# Novel mutations and findings in a cohort of McLeod neuroacanthocytosis, an X-linked HD phenocopy

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**Background** McLeod syndrome (MLS) is an ultra-rare neurodegenerative X-linked disease caused by mutations in the *XK* gene, classified as neuroacanthocytosis syndrome. Together with the clinically very similar chorea-acanthocytosis it belongs to the heterogeneous group of “Huntington's disease (HD) phenocopies”.

**Aims & Methods** To characterize a cohort of HD phenocopies with the genetically confirmed diagnosis of MLS. This is a retrospective and prospective multi center analysis of genotype and phenotype of sixteen MLS cases from Germany. The study was approved by the IRB of the LMU Munich (No. 19-843).

## Results

| Case | I | II | III | IV | V | VI | VII | VIII | IX | X | XI | XII | XIII | XIV | XV | XVI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mutation** (* novel) | c.144C>A p.Cys48Ter (*) | c.397C>T p.R133X (XK*N.17) | c.397C>T p.R133X (XK*N.17) | c.451dupC p.Gln151ProfsTer48 (XK*N.10) | c.451C>T stop codon at Q151Stop (*) | c.686+687delTT p.F229Y + fs 264X (XK*N.11) | c.719dupT p.Ile241Asnfs*25 (*) | c.757delT p.W253fs (*) | c.771G>A stop codon at W257X (*) | c.977C>T p.Q299X | c.941G>A p.Trp314* (XK*N.21) | c.962T>C p.Cys294Arg | c.1078 T>C p.C360R (*) | Deletion of *XK* and *PRRG;* Xp21.1 (35975369_ 37731812)x0 | Deletion of *XK*, *CYBB*, *DYNLT3*; Xp21.1 (37423614_ 37690981)x0 | Deletion of *XK*, *CYBB*, *DYNLT3;* Xp21.1 (.37586289_ 37712292)x0 |
| **Movement disorder** | Generalized chorea | Generalized chorea, tics, vocalizations/ echolalia | Generalized chorea, orofacial dyskinesia, tics/vocalizations, resting/posture tremor of the arms, parkinsonism, bending in the knees | Generalized chorea | Orofacial dyskinesia | Mild vocal tics | N/A | N | Akathisia, orofacial dyskinesia | Generalized chorea | N | Generalized chorea aged orofacial dyskinesias, dystonic and athetoid movements, vocalizations | Generalized chorea, tremor (side effect), postural tremor, dystonia, bradykinesia | Vocalizations | N | N |
| **Cognitive impairment** | Y | N | Perseveration | Y | MCI | N; MOCA: 29/30 | N/A | N | N | N | N | Y, IQ below 80 | Perseveration, cognitive decline | N | N | N |
| **Neuro-psychiatric manifestation** | Severe psychosis, zonesthesia | Depression | Severe Depressions, obsessive compulsive behavior with coprolalia, perseveration, irritability, agitation, sleep disorder | Paranoid hallucinatory syndrome | Depression | BDI-II: 0 mild obsessive behaviour | N/A | N | Dissociative disorder, depression, received neuroleptics in the past | Compulsive behavior, paranoia, restlessness | N | Depression, insomnia, personality changes, etc. | Depression, irritability, restlessness, verbally aggressive behavior, mood swings, sleep disturbances, apathy and binge eating | “Increased nervousness“ | N | N |
| **Seizures** | N | N | N | N | N | Y (since childhood) | N/A | N | N | Y | N | Y | Y (since childhood) | N | Y (following stroke) | N |
| **Myopathy** | N | N/A | No signs for myopathy in EMG | Y (rhabdomyolysis) | N/A | Y | N/A | Mild | No signs for myopathy in EMG | Mild myopathy | N | Muscle weakness | No signs for myopathy in EMG | „Degenerative“ myopathy | N | N |
| **Neuropathy** | Axonal sensory PNP | Peripheral axonal sensory<motor PNP | Peripheral axonal-demyelinating sensory-motor PNP | Peripheral axonal PNP | Peripheral axonal PNP | Peripheral axonal sensory neuropathy | N/A | Peripheral axonal PNP | Severe axonal-demyelinating sensory-motor PNP | Axonal- demyelinating sensory and motor PNP | N | N | Axonal sensory-motor PNP | N/A | N | N |
| **Cardio-myopathy** | N/A | Myocarditis?, concentric left ventricular hypertrophy | pathological speckle tracking echocardiography | N/A | Dilated cardiomyopathy, atrial fibrillation | N | N/A | Dilated (inflammatory) cardiomyopathy, atrial fibrillation | N/A “sudden cardiac death” | N | N | Slight left ventricular hypertrophy, constant sinus tachycardia 100 bpm | Dilated cardiomyopathy ICD Implantation | N | Dilatated cardiomyopahty (toxic after stem cell transplantation?) | Pathological speckle tracking echocardiography (toxic after stem cell transplantation?) |
| **Laboratory results** | CK 479-652 U/l | CK 949-2422 U/l Acanthocytes 8-15 % | CK 55-10855 U/l Acanthocytes 15% | CK 2579-14795 U/l Acanthocytes N/A | CK 685 – 3374 U/l Acanthocytes + | CK 300-6000 U/L Acanthocytes 36 % | N/A | CK 165-3514 U/l Acanthocytes + | HyperCKemia | CK 279 – 1270 U/l | CK 474-18099 U/l | CK 93-337 U/l Acanthocytes 5-8% | HyperCKemia, Acanthocytes - | CK 358-2940 U/l Acanthocytes 23 % | CK 578 U/l | CK 1279-2453 U/l Acanthocytes - |
| **Neuro-imaging** | MRI: caudate atrophy as well as atrophy of the parietal cortex | MRI: cerebral microangiopathy, zystic lesion of the pituitary gland | MRI: mild leukoencephalopathy | MRI: caudate atrophy | MRI: caudate atrophy (caput) | MRI: vestibular schwannoma, FDG-PET: reduced metabolism in basal ganglia (left>right) | N/A | N/A | MRI scan normal | Normal CT | MRI: typical MS lesions supra- and infratentorial | Caudate atrophy | MRI/CT: generalized atrophy, caudate atrophy Scintigraphy: striatal degeneration | N/A | CT prior to conditioning for HSCT: normal | MRI prior to conditioning for HSCT (age 10 years): normal |
| **Others** | N | Implantable cardioverter-defibrillator | Dysarthria/dysphagia with questionable feeding dystonia (PEG), Hepatitis C | Dysarthria | Hepatosplenomegaly, OSAS, implantable cardioverter-defibrillator | OSAS, vestibular schwannoma | N/A | Implantable cardioverter-defibrillator | Testicular carcinoma with orchiectomy and radiation; caused traffic accident due to akathisia | Spinal dermoid cyst at lumbar vertebrae 2/2 | Multiple sclerosis | Died of recurring aspiration pneumonias | Dysarthria, implantable cardioverter-defibrillator | Hepatosplenomegaly OSAS, vitiligo | Hematopoietic stem cell transplantation for chronic granulomatous disease | Hematopoietic stem cell transplantation for chronic granulomatous disease |

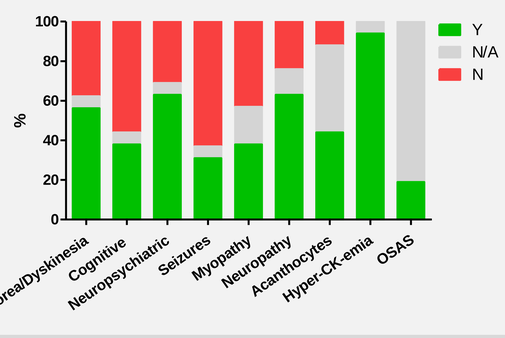


**Fig. 1** Frequency of symptoms and clinical findings

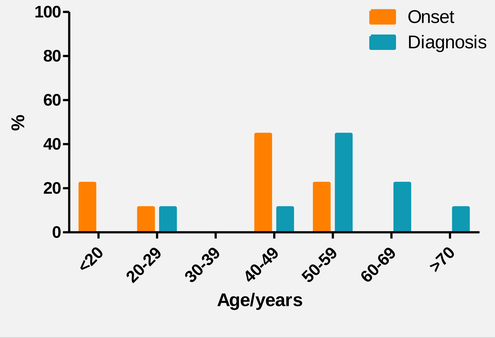


**Fig. 2** Age of onset (first symptom) and age at diagnosis

## Conclusions

We longitudinally characterized the second largest MLS cohort known to date. We identified novel *XK* mutations as well as a deletion that extend into the *PRRG1* gene (novel) and describe two contiguous gene deletion cases of MLS with X-linked chronic granulomatous disease (deletion also effecting the *CYBB* gene). This study confirms core features of MLS such as late onset hyperkinetic movements in association with neuro-/myopathy, neuropsychiatric impairment, cardiac involvement, hyperCKemia. Novel aspects in this MLS series seem obstructive sleep apnea and epileptic seizure onset in childhood.

Our study expands the limited knowledge on the variable course, the various clinical manifestations and the genetic spectrum of a hereditary HD phenocopy syndrome.