

## Detection of proximally extended D4Z4 deletion in FSHD

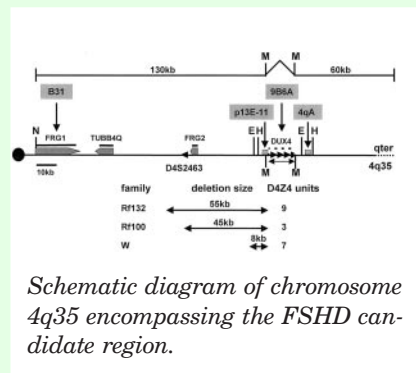
Lemmers et al. studied three FSHD families with proximally extended deletions spanning the D4F104S1 region and D4Z4 repeat. The deletions differ in size among the three affected individuals. A method is presented to identify large deletions involving both D4Z4 and D4F104S1 using conventional gel electrophoresis.

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## Facioscapulohumeral muscular dystrophy: Untangling a molecular enigma

Commentary by Rabi Tawil, MD

More than a decade after the discovery of the genetic lesion in FSHD, the molecular mechanism and the gene or genes involved in disease pathogenesis are not known. FSHD is caused by a deletion of a critical number of a 3.3 Kb (D4Z4) repetitive element in the subtelomeric region of chromosome 4q (4q35).<sup>1</sup> The initial assumption, in accordance with the classical Mendelian model, was that the FSHD gene was contained within the deleted repeats. However, no transcribed sequences could be found within the D4Z4 repeat elements. This led investigators to propose that FSHD was caused by a "position effect," whereby deletions of a critical number of D4Z4 repeats lead to a spread of telomeric heterochromatin upstream, turning off expression of genes on 4q35. But silencing of these genes is not the likely mechanism because chromosomal aberrations resulting in loss of 4q35 do not cause FSHD. Therefore, contraction of the repeats to below a threshold number must result in a deleteri-



ous gain of function. Support for this hypothesis came from the recent demonstration that 4q35 genes are inappropriately overexpressed in FSHD muscle and that D4Z4 units contain a sequence that binds a transcriptional repressor complex.<sup>2</sup>

In the current article, Lemmers et al. describe the clinical phenotype and establish a molecular diagnostic method for patients with FSHD with deletions that span the region just proximal to the D4Z4 recognized by p23E-11, the probe commonly used by FSHD molecular diagnosis. The article demonstrates the limits of conventional molecular diagnostic

testing in FSHD and provides additional insights into the complex mutational process involved in this disease. Perhaps of equal importance is the exclusion of FRG2 as a candidate gene for FSHD. One of the families described, with a typical FSHD phenotype, harbors a deletion that extends proximally to include the FRG2 gene. This gene is one of several 4q35 genes reported to be overexpressed in FSHD muscle.<sup>2</sup> FRG2 overexpression is clearly not necessary for a patient to have characteristic clinical findings of the FSHD phenotype. We know the chromosome lesion in virtually 100% of FSHD cases, but the search is still on for the genetic mechanism of the disease.

### References

1. Wijmenga C, Hewitt JE, Sandkuijl LA, et al. Chromosome 4q DNA rearrangements associated with facioscapulohumeral muscular dystrophy. *Nat Genet* 1992;2:26-30.
2. Gabellini D, Green MR, Tupler R. Inappropriate gene activation in FSHD: a repressor complex binds a chromosomal repeat deleted in dystrophic muscle. *Cell* 2002;110:339-348.

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## Medication-overuse headache

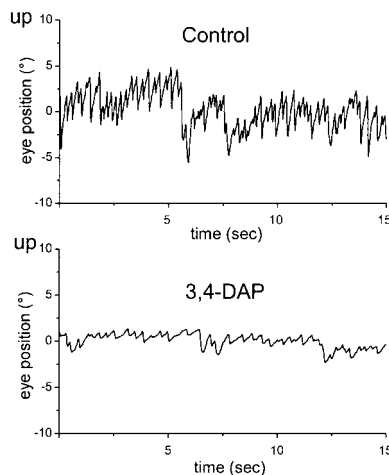
Zwart et al. showed in a large prospective population-based study conducted in Norway (1984–1986/1995–1997) that overuse of analgesics strongly predicted chronic pain and chronic pain associated with analgesic overuse 11 years later, especially among those with chronic migraine. “Because the association [with chronic analgesic use] was stronger for chronic migraine than other pain disorders—the association may be causal.”

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*In the accompanying editorial, Lipton and Bigal focus on the relationship between chronic daily headache and analgesic overuse. Chronic daily headache affects 4% of the population; chronic migraine is its most common subtype. Risk factors for chronic migraine include female sex, obesity, stressful events, hypertension, alcohol overuse, snoring, and the most important—overuse of analgesics. Analgesic overuse is neither necessary nor sufficient to induce chronic daily headaches, exemplified by another study in which 92% of people in an arthritis clinic who were taking analgesics did not develop chronic daily headaches—the 8% who did all had a history of migraine.*

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## Treatment of downbeat nystagmus with 3,4-diaminopyridine



Downbeat nystagmus is the most common form of persistent nystagmus. Medical treatment is difficult. In the placebo-controlled study by Strupp et al., the potassium channel blocker 3,4-diaminopyridine (3,4-DAP) decreased downbeat nystagmus in half of the subjects.

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*The accompanying editorial by R. John Leigh reviews current drug treatments for nystagmus, noting that an effect on ion channels in the cerebellum is likely to be an important mechanism of action. The benefit of acetazolamide in episodic ataxia type 2 as well as this article's report of 3,4-DAP benefit may result from an effect on cerebellum since the cerebellum selectively inhibits upward and not downward vestibular eye movements.*

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## Responders to interferon therapy for relapsing MS

Waubant et al. report that one-third of 262 patients with relapsing MS experienced higher or identical relapse rate on interferon beta. Responders had higher relapse rates the year before interferon therapy. Responders were also older and had longer disease duration when interferon was initiated compared to nonresponders.

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## Ethnic and sex disparities in childhood stroke

Using a statewide discharge diagnosis database, Fullerton et al. found that boys had higher risk of stroke than girls and that black children had a higher risk than white or Asian children. Sickle cell disease did not fully account for the ethnic disparity, and trauma did not fully account for the excess risk in boys.

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## Cholesterol and Alzheimer disease amyloid pathology

Studying the relationship between cholesterol levels and Alzheimer disease (AD), Pappolla et al. demonstrated that early mild elevations of blood cholesterol in middle age are associated with a higher risk for developing the amyloid pathology characteristic of AD.

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## Effect of reading instruction on fMRI dyslexia

Aylward et al. assessed fMRI during specific language tasks in children with dyslexia vs normal readers. After 28 hours of instructional treatment, the brain activation in dyslexic children was similar in location and quantity to that of the control children.

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## Seven-year survival in glioblastoma after gene therapy

Floeth et al. studied a patient with recurrent glioblastoma who was treated by open resection, followed by local gene therapy. After 7 years there is no evidence of tumor relapse.

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## ■ X-linked mental retardation

### **XLAG: A novel candidate of ARX-related disorders**

Uyanik et al. genetically assessed pedigrees with X-linked lissencephaly with abnormal genitalia (XLAG). Two distinct mutations within the ARX gene lead to the severe clinical XLAG phenotype within the ARXopathy spectrum.  
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## **ARX and infantile spasms**

Kato et al. report a boy with cryptogenic infantile spasms in whom they identified a mutation of the X-linked ARX gene. This observation should lead to improved diagnosis and genetic counseling. It also suggests treatment strategies with GABA agonists, as mutant mice are deficient in GABAergic and other inhibitory interneurons.

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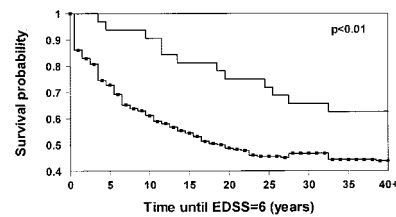
*The accompanying editorial by Patterson and Zoghbi reviews X-linked mental retardation (XLMR). Mutations in the X chromosome probably account for the higher incidence of MR in males. They focus on 3 of the over 35 XLMR loci whose mutations have been identified: fragile X syndrome (the commonest), MECP2 (also responsible for Rett syndrome), and the ARX gene. Mutations in the ARX gene produce a bewildering array of phenotypes. They note the challenge of deciding which patients to investigate for these and other gene lesions in routine assessment of MR in boys.*

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## ■ Seizures after stroke

Devuyst et al. studied the clinical features of 3628 patients presenting seizures before and after a first-ever stroke. The majority of poststroke seizures occur <3 hours later and adversely influence the consciousness level but not the short-term outcome. Patients with hypercholesterolemia were less likely to have seizures.  
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## ■ Mutated CCR5 gene may confer favorable prognosis in MS



*A slower progression to disability is demonstrated in the 32 patients with MS carrying the  $\Delta 32$ CCR5 mutation (solid line), compared with the 224 patients with MS carrying the wild-type CCR5 genotype (broken line) ( $p < 0.01$ ).*

Kantor et al. studied 256 patients with MS for the  $\Delta 32$ CCR5 mutated allele of the chemokine receptor CCR5 and found a frequency of 7.4%. Patients carrying the mutated allele had a slower progression of MS disability vs those with the wild-type genotype.

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## July 22 Highlights

*Neurology* 2003;61;151-153  
DOI 10.1212/WNL.61.2.151

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