In the interior of larger clusters and in bulk water, the hydrated electron may not be bound in the vicinity of double-acceptor water molecules. However, this type of arrangement could very well occur on ice surfaces or at the surface of large water clusters. The application of the vibrational predissociation technique of Hammer *et al.* to larger clusters may elucidate the location (surface or interior) of the excess electron.

These new experimental results for negatively charged water clusters are important benchmarks for theoretical studies of the structure and dynamics of excess electrons in aqueous environments. Recent theoretical studies have shown that dispersion interactions between the excess electron and the electrons of the water molecules make an important contribution to the binding energy of the former (*12*). Such interactions could play a role in determining whether the excess electron is surface- or interior-bound and could also affect its dynamics.

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GENETICS

The Critical Region in Trisomy 21

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Manipulating mice to model human genetic disorders has become routine since the development of methods to introduce targeted mutations by homologous recombination. Although excellent mouse models exist for many human single-gene disorders such as hemophilia or Zellweger syndrome, mouse models for other diseases only partially mimic or sometimes fail to recapitulate any aspect of the human syndrome. It is therefore surprising that some mouse models of human conditions that are caused by chromosome-scale anomalies have proved valuable. Perhaps the most ambitious of these efforts is the creation of mouse models for Down syndrome (DS), a developmental abnormality characterized by trisomy of human chromosome 21. It has been presumed that several dosage-sensitive genes in a section of human chromosome 21 called the Down syndrome critical region (DSCR) are responsible for many of the features of this disease, including craniofacial abnormalities. On page 687 of this issue, Olson *et al.* (*1*) put this theory to the test with their study of mice engineered to be trisomic but only for those sections of the mouse genome that are orthologous to the human DSCR. In this way, the investigators hoped to more closely model the effect of carrying three copies of genes in this region in an intact animal. Surprisingly, they discovered that three copies of the DSCR genes are not sufficient to cause the cranial anomalies characteristic of Down syndrome. These findings allow a firm refutation of the notion that trisomy of the DSCR is the sole cause of the craniofacial aspect of the Down syndrome phenotype.

Down syndrome, or trisomy 21, is the most common genetic cause of mental retardation, with a worldwide frequency of 1 in 700 births. Trisomy results from sporadic nondisjunction of chromosome 21 leading to three copies of the smallest human chromosome. Although the vast majority of individuals with Down syndrome have three copies of the entire chromosome (and all of the genes it contains), rare individuals with Down syndrome have smaller portions triplicated because of unbalanced translocations. Comparison of the chromosome anomalies and physical characteristics shared among these patients has led to the concept of a critical region for certain features of Down syndrome (*2*). Although controversial, the idea of a DSCR implies that much of Down syndrome could be caused by extra copies of one or a small number of genes in this region (*3*). The notion that a few genes might be of critical importance in this syndrome is particularly attractive because such a simple model would bode well for possible therapeutic intervention.

The development of a mouse model for Down syndrome has not been easy. Human chromosome 21 carries about 231 defined genes across the 33.5 million bases (Mb) of its long arm. The orthologous genes in the mouse are distributed across three chromosomes: 10, 16, and 17. Mouse chromosome 16 contains orthologs of most of the human chromosome 21–linked genes, but it also carries orthologs of genes found on three other human chromosomes. Presumably as a result of these additional genes, mice with trisomy 16 are not viable postnatally. This has necessitated the development of segmental trisomy mouse models of Down syndrome. The Ts65Dn mouse—derived by Davisson and colleagues using translocation chromosomes—exhibits segmental trisomy for orthologs of 104 human chromosome 21–linked genes, and this mouse remains viable into adulthood (*4*). A second partial trisomy mouse model, Ts1Cje, carries a smaller segment containing 81 genes in 10.3 million bases (*5*). Although neither mouse perfectly models human trisomy 21, there are substantial similarities in phenotype, notably craniofacial changes that mimic the human condition, along with electrophysiological differences in brain activity and altered behavior.

Olson *et al.* (*1*) exploited the ability to create defined deletions and duplications in mouse chromosomes by introduction of *Cre* recombinase recognition sequences through homologous recombination in mouse embryonic stem cells. Pioneered by Bradley's group, this method enables the generation of specific deletions and duplications spanning tens of millions of bases (*6*). A particularly successful application of this technique by Baldini and colleagues led to the creation of mouse deletions similar to those found in human DiGeorge syndrome (*7*). However, so far, these methods have not been widely applied to creating mouse models of human diseases, although this may change with the recent description by Adams *et al.* of a new resource to facilitate manipulation of the mouse genome (*8*).

In the new work, Olson and co-workers engineered mice to carry either a duplication or deletion of a 3.9-Mb segment of mouse chromosome 16 containing the 33 orthologs of genes found in the human DSCR. The authors analyzed the phenotype of these mice. They then bred animals with the deleted chromosome segment with those carrying existing segmental trisomies (the Ts65Dn and Ts1Cje mice). This enabled analysis of animals that were trisomic for most of the genes in the Ts65Dn or Ts1Cje mice, but disomic for the 33 DSCR genes. They found that three copies of these 33 genes alone were not

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sufficient to generate the cranial changes found in mouse models of Down syndrome with larger numbers of triplicated genes. Furthermore, reducing trisomy of these 33 genes to disomy in the Ts65Dn mouse did not eliminate the phenotype.

Breeding mice with the deleted chromosome segment with trisomy mouse models is a particularly elegant approach to testing the role of the DSCR segment in Down syndrome. It would appear that triplication of the 33 DSCR genes is not necessary at least for the craniofacial alterations characteristic of the disease, thus reducing the likelihood of a contiguous critical region for this aspect of Down syndrome. The authors favor a model in which individual or small numbers of genes can make a "critical" contribution to Down syndrome, but where the effect is highly contextual, depending on the combined effects of altering the dosage of other genes.

The generation of these new mouse models will allow additional study of the association of these 33 genes with other Down syndrome abnormalities associated with behavior, electrophysiology, and loss of cerebellar granule cells (*9*). It will also be interesting to increase the size of the duplicated chromosome segments to more closely mimic the human disorder, although if Olson *et al*. are correct that combinations of genes of small (or no) individual effect can contribute to the overall phenotype, the numbers of permutations are daunting.

Mice remain our most useful genetic relative for modeling human disorders, despite numerous differences that complicate analysis. For diseases involving mental retardation, this is a particularly acute problem, as alterations in behavior and learned tasks must suffice to flag differences in mental acuity between mutant mice and their normal counterparts (*10*). Another challenge is the difference in colinearity of the human and mouse genomes, and the lack of conservation of gene order. Even though we now have complete genome sequences for both species, there are still many sequences not currently recognized as genes that could prove to be of great importance when designing mouse models of human disorders. Mouse models such as those described here may offer one of the best ways to understand whether such sequences contribute to phenotype.

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CLIMATE

The Real Color of Climate Change?

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How sensitive is the climate to changes in solar irradiance, atmospheric aerosols, greenhouse gases, and other climate forcings? To answer this question, we first need to know the true extent of past climate fluctuations. The changing temperatures over past centuries and millennia have been reconstructed by regressing annually resolved climate proxy records—for example, from ice cores and tree rings—against recent thermometer measurements. On page 679 of this issue, von Storch *et al.* (*1*) investigate whether climate changes over decades and longer are likely to have been captured realistically in such reconstructions of Northern Hemisphere (NH) mean temperature.

The likelihood that reconstructions of this kind represent accurate "hindcasts" of past climate is usually assessed by verification against a short period of independent thermometer data. Such verification is only possible for short-term (annual to decadal) climate variability, because the instrumental climate record is too short to sample longer (decadal to centennial) time scales adequately.

To overcome this limitation, von Storch *et al.* use a 1000-year simulation from a coupled ocean-atmosphere model as a testbed in which the (simulated) NH temperature is known. They then generate pseudo-proxy records by sampling a small selection of the model's simulated grid-box temperatures (replicating the spatial distribution of existing proxy records) and degrading them with statistical noise.

The authors show that most of their attempts to reconstruct the model's NH temperature with the pseudo-proxies result in significant underestimates of the amplitude of fluctuations over the last millennium. Published temperature reconstructions for the real world, based on similar calibration methods, may suffer from the same limitation.

Although von Storch *et al.* focus their discussion on the reconstruction method of Mann *et al.* (*2*), their conclusions are relevant to other attempts to reconstruct NH temperature history. They demonstrate even greater loss of long-term variations with a simple regression-and-averaging method [this observation was also made in (*3*)]. The results may apply to all regression-based methods. Accepting von Storch *et al.*'s results does not mean that we must also accept that their simulated temperature history is close to reality—merely that it is a reasonable representation of climate behavior for which any valid reconstruction method should perform adequately.

The underestimated long-term variability obtained by von Storch *et al.* is not a result of problems with proxy data or the ability of the proxies to retain information on these time scales (*4*), because the pseudo-proxies were generated free from such biases. Neither is it simply due to the usual loss of variance associated with any regression-based prediction (this loss already forms the basis for published estimates of reconstruction error). This usual loss of variance is often modeled as a random error, and although a reconstruction may not be perfect, it cannot be scaled by a simple multiplier to achieve a better fit (that is, the reconstruction and its error are uncorrelated) during the calibration period. It is clear from figure 1 of (*1*) that the underestimation of long-term temperature variability is systematic rather than random: At these time scales, a better fit to the actual NH temperature can be achieved by scaling a reconstruction by a simple multiplier (>1), because the reconstruction and its error are correlated. Such error is not incorporated in the uncertainties associated with any published NH temperature reconstruction.

The source of this systematic error can be traced to differing shapes of the variance spectra of the NH temperature and of the pseudo-proxy data. The authors constructed pseudo-proxies by adding white noise to the simulated temperatures. Doing so alters the variance spectra and leads to a deficiency in variance at longer time scales, even after calibration (see the figure). Hence, for climate reconstructions to be optimal on all time scales, proxy data must have variance spectra that are similar to those of the climate data that they are presumed to represent. It is not only through the noise inherent in proxy records that this requirement may be violated. Using

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