Joining mainstream research on Facioscapulohumeral Dystophy: disease prevalence in China

*Frédérique Magdinier**

Aix Marseille Univ, INSERM, Marseille Medical Genetics, MMG, Marseille, France

The Lancet Regional Health - Americas 2022;18: 100328
Published online xxx
https://doi.org/10.1016/j.lanwpc.2021.100328

Based on the exploration of different cohort in occidental countries, Facioscapulohumeral Dystrophy (FSHD) has been estimated around 1:8000 to 1:12 000.[1,2]

This autosomal dominant inherited disorder is characterized by a typical clinical presentation with a progressive weakness of specific groups of muscles of the face, shoulder girdle, upper arm and lower limbs. Disease severity is heterogenous ranging from a minimal clinical manifestation to a severe muscle weakness and wheelchair dependency. An early onset of the disease is usually associated with higher disease severity.[3] As life expectancy is considered as normal, disease duration and progression is long, posing societal and socio-economic burden for patients and their families.

In their nationwide population-based study, Wang and colleagues provided a comprehensive study of the prevalence of FSHD in the Chinese population.[4] Data were collected between 2001 and 2020 across different provinces with a discrepancy in the period of recruitment between provinces, that highlights the importance of establishing competent centers for medical evaluation and follow up. This bias in the recruitment between Chinese provinces also indicates that the number of patients suffering from FSHD nationwide is likely underestimated. Furthermore, as FSHD is characterized by a late onset and a high clinical variability, a considerable number of individuals remains probably undiagnosed to date.

A total of 1802 cases collected were collected; 1744 were tested for FSHD1 by Pulse Field Gel Electrophoresis and Southern blotting[3] at the Fujian Neuromedical Center, the clinical genetic test hospital for FSHD in China. The size of the D4Z4 array was determined together with the presence of A-type haplotype. Molecular diagnostics was completed with DNA methylation analysis. Out of these 1744 cases, 58 (3.2%) were excluded due to an incomplete genetic testing, 997 (57.2%) individuals from 620 families were diagnosed with FSHD1; 0.3% (5 cases) are carrier of a *SMCHD1* variant and met the criteria for FSHD2. Out of the 742 negative cases, 591 individuals were relatives of genetically confirmed FSHD1 patients.

The prevalence was estimated at 0.75 per million with a higher prevalence in males than in females (0.78 versus 0.71, respectively), as reported in occidental populations. The prevalence in the Chinese population is lower than in the Italian (6.1 per million[2]), Japanese (3 to 3.9 per million[5]), Israelian (5.3 per million[6]) or Dutch (120 per million[1]) populations. When parental testing was possible, the prevalence of *de novo* cases was estimated around 0.08 per million. Somatic mosaicism was found in 4% of FSHD1 mutation carriers. As reported,[7–9] hypomethylation was correlated with disease penetrance and age of onset.

Strikingly, the number of paediatric cases was high in this population, with a median onset age of 16 at first clinical signs. The mean age of onset is younger in China (18 years of age) compared to the age of 20 in the Netherlands[1], 33 in Italy[2] but older compared to the Korea with a mean age of 13.[10] The median number of contacted alleles is estimated at 5 units, lower than in other populations (5.8 units in adults in the Dutch population). This might be explained by the high number of paediatric cases reported by Wang et al. (526 cases, mean size 3.6 units versus 310 adult patients, mean size 4.7 units), as early onset is often associated with a short D4Z4 array.[4]

For all patients, the clinical phenotype was assessed using the Comprehensive Clinical Evaluation Form (CCEF).[11] Disease severity was estimated using the Clinical Severity Score (CSS) and age-corrected Clinical Severity Score (ACSS). The majority of patients had a typical phenotype with facial and upper limb muscle weakness (69.9%, category A); 6.6% were of category B (± facial weakness and/or upper limb involvement); 20.8% of category C (presence of at least one typical sign) and 6.7% of category D (presence of at least one uncommon feature). The duration between disease onset and loss of independent ambulation (12% of cases), determined using the modified Rankin Scale (mRS) is estimated around the age of 40, with a higher proportion of females (62.4%, p-value < 0.001) and paediatric patients (69.2%).

Overall, this article that describes the largest cohort analyzed to date for FSHD underlines the importance

Abbreviations: FSHD, Facioscapulohumeral Dystrophy; SMCHD1, structural maintenance of chromosomes flexible hinge domain containing 1.; CCEF, Comprehensive Clinical Evaluation Form; CSS, Clinical severity score; ACSS, Age-corrected clinical severity score

*Corresponding author's address: Marseille Medical Genetics, U1251, INSERM; Aix Marseille University, Faculté des Sciences Médicales et Paramédicales de la Timone. 27, Bd Jean Moulin 13005 Marseille, France, phone: +33 4 91 32 49 08

E-mail address: frederique.magdinier@univ-amu.fr

of expert centers for the diagnosis of this disease together with the importance of patient's registries for data collection but also patients advocacy groups for disease awareness. Given the societal burden associated with rare diseases in general, standardized and exhaustive disease registries together with associated medical records appear as a critical resource to define the disease natural history, outcome measures and clinical trial readiness. The analyses reported by Wang *et al.* pave the way for further investigations only possible in large-scale population studies for estimating non-muscular symptoms commonly associated with FSHD such as hearing loss and retinopathies, but also for identification of underreported signs and definition of their respective prevalence or importance in patient's life.[4] It also opens further perspectives for inclusion of patients in clinical trials at a time where therapeutic developments are being pursued to cure FSHD.

Declaration of Competing Interest

The authors have no conflict of interest to declare

References

1 Deenen JC, Arnts H, van der Maarel SM, et al. Population-based incidence and prevalence of facioscapulohumeral dystrophy. Neurology 2014;83(12):1056–9.

2 Mostacciuolo ML, Pastorello E, Vazza G, et al. Facioscapulohumeral muscular dystrophy: epidemiological and molecular study in a north-east Italian population sample. Clin Genet 2009;75(6):550–5.

3 Magdinier F UM. Facioscapulohumeral Muscular Dystrophy: Genetics. Encyclopedy of Life Science 2018 accessed.

4 Wang N, Wang Z, Qiu L. Prevalence and disease progression of genetically-confirmed facioscapulohumeral muscular dystrophy type 1 (FSHD1) in China between 2001 and 2020: a nationwide population-based study. The Lancet Regional Health - Western Pacific 2021. doi: 10.1016/j.lanwpc.2021.100323.

5 Araki S, Uchino M, Kumamoto T. Prevalence studies of multiple sclerosis, myasthenia gravis, and myopathies in Kumamoto district, Japan. Neuroepidemiology 1987;6(3):120–9.

6 Kott E, Golan A, Don R, Bornstein B. Muscular dystrophy: the relative frequency in the different ethnic groups in Israel. Confin Neurol 1973;35(3):177–85.

7 Lemmers RJ, Goeman JJ, van der Vliet PJ, et al. Inter-individual differences in CpG methylation at D4Z4 correlate with clinical variability in FSHD1 and FSHD2. Hum Mol Genet 2015;24(3):659–69.

8 Gaillard MC, Roche S, Dion C, et al. Differential DNA methylation of the D4Z4 repeat in patients with FSHD and asymptomatic carriers. Neurology 2014;83(8):733–42.

9 Salort-Campana E, Nguyen K, Bernard R, et al. Low penetrance in facioscapulohumeral muscular dystrophy type 1 with large pathological D4Z4 alleles: a cross-sectional multicenter study. Orphanet J Rare Dis 2015;10:2.

10 Park HJ, Hong JM, Lee JH, et al. Low D4Z4 copy number and gender difference in Korean patients with facioscapulohumeral muscular dystrophy type 1. Neuromuscul Disord 2015;25(11):859–64.

11 Ricci G, Ruggiero L, Vercelli L, et al. A novel clinical tool to classify facioscapulohumeral muscular dystrophy phenotypes. J Neurol 2016;263(6):1204–14.