the expression of *CNTNAP2*, a gene that encodes a neurexin-related protein and is expressed during the development of the human cortex. Of note is that neurexin is a protein whose functions include adhesion of neurons at a synapse to ensure signal transduction/transmission. Also of note is that the genetic variation in *CNTNAP2* is associated with a more narrowly defined form of linguistic phenotype than that found in the KE family, SLI, especially through its nonword repetition facet [4••]. Yet, this evidence was received by the field with some reservation [33]; more work is needed to support this first report of the involvement of *CNTNAP2* with SLI, and to differentiate this involvement from the previously reported association of this gene with ASDs [34–36]. However, although not fully processed by the field, this work brings up three interesting observations. First, it is possible that the genetic disruptions observed in rare Mendelian families, although not generalizable to the common forms of developmental disorders, might offer insights into the pathways in which these genes are involved. Also, the variation in the gene members of these pathways might, in turn, inform our understanding of the genetic bases of common developmental disorders. Second, it is quite interesting that the reported associations are not with the holistic phenotype of SLI, but with its componential aspect, nonword repetition, the same phenotype that best differentiated affected and unaffected members of the KE family. This observation brings us back to the discussion of study outcomes and their replicability with regard to genetic studies of common disorders and common variants. The holistic-componential debate has not penetrated even the field of rare variants. Finally, of note is that the variant of the *CNTNAP2* gene that has been associated with the trait of nonword repetition is in a noncoding, intronic area of the gene [i.e., the most strongly associated single-nucleotide polymorphism (SNP) is rs17236239]. This observation is quite intriguing and draws the field away from its conventional expectation of associating functional variants with phenotypes of interest. Yet, this is not the first time the field has been taken by surprise and, thus, this finding deserves the attention of the field, even while awaiting replication.

Conclusion

Here, I comment selectively on recent publications on the genetics of neurodevelopmental disorders, focusing on two contentious issues: whether the genetic mechanisms discovered for these disorders are expected to be disorder (and even disorder-component) general or disorder-specific, and whether this set of genetic mechanisms will include mostly rare ones or few common ones. At this point, our knowledge of the genetic mechanisms involved in the manifestation of developmental disorders is far from advanced, but neither are we entirely ignorant. We know there are likely genetic factors of general and specific impact that follow a certain hierarchy: disruptions in genes of major impact are rare, lead to severe phenotypic deficiencies that are not specific, and do not seem to account for common less severe forms or disorders or for individual differences in related traits in the general population; disruptions in genes expressed early in development are infrequent, result in a jeopardized or atypically structured anatomical foundation and brain function, which are then recruited in the development of higher order psychological processes and might account for common disorders

in combination with specific environmental exposures; and variations in genes expressed later in development and throughout the life span are common, characterized by small or very small effects in isolation, and contribute to ‘orchestras’ of genetic and environmental effects forming the texture of individual differences in the general population. The challenge of the ‘next step’ is to figure out what these mechanisms actually are and how they relate to each other, and to reconstruct, using animal models and clinical illustrations, the machinery they operate.

Acknowledgments

Preparation of this article was supported in part by the following research grants from the National Institutes of Health: R01 DC007665 and PO HD052120. Grantees undertaking such projects are encouraged to express their professional judgment freely. Therefore, this article does not necessarily reflect the position or policies of the National Institutes of Health, and no official endorsement should be inferred. For further development of some of the ideas presented here, see [37,38] I am thankful to Ms Mei Tan for her editorial assistance.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

- 1••. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. *Science* 2007;316:445–449. [PubMed: 17363630] This article delivered substantial evidence on the importance of copy number variation (CNV) in ASDs, especially de-novo CNV. Of interest also is that CNV appears at higher rates among sporadic and at lower rates in familial cases of ASDs. The identified mutations were highly diverse in terms of their type, size, and placement in the genome. This de-novo CNV appears at higher rates among women than in men. A specific illustration of one of such de-novo deletion in a child with the diagnosis of Asperger syndrome involved nearly 27 genes, including the oxytocin gene *OXT*, a gene previously implicated in the regulation of social cognition.
- 2••. The Autism Genome Project (Agp) Consortium. Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, et al. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet* 2007;39:319–328. [PubMed: 17322880] This is a report on a whole-genome linkage/association study ($n = 10\,000$ SNPs) of the largest, so far, sample of multiplex families ($n = 1168$) of probands with ASDs. This report highlighted three important findings: the heterogeneity of ASDs appears to be so large that the P values for the linkage/association results even in a sample of this size are rather unimpressive; various chromosomal aberrations (copy number variation) appear to be of importance in ASDs; and linkage and copy number variation analyses implicate chromosome 11p12–p13 and neurexins, respectively, among other candidate loci.
- 3••. Morrow EM, Yoo SY, Flavell SW, et al. Identifying autism loci and genes by tracing recent shared ancestry. *Science* 2008;321:218–223. [PubMed: 18621663] This research focused on rare families from the Arabic Middle East, Turkey, and Pakistan ($n = 104$) of probands with ASDs whose parents share ancestors. Multiple and diverse loci, containing large, inherited, homozygous deletions of genetic material, were identified with regard to their putative causal link to ASDs. The largest deletions implicated genes, including *PCDH10* (protocadherin 10) and *DIA1* (deleted in autism1, or c3orf58), whose level of expression changes in response to neuronal activity, a marker of genes involved in synaptic changes that underlie learning.
- 4••. Vernes SC, Newbury DF, Abrahams BS, et al. A functional genetic link between distinct developmental language disorders. *N Engl J Med* 2008;359:2337–2345. [PubMed: 18987363] This research further unfolds the involvement of *FOXP2* in disorders of language, in this particular case, SLI. Specifically, it presents evidence that *FOXP2* influences the expression of *CNTNAP2*, a gene

that encodes a neurexin-related protein and is expressed during the development of the human cortex (see discussion of the involvement of neurexin in ASDs in [2]). Moreover, it further specifies the facet of the SLI phenotype that demonstrates genetic association with *CNTNAP2*, that is, nonword repetition.

5. Spence SJ, Cantor RM, Chung L, et al. Stratification based on language-related endophenotypes in autism: attempt to replicate reported linkage. *Am J Med Genet B Neuropsychiatr Genet* 2006;141:591–598. [PubMed: 16752361]
6. Bartlett CW, Flax JF, Logue MW, et al. Examination of potential overlap in autism and language loci on chromosomes 2, 7, and 13 in two independent samples ascertained for specific language impairment. *Hum Hered* 2004;57:10–20. [PubMed: 15133308]
7. Smith SD, Pennington BF, Boada R, Shriberg LD. Linkage of speech sound disorder to reading disability loci. *J Child Psychol Psychiatry* 2005;46:1057–1066. [PubMed: 16178929]
8. Stein CM, Schick JH, Taylor GH, et al. Pleiotropic effects of a chromosome 3 locus on speech–sound disorder and reading. *Am J Hum Genet* 2004;74:283–297. [PubMed: 14740317]
9. Willcutt EG, Pennington BF, Smith SD, et al. Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for attention-deficit/hyperactivity disorder. *Am J Med Genet* 2002;114:260–268. [PubMed: 11920845]
10. Alarcon M, Yonan AL, Gilliam TC, et al. Quantitative genome scan and Ordered-Subsets Analysis of autism endophenotypes support language QTLs. *Mol Psychiatry* 2005;10:747–757. [PubMed: 15824743]
11. Veenstra-Vanderweele J, Christian SL, Cook EHJ. Autism as a paradigmatic complex genetic disorder. *Annu Rev Genom Hum Genet* 2004;5:379–405.
12. Somerville MJ, Mervis CB, Young EJ, et al. Severe expressive-language delay related to duplication of the Williams–Beuren locus. *N Engl J Med* 2005;353:1694–1701. [PubMed: 16236740]
13. Grigorenko, EL.; Naples, AJ. The devil is in the details: decoding the genetics of reading. In: McCardle, P.; Pugh, K., editors. *Helping children learn to read: current issues and new directions in the integration of cognition, neurobiology and genetics of reading and dyslexia*. Psychological Press; New York, NY: (in press)
14. Grigorenko EL. A conservative meta-analysis of linkage and linkage-association studies of developmental dyslexia. *Sci Stud Read* 2005;9:285–316.
15. Grigorenko EL. Genetic bases of developmental dyslexia: a capsule review oheritability estimates. *Enfance* 2004;3:273–287.
- 16•. Monaco AP, The SLI Consortium (SLIC). Multivariate linkage analysis of specific language impairment (SLI). *Ann Hum Genet* 2007;71:660–673. [PubMed: 17388790] This article presents a multivariate variance-components approach to the previously published data from whole-genome scans of SLI, using the multiple correlated quantitative traits that form facets of this disorder. Two previously reported regions (16q and 19q) were confirmed and a new region on chromosome 10 was introduced. Quantitative analyses demonstrated that the effect of 16q on nonword repetition was equally as strong on reading and spelling phenotypes, whereas the effect of 19q appeared to influence a selection of expressive and receptive language phenotypes in addition to nonword repetition, but did not show linkage to literacy phenotypes. This work further emphasizes the importance of providing componential characterization of neurodevelopmental disorders while searching for their genetic bases.
- 17•. Yrigollen CM, Han SS, Kochetkova A, et al. Genes controlling affiliative behavior as candidate genes for autism. *Biol Psychiatry* 2008;63:911–916. [PubMed: 18207134] Unlike studies [1–3], where only holistic categorical definitions of ASDs were used, this article capitalizes on facets of the disorder, stressing the importance of splitting the phenotype into its components. This is a candidate-gene study, where a number of genes previously implicated in social cognition are tested for their association with various facets of ASDs. Similar to [1], the results indicate the putative involvement of variations in genes associated with oxytocin in the genetics of ASDs.
- 18•. Lasky-Su J, Anney RJ, Neale BM, et al. Genome-wide association scan of the time to onset of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* 2008;147:1355–1358. [PubMed: 18937294] Similar to [2], this work presents a large-scale linkage/association study of a neurodevelopmental disorder, ADHD. As in [2], the obtained *P* values for linkage and association analyses do not meet expectations, probably due to the genetic heterogeneity of the

sample. Once again, this article illustrates that finding quantitatively distributed aspects of a disordered phenotype (in this particular case – a time to onset) opens novel opportunities for interpreting and understanding genetic foundations of complex neurodevelopmental disorders.

19. Plomin R, Kovas Y. Generalist genes and learning disabilities. *Psychol Bull* 2005;131:592–617. [PubMed: 16060804]
20. Hurst JA, Baraitser M, Auger E, et al. An extended family with a dominantly inherited speech disorder. *Dev Med Child Neurol* 1990;32:352–355. [PubMed: 2332125]
21. Watkins KE, Dronkers NF, Vargha-Khadem F. Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain* 2002;125:452–464. [PubMed: 11872604]
22. Belton E, Salmond CH, Watkins KE, et al. Bilateral brain abnormalities associated with dominantly inherited verbal and orofacial dyspraxia. *Hum Brain Map* 2003;18:194–200.
23. Lai CS, Fisher SE, Hurst JA, et al. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 2001;413:519–523. [PubMed: 11586359]
24. Fisher SE, Lai CS, Monaco AP. Deciphering the genetic basis of speech and language disorders. *Annu Rev Neurosci* 2003;26:57–80. [PubMed: 12524432]
25. Kaufmann E, Knöchel W. Five years on the wings of fork head. *Mech Dev* 1996;57:3–20. [PubMed: 8817449]
26. MacDermot KD, Bonora E, Sykes N, et al. Identification of FOXP2 truncation as a novel cause of developmental speech and language deficits. *Am J Hum Genet* 2005;76:1074–1080. [PubMed: 15877281]
27. White SA, Fisher SE, Geschwind DH, et al. Singing mice, songbirds, and more: models for FOXP2 function and dysfunction in human speech and language. *J Neurosci* 2006;26:10376–10379. [PubMed: 17035521]
28. French CA, Groszer M, Preece C, et al. Generation of mice with a conditional Foxp2 null allele. *Genesis* 2007;45:440–446. [PubMed: 17619227]
29. Newbury DF, Bonora E, Lamb JA, et al. FOXP2 is not a major susceptibility gene for autism or specific language impairment. *Am J Hum Genet* 2002;70:1318–1327. [PubMed: 11894222]
30. Meaburn E, Dale PS, Craig IW, Plomin R. Language-impaired children: no sign of the FOXP2 mutation. *Cogn Neurosci Neuropsychol* 2002;13:1075–1077.
31. O'Brien EK, Zhang X, Nishimura C, et al. Association of Specific Language Impairment (SLI) to the region of 7q31. *Am J Hum Genet* 2003;72:1536–1543. [PubMed: 12721956]
32. Bartlett CW, Flax JF, Logue MW, et al. A major susceptibility locus for specific language impairment is located on 13q21. *Am J Hum Genet* 71:45–55. [PubMed: 12048648]
33. Stromswold K. The genetics of speech and language impairments. *N Engl J Med* 2008;359:2381–2383. [PubMed: 18987364]
34. Alarcón M, Abrahams BS, Stone JL, et al. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *Am J Hum Genet* 2008;82:150–159. [PubMed: 18179893]
35. Bakkaloglu B, O'Roak BJ, Louvi A, et al. Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. *Am J Hum Genet* 2008;82:165–173. [PubMed: 18179895]
36. Arking DE, Cutler DJ, Brune CW, et al. A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *Am J Hum Genet* 2008;82:160–164. [PubMed: 18179894]
37. Grigorenko EL. Understanding the etiology of complex traits: symbiotic relationships between psychology and genetics. *Mind Brain and Educ* 2007;4:193–199.
38. Grigorenko EL. Speaking genes or genes for speaking? Deciphering the genetics of speech and language. *J Child Psychol Psychiatry* 2009;50:116–125. [PubMed: 19220595]