

# Predicting hearing loss in facioscapulohumeral muscular dystrophy

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Facioscapulohumeral muscular dystrophy (FSHD) has an estimated prevalence of 4–7 per 100,000 population, making it the third most common type of muscular dystrophy. The classic form of FSHD is characterized by weakness that is slowly progressive and often asymmetric in the face, scapulae, upper arms, lower legs, and abdomen. The age at onset of symptoms varies from infancy to middle age, and life expectancy is normal or almost normal. Aside from muscle weakness, other manifestations include chronic pain, hearing loss, retinal telangiectasias and exudation (Coats syndrome) that can progress to retinal detachment and vision loss, cardiac arrhythmias, cognitive impairment, and epilepsy.<sup>1</sup> There seems to be an increased prevalence of hearing loss in FSHD compared with the general population. Hearing loss has been described particularly in patients with infantile-onset FSHD but also in typical cases.<sup>2</sup> In severe infantile-onset cases, the hearing loss can be profound, and if not detected may lead to delayed language development and even the false perception of cognitive impairment. Consensus-based recommendations suggest routine hearing testing in infants and preschool-age children diagnosed with FSHD.<sup>3</sup>

FSHD manifests in 2 clinically identical types; both types are related to inappropriate expression of DUX4 protein in muscle cells, which leads to the development of FSHD by a toxic gain of function mechanism. DUX4 expression has a different cause in each type. FSHD type 1 (FSHD1), which is inherited in an autosomal dominant fashion, accounts for about 95% of cases. In FSHD1, inappropriate DUX4 expression is caused by contraction of a region on chromosome 4q35 known as D4Z4. In the general population, D4Z4 consists of 11–100 repeated DNA segments. In FSHD1, one D4Z4 allele is contracted (1–10 repeats, EcoRI fragment less than 38 kb, EcoRI/BlnI fragments less than 35 kb) and the other D4Z4 allele has the normal number of repeat units. The contraction results in a more open chromatin structure and if it occurs on a permissive chromosomal background (4qA haplotype), DUX4 transcription is activated.<sup>4,5</sup> In the less common FSHD type 2 (FSHD2), seen in fewer than 5% of

patients, the D4Z4 region is not contracted. Instead, in about 80% of FSHD2 cases, the abnormal DUX4 expression is caused by mutations in the *SMCHD1* gene that affect the D4Z4 chromatin structure.<sup>6</sup> The inheritance of FSHD2 is related to the interaction between the independent inheritance of an *SMCHD1* mutation on chromosome 18 and a permissive 4qA haplotype.<sup>6</sup>

In this issue of *Neurology*®, Lutz et al.<sup>7</sup> describe the hearing loss in FSHD and its relationship to genotype. In a cohort of 59 individuals with FSHD, 11 had substantial hearing loss diagnosed from birth to 7 years. In 2 patients, hearing loss was identified by newborn hearing screen, and 3 patients had progression of hearing loss. In 53 participants, information regarding the contracted EcoRI/BlnI fragment, which reflects the number of residual repeats, was available, and a negative association was detected between hearing loss and fragment size. There was no hearing loss in patients with EcoRI/BlnI fragment size of more than 20 kb (i.e., 4–10 repeats). In the cohort with EcoRI/BlnI fragment less than 20 kb reflecting a larger repeat contraction (i.e., 1–3 residual repeats), about one-third (10/31) of patients had hearing loss.

It seems that FSHD-associated hearing loss may worsen over time, as reported before, while some individuals can have stable hearing loss over long periods of time. Why hearing loss is stable in some patients while progressive in others is not clear. The authors' data provide support for the current testing recommendations, which can be outlined as follows:

- FSHD is one possible etiology of hearing loss in the newborn.
- Repeat hearing screenings should be conducted in children with FSHD even if they passed newborn hearing screening.
- FSHD-associated hearing loss may occur after acquisition of language in preschool- and even school-age children. Therefore, hearing screens should be continued until school age, particularly in young children with a small EcoRI/BlnI fragment size (less than 20 kb, i.e., 1–3 residual

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repeats), even if they have passed newborn hearing screening.

Older-aged children with FSHD and normal language development who pass routine hearing screens in school do not require an audiogram. Similarly, adults with FSHD do not need audiograms if they are asymptomatic.<sup>3</sup>

Recently, animal models of FSHD have been created.<sup>8,9</sup> Misexpression of human DUX4 protein in zebrafish development recapitulates features seen in the human FSHD phenotype. Injection of DUX4 protein in zebrafish embryos results in asymmetric abnormalities of fin muscle (corresponding to arms), facial musculature or trunk muscle, eyes, and ears; the number, size, and position of otoliths in the ears were altered. These abnormalities are of interest because in human FSHD, asymmetric involvement of muscles can be striking, and audiologic studies have indicated a cochlear origin of hearing loss. Animal models thus offer a key pathway toward improved understanding of the pathogenesis of FSHD in humans.

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