WEB WATCH

Self-improving GBuilder

The European Bioinformatics Institute (EBI) has recently published improvements to GBuilder (once called GenomeBuilder), a program for analysing DNA-sequence clusters and assemblies. It aims to help researchers to combat the sequence-analysis problems posed by expressed sequence tags (ESTs) because of their poor sequence quality, high rates of chimerism, high redundancy and alternatively spliced forms, which cause alignment mismatches. Sequence data can be analysed and visualized in GBuilder in many ways. For example, aligned sequences can be colour coded according to annotation properties or to highlight vector sequence.

GBuilder's key feature is that it uses CORBA (common object request broker architecture) to allow it to connect to database and analysis-application servers at EBI (or elsewhere where the same CORBA interfaces are used). This allows it to access different data sources and applications on the internet, or at a user's own site, and to integrate this additional data and functionality into itself.

GBuilder runs from the EBI, but the program's main developer, Juha Muilu, recommends that users download the program for their own use for several reasons, one being that the EBI-run version cannot provide all the program's features. This might prevent the less computer literate from making the most of this program, however, it allows the computer savvy to customize GBuilder to access their favourite databases by providing the program's configuration file with the appropriate URLs. Future additions to the program are in the pipeline, such as more sequence-analysis tools.

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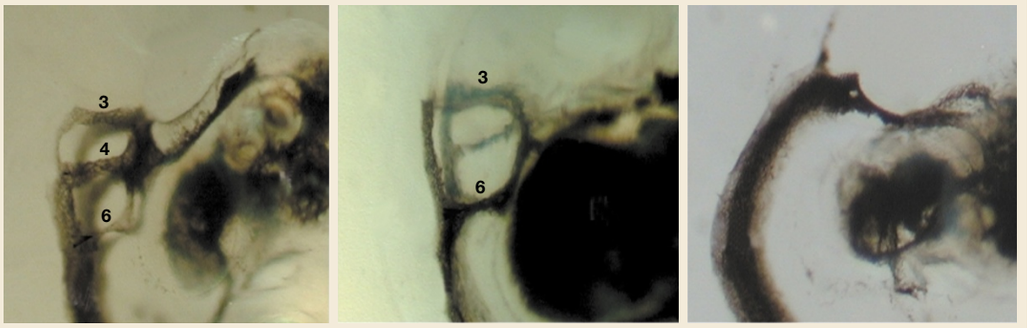
FURTHER READING Muilu, J. *et al.* GBuilder — an application for the visualization and integration of EST cluster data. *Genome Res.* **11**, 179–184 (2001)



Ink injections showing pharyngeal arch arteries (PAAs) in wild-type (left), *Tbx1*$^{+/-}$ (middle) and *Tbx1*$^{-/-}$ (right) mutant mouse embryos. Wild-type embryos have three pairs of PAAs (3–6), *Tbx1*$^{+/-}$ embryos have small or absent 4th PAAs, and in *Tbx1*$^{-/-}$ mutants, PAAs 3–6 do not develop. Courtesy of E. Lindsay, Baylor College of Medicine, USA.

HUMAN GENETICS

Genes at the heart of DiGeorge

DiGeorge syndrome (DGS), a complex congenital disorder, is partly characterized by cardiovascular (CVS) defects, lack of parathyroid and thymus glands, and facial abnormalities. Despite the common embryological origins of affected tissues — many derive from the pharyngeal arches — elucidating the genetic basis of DGS has proved a challenge. This is because most DGS patients are heterozygous for a 3-Mb, chromosome 22 deletion, in 22q11, that encompasses many genes. The race to discover the genes that underlie DGS has been intense, as shown by four recent publications, three of which report that mutations in the T-box gene, *Tbx1*, cause DGS-like CVS defects in mice. The fourth paper implicates another 22q11 gene, *CRKL*, in the disease.

Deletions that had previously been made in the region of mouse chromosome 16 (MMU16) that is homologous to the DGS region on 22q11 set the stage for the recent findings. In particular, two independently generated, partially overlapping deletions, *Df(16)1* and *Idd–Arvcf*, defined a candidate region for the CVS defects. In their latest study, Lindsay and colleagues used Cre-*loxP* technology to engineer additional MMU16-deletion and -duplication alleles. They found that loss of a critical interval, encompassing ~700 kb, caused fully penetrant CVS defects. A duplication of this interval rescued the CVS phenotype — this ruled out a role for the action of long-range regulatory elements in this phenotype and indicated that it was caused by a dosage-sensitive gene in this region. The authors then identified a 140-kb PAC that rescued the CVS phenotype caused by the *Df(16)1* deletion. Of the four genes on this PAC, only *Tbx1* was strongly expressed in mouse pharyngeal arches, and so Lindsay *et al.* knocked it out. The *Tbx1*$^{+/-}$ mutants had an identical DGS-like CVS phenotype to *Df(16)1*/+ mutants, and *Tbx1*$^{-}$/*Df(16)1* compound mutants fully reiterated the *Tbx1*$^{-/-}$ phenotype.

These and other findings strongly implicated *TBX1* deficiency as the cause of CVS defects in DGS. Merscher *et al.* also generated a large MMU16 deletion, which caused DGS-like CVS defects in 50% of heterozygous mutants and parathryroid abnormalities in some animals. The failure of a duplication of the *Idd–Arvcf* interval to rescue this deletion phenotype further narrowed down the candidate interval, and a human BAC from this region partially rescued the deletion phenotype. This BAC contained *TBX1*. Confirmation of *TBX1*'s role came when the authors knocked out *Tbx1* in mice and generated mutants with DGS-like CVS defects. Jerome and Papaioannou also knocked out *Tbx1* in a candidate-gene approach to studying DGS. They report that their *Tbx1*$^{-/-}$ mutants develop CVS defects and other DGS features, such as thymus, parathyroid and facial abnormalities. It is not known whether *TBX1* mutations in humans underlie the whole DGS phenotype, but these abnormalities in *Tbx1* nulls — as also reported by Lindsay *et al.* — indicate this should not be excluded.

But what of the other genes in the region? Guris *et al.* report that loss of another 22q11 homologue in mice, *Crkol*, causes post-migratory defects in neural crest cells, which contribute to many of the tissues affected in DGS — null mutants have CVS, parathyroid and thymus, and facial defects. As *Crkol* lies outside the *Df(16)1* interval, this study indicates that independent loci might contribute to the DGS phenotype — a possibility as *TBX1* mutations in DGS patients have not been found. However, Lindsay *et al.* suggest that DGS might be caused — not by neural-crest-cell defects — but by loss of a pharyngeal-arch-segmentation function of *Tbx1*. Only time and additional studies will tell.

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References and links

ORIGINAL RESEARCH PAPERS Lindsay, E. A. *et al. Tbx1* haploinsufficiency in the DiGeorge syndrome region causes aortic arch defects in mice. *Nature* **410**, 97–101 (2001) | Merscher, S. *et al. TBX1* is responsible for cardiovascular defects in velo-cardio-facial/DiGeorge syndrome. *Cell* **104**, 619–629 (2001) | Jerome, L. A. & Papaioannou, V. E. DiGeorge syndrome phenotype in mice mutant for the T-box gene, *Tbx1*. *Nature Genet.* **27**, 286–291 (2001) | Guris, D. L. *et al.* Mice lacking the homologue of the human 22q11.2 gene *CRKL* phenocopy the neurocristopathies of DiGeorge syndrome. *Nature Genet.* **27**, 293–298 (2001)