Genetic Specificity of Linguistic Heritability

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TWIN STUDIES OF LANGUAGE

The logic of twin studies

The most common method used to study the role of genetic factors in development is to determine whether monozygotic (MZ) cotwins are linguistically more similar to one another than dizygotic (DZ) cotwins. Because MZ and DZ cotwins share essentially the same pre- and postnatal environment, whereas MZ cotwins share 100% of their DNA and DZ cotwins share only 50% of their DNA, if MZ cotwins are linguistically more similar than DZ cotwins, this suggests that genetic factors play a role in language. If, on the other hand, MZ cotwins are no more similar to one another than DZ cotwins, this suggests that genetic factors play a negligible role for language. Putting aside the possibility of interactions and correlations between genetic and environmental factors, the variation in linguistic abilities in a population (the phenotypic variance) is due to genetic variance plus environmental variance. Heritability is a measure of the proportion of the phenotypic variance that is due to genetic variance. In twin studies, environmental factors that

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may contribute to phenotypic variance are divided into those environmental factors that co-twins do and do not share. Shared environmental factors include the linguistic input children receive (assuming parents of twins speak the same way to both cotwins), and nonshared environmental factors include illnesses or accidents that only occur to one cotwin.

Concordance rates for language disorders

One way to determine whether MZ cotwins are linguistically more similar than DZ cotwins is to compare the MZ and DZ concordance rates for developmental language disorders. Twins are concordant for a language disorder if both cotwins are impaired, and discordant if only one cotwin is language-impaired. If the concordance rate for language disorders is significantly greater for MZ than DZ twins, this suggests that genetic factors play a role in language disorders such as dyslexia and specific language impairment (SLI). Stromswold (2001) performed meta-analyses of 10 twin studies of written or spoken language disorders. In these 10 studies, the mean proband-wise concordance rate was 80% for MZ twins and 46% for DZ twins. In all 10 studies, concordance rates were greater for MZ than DZ twin pairs, with the differences being significant in all but one study. When the twin pairs from the studies were pooled together, the overall concordance rate was significantly higher for MZ twins (80%) than DZ twins (46%). In the 5 twin studies of written language disorders, the mean concordance rate was 76% for MZ twins and 41% for DZ twins, with the overall concordance rate for MZ twins (75%) being significantly greater than for DZ twins (43%). For the 5 twin studies of spoken language disorders, the mean concordance rate was 84% for MZ twins and 52% twins, with the overall concordance rate for MZ twins (84%) being significantly greater than for DZ twins (50%). One can obtain an estimate of the role of heritable factors for a disorder by doubling the difference in MZ and DZ concordance rates for the disorder. For example, if the concordance rate for spoken language impairments is 84% for MZ twins and 50% for DZ twins, the heritability of spoken language impairments is 68%. An estimate of the role of shared environmental factors is obtained by subtracting the heritability estimate from the MZ concordance rate (84%-68% = 16%), and an estimate of the role of non-shared (twin-specific) environmental factors is obtained by subtracting the MZ concordance rate from 100 (100-84% = 16%).

Heritability estimates that are based on concordance analyses have a number of limitations. First, they are only as valid as the diagnoses given to twins. If non-impaired twins are incorrectly diagnosed as being language impaired, or if language-impaired twins fail to be diagnosed, this can dramatically affect heritability estimates. Secondly, the estimates are only as specific as the diagnoses twins receive. If (some of) the twins' linguistic impairments are secondary to non-linguistic deficits, then the

estimates obtained will not be good estimates of the heritability of linguistically-specific impairments. A third limitation of heritability estimates obtained from twin concordance analyses is that they are estimates of broad-sense heritability, and as such include the influence of gene dominance, epistasis (interactions between genes) and interactions between genes and environment.

Univariate analyses of normal twins' linguistic abilities

There are two additional drawbacks that are fairly specific to concordance-based heritability estimates. The first drawback has to do with the fact that concordance analyses take what is likely to be a continuous variable (linguistic ability) and artificially categorize people as either impaired or not impaired. Inevitably, there will be cases in which one twin scores just a few points higher than his or her cotwin, but this small difference is enough for one twin be labeled "normal" and the other impaired. The second drawback is that twin concordance studies can only be used to study the heritability of language impairments, and not the heritability of normal linguistic function. This is important because it is becoming increasingly clear that there isn't perfect overlap in heritable factors that affect language development and proficiency in people who have normal language versus impaired language (see Stromswold, 2001). In cases where the data obtained are more or less continuous (e.g., scores on language tests, age of acquisition of linguistic milestones) rather than dichotomous (presence or absence of a language disorder), one can address both of these drawback by comparing the similarity of normal MZ and DZ cotwins' language scores.

In univariate analyses, a twin's performance on test A is compared with his cotwin's performance on that same test. In meta-analyses of 8 studies of typically-developing twins' vocabulary development, Stromswold (2001) found that the mean weighted correlation coefficient was .93 for MZ twins (as compared to .76 for DZ twins). For phonemic awareness, the MZ correlation coefficient was .90 (compared to .56 for DZ twins). For articulation, the correlation coefficient was .92 for MZ twins and .85 for DZ twins. For reading, the coefficient for MZ twins was .86 (as compared to .66 for DZ twins). For spelling, the coefficient was .78 for MZ twins (as compared to .48 for DZ twins). Stromswold (2001) reported the results of 12 twin studies in which 36 tests of morphosyntax were administered. Unfortunately, the variability among these tests precluded calculating mean correlation coefficients. However, it is worth noting that in 33 of the 36 tests, the MZ correlation coefficient was larger than the DZ twins, with the difference being significant for 12 of the 36 morphosyntactic tests. Falconer's (1960) estimate of the effect of heritable factors is calculated by doubling the difference between the MZ and DZ intra-twin correlation coefficients. The role of shared environmental factors is computed by subtracting

Falconer's heritability estimate from the MZ correlation coefficient and the role of non-shared environmental factors is calculated by subtracting the MZ correlation from one. We can use these formulas to estimate, for example, that 68% of phonemic awareness is due to heritable factors, 22% is due to shared environmental factors, and 10% is due to nonshared environmental factors.

Univariate analyses clearly reveal that for a wide range of linguistic tasks, normal MZ cotwins perform more similarly to one another than DZ cotwins do. This suggests that heritable factors play a substantial role in the linguistic abilities of normal people. However, like heritability estimates based on twin concordancy, Falconer's heritability estimates are estimates of broad sense heritability. A second limitation of univariate twin analyses is that they do not allow one to tell whether the heritable factors that affect language are specific to language. It is possible, for example, that the heritable factors that affect phonemic awareness also influence other cognitive, linguistic or motor abilities.

Multivariate analyses of normal twins' linguistic abilities

Bivariate analyses can help determine how specific-to-language the genetic factors that influence language are.[1] In bivariate analyses, a twin's performance on test A is compared with his cotwin's performance on test B. Genetic influence on the phenotypic correlation between test A and B (bivariate heritability) is estimated by the extent to which the MZ cross-twin correlation is greater than the DZ cross-twin correlation. In contrast, the genetic correlation estimates the extent to which the same genetic factors affect A and B regardless of their contribution to the correlation between A and B. Genetic correlation may be high, yet bivariate heritability low and vice versa. For example, genetic factors might play a substantial role for both gross motor abilities and linguistic abilities, but if completely different genetic factors are responsible for gross motor and linguistic abilities, the genetic correlation will be zero. Conversely, genetic factors might play only a modest role for gross motor and linguistic abilities, but if the same genetic factors are responsible for both abilities, the genetic correlation will be high. One limitation of multivariate analyses is that they only allow one to determine the extent to which there is genetic overlap for the particular behavioral traits one has assessed. For example, researchers involved in the U.K Twins Early Development Study (TEDS) have used multivariate analyses to determine the specificity of genes that affect verbal and nonverbal abilities. In addition to heritable factors that influence both nonverbal

[1] Using Cholesky decomposition modeling, bivariate analyses can be extended to investigate relationships among more than two variables (see de Jong, 1999).

cognitive abilities and verbal abilities, there appear to be genetic factors that influence verbal abilities but not nonverbal cognitive abilities (e.g., Price et al., 2000). It is possible, however, that these latter genetic factors affect more than just verbal abilities. For example, genetic factors that affect verbal abilities but not nonverbal cognitive abilities could nonetheless affect oral motor abilities, fine motor abilities, gross motor abilities, social-emotional abilities, short term memory, attention, auditory processing, etc.. The only way to rule this out is to assess all of these abilities in the same group of subjects, and perform the appropriate analyses. Unfortunately, in order to have the statistical power to do so, one must have data from a very large number of twins. We have begun such a twin study and, as of December 2003, we have assessed the gross motor, fine motor, oral-motor, cognitive, personal-social, and linguistic abilities of 400 sets of twins (Stromswold, 2003).

A second limitation is that the estimates of the genetic correlation for two behavioral traits are only as good as the behavioral tests used to assess the two traits. For example, analyses of the TEDS data suggest that the same genes affect vocabulary development and syntactic development, and that no vocabulary- or syntax-specific genetic factors exist (Dale, Dionne, Eley, & Plomin, 2000). However, this might reflect limitations in the way syntax and vocabulary development were assessed. In the TEDS study, parents assessed their twins' vocabularies by indicating whether they said each of 100 words. Parents then assessed their twins' syntax by choosing which sentence in 12 pairs of sentences (e.g. baby crying, baby is crying) sounded more like something that their twins might say. It seems plausible that, during the early stages of language learning, parents are fairly good at recalling whether their child says particular words and, hence, that the TEDS vocabulary measure is probably adequate. The same is not necessarily true of the TEDS syntax measure. It is very unlikely that a child has said the exact sentences listed, so to complete the syntax measure, parents must act as amateur developmental linguists. Furthermore, parents complete the syntax section immediately after completing the vocabulary checklist. Therefore, one worry is that parents who check off lots of words on the vocabulary test might (unconsciously) be biased to choose the "better" of the sentences in each pair, whereas parents who check off few words might be biased to choose the "worse" sentence in each pair, and this bias accounts for the high genetic correlation for vocabulary and syntax. In our ongoing twin study (Stromswold, 2003), we address this problem by supplementing parents' reports of when their twins acquired linguistic milestones (babbling, first word, first sentence, and clear articulation) and whether (and how much) written and spoken language therapy their twins received, with direct assessment of key linguistic skills (Stromswold, 2002). For example, articulation is assessed via a word repetition task, lexical access is assessed via a rapid naming task, and syntax is assessed via a picture-pointing comprehension test of

semantically reversible sentences. (A sample test may be found at: http://ruccs.rutgers.edu/~karin/PERINATAL/PALS/PAL4.pdf)

The role of environment on language development

Twin studies are usually used to explore whether genetic factors affect a phenotypic trait, but it is equally valid to use twin studies to examine how environmental factors influence a trait. A limitation shared by concordance, univariate, and multivariate twin studies, however, is that estimates of the phenotypic effects of shared and non-shared environment completely conflate the effects of prenatal and postnatal environment. Seventy years of research has confirmed that even when impaired twins are excluded, twins' language development is 2 to 3 months delayed compared to singletons (see Dale et al., 2000). This delay is believed to reflect the special environmental hardships twins face. The (often unspoken) assumption in most twin studies is that when one refers to the role of environmental factors in language development, one is referring to the role of postnatal factors such as the quantity or quality of adult linguistic input that children receive. Indeed, several studies have shown that twins typically receive less adult linguistic input than singletons (for a review, see, Reznick, 1997; Stromswold, 2001).

Conway et al. (1980) found that maternal speech variables (amount of maternal speech, amount of maternal child-directed speech, and complexity of maternal speech) accounted for 15% of the variance in twins' language development, whereas neonatal variables (Apgar scores,[2] gestational age, and birth weight) accounted for 8% of the variance. These results are often cited as proof that postnatal factors affect language development much more than prenatal factors. However, Conway et al.'s (1980) findings should be viewed with great caution for several reasons. First, the study had only 24 twins. Second, the twins had atypically benign perinatal histories (they were born an average of 2 weeks later and 400 grams heavier than the mean for U.S.-born twins). Third, there was considerably less variance for neonatal variables than maternal variables, and this may have decreased the predictive power of

[2] Apgar scores are commonly used to rate the physical well-being of neonates on a 0 to 10 scale, with 10 being the best score possible. Five physical parameters are given a score of 0, 1, or 2, and these subscores are summed to give a neonate's Apgar score. The word 'Apgar' is both an eponymic tribute to its inventor (Virginia Apgar) and a mnemonic for the five parameters that are assessed (Appearance or color, Pulse rate, Grimace or reflex irritability, Activity or muscle tone, and Respiration). Some studies have shown that low scores (e.g., 5 minute Apgar scores of less than 7) are associated with neurodevelopmental delay (Thorngren-Jerneck & Herbst, 2001) and linguistic delay (Cusson, 2003).

the neonatal variables. Fourth, because the study didn't distinguish between MZ and DZ twins, and twin and singleton data were collapsed in the regression analyses, these data cannot be used to evaluate the relative importance of neonatal versus maternal variables on twins' language. There is another reason to suspect that postnatal environment may not play a major role in language development. If postnatal environment *did* play a major role, we would expect that twins who are reared apart would have less similar linguistic abilities than twins reared together. Contrary to this prediction, Pedersen et al. (1994) found that the heritability estimates for vocabulary size were quite similar for elderly twins who were reared together or apart.

The effects of perinatal environment

For over 50 years, researchers have known that twins suffer from more pre- and perinatal complications than singletons, and MZ are at greater risk for many of these complications than DZ twins (for a historical perspective, see Lenneberg, 1967). Twins are 5 time more likely to be born prematurely (before 37 weeks gestation) and 10 times more likely to be born at low birth weights (less than 2500 grams) than singletons (Center for Disease Control, 1999), both of which are major risk factors for language impairments. Furthermore, twins (especially MZ twins) are more likely to suffer perinatal complications such as hypoxic/ischemic brain injuries, fetal growth restriction, prolonged labor, umbilical cord incidents, and hyperbilirubinemia. The special perinatal environmental factors associated with twinning result in perinatal mortality rates for twins who share a placenta being twice as great as for twins who do not share a placenta[3] and 4 times as high as for singletons; congenital malformations being more common in twins (particularly MZ twins) than singletons; discordance for congenital malformations being more common in MZ twins than DZ twins; and neurodevelopmental disabilities being more common in twins than singletons, with certain disabilities (e.g., cerebral palsy) being more common in MZ twins than DZ twins. (For a discussion of perinatal risk factors associated with twinning, see Stromswold, 2004 and references therein.)

There are at least two reasons why children who experience perinatal hardships may be more likely to exhibit language delays than children who don't experience these hardships. The first reason is that, because language is one of the most complicated tasks that children must master, children with subtle (but non-specific) neurodevelopmental dysfunction are likely to exhibit language delays. The second reason is

[3] DZ twins never share a placenta, whereas 75-80% of MZ twins do share a placenta (see Stromswold, 2004).

that the neural substrates of language may be particularly vulnerable to the effects of these perinatal hardships. Consider, for example, the effects of excess bilirubin. Excess bilirubin causes neonatal jaundice and, in severe cases, can lead to bilirubin encephalopathy in which cerebral grey matter is destroyed (Volpe, 1995). Although hyperbilirubinemia can affect any part of the central nervous system, the auditory pathways are particularly sensitive to the effects of bilirubin (e.g., Shapiro, 2002), and even modestly elevated bilirubin in the neonatal period is associated with mild sensorineural hearing loss and auditory dysfunction (e.g., Amin et al., 2001). Recent studies suggest that children with minimal hearing losses (hearing thresholds of between 16 and 25 dBs) are more likely to suffer from language delays and impairment than children with normal hearing (e.g., Bess, Dodd-Murphy, & Parker, 1998). This is important for genetic studies of SLI because the hearing thresholds generally used to ensure that hearing impaired children aren't labeled SLI would miss some children with minimal hearing losses (see Stromswold, 1997).

Teasing apart the effects of pre- and post-natal environments

Birth weight discrepancies in twin pairs may provide a way of teasing apart the effects of prenatal and postnatal environment. Here's why. Because DZ twins share only 50% of their DNA, birth weight differences in DZ twin pairs reflect differences in the genetic endowment of twin pairs (one twin might be genetically predisposed to be bigger than his cotwin) *and* differences in the prenatal environment. In contrast, because MZ twins share 100% of their DNA, differences in MZ twin pairs' birth weights *solely* reflect differences in the cotwins' prenatal environments. By comparing MZ cotwins who have very similar birth weights with MZ cotwins who have very dissimilar birth weights (i.e., birthweights that differ by at least 15 or 20%, Charlemaine et al., 2000), we can obtain an estimate of the effect of intrauterine environment on later development. To the extent that MZ cotwins who have very similar birth weights are linguistically more similar to one another than MZ cotwins who have very different birth weights, this is a measure of the effect of intrauterine environment on language development. Estimates of the effect of intrauterine environment can be calculated using slight variants of the methods traditionally used to calculated heritability estimates. However, instead of contrasting the linguistic similarity of MZ and DZ cotwins, we compare the linguistic similarity of MZ cotwins who have similar and dissimilar birth weights. The size of interactions between genetic and intrauterine environmental factors can be estimated by comparing how great an effect having very different birth weights has for MZ and DZ cotwins (in essence calculating a difference of a difference score).

The best biologic predictors of developmental delays in prematurely-born and intrauterine growth restricted children are

hypoxic-ischemic perinatal brain injuries and subnormal brain growth (see Berg, 1989 and references therein). Brain growth is typically spared in intrauterine growth restriction, but when this protective mechanism fails, the risk of neurodevelopmental delay is high (Kramer et al., 1989). This is especially true when head size (a proxy for brain growth) fails to normalize during infancy and childhood (e.g., Hack et al., 1991). Neonatologists and pediatricians routinely record infants' head circumferences, and it is trivial to obtain this measurement on older children and adults. Therefore, one could investigate the role of perinatal brain injuries on linguistic abilities by testing whether discrepancy in head circumference in MZ cotwins is associated with linguistic discordance in these twins. Because there are well-normed growth curves for head circumference, one could also test whether MZ twins whose head circumferences are persistently discrepant are more likely to be linguistically discordant than MZ twins whose head circumferences become more similar with time. Following the logic outlined for birth weight discrepancy, size of interactions between genetics and intrauterine factors can be estimated by comparing how having very different head sizes affects linguistic similarity in MZ and DZ cotwins. Neonatal neural ultrasounds are routinely obtained on neonates admitted to neonatal intensive care units. Neural ultrasounds are used primarily to detect and determine the severity of intraventricular hemorrhages (IVHs). One can easily tell whether (and how severe) an IVH a neonate has suffered for each side of the brain. Therefore, another way to investigate the extent to which perinatal brain injuries affect language development is to compare the linguistic abilities of MZ cotwins who are concordant or discordant for IVHs.

Mothers are usually able to recall the complications and interventions that occur during labor and delivery. For example, over 90% of the mothers of twins in our study are able to report whether each of their twins was breech, how long they were in labor, what drugs they received during labor, how much time passed between the delivery of the first twin and the second twin, whether forceps or vacuum extraction was used for each twin, and whether there were any cord complications (Stromswold, 2003). These data could easily be used to estimate the impact of intrapartum complications on language development in twins.

Interactions among genetic and environmental factors

Prenatal factors might affect twins differentially according to their genetic make up. A relatively minor ischemic injury to brain areas involved in language or a mild sensorineural hearing loss might have devastating effects on a twin genetically at risk for language impairments, yet have no discernible adverse affect on a twin who is not genetically at risk. Postnatal environmental factors could also have different effects on different people depending on their genetic makeup.

A child who is genetically at risk for developing language disorders may be particularly sensitive to subtly impoverished linguistic environments. Because the genetically-at-risk child is likely to have relatives who are language impaired, he is likely to be reared in linguistically impoverished environments. A child who is linguistically less adept (for genetic and/or environment reasons) may respond less to linguistic input. His parents might unconsciously respond by providing less (or less complex) linguistic input, which might further impede his language acquisition. The less linguistically-adept child might unconsciously avoid linguistically challenging situations, choosing instead activities and friends that make fewer linguistic demands of him, thereby further slowing his language development. At the other end of the spectrum, if there are synergistic interactions between genetic and postnatal environmental factors, a child who has the genetic propensity to succeed at language might benefit more from enriched environments (and better tolerate impoverished environments). Because a genetically well-endowed child is more likely to have relatives who are linguistically able, he is more likely to be reared in linguistically enriched environments. In addition, such a child might seek out environments that are linguistically challenging, thereby further accelerating his language development. Genetic-postnatal environmental interactions do not necessarily have to involve psycho-social environmental factors. A child who is genetically at risk for language delay may be more susceptible to the adverse effects of malnutrition, environmental toxins, or postnatal head injury, whereas a child who is not genetically at-risk may be more resilient to the effects of such insults.

Prenatal and postnatal environmental factors may be correlated (e.g., pre- and post-natal malnutrition in poor families) or interact with one other. For example, as mentioned above, children with mild hearing losses due to perinatal factors may seek out linguistically less challenging environments and/or receive less linguistic input either because they cannot hear what is said to them or their parents limit what they say to their child (Nelson & Soli, 2000). In addition, children with mild hearing losses may be more susceptible to the effects of slightly impoverished linguistic input (prenatal-postnatal interaction).

Gene-gene interactions could also be phenotypically important for language. Bivariate analyses of the data from 1937 same-sex TEDS twin pairs at age 2 reveals that only 21% of the variance in expressive vocabulary size can be explained by scores on a parent-administered nonverbal cognitive test, and the genetic correlation between nonverbal and expressive vocabulary measures is only .30 (Price et al., 2000). At age 4, one-sixth of the TEDS twins were tested on a battery of language and nonverbal cognitive tests. Bivariate analyses of these data reveal a genetic correlation of .46 for language and nonverbal abilities (Colledge et al., 2002). Taken together, these results suggest that, as children get older, the overlap in genetic factors affecting language and nonverbal

abilities becomes more apparent. This increase could reflect the impact of gene-gene or gene-environment interactions.

MOLECULAR GENETIC STUDIES OF LANGUAGE

The logic of molecular genetic studies

In most molecular genetic studies of language, parametric and nonparametric linkage analysis techniques are used to compare the genomes of language-impaired people and their normal relatives, and determine how the genomes of affected people differ from those of unaffected relatives. This is usually done by finding large multiplex families (multi-generational families in which several family members suffer from the same disorder, and this disorder appears to have simple Mendelian transmission) and comparing the DNA of affected and unaffected family members. In parametric linkage analyses, the transmission of marker alleles through multiple generations is compared with the transmission of the trait phenotype to determine whether the marker locus and trait locus assort independently, or whether they show decreased recombination (which would indicate that the two loci are near each other on the same chromosome).

Because language-disordered multiplex families are rare (Stromswold, 1998), geneticists also compare the DNA of sibling pairs in which one sibling is affected and the other is unaffected. In non-parametric sibling-pair analyses, the proportion of marker alleles that are identical in pairs of siblings is compared with the phenotypic similarity between the siblings. For example, siblings share 0, 1, or 2 alleles at a particular locus. If the trait locus is closely linked to a marker allele, similarity between the siblings for the marker alleles should correspond to similarity for the trait phenotype, regardless of mode of transmission or penetrance for the disorder.[4] Sibling-pair linkage analyses have several possible advantages over multiplex family analyses. First, because sibling-pair analyses are usually nonparametric, they are more likely to reveal associations, particularly with traits with variable expressivity. Second, one does not need to specify the mode of transmission in sibling-pair analyses. Third, sibling-pair analyses can reveal linkage even when penetrance is incomplete. Fourth, because it is easier to locate affected-unaffected sibling pairs than multiplex families,

[4] Mode of transmission refers to the way in which a genetic disorder is passed from one generation to the next (e.g., autosomal dominant, autosomal recessive, X-linked recessive, multifactorial-polygenic). Penetrance is the fraction of individuals with a given genotype who exhibit the disorder.

the sample size (and statistical power) is likely to be greater for sibling-pair than multiplex family analyses. Fifth, because most cases of developmental language disorders do not appear to follow simple Mendelian transmission patterns (Stromswold, 1998), linkage analyses conducted on multiplex families may implicate genes that *can* cause language disorders but rarely do (Stromswold, 2001). This appears to be the case for the FOXP2 gene, the mutation of which is clearly associated with speech dyspraxia (and a myriad of other disorders) in the members of the KE family (Lai et al., 2001). In 4 large studies of people with spoken language impairments (Bartlett et al., 2002; Meaburn, Dale, Craig, & Plomin, 2002; Newbury et al., 2002; O'Brien et al., 2003), the FOXP2 mutation has not been found in a single language impaired person.

Written language impairment loci

To date, at least 8 loci (1p34-36, 2p15-16, 3p12-q13, 6p21.3, 6q12-13, 11p15.5, 15q21, and 18p11.2) and possibly 9 (7q32, Kaminen et al., 2003) have been linked to written language disorders (for a review, see Fisher & DeFries, 2002; Stromswold, 2001).[5] Recently, Taipale et al. (2003) have identified a candidate gene for dyslexia at the 15q21 locus. If genes at all of these loci can cause dyslexia, what does this say about the genetic specificity of dyslexia? One possibility is that the different dyslexia loci contain genes that affect different aspects or component skills of reading. For example, Grigorenko (2001) has argued that the 15q21 locus is associated with orthographically-based (or surface) dyslexia and the 6p21 locus is associated with phonologically-based dyslexia. This association has not generally been found and, at this point, the preponderance of the evidence does not suggest that there is a simple relationship between dyslexia loci and subcomponents of reading (see Fisher & DeFries, 2002; Stromswold, 2001). The specificity of putative dyslexia loci is further undermined by the observation that *most* of these loci are also linked to other neuropsychological disorders.[6] The 2p15 dyslexia locus is also (weakly) linked to schizophrenia (Shaw et al., 1998), the 6p21 locus is also linked to attention deficit-hyperactivity disorder (ADHD) and schizophrenia (see references in Stromswold, 2001), the 6q13 locus is also linked to schizophrenia (e.g., Cao et al., 1997; Straub et al., 2002), the 7q32 locus is also linked to autism (see Bonora et al., 2002; Collaborative

[5] Humans have 22 pairs of autosomal and 2 sex (X, Y) chromosomes. Autosomal chromosomes are numbered from 1 to 22 by size, with 1 being the largest. Each chromosome has an asymmetrically placed constriction that is used to define a short arm (p) and a long arm (q) of the chromosome. Thus, for example, 15q21 refers to staining band 21 on the long arm of chromosome 15.

[6] Because loci encompass thousands of genes, the overlap in loci for language disorders and other neurodevelopmental disorders could merely be coincidental.

Linkage Study of Autism, 2001 and references therein), the 11p11.5 locus is also linked to ADHD (see Langle et al., 2004 and references therein); bipolar disorder (see Zandi et al., 2003 and references therein) and autism (Trottier, Srivastava, & Walke, 1999); the 15q21 locus is also linked to ADHD (Bakker et al., 2003), and the 18p11 locus is also linked to bipolar disorder and schizophrenia (Kikuchi et al., 2003; Reyes et al., 2002).

Spoken language impairment loci

At least 6 loci or genes have been linked to spoken language impairments: the FOXP2 gene on 7q31 (Lai et al., 2001), a region near the CFTR gene at 7q31 (Bartlett et al., 2004; O'Brien et al., 2003), a region near D7S3052 at 7q31 (Bartlett et al., 2004; O'Brien et al., 2003), 13q21[7] (Bartlett et al., 2004; Bartlett et al., 2002), a locus at 16q24 (SLI Consortium, 2002), and a locus at 19q13 (SLI Consortium, 2002). There are also some data that suggest spoken language impairment loci at 2p22 (Bartlett et al., 2004; Bartlett et al., 2002) and at 1p36, 2p15, 6p21, and 15q21 (Bartlett et al., 2000), and there are case reports of mutations associated with spoken language impairments that implicate loci at 15q13, 1p22 and/or 2q31 (see Stromswold, 2001 and references therein). As is the case with dyslexia loci, many of the spoken language impairment loci are also linked to other neurodevelopmental disorders. The D7S3052 loci on 7q31 is near the IMMP2L gene that has been implicated in Tourette syndrome (Petek et al., 2001). The CFTR region of 7q31 has been implicated in autism (Wassink et al., 2001), as have the loci at 13q21 (Collaborative Linkage Study of Autism, 2001) and 19q13 (Liu et al., 2001). Furthermore, although the FOXP2 mutation segregates perfectly with affectedness in the KE family, it is unclear how phenotypically specific the effects of the mutation are as affected family members suffer from grammatical deficits, speech dyspraxia (difficulty making the complex, oral motor movements necessary for speech), depressed nonverbal IQ, and developmental learning disorders that do not appear to be verbal in nature (see Stromswold, 2001 and references therein).

Problems associated with genotype-phenotype mapping

Phenocopy is the term used to describe the situation when different genotypes can result in the same phenotype. The fact that 9 distinct loci have been linked to dyslexia and a dozen loci have been linked to spoken language impairments clearly indicates that different genotypes can

[7] Fisher et al. (2003) have argued that the 13q21 locus might be better characterized as a dyslexia locus because the phenotype that links to 13q21 is reading impairment and not spoken language impairment.

cause at least broadly-defined phenotypes such as written and spoken language impairments. Even rather specific language impairment phenotypes may have different causes, and hence may be due to different genotypes. Consider a phenotype that is characterized by the selective omission of grammatical morphemes. This phenotype could be the result of a genetic disorder that selectively impairs syntax, a genetic disorder that specifically impairs control of rapid, complex oral motor movements necessary for language (speech dyspraxia), a genetic disorder that specifically impacts some component of auditory processing (e.g., auditory short term memory, auditory sequencing, rapid auditory processing), or a genetic disorder that affects multiple aspects of language but not nonverbal cognition (see Stromswold, 1997).

Pleiotropy is the term that is used when the same genotype results in different phenotypes. A particularly clear example of pleiotropy is incomplete penetrance, when family members share a mutation for a disorder, but only some of these family members are clinically affected. Another type of pleiotropy is when all family members who have a mutation are affected, but the nature of the disorder varies among family members. Consider again a genetic mutation that affects people's abilities to coordinate complex oral motor movements (oral motor apraxia). A person with such a genotype could present as someone who is unwilling or unable to speak in any situation (mutism) or in selective situations (selective mutism), as someone with speech dyspraxia, as someone who has a dysfluency or stutter, or as someone who omits phonologically unstressed elements (i.e., grammatical morphemes) and, hence, appears to have a grammatical deficit.

In addition to dealing with the problems of phenocopy and pleiotropy, geneticists must grapple with the problem that a genotype may be expressed phenotypically in different ways at different points of development. Returning again to the oral motor apraxia mutation, an infant with such a mutation might have difficulty coordinating suck and swallow, and might present as having a feeding disorder or failing to grow adequately. As a toddler, the child might have outgrown his feeding disorder, but be unwilling to speak. By the time he is school-aged, he might speak but selectively omit phonologically unstressed eliments. As an adult, his impairment might not be readily apparent, but he might nonetheless avoid linguistically-taxing social or professional settings, and hence might seem shy. In a similar fashion, a child who starts out with a fairly language-specific deficit might over time begin to show additional secondary deficits. For example, because he has difficulty understanding what is said to him, he might appear to have attention deficit disorder. Eventually, the child's difficulty understanding spoken language is likely to result in poor school performance, and perhaps even lowered nonverbal IQ.

FUTURE DIRECTIONS

Over 20 years ago, Ludlow and Cooper (1983) edited a volume entitled "Genetic Aspects of Speech and Language Disorders". Thirteen years later, Rice (1996) chose the somewhat more cautious title "Towards a genetics of language" for her edited volume on the genetics of language. Despite an explosion of knowledge in the 8 years since Rice published her book, we are still moving towards an understanding of how genetic and environmental factors working together allow us to acquire and use language. How can we increase the rate of progress toward greater understanding of the genetic and environmental bases of language?

One way to simplify the task of identifying loci and genes that affect language is by analyzing the DNA of MZ and DZ twins. We can perform fine-grained molecular genetic analyses to determine whether linguistically discordant MZ twin pairs differ more genetically (e.g., in terms of frequency of spontaneous mutations) or epigenetically (e.g., in terms of methylation patterns) than linguistically concordant MZ twin pairs. We can also perform linkage analyses of DZ twins. Although DZ twins are, on average, no more genetically similar than full siblings, linkage analyses of twins are more likely to be fruitful than linkage analyses of siblings for several reasons. First, the environments of DZ twins are almost certainly more similar than the environments of nontwin siblings. Thus, environmental differences between DZ twins are less likely to obscure the effects of genetic factors. Second, because DZ cotwins are the same age, the same tests and measures can be used to evaluate their linguistic function, thus eliminating a huge source of noise in linkage analyses. Third, the concern that the language-disordered genotype may be expressed differently at different ages (the developmental problem) does not apply.

We can use data from twins to simplify the task of identifying which prenatal and postnatal factors affect language development (either acting alone or in concert with genetic factors). We can explore the effects of pre- and perinatal environmental factors by measuring the linguistic similarity of MZ cotwins and DZ cotwins that are concordant and discordant for birth weight, head circumference, brain injuries and intrapartum complications. Similarly, we can explore the impact of postnatal environmental factors on language by measuring the linguistic similarity of MZ and DZ cotwins that have been exposed to different biological (e.g., head injuries, neurological illnesses, neurotoxins), psychosocial, or linguistic environments.

Recently Becker (2004) proposed the Common Variant/ Multiple Disease (CV/MD) hypothesis to account for pleiotropy and phenocopy in autoimmune disorders, metabolic disorders (type 2 diabetes and obesity) and schizoid disorders (schizophrenia and bipolar disorders), According to the CV/MD hypothesis, common alleles that contribute to a particular disease under particular genetic and environmental conditions

may result in a different disease under other genetic and environmental conditions. For a group of related disorders (e.g., autoimmune disorders such as thyroiditis, systemic lupus erythematosus, and multiple sclerosis), there are some genetic and environmental factors that are unique to a particular disease and other genetic and environmental factors that are shared by several diseases. The CV/MD hypothesis could explain why *most* of the loci that have been linked to written and spoken language disorders have also been linked to other neurodevelopmental disorders, why most cases of familial language disorders do not have simple Mendelian patterns of transmission, why different people with the same genetic mutation have different clinical pictures, and why linkage analyses of people with familial language disorders often fail to identify susceptibility loci, including loci that have been previously identified. By adopting the CV/MD hypothesis that developmental language disorders belong to a larger class of neurodevelopmental disorders, we will have a framework in which we can better explore, understand, and explain how genetic and environmental factors affect language.

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