Disorders that disrupt the development of speech, language, or reading have substantial effects on social function. Researchers have implicated specific genetic variants in monogenic speech disorder, common language impairments, and dyslexia. With the report by Kang and colleagues in this issue of the Journal, stuttering joins the fray.

Stuttering is a disorder in which speech fluency can be severely compromised. It is characterized by the involuntary repetition or prolongation of sounds, syllables, words, or phrases, as well as frequent pauses, impeding the rhythmic flow of speech. Onset is typically between 3 and 6 years of age, and approximately 5% of preschool children are affected. The majority of young children who stutter go on to make a full recovery. For a considerable number, however, the disorder continues unabated, resulting in a prevalence of about 1% among adults.

The primary causes of stuttering and the high rates of spontaneous recovery, as well as the etiologic distinctions between persistent and resolved forms, have resisted explanation. Familial clustering is extensively documented, and twin studies carried out in different countries and cultures show a high degree of heritability. Nevertheless, it is clear that genetic susceptibility to stuttering is complex, multifactorial, and heterogeneous. Genomewide scans have yielded suggestive evidence of linkage at multiple chromosomal sites, with little overlap among independent data sets. A rare example of significant linkage (with a locus on chromosome 12q) was found in a study of stuttering in 46 consanguineous families from Pakistan.

Kang and colleagues now describe an elegant follow-up to this familial study and conclude that persistent stuttering, at least in a subgroup of affected subjects, may be related to disturbances in a metabolic pathway. In pursuing the chromosome 12 locus, they focused on Family PKST72, the largest family described in their earlier report, and expanded their study by recruiting additional relatives and performing new linkage analyses. They carried out a search for mutations across the interval with strongest linkage, sequencing promoters, exons, and untranslated regions of 45 genes in several affected persons, including three members of Family PKST72. They zeroed in on a single nucleotide change (G3598A) in the GNPTAB gene, which encodes both alpha and beta subunits of GlcNAc-phosphotransferase (GNPT). This variant predicts the substitution of lysine at a glutamic acid residue, which is conserved across species, and showed the clearest evidence of cosegregation with stuttering in Family PKST72. The investigators went on to sequence GNPTAB in 123 unrelated Pakistani subjects who stuttered (one from each family that had been included in the previous study, together with newly ascertained singletons), and they identified 5 additional people who were heterozygous or homozygous for G3598A. In 96 matched Pakistani control subjects, only one person carried this variant. Kang and colleagues also found G3598A alleles in one person of Asian Indian ancestry from a panel of 270 North American and British people who stuttered but not in 276 North American control subjects. Furthermore, the screening uncovered three additional putative mutations that were present in four unrelated Pakistani and North American subjects who stuttered, but were absent in the control subjects.

The authors went on to sequence GNPTG,
which encodes the gamma subunit of GNPT, as well as NAGPA, which encodes another enzyme acting in the same pathway. They identified several different potential mutations in the affected persons from North America (three GNPTG variants, found in four unrelated cases, and three NAGPA variants, found in six unrelated cases). They did not observe these mutations in the affected Pakistani subjects or in either control group.

This work illustrates how studying large families with many affected relatives can shed light on the molecular cause of a disorder. Most support for the chromosome 12 linkage came from a single family, PKST72. It was the discovery of the G3598A variant in this family that drove the team to sequence GNPTAB, GNPTG, and NAGPA in unrelated cases. At the same time, the findings emphasize the complexities of the genetics of stuttering: 36 genotyped members of Family PKST72 carried at least one G3598A risk allele; 25 of them had a diagnosis of stuttering, but the other 11 (including 2 homozygotes) were unaffected. Moreover, 3 affected PKST72 family members, on sequencing, turned out to carry no mutations in GNPTAB. Thus, there is evidence of both incomplete penetrance (i.e., carriers of the genetic risk factor can remain unaffected) and pheno-copy (i.e., affected persons may not carry the genetic risk factor). Additional unknown factors must modulate the relationship between the risk allele and stuttering in this family, and presumably in others with similar variants.

The GNPTAB, GNPTG, and NAGPA variants were found in only a small proportion of cases, together accounting for 21 of 393 cases in unrelated, affected subjects — a finding that is consistent with the genetic heterogeneity that underlies stuttering. Causative factors in the remaining 95% of cases remain to be elucidated. Because the identified variants are rare, they would have escaped detection on a standard genomewide association screen.

A remarkable feature of this study is the nature of the implicated biologic pathway — an unlikely culprit to explain stuttering. Lysosomes, which are membrane-bound organelles within the cytoplasm of most eukaryotic cells, break down intracellular waste products and ingested macromolecules through a variety of hydrolytic enzymes. These hydrolases, initially synthesized in the endoplasmic reticulum, must be modified by means of a mannose-6-phosphate tag to be properly transported to the lysosome. GNPT and NAGPA catalyze the two-stage process that adds the mannose-6-phosphate signal to the appropriate enzymes. Failure of this pathway can have dramatic consequences. For example, an absence of GNPT activity results in the loss of lysosomal targeting in multiple tissues, causing mucolipidosis type II, a severe disorder that usually involves delayed development; skeletal, respiratory, and cardiovascular abnormalities; and death within the first decade.

The affected subjects studied by Kang et al. stuttered but were otherwise normal and did not display the symptoms that are most typical of lysosomal malfunction. A possible explanation is that the efficiency of lysosomal targeting is only partially reduced by the mutations that these researchers identified. Now it is important to directly test the properties of the variant forms of GNPT and NAGPA enzymes with the use of standard biochemical assays.

Are mutations that affect this pathway present in independent cohorts of people who stutter? Why would dysfunction of a basic process found in many cell types selectively affect the neural circuits involved in speech fluency? Do other undiscovered genes associated with stuttering have roles in metabolic pathways? Can these data explain whether early stuttering will persist? Where are new prospects for treatment? As with other neurodevelopmental disorders that affect speech, the task of connecting the dots between genes and stuttering is just beginning.

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Another Selective Estrogen-Receptor Modulator for Osteoporosis
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Selective estrogen-receptor modulators are non-steroidal compounds that act as estrogen agonists in some tissues and as estrogen antagonists in others. Thus, they are uniquely suited for postmenopausal women. An ideal selective estrogen-receptor modulator would offer postmenopausal women the benefits of estrogen therapy (i.e., a reduced risk of fracture, urologic and vaginal atrophy, and hot flushes) without the risks (i.e., an increased risk of breast cancer, endometrial cancer, coronary heart disease, stroke, and venous thromboembolic events).

Tamoxifen and raloxifene, the two selective estrogen-receptor modulators currently marketed for postmenopausal women in the United States, offer both benefits and drawbacks. Tamoxifen is associated with a reduced risk of estrogen-receptor (ER)-positive breast cancer but an increased risk of endometrial cancer. Raloxifene reduces the risk of osteoporotic fracture and breast cancer, has a neutral effect on the risk of endometrial cancer, and does not reduce the risk of coronary heart disease or stroke. Both drugs are associated with increased risks of venous thromboembolic events and hot flushes, and neither improves urologic and vaginal atrophy.

In this issue of the Journal, Cummings et al. report the results of the Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) Study (ClinicalTrials.gov number, NCT00141323), an international, placebo-controlled trial in which 8556 postmenopausal women with osteoporosis were randomly assigned to lasofoxifene (at a dose of either 0.25 or 0.5 mg per day) or placebo. The primary end point after 3 years was vertebral fracture, a key secondary end point at 3 years. In contrast, in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (NCT00670319), raloxifene was associated with a significant relative risk reduction in radiographic vertebral fractures and new clinical findings of vertebral fractures.

In the PEARL study, lasofoxifene had no significant effect on the risk of nonvertebral fracture at 3 years but was associated with a reduction of 25% in the risk of major nonvertebral fracture at 5 years. There were significant reductions in nonvertebral fractures by 3 years in a subgroup of women with osteoporosis at the spine. Raloxifene has not been associated with a reduction in the risk of nonvertebral fracture, even after 5 to 7 years.

A close look at the data from the PEARL study shows that nearly all the reductions in major nonvertebral fractures appear to be due to a decrease in forearm and wrist fractures. At 5 years, there were 112 forearm and wrist frac-