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Novel Xp21.1 deletion associated with unusual features in a large McLeod syndrome kindred

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1. Introduction

McLeod syndrome (MLS) is a rare adult-onset, progressive and incurable X-linked multisystemic disorder characterized by chorea, cognitive decline, seizures, polyneuropathy, myopathy and dilated cardiomyopathy with subsequent heart failure and increased risk for arrhythmia [1]. Variable psychiatric symptoms are common; the presence of acanthocytes on blood smears, elevated CK levels and striatal atrophy are other features. MLS is caused by mutation in the *XK* gene which encodes a membrane transport protein containing the Kx erythrocyte antigen [1]. So far, less than 200 MLS cases have been reported. In general, women harboring *XK* mutations rarely manifest symptoms. In addition, myoclonus has not been described in association with MLS and functional imaging studies are scarce.

2. Methods

All the examined patients consented to participate in this characterization which was approved by the local ethics committees in Vasa, Finland and in Stockholm, Sweden.

2.1. Patients

The family is from the Ostrobothnia region in Western Finland (Pedigree in Fig. 1A).

2.2. Clinical investigations

Comprehensive clinical characterization, analysis of blood smears, Kx and Kell antigens as well as genotyping. Brain MRI was performed in 2 symptomatic males, the index case underwent brain FDG-PET. Neuropathology was performed in his affected cousin. In addition, 4 women were examined by neurologists (B.U., O.S. and M.P.), phenotype assignment in some was based on history provided by relatives.

2.3. Genetics

Targeted analysis of the XK gene was performed using the stepwise partitioning method [2].

3. Results

3.1. Clinical features and neurophysiological tests

The clinical features are summarized in Table e−1. Briefly, intrafamilial heterogeneity is in line with previous descriptions [1,3]. The index case (IV:2) is a 72-years-old man who presented with insidious onset of involuntary movements with vocalizations, eating difficulties and personality change at age 45. Reduced short term memory, lack of insight, perseveration and severe insomnia were also reported; his CK was mildly elevated and ENMG displayed a mild demyelinating sensorimotor polyneuropathy and proximal myopathy. ECG revealed first-degree AV block at age 69 and echocardiography demonstrated dilated cardiomyopathy with reduced ejection fraction (30–35%). An ACE inhibitor was started and a pace maker was inserted later. Range for age at onset in males was 35–45 years, disease duration was slow (16–27 years) and age at death ranged between 56 and 72 years. Two men in this family succumbed to sudden death (II:1 and IV:7). Myoclonus was the first symptom in IV:7. Neurophysiology demonstrated sensorimotor polyneuropathy in IV:7 and in the index case (IV:2), in the latter signs of proximal myopathy abnormalities were also evident. Patient IV:7 suffered from severe behavioral and psychiatric symptoms. Patients II:1, III:6 and III:8 never sought medical care. Neither did 2 females (III:5 and III:7) affected by involuntary movements suggesting chorea. Botulinum toxin injections in both genioglossus muscles (7.5 U) attenuated feeding dystonia in the index case (Video file).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.014.

3.2. Biochemistry

Acanthocytes, compensated hemolysis, elevated CK were present in VI.2 and IV:7 (Table e−2). Immunohemathlogical analyses in both patients demonstrated absence of Kx antigen and weak reactions to the Kell antigens k, Kpb and Jsb.

3.3. Genetics

A 1.94 mbp deletion in Xp21.1 starting 23.306 bp 5' of the A of ATG of the *MAGEB16* gene and contiguous into intron 2 + 22.197 bp of the *XK* gene was detected in the 2 affected males (IV:2 and IV:7) and in 4

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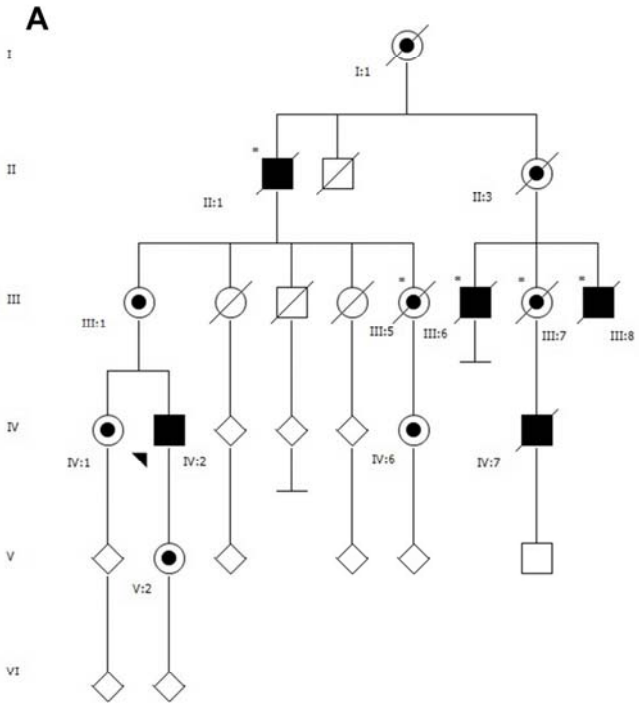

Fig. 1A. Pedigree of a large Finnish family harboring a large Xp21.1 deletion. *Phenotype assignment based on history provided by relatives.

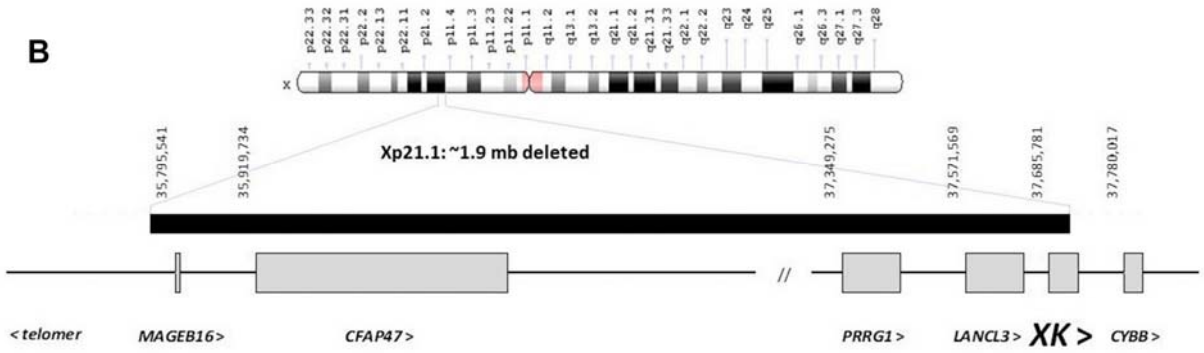

Fig. 1B. Schematic representation of the ~1.94 mbp contiguous gene deletion at Xp21.1 found in two affected men, involving an area from 23.312 kb 5′ of ATG of *MAGEB16* to intron 2 + 22.198 kb of *XK* is shown as a black bar. Below, genes with known expression of proteins are displayed as gray boxes. Their name is given and their orientation of transcription is indicated by arrows. Locations according to build GRCh38.p7 primary assembly for chromosome X are given for the initiation of transcription of the respective genes.

asymptomatic females (Fig. 1B). The resulting sequence is differing from all other 17 cases with contiguous gene deletions, reported so far. The diagnostically relevant breakpoint sequence will be submitted to the European Nucleotide Archive (ENA).

3.4. Neuroimaging and neuropathology

In the index case, progressive striatal atrophy (MRI exams done at age 61 and 70) and bilateral atrophy of the hippocampus was found. Marked hypometabolism in the striatum, temporal, parietal, occipital lobes, and prefrontal regions was evident. In addition, metabolism was enhanced in the primary motor cortex, supplementary motor area and vermis (Fig. e−1 and e−2). Patient IV:7 had severe striatal atrophy and hyperintensities in the caudate nuclei (Fig. e−1); severe neuronal loss was found in the striatum, in addition the striatal hyperintensities were corresponded by neuronal loss and severe gliosis (Fig. e−3). Muscle biopsy in IV:7 indicated myopathy (Fig. e−4).

4. Discussion

This large Finnish kindred, the first report of MLS in Scandinavia, had a 1.94 mbp novel deletion at Xp21.1. New findings for MLS are the neuroimaging abnormalities and the presence of myoclonic jerks at onset in one male. Progressive striatal atrophy and widespread white matter abnormalities have been reported before in MLS [3,5] but hyperintensities in the caudate nuclei are new, corresponding to severe gliosis on neuropathology. Only 5 publications have provided data on functional imaging in MLS (Appendix). Danek et al. found reduced D2 receptor density and striatal hypometabolism in 1 MLS patient [4]. A similar pattern of hypometabolism, which correlated with disease duration, was reported in 5 patients from the largest MLS family so far reported [5]. Similar findings were documented in 2 additional patients; one of them, presymptomatic, another MLS patient with predominant hypokinesia had reduced DAT binding but limited response to levodopa (References 10 and 11 in Appendix). Hypometabolism in the occipital lobes was also found in a previous study (Appendix), however the degree of widespread hypometabolism in our index case is a new finding and likely reflects longstanding disease with dementia.

Elevated metabolism in motor cortices has not been reported before for MLS, but it has been described in hyperglycemia-induced chorea [6]. This phenomenon may represent a compensatory activity in chorea.

The core neuroacanthocythosis syndromes MLS and chorea-acanthocytosis (ChAc) overlap with each other, but the presence of dilated cardiomyopathy and loss of the public red blood cell antigen Kx differentiate MLS from ChAc. Two patients in the Finnish MLS family died suddenly likely due to cardiac arrhythmia illustrating the importance of cardiac management for survival in this disease. Unmatched blood transfusions constitute another potential hazard for MLS patients [1]. Feeding dystonia is sometimes a disabling feature of neuroacanthocytosis syndromes, in particular in ChAc. The condition is usually refractory to pharmacological treatment; however, treatment with botulinum toxin injections can be beneficial as demonstrated in this work.

Some missense *XK* mutations are associated with a milder phenotype [1]. Large deletions of variable size at Xp21.1 affecting *CYBB*, *RPGR*, *DMD* and *OTG* may cause chronic granulomatous disease (X-CGD), retinitis pigmentosa, Duchenne muscular dystrophy and urea cycle defects in addition to neuroacanthocytosis [1]. Larger Xp21 deletions affecting *XK* and other genes but sparing *CYBB*, *RPGR*, *DMD* and *OTG* are not necessarily associated with a more severe MLS phenotype as demonstrated previously and supported by our work. Females harboring a heterozygous *XK* mutation may develop symptoms likely correlated to the degree of skewed X-chromosome inactivation [1]. So far 39 small nucleotide variants and 17 cases with a partial, or complete deletion of *XK* plus contiguous gene deletions (6 of 17 with full characterization on the molecular level) are recognized by the International Society for Blood Transfusion (ISBT), representing the most complete repository of *XK* variants with an associated MLS phenotype. Five *XK* point mutants have been reported to be found in more than one study, all others were reported from single patients or family groupings only.

In conclusion, the main novel findings we describe for MLS-hyperintensities in the striatum and widespread brain hypometabolism-appear to be unique for the 1.94 mbp deletion in Xp21.1. However, this possibility has to be nuanced by the lack of longitudinal functional imaging, scarce longitudinal structural imaging studies on a few MLS patients [3,5] and because the impact of gene modifiers for this disease remains largely unexplored.

Author contributions

M. Paucar, B. Udd, O. Sveinsson, C. Engström and B. Frey: study concept, data collection and writing of the manuscript; M. Paucar wrote the first draft. C. Gassner carried out the genetic analysis; C. Engström and B. Frey performed the immuohematological analyses; I. Savitcheva contributed with imaging data; G. Solders performed the neurophysiology in the index case; S. Hertegård treated the patient for feeding dystonia. H. Jung and M. Tolnay performed the neuropathological assessment. O. Sveinsson, P. Svenningsson, C. Gassner, C. Engström, J. Laffita-Mesa, G. Solders, S. Hertegård, I. Savitcheva, H. Jung, M. Tolnay and B. Frey: editing of the manuscript.

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Disclosures

The authors report no disclosures relevant to the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.09.014.

References

[1] H.H. Jung, A. Danek, R.H. Walker, et al., McLeod neuroacanthocytosis syndrome, in: M.P. Adam, H.H. Ardinger, R.A. Pagon, S.E. Wallace, L.J. Bean, H.C. Mefford, et al. (Eds.), GeneReviews® [Internet], University of Washington, Seattle, Seattle (WA), 1993[cited 2018 April 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1354/.

[2] C. Gassner, C. Brönnimann, Y. Merki, et al., Stepwise partitioning of Xp21: a profiling method for XK deletions causative of the McLeod syndrome, Transfusion 57 (9) (2017 Sep) 2125–2135.

[3] A. Danek, J.P. Rubio, L. Rampoldi, et al., McLeod neuroacanthocytosis: genotype and phenotype, Ann. Neurol. 50 (6) (2001 Dec) 755–764.

[4] H.H. Jung, M. Hergersberg, S. Kneifel, et al., McLeod syndrome: a novel mutation, predominant psychiatric manifestations, and distinct striatal imaging findings, Ann. Neurol. 49 (3) (2001 Mar) 384–392.

[5] P.O. Valko, J. Hänggi, M. Meyer, et al., Evolution of striatal degeneration in McLeod syndrome, Eur. J. Neurol. 17 (4) (2010 Apr) 612–618.

[6] Ba D. Nguyen, Brain and upper extremity PET/CT findings of hyperglycemia-induced hemiballism-hemichorea, Clinical Nuclear Medicine Issue, 32 August 2007, pp. 643–645.

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