Novelty Journals

ISSN 2394-966X

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

MARINESCO-SJOEGREN SYNDROME: A RETROSPECTIVE EVALUATION OF A RARE ENTITY OF TWO FEMALE SIBLINGS WITH WELL-PRESERVED COGNITIVE MILESTONES AND INTELLECTUAL ABILITIES. REVIEW OF THE LIETRATURE WITH MAIN FOCUS ON MOLECULAR BIOLOGY AND GENETICS

Munthir Al-Zabin[1], MD, PhD; Herbert Wachtermann[2], MD, PhD

[1]Correspondence author; Doctor of Neurosurgery, Neurosurgical Intensive Care and Emergency Medicine, PhD in Molecualr Neurobiology.

Former Head Of Neurosurgical Unit, Ibra Hospital, Sultanate of Oman.

Currently at Department of Orthopaedics and Neurosurgery, BDF, RMS, Military Hospital, Kingdom of Bahrain.

[2]Professor of Paediatric Neurology and Paediatric Intensive Care, PhD in Experimental Paediatric Immunology, Former Head Of Paediatric Department Of The Catholic Hospital in Saarbruecken / Germany.

Abstract: **Marinesco-Sjögren syndrome (MSS) is a rare autosomal recessive, multiorgan disorder with cardinal features of cerebellar ataxia, congenital or early childhood cataracts, psychomotor retardation, and myopathy. Additional features include hypergonadotropic hypogonadism, various skeletal abnormalities and deformities due to muscle weakness, short stature, and strabismus. The neuroradiologic hallmarks are hypoplasia of both the vermis and cerebellar hemispheres. The histopathologic findings include severe cerebellar atrophy and loss of Purkinje and granule cells. The common pathologic findings in muscle biopsy are variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation. The presence of marked cerebellar atrophy with myopathy distinguishes MSS from another rare syndrome, the congenital cataracts, facial dysmorphism, and neuropathy syndrome (CCFDN). Mutations in the SIL1 gene on chromosome 5q31 were demonstrated to cause MSS, which is caused by homozygous or compound heterozygous. MSS is genetically distinct from congenital cataracts, facial dysmorphism, and neuropathy, which is caused by mutation in the CTDP1 gene on chromosome 18q23; MSS can share some overlapping features with other sundromes, including congenital cataracts, delayed psychomotor development, and ataxia. The major distinguishing clinical features of MSS are the presence of peripheral neuropathy, facial dysmorphism, and microcornea (Lagier-Tourenne et al., 2003). Patients with a subtype of MSS with myoglobinuria and neuropathy have been linked to chromosome 18q23r, and recently a locus for classical MSS has been localized on chromosome 5q31. The importance of myopathy has been determined in**

Novelty Journals

ISSN 2394-966X

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

this disorder apart from the CNS based disability. Pattern of muscle involvement and degree of its severity have been established. Muscle computed tomography (CT) investigations were carried out in many MSS patients homozygous for markers around the MSS locus on chromosome 5q31. Patients with severe clinical disability showed severe and generalized muscle degeneration. Muscle CT findings in patients with relatively severe clinical picture were characterized by severe involvement of the posterior thoracic and pelvic muscles, and almost all thigh muscles. In the legs, the peronei and posterior compartment muscles were severely degenerated. The group of patients with moderate severity of disease showed the same pattern of involved muscle, albeit with lower degree of muscle degeneration. Patients with MSS linked to chromosome 5q31 have a severe progressive myopathy, the extent of which may remain largely unrecognized because of the CNS involvement. In this case study, two female siblings were reported with typical symptoms of MSS; but however without any cognitive or intellectual deficits and with stable and normal mental development. A review of the literature was performed for understanding of the history and assessment of the disease and possible management and treatment. MSS is genetically heterogeneous, and mutations of SIL1 are often not evident. Consequently, new genes for MSS await discovery and they hold the promise of furthering the mechanistic understanding of the condition, enabling clinically meaningful genetic classification schemes to be designed.

Keywords: **Marinesco–Sjoegren syndrome (MSS); SIL1 gene; Bradykinetic movement disorder; Motor neuronopathy; Multisystem disorders; Autophagy; Ataxia; clinical scale; DNA repair; ion channel dysfunction; mitochondrial dysfunction; polyglutamine disorders.**

1. INTRODUCTION

The practice to use ataxia to designate a disease goes back to the middle of the 19th century, when Duchenne coined the term locomotor ataxia for tabes dorsalis. In the 20th century, a neuropathological approach to the ataxias inspired by the seminal work of Holmes and Greenfield prevailed, and classifications based on neuropathological categories, such as olivopontocerebellar atrophy, cerebellar cortical atrophy, or spinocerebellar degeneration, were in common use. However, a consensus on the proper classification of cerebellar degenerations was never reached. [1-9, 13, 17-22, 29-30, 35]

TABLE 1: Classification of ataxias.

1. Hereditary ataxias
   - 1.1. Autosomal recessive ataxias
     - 1.1.1. Friedreich ataxia (FRDA)
     - 1.1.2. Ataxia telangiectasia (AT)
     - 1.1.3. Autosomal recessive ataxia with oculomotor apraxia type 1 (AOA1)
     - 1.1.4. Autosomal recessive ataxia with oculomotor apraxia type 2 (AOA2)
     - 1.1.5. Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)
     - 1.1.6. Ataxia with isolated vitamin E deficiency (AVED)
     - 1.1.7. Marinesco–Sjögren syndrome (MSS)
     - 1.1.8. Autosomal recessive ataxias due to POLG mutations (MIRAS, SANDO)
     - 1.1.9. Cerebrotendinous xanthomatosis (CTX)
     - 1.1.10. Refsum disease
     - 1.1.11. Abetalipoproteinemia
     - 1.1.12. Other autosomal recessive ataxias
   - 1.2. Autosomal dominant ataxias
     - 1.2.1. Spinocerebellar ataxias (SCA)
     - 1.2.2. Episodic ataxias (EAs)
   - 1.3. X-linked ataxias
     - 1.3.1. Fragile X–associated tremor/ataxia syndrome (FXTAS)
     - 1.3.2. Other X-linked ataxias
   - 1.4. Ataxias due to mitochondrial mutations
2. Nonhereditary degenerative ataxias
   - 2.1 Multiple system atrophy, cerebellar type (MSA-C)
   - 2.2 Sporadic adult-onset ataxia of unknown origin (SAOA)
3. Acquired ataxias
   - 3.1. Alcoholic cerebellar degeneration (ACD)
   - 3.2. Ataxia due to other toxic reasons
   - 3.3. Ataxia due to acquired vitamin deficiency
   - 3.4. Paraneoplastic cerebellar degeneration
   - 3.5. Other immune-mediated ataxias
   - 3.6. Ataxia in chronic CNS infection
   - 3.7. Superficial siderosis

The situation changed with the work of Harding in the early 1980s. Harding clearly recognized the inconsistencies of the neuropathological classifications, in particular that hereditary diseases manifesting in a single family often had to be assigned to different neuropathological categories, whereas, on the other hand, disorders that were clinically and genetically distinct were put into the same category. Consequently, Harding proposed a new classification that was based mainly on clinical and genetic criteria. The new classification was not only widely accepted but paved the way for a renewed interest of clinical neurologists in ataxias. (Table 1).

1.1. Genetics:

Among all disciplines, genetics had the strongest impact on the development of the ataxia field in the past 25 years. During this period, linkage of numerous ataxia disorders to chromosomal loci was demonstrated, and in most cases, the mutations causing these disorders were subsequently found. The identification of mutations causing dominantly inherited spinocerebellar ataxias (SCAs) started in 1993 with the discovery that an unstable expansion of a translated CAG repeat underlies SCA1.4 This finding placed SCA1 in the group of polyglutamine disorders that at that time included spinobulbar muscular atrophy (SBMA) and Huntington's disease (HD).

1.2. Pathology:

In the past 25 years, however, clinicians and geneticists rather than neuropathologists left their marks on ataxia research. Numerous new insights came from neuropathological studies, the most important one being the recognition of intracellular proteinaceous inclusions as pathological hallmarks of a number of ataxia disorders.

In brains of patients with the polyglutamine ataxias SCA1, SCA3, SCA7, and SCA17, neuronal intranuclear inclusions (NIIs) containing the expanded disease protein were observed.19 On the other hand, NIIs are less frequent or absent in SCA2 and SCA6, disorders that also belong to the group of polyglutamine diseases.

Although most scientists agree that the large inclusions seen inside neurons in brain disease are not the primary culprits causing neurons to die, they do represent a pathological hallmark reflecting a chronic problem with protein homeostasis. Following the clinical delineation of MSA as a disease entity, glial cytoplasmic inclusions (GCIs) were discovered in oligodendroglial cells of MSA brains.

A major component of GCIs is a-synuclein, an observation that placed MSA in the group of synucleinopathies together with Parkinson disease and Lewy body dementia. [1-5, 14-17, 20-31, 34]

1.3. Epidemiology:

In the past 25 years have seen a number of epidemiological studies that attempted to determine the prevalence of certain ataxias in defined regions. Nevertheless, a reliable estimation of the prevalence of all ataxias is still not possible. In Europe, FRDA is the most frequent recessive ataxia with a prevalence ranging between 1.7 and 3.7 per 100,000,22 whereas it is almost absent in the East Asian population.

Dutch and Norwegian surveys found a prevalence of dominantly inherited SCAs of 3.0 and 4.2 per 100,000, respectively.23,24 Studies of sporadic ataxia performed in the Aosta valley (Italy) and in south eastern Wales (United Kingdom) reported a prevalence of 6.9 and 8.4 per 100,000, respectively. In the Japanese population, the prevalence of sporadic ataxias including MSA was determined to be 18.5 per 100,000.27 Epidemiological studies of acquired ataxias are widely lacking. On the basis of the available figures, it can be estimated that the overall prevalence of ataxias is at least 15 per 100,000 and may approach 20 per 100,000. Thus, ataxia appears to be more frequent than generally assumed. Nevertheless, ataxia remains an orphan disease according to current definitions of the National Institutes of Health and the European Commission. (Tables 2 and 3). [15-17, 20, 24, 35]

Therapeutic: Although the genetic defects of many hereditary ataxias were discovered in the past 25 years, this has not yet led to new therapies. (Tables 2 and 3) Etiological treatment approaches are available only for some rare forms of ataxia with known biochemical defects, such as Refsum's disease, CTX, and AVED. In most other types of hereditary and nonhereditary degenerative ataxias, only supportive treatment is possible. Repeated claims that centrally acting drugs such as 5-hydroxytryptophan, buspirone, physostigmine, thyrotropin-releasing hormone, and D-cycloserine have an antiataxic action and temporarily improve cerebellar ataxia, often based on uncontrolled observations in small patients samples, did not stand up to subsequent larger trials.

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

TABLE 2: Spinocerebellar ataxias (SCAs): molecular genetics and clinical phenotype

Disorder	Mutation	Gene product	Clinical phenotype
SCA1	Translated CAG repeat expansion	Ataxin-1	Ataxia, pyramidal signs, neuropathy, dysphagia, restless legs syndrome
SCA2	Translated CAG repeat expansion	Ataxin-2	Ataxia, slow saccades, neuropathy, restless legs syndrome
SCA3/Machado-Joseph disease (MJD)	Translated CAG repeat expansion	Ataxin-3	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia, restless legs syndrome
SCA4	Unknown	Unknown	Ataxia, sensory neuropathy
SCA5	Point mutation	Beta-III spectrin (SPTBN2)	Almost purely cerebellar ataxia
SCA6	Translated CAG repeat expansion	Calcium channel subunit (CACNA1A)	Almost purely cerebellar ataxia
SCA7	Translated CAG repeat expansion	Ataxin-7	Ataxia, ophthalmoplegia, visual loss
SCA8	3′ Untranslated CTG repeat expansion	Ataxin-8	Ataxia, sensory neuropathy, spasticity
SCA10	Intronic ATTCT repeat expansion	Ataxin-10	Ataxia, epilepsy
SCA11	Insertion, deletion	Tau tubulin kinase 2 (TTBK2)	Almost purely cerebellar ataxia
SCA12	5′ Untranslated CAG repeat expansion	Phosphatase subunit (PP2A-PR55β)	Ataxia, tremor
SCA13	Point mutation	Potassium channel (KCNC3)	Ataxia, mental retardation
SCA14	Point mutation	Protein kinase C γ (PKCγ)	Ataxia, myoclonus, dystonia, sensory loss
SCA15/16	Deletion	Inositol 1,4,5-triphosphate receptor, type 1 (ITPR1)	Almost purely cerebellar ataxia
SCA17	Translated CAG repeat expansion	TATA binding protein (TBP)	Ataxia, dystonia, chorea, dementia, psychiatric abnormalities
SCA18	Unknown	Unknown	Ataxia, sensory neuropathy, neurogenic muscle atrophy
SCA19/22	Unknown	Unknown	Ataxia, myoclonus, cognitive impairment
SCA20	Unknown	Unknown	Ataxia, dysphonia
SCA21	Unknown	Unknown	Ataxia, parkinsonism
SCA23	Unknown	Unknown	Ataxia, sensory neuropathy, pyramidal signs
SCA25	Unknown	Unknown	Ataxia, sensory neuropathy
SCA26	Unknown	Unknown	Almost purely cerebellar ataxia
SCA27	Point mutation	Fibroblast growth factor 14 (FGF14)	Ataxia, tremor, mental retardation
SCA28	Missense	ATPase family gene 3-like 2 (AFG3L2)	Ataxia, ophthalmoparesis, pyramidal signs
SCA30	Unknown	Unknown	Almost purely cerebellar ataxia
SCA31	Pentanucleotide (TGGAA) repeat insertion	Unknown	Almost purely cerebellar ataxia

Understanding of Molecular Pathogenesis: Some repeatexpansion diseases result in expansions in the encoded proteins, whereas others occur in non-protein-coding regions of the gene. Although it is not yet certain how noncoding repeat expansions cause neurodegeneration, the prevailing theory is that at least some of them act through a dominant toxic mechanism occurring at the RNA level, much like myotonic dystrophy.36 Fragile X–associated tremor ataxia syndrome (FXTAS) belongs to this class of diseases. Another noncoding repeat disease is SCA8, which is associated with a large CAG/CTG repeat expansion. 12-20, 22, 24, 26, 29, 31, 33

TABLE 3: Autosomal recessive ataxias: gene products and function

Disorder	Gene product	Function
Mitochondrial/oxidative stress		
Friedreich ataxia (FRDA)	Frataxin	Synthesis of iron–sulfur clusters
Mitochondrial recessive ataxia syndrome (MIRAS)	Polymerase gamma (POLG)	Mitochondrial DNA proofreading
Infantile onset spinocerebellar ataxia (IOSCA)	Twinkle	Mitochondrial DNA proofreading
Autosomal recessive cerebellar ataxia type 2 (ARCA2, SCAR9)	ADCK3	Coenzyme Q10 synthesis
Ataxia with isolated vitamin E deficiency (AVED)	α-Tocopherol transport protein	Vitamin E
Abetalipoproteinemia	Microsomal triglyceride transfer protein	Vitamin E
DNA repair		
Ataxia telangiectasia (AT)	ATM protein	Phosphoinositol-3 kinase activity: cell-cycle checkpoint control and DNA repair
Ataxia telangiectasia-like disorder (ATLD)	MRE11	Double-stranded DNA repair
Ataxia with oculomotor apraxia type 1 (AOA1)	Aprataxin	Single-stranded DNA repair
Ataxia with oculomotor apraxia type 2 (AOA2, SCAR2)	Senataxin	Single-stranded DNA repair
Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1)	Tyrosyl-DNA phosphodiesterase-1 (TDP1)	DNA replication
Other mechanisms		
Refsum disease	Phytanoyl–CoA hydroxylase	Oxidation of phytanic acid
Cerebrotendinous xanthomatosis (CTX)	Sterol-27 hydroxylase	Sterol hydroxylation
ARSACS	Sacsin	Proteasomal system
Marinesco-Sjögren syndrome (MSS)	SIL1	ER glycoprotein
Autosomal recessive cerebellar ataxia type 1 (ARCA1, SCAR8)	SYNE1	Member of spectrin family
Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)	ABHD12	Endocannabinoid metabolism: hydrolysis 2-arachidonoyl glycerol (2-AG)

Future Directions: The greatest challenge for ataxia research is the development of effective therapies. So far, only idebenone in FRDA has made its way to a phase III trial, which then unfortunately failed.42 In the future, it will be of vital importance for academic research and the pharmaceutical industry to join forces to establish an effective research pipeline including development of standardized criteria for the rigorous evaluation of molecular targets, of pathogenic mechanisms, and of therapeutic approaches that will finally result in successful clinical trials. The possible therapeutic strategies are diverse and range from conventional pharmaceutical approaches to gene therapy. Silencing of disease genes using RNA interference (RNAi) is a novel experimental therapeutic approach that appears to be specifically suitable for polyglutamine SCAs. The therapeutic value of this approach in SCAs has already been shown in transgenic disease models. [2-9, 17-20, 28, 30, 33, 35]

An alternative approach is treatments that aim to normalize disturbed neuronal activity in the cerebellum and thereby exert a ‘‘symptomatic’’ antiataxic effect. [2-7, 18, 20, 23, 29, 33, 35]

1.4. History of the disease description:

Marinesco-Sjögren syndrome is a recessively inherited disorder characterized by cataract and ataxia. Cataract may be present at birth or develop within the first two years of life. Mental retardation is an associated feature and can be mild to severe. The disorder was initially described by Moravscik in 1904 and later by Marinesco et al. and Sjögren. In addition to the main characteristics of the syndrome, numerous other features have been reported in individual patients indicating that Marinesco-Sjögren syndrome is a multisystem disorder.

Many authors have described the disease in the past:

*G. Marinescu, S. Draganescu and D. Vasiliu announced in 1931 in their French publication about a new congenital disease, which was characterized by congenital cataract and delayed mile stones in the somato-neuro-psychiaric development:

«Nouvelle maladie familiale caractérisée par une cataracte congénitale et un arrêt du dévelopement somato-neuro-psychique.»

The authors in the publication in L'encéphale, Paris, 1931, 26: 97-109, they described a new syndrome with congenital cataract and delay of the somato-neurological and psychological development.

**The publication by T. Sjögren in Berlin in 1935, written in German, reported similar investigations about clinical and hereditary assessment of patients with congenital cataract and oligophrenia:

«Klinische und vererbungsmedizinische Untersuchungen über Oligophrenie mit kongenitaler Katarakt.

Zeitschrift für die gesamte Neurologie und Psychiatrie, Berlin, 1935, 152: 263-292.»

***T. Sjögren pulished again in 1947 about the disease:

Hereditary congenital spinocerebellar ataxia combined with congenital cataract and oligophrenia.

Acta psychiatrica et neurologica scandinavica, Copenhagen, 1947, 46 (Suppl): 286-289. And again the same author wrote in 1950 his famous paper about :

Hereditary congenital spinocerebellar ataxia accompanied by congenital cataract and oligophrenia. A genetic and clinical investigation.

Confinia Neurologica, Basel, 1950, 10: 293-308.

****H. Garland, D. Moorhouse published in 1953:

An extremely rare recessive hereditary syndrome including cerebellar ataxia, oligophrenia, cataract and other features. Journal of Neurology, Neurosurgery and Psychiatry, London, 1953, 16: 110-116. Superneau et al. (1985) pointed to a description of this syndrome reported in the Hungarian medical literature in 1904. Chudley (2003) provided a biographic sketch of Georges Marinesco (1863-1938).

1.5. Clinical, genetical Mapping and molecular genetics of MSS:

Cerebellar ataxia, congenital cataracts, retarded somatic and mental maturation are the cardinal features of MSS. Alter et al. (1962) suggested the designation 'hereditary oligophrenic cerebellolental degeneration.' Garland and Moorhouse (1953) published a striking pedigree. In a boy almost 5 years old, Todorov (1965) found the brain lesions limited almost exclusively to the cerebellum which showed massive cortical atrophy. Many of the Purkinje cells that remained were vacuolated or binucleated. Skre and Berg (1977) observed 10 persons with Marinesco-Sjögren syndrome in 2 kindredships; 9 of whom also had hypogonadism. The observations of Wertelecki (1986) also suggested that the association of hypergonadotropic hypogonadism is a pleiotropic manifestation of the MSS gene. [19, 21, 23, 25, 27, 30-32, 34] In an inbred, triracial (Indian, black, white) isolated in southwestern Alabama, Wertelecki (1986) found hyper gonadotropic hypogonadism as a frequent feature among the many cases observed. And in the same inbred group, Superneau et al. (1987) found progressive muscular weakness, hypotonia and atrophy to be among the cardinal symptoms and signs. Most of the 17 patients studied had elevated serum creatine kinase (CK) levels and muscle biopsies showed myopathic changes. Conspicuous myopathy was present in 2 young children, indicating that myopathy is an early sign. Walker et al. (1985) suggested that MSS may be a lysosomal storage disorder. In 4 patients from 2 different families and ethnic groups, they found, by electron microscopy, numerous enlarged lysosomes containing whorled lamellar or amorphous inclusion bodies. By homozygosity mapping in 2 large consanguineous families with MSS, one of Turkish and one of Norwegian origin, Lagier-Tourenne et al. (2003) localized the MSS locus to chromosome 5q31. In a Finnish family, Anttonen et al. (2005) confirmed linkage of the disease phenotype to 5q31; meiotic and historical recombinations defined a 3.52-Mb region with a shared haplotype in Finnish individuals with MSS. Further studies narrowed the region to 1.98 Mb, which excluded the gene SAR1B, also called SARA2 (607690), which had been suggested as a candidate. Anttonen et al. (2005) selected genes from the 1.98-Mb region for sequencing on the basis of tissue expression or predicted function.

2. MSS – A PROTEIN MISFOLDING AND ACCUMULATION DISEASE?

Several data suggest that MSS pathogenesis is linked to abnormal protein quality control in the ER. Chaperone GRP78 has multiple roles in processing proteins targeted to the secretory pathway (Hendershot 2004). As cochaperone, SIL1 regulates the ATPase cycle of GRP78. Most of the SI L 1 mutations described so far are predicted to lead to nonfunctional or absent SIL1 and are thus likely to result in decreased rates of GRP78 hydrolysis and abnormal protein translocation and folding (Figure 10). The accumulation of unfolded proteins in the ER causes ER stress, and if stressful conditions are not alleviated this may lead to cell death (Ma et al. 2004). In addition to the prior pathogenetic mechanisms, our results in the mutant SIL1 expression studies imply that missense changes and some truncations in the SIL1 polypeptide may lead to conformational alterations making the polypeptide prone to aggregation and thus nonfunctional. The hypothesis of defective protein folding in MSS is supported by data from the w z mouse. In the w z Purkinje cells loss-of-function of SIL1 causes induction of the unfolded protein response and abnormal accumulation of proteins, which is followed by neurodegeneration (Zhao et al. 2005). The accumulations in w z Purkinje cells contain several ER chaperones, including GRP78 and GRP94, but it remains to be studied whether truncated SIL1 could also be present. Another interesting aspect is the survival of a subset of cerebellar Purkinje cells in MSS and in the w z mouse mutant.

2.1. CASE REPORT (1)

The 5-year-old girl of first-cousin healthy parents presented at the age of 6 months with global developmental delay, hypotonia, and weakness. She was the first child of a distantly related Chinese couple. She was born at 39 weeks in good condition, and weighed 2.97 kg (9–25th centile). Her gross motor milestones were delayed; at six months of age she had poor head control, and could not roll over. She was setting unaided at 15 months, profound bradykinesia was noted at the age of two years, and she took steps with the support of a frame at three years. At four years she could walk short distances with the support of a Kaye-walker, however she remained very bradykinetic. Fine motor skills were also impaired. Speech development was delayed, however less significantly than gross and fine motor skills; at two years of age she had 20 words, continued to make significant progress and at the age of five years was bilingual. There were no concerns about her hearing and cognitive abilities. Concerns about her vision were raised at three years of age when she was found to have bilateral cataracts, which required surgical removal. She currently attends mainstream school with support.

On examination at 4 years of age; height, weight and head circumference were all below the 0.4th centile. She was not dysmorphic and had a full range of eye movements. The most striking features were profound facial hypomimia, and marked generalized paucity of movement. There was a degree of weakness, and mainly truncal ataxia, although this was not as prominent. There was no tremor. Reflexes were absent, and plantars were downgoing. On further examination at 4 years and 6 months of age, her ataxia had evolved but hypomimia and difficulties initiating and executing movements remained the most prominent neurological feature. Laboratory investigations included mildly elevated CK levels ranging from 283 to 431 IU/l. Endocrine tests performed for her short stature and poor growth revealed growth hormone deficiency and low insulin-like growth factor levels, prompting initiation of growth hormone therapy. MRI of the brain revealed cerebellar atrophy (Figure 1). CSF neurotransmitter studies were normal. Nerve conduction studies showed normal sensory and motor responses with appropriate velocities for age. Motor unit duration estimation of the EMG showed an excess of long duration units in the tongue and, to a slightly lesser degree, tibialis anterior. This combination of findings was interpreted as indicating the presence of a motor neuronopathy with the cranial nuclei affected more than spinal neurones. Muscle biopsy featured an increase in endomysial connective tissue, abnormal variability in fibre size and occasional fibres with basophilic-rimmed vacuoles in the subsarcolemmal region, which appeared positive for p62 on immunohistochemical stains (Figure 1). Electron microscopy showed some small collections of membranous debris and mild myonuclear lobulation but no well-formed vacuoles (not shown). Whole exome sequencing (WES) of the patient was performed within the NeurOmics project (REC reference 13/EE/0398). The data analysis, using Clinical Sequence Miner tool (deCODE Genetics), revealed a homozygous frameshift mutation in SIL1, c.512_513delTT (p.Phe171Ter). The mutation was not present in Exome Variant Server (http://evs.gs.washington.edu/EVS/) or ExAC (http://exac.broadinstitute.org/) data bases. Subsequent Sanger sequencing verified the SIL1 mutation previously identified on WES. With a view to the unusual clinical findings in our patient, we interrogated WES data for variants in genes known to be associated with inherited neuropathies and early-onset dyskinesia and Parkinsonism, and did not find any additional pathogenic variants. We only identified a not previously reported heterozygous missense variant in the neuralgic amyotrophy associated gene SEPT9 [5], unlikely to be relevant considering asymptomatic consanguineous parents and a discordant clinical phenotype. Both parents were found to be heterozygous carriers of the homozygous SIL1 mutation identified in their daughter.

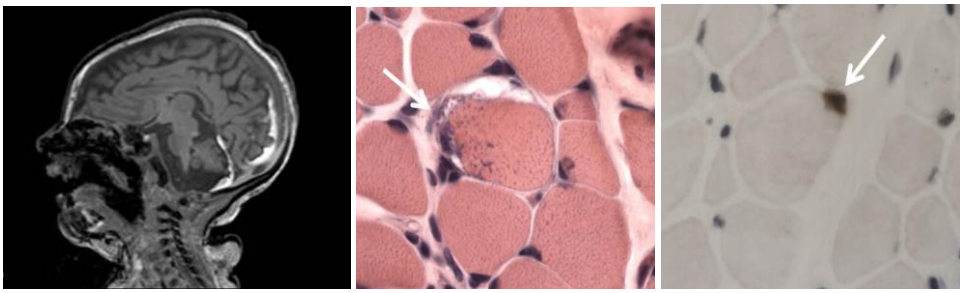

Figure 1: Left: MRI of the brain, T1-weighted images, sagittal sections, showing marked cerebellar atrophy of the patient with SIL1-related MSS at 3 years of age. Middle: Muscle biopsy from the quadriceps, transverse sections, H&E stain, showing a basophilic-rimmed subsarcolemmal vacuole (arrow) and Right: staining positively with antibody to the ubiquitin-binding protein p62 (arrow).

Discussion of the case: To date, more than 100 patients with SIL1-related Marinesco–Sjoegren syndrome (MSS) have been reported in the literature, associated with a consistent phenotype of ataxia, myopathy, and cataracts with onset typically within the first decade of life. Here we present a case of SIL1-related MSS, with an associated motor neuronopathy and a bradykinetic movement disorder preceding the onset of ataxia. This case expands the current spectrum of SIL1-related MSS and suggests a continuum with other early-onset multisystem disorders with overlapping clinico-pathological features and putatively linked in the same cellular pathways.

An associated motor neuronopathy to our knowledge has not been previously reported in SIL1-related MSS and is indeed considered an exclusion criterion by some authors. Neuronal involvement manifesting as an associated (demyelinating, sensory) neuropathy is however a consistent feature in clinically closely related conditions, for example CCFDN (Congenital Cataracts, Facial Dysmorphism and Neuropathy) [OMIM 604168] due to an Eastern European founder mutation in CTDP1 [8], and in patients with genetically unresolved early-onset cerebellar ataxia (EOCA) [9], Friedreich's

ataxia and distinct subgroups of the spinocerebellar ataxias (SCAs). In addition, histopathological evidence of segmental demyelination and axonal degeneration has been reported in one genetically unresolved patient with typical clinical features of MSS. Moreover, Filézac de L'Etang and colleagues demonstrated recently that loss of a functional SIL1 allele results in exacerbation of motor neuron dysfunction and denervation in a mouse model of amyotrophic lateral sclerosis (ALS), providing further supportive evidence for a neuronal phenotype associated with sil1 deficiency. Abnormalities of the lysosomal–autophagic pathway, one of the pathological mechanisms also identified in SIL1-related MSS [4], have recently emerged as a common denominator of a group of neurodevelopmental, neurodegenerative and neuromuscular disorders with substantial overlap. Other neurodevelopmental disorders within this group include Vici syndrome (VS) [OMIM 242840] due to recessive mutations in EPG5, encoding a key autophagy regulator involved in autophagolysosome formation, and Chediak–Higashi syndrome (CHS) [OMIM 214500] due to recessive mutations in LYST, encoding a lysosomal trafficking regulator with a proposed role in autophagosome–lysosome biology. As in our patient with MSS, neuronal involvement has also been found in a subset of patients with CHS and VS (unpublished personal observation). MSS, VS and CHS also share a skeletal muscle myopathy with prominent vacuoles, the hallmark of myopathies due to primary autophagy defects, further indicating a communality of muscle and nerve involvement in disorders with abnormalities of the lysosomal–autophagic pathway. Marked bradykinesia, hypomimia and difficulties initiating movements were the predominant features in our patient before the ataxia typically associated with SIL1-related MSS became more prominent. Interestingly, an early-onset bradykinetic movement disorder with prominent Parkinsonian features has also been reported in a subset of patients with CHS, and features of neurodegeneration evolving over time have been observed in humans with EPG5-related Vici syndrome and animal models of epg5 deficiency. Taken together, these findings suggest an intriguing link between early-onset neurodevelopmental disorders such as VS, CHS and MSS associated with defective autophagy, and the increasing number of adult-onset neuro-degenerative disorders including dementia, ALS and Parkinson's disease (PD) due to defects in the molecular machinery involved in autophagic and lysosomal degradation. Such a link is further supported by the recent observation of sil1 downregulation as a contributory factor to the neuronopathy in SOD1/ALS mice, very specifically indicating this protein as a key player in neurodevelopmental and neurodegenerative disorders with peripheral nerve involvement. Conclusion: This case indicates that an associated motor neuronopathy may be part of the spectrum of SIL1-related MSS and should be actively investigated in genetically confirmed cases. The additional observation of a bradykinetic movement disorder suggests an intriguing continuum between neurodevelopmental and neurodegenerative multisystem disorders intricately linked in the same cellular pathways. MSS may be considered part of an increasing spectrum of conditions combining neuropathic and Parkinsonian features.

2.2. CASE REPORT (2)

The proband was a 12-year-old female sibling of the patient of case 1, the oldest child of first-cousin healthy parents, who presented with developmental delay, speech delay, ataxia and bilateral cataracts. She was born at term through normal vaginal delivery following an uncomplicated pregnancy with a birth weight of 3.5 kg. There were no postnatal problems. At 12 years his weight was 33 kg (10th to 25th centile), height was 147 cm (25th centile), and head circumference was 53 cm (50th to 75th centile). The parents reported that she was an active and cooperative girl. She had subtle dysmorphic features, including bushy eyebrows and a flat mid face with a high arched palate. She had an ataxic gait, with dysmetria, intention tremor and dysdiadochokinesia.

A convergent squint was present in the left eye. Her muscle tone was normal and deep tone reflex was elicited. Pectus carinatum was observed, and the patient was noted to have bilateral clinodactyly of the fifth fingers as well as flat feet. A skeletal survey was normal, except for a mild kyphosis seen at the lower thoracic spine. She was able to stand with support, and walked with support with an ataxic gait. A developmental assessment at 8 years of age showed that she was able to say full sentences, but with poor articulation, and needed help with dressing and feeding. She was observed clinically to be unremarkable in sensce of hearing, understanding and cognitive features and abilities. She had also been diagnosed with infantile bilateral cataract, which had been surgically corrected. X-ray, computer tomography, and magnetic resonance imaging of the brain revealed cerebellar atrophy with a dilated 4^{th} ventricle (Figures 2 and 3). All other investigations were normal and the family history was unremarkable. The patient's four living siblings were all healthy. The mother had had one spontaneous abortion. Based on the clinical features, a tentative diagnosis of MSS was made. Informed written consent was obtained and genomic DNA was extracted from the patient and both of her parents.

Ten millilitres of venous blood was drawn from each of the individuals and sampled in EDTA tubes. The coding region of exons 2–10 and the exon-intron boundaries of the SIL1 gene were amplified by polymerase chain reaction (PCR) and sequenced directly by Bioscientia (Ingleheim, Germany).

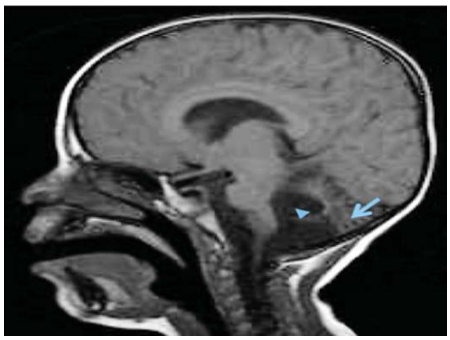

Figure 2: Magnetic resonance imaging scan of the patient. The arrow indicates cerebellar atrophy, while the arrowhead points to the dilated 4th ventricle.

For confirmation of the results, an independent PCR product was sequenced, also by Bioscientia. The sequencing of SIL1 revealed a homozygous deletion from the 5′ untranslated region (UTR; c.-197) to exon 1 (c.90). Instead of the deleted bases, there was a homozygous insertion of one base (C) of unclear origin and 20 bases from intron 1. Both parents turned out to be heterozygous carriers of the same c.-197_90delin sCTGTACTTTCTCAGTTCACT mutation (Figure 3). This mutation was not found in the EXAC Browser or in the GalaxC TM Allele Frequency Database, which contains >2.5 million unique Middle Eastern pathogenic mutations and variants.

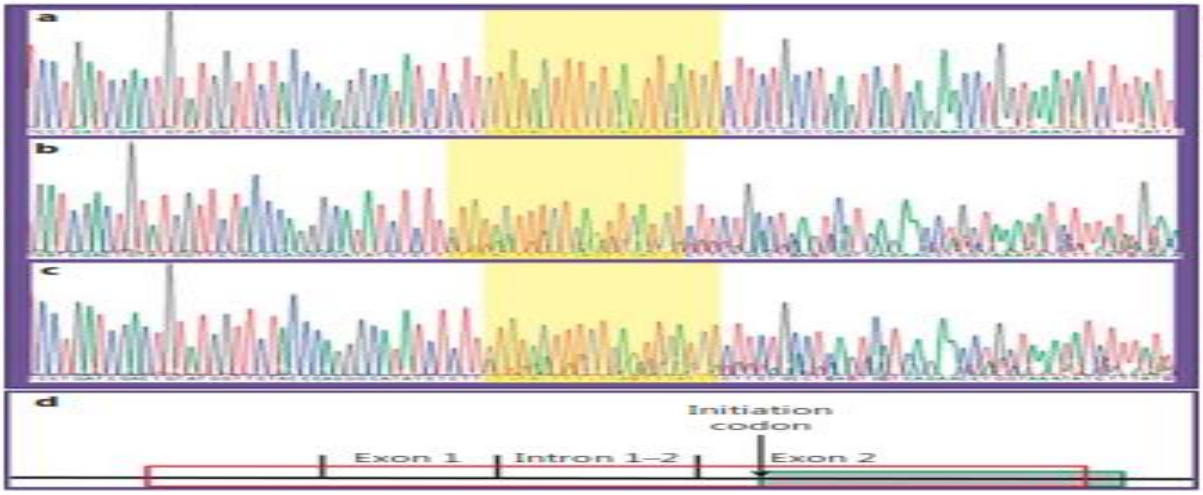

Figure 3: Chromatograms of the patient (a), mother (b) and father (c) showing the indel mutation. d Schematic diagram showing the deletion in the context of the gene structure. The box with a red outline represents the deletion, while the shaded box with a green outline shows the ER signal sequence.

Discussion of the case: This was a case of deletion in the SIL1 gene that led to MSS. The mutation was expected to result in the loss of the start codon and the first 30 amino acids of the protein, as well as the entire 5′ UTR, and part of the region upstream of it. The deleted sequence included the initiation codon as well as the ER targeting sequence. Most mutations so far detected in the SIL1 gene leading up to MSS are concentrated in either intron 9 or exons 6, 9, and 10. It has been speculated that exons 6 and 9 play a pivotal role in mediating the interaction between BAP and BiP, and that exon 10 supports this interaction. This view is supported by the fact that the key amino acid residues that are involved in the interaction between SIL1 and BiP are located within these regions. This mutated protein lacking the ER targeting sequence remains in the cytosol and is thereby unable to carry out the chaperoning activities required of it. Conclusion: This was a case of a mutation in the SIL1 gene affecting the initiation codon and the ER targeting sequence that leads to a phenotype of MSS. Protein level studies would help in the further characterization of this mutation and to assess its functional impact.

Novelty Journals

ISSN 2394-966X

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

3. DISCUSSION

Cerebellar ataxias are a heterogeneous group of neurodegenerative disorders. The hereditary ataxias are all characterized by motor incoordination due to cerebellar dysfunction and the group consists of a large number of autosomal dominant ataxias and ataxias with autosomal recessive, X-linked, or mitochondrial inheritance. Different types of hereditary ataxia have overlap in their clinical presentation and it may be difficult to distinguish between them even when the family history is known (Opa et al. 2002). (Table 4). Friedreich's ataxia (FRDA, MIM 229300) is world wide the most common form of autosomal recessive ataxia, but in Finland its incidence is much lower (Juvonen et al. 2002). In a typical case, symptoms begin in late childhood or adolescence and the death typically occurs in the fourth decade.

TABLE 4: Characteristics of selected autosomal recessive cerebellar ataxias. (Modified from Breedveld et al. 2004).

Disease	Locus	Gene *	Protein **	Age at onset (years)	Distinguishing features	OMIM number	References
Ataxia-telangiectasia (AT)	11q22.3	*ATM*	Serine-protein kinase ATM	0 - 20	Telangiectasia, immune deficiency, cancer, elevated AFP	208900	(Savitsky *et al.* 1995)
Ataxia with vitamin E deficiency (AVED)	8q13.1-q13.3	*TTPA*	Alpha-tocopherol transfer protein TTPA	2 - 52 (<20)	As FRDA, but cardiomyopathy and diabetes are rare; head titubation	183090	(Ouahchi *et al.* 1995)
Friedreich's ataxia (FRDA)	9q13	*FXN*	Frataxin, mitochondrial FRDA	4 - 40	Cardiomyopathy, diabetes	229300	(Campuzano *et al.* 1996)
Infantile onset spinocerebellar ataxia (IOSCA)	10q24	*C10orf2*	Twinkle protein, mitochondrial PEO1	~ 1	Oftalmoplegia, hypacusis, athetosis, peripheral neuropathy, epilepsy	271245	(Nikali *et al.* 2005)
Marinesco-Sjögren syndrome (MSS)	5q31	*SIL1*	Nucleotide exchange factor SIL1	Childhood	Cataract, myopathy, mental retardation, hypergonadotropic hypogonadism	248800	Study II
Mitochondrial recessive ataxia syndrome (MIRAS)	15q24	*POLG*	DNA polymerase subunit gamma-1 DPOG1	5 - 50	Myoclonus, epilepsy	-	(Hakonen *et al.* 2005)

AFP: α-fetoprotein
* Gene abbreviations are according to the HUGO Gene Nomenclature Committee (HGNC) recommendations (www.genenames.org).
** Protein names and abbreviations are according to the UniProt database (beta.uniprot.org).

The age of onset is commonly around 10 years, and in its classical form AVED is very similar to FRDA. The absence of cardiomyopathy and diabetes in AVED distinguishes it from FRDA. Diagnosis is based on low levels of vitamin E in serum. The condition is treatable with vitamin E supplementation (Koenig 2003). [7, 13, 15-19, 23-31]

3.1 Clinical Manifestations:

Marinesco-Sjögren syndrome (MSS, MIM 248800) is an autosomal recessive disorder with marked phenotypic variability (Williams et al. 1996; Lagier-Tourenne et al. 2003; Slavotinek et al. 2005). The syndrome is a panethnic disease with 200 published cases (Orphanet Reports Series 2007), but exact prevalence figures are not available. Clinically, the patients described in the literature form a heterogeneous entity, and can be divided into classical MSS and MSS-like groups. (Table 5).

TABLE 5: Clinical features of MSS.

	(Slavotinek *et al.* 2005) 75 cases	(Williams *et al.* 1996) 125 cases
Cerebellar signs		
Truncal / limb ataxia	72%	>98% cerebellar dysfunction
Dysarthria	45%	
Nystagmus	36%	
Intention tremor	16%	
Ophthalmological features		
Cataracts	91%	98%
Strabismus	44%	
Other neurological signs		
Truncal / limb hypotonia	53%	89% hypotonia, muscle weakness or atrophy
Muscle atrophy	51%	
Muscle weakness	36%	
Ortopedic manifestations		
Pes planus / planovalgus	28%	46% skeletal anomalies
Genu valgum	20%	
Scoliosis	19%	
Kyphoscoliosis	16%	
Joint contractures	17%	
Pectus deformities	9%	

The neuromuscular manifestations described so far show considerable variation. Hypotonia, slowly progressive muscle weakness, and atrophy suggesting chronic myopathy have been the most frequent findings (Andersen 1965; Alter et al. 1968; Herva et al. 1987; Superneau et al. 1987). Electromyography (EMG) typically shows only myopathic features (Chaco 1969; Komiyama et al. 1989; Torbergsen et al. 1991b). Demyelinating polyneuropathy (Zimmer et al. 1992), axonal polyneuropathy (Skre et al. 1976) or both (Alexianu et al. 1983; Müller Felber et al. 1998) have also been described. Serum creatine kinase (CK) concentrations are normal (Superneau et al. 1987; Torbergsen et al. 1991a) or moderately increased, usually 2– 4 fold the upper normal limits. [3, 6, 9, 11-14, 19-25, 27-32, 33-34] The bilateral cataracts have been stated as congenital, but there are several reports on rapid postnatal development of lens opacities (Herva et al. 1987; Ishikawa et al. 1993; McLaughlin et al. 1996; Farah et al. 1997; Slavotinek et al. 2005). In only a few cases has the type of cataract been stated.

Natural history: MSS patients are usually born after uncomplicated pregnancies. Muscular hypotonia is typically noted in early infancy. The development of a child sometimes deteriorates after febrile illness (Slavotinek et al. 2005). Muscular weakness is already noticed during the first decade of life in the distal muscles of the extremities, and some patients are never able to walk without assistance (Alter et al. 1968; Herva et al. 1987; Superneau et al. 1987). Later, patients show truncal ataxia, dysdiadochokinesia, and dysarthria. The motor functions of the patients worsen progressively, followed by stabilization of the functional state at varying ages and at variable degrees of severity. Patients show delayed developmental milestones and their mental performance varies usually from mild to moderate mental retardation (Lagier-Tourenne et al. 2003). Although many of the patients are severely handicapped in their adulthood, the life span of patients with MSS is near to normal. [1, 4, 7, 10, 13-1719-35]

3.2 Histopathologic findings:

Under light microscopy variation in muscle fiber size, atrophic fibers, fat accumulation, and rimmed vacuole formation are observed (Herva et al. 1987; Sewry et al. 1988; Suzuki et al. 1997). Rimmed vacuoles were most evident in samples taken at older ages (Herva et al. 1987). In electron microscopy, autophagic vacuoles with myeloid bodies beneath the sarcolemma or near the nucleus, and a perinuclear dense double-membrane structure suggested to be specific to MSS, are seen (Herva et al. 1987; Sewry et al. 1988; Sasaki et al. 1996). Sural nerve biopsy has been performed on four MSS patients. The findings have been presence of segmental demyelination (Hakamada et al. 1981; Alexianu et al. 1983; Farah et al. 1997), and features of chronic axonal degeneration (Farah et al. 1997), which was proposed to be secondary to the segmental demyelination (Alexianu et al. 1983).

Differential diagnosis: Other syndromes presenting with cerebellar atrophy and ataxia (see above) should be considered as differential diagnoses. This is especially true in a case of an affected child without family history, when all MSS features, e.g. cataract and hypergonadotropic hypogonadism, may not be present (McLaughlin et al. 1996). In MSS, the degree of mental retardation may vary as well as the myopathic features. The congenital cataracts, facial dysmorphism, and neuropathy syndrome (CCFDN, MIM 604168) share with MSS the key features of ataxia, cataracts, psychomotor delay and hypogonadism (Tournev et al. 1999).

Molecular genetics: Two loci have been linked to MSS. LagierTourenne et al. 2003 used a homozygosity mapping strategy in two large consanguineous families of Turkish and Norwegian origin with the strict clinical features of MSS. They localized the M S S locus to a 9.3 cM interval on chromosome 5q31 between markers D 5 S 1 9 9 5 and D 5 S 4 3 6 . A second locus on chromosome 18qter was identified in three Roma families with the phenotype of MSS with myoglobinuria and demyelinating neuropathy (Merlini et al. 2002).

3.3 Link age analysis – defining the gene location:

The recombination fraction (θ) indicates the probability that a recombination, that is a crossing-over event during meiosis, is observed between the two loci. Two loci are genetically linked when θ is less than 0.5 (or 50%). The genetic distance between two loci is measured in centiMorgans (cM). If two loci are 1 cM apart from each other, there is a 1% chance of recombination between these loci as the chromosome is passed to the next generation. In other words, 100 meioses are required to observe one recombination. (Kong et al. 2002; Coop et al. 2007) and (Coop et al. 2007). A statistical method is used to evaluate the results obtained in a linkage study. Calculation of the lod score (Z; logarithm of odds) represents the most efficient statistical test for proving that the result is not simply due to chance (Morton 1955). lod score gives a

Novelty Journals

ISSN 2394-966X

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

logarithm based likelihood ratio of a pedigree on two alternative hypotheses: is linkage with a recombination fraction of θ more likely or is it more likely that the two loci are not linked (θ = 0.5) (Terwilliger et al. 1994). In a set of families the overall lod score is obtained by simply adding up individual lod scores for each family: lod score calculation can be represented as a formula:

$$Z = \log 10 \frac{(1-\theta)^n \theta^r}{0.5^{n+r}}$$

n = number of non-recombinant offspring
r = number of recombinant offspring

For a disease with autosomal inheritance lod scores of 3.0 or higher are taken as evidence of linkage with a 5% chance of error (p = 0.05), and linkage can be rejected if lod score is < -2.0. Lod scores between -2 and +3 do not give conclusive results. In parametric, model based linkage analysis requiring detailed information on the mode of inheritance, gene frequencies, and penetrance, computer programs such as MLINK (Lathrop et al. 1984) and Genehunter (Kruglyak et al. 1996) are widely used. MLINK is part of the LINKAGE program package, which analyzes limited numbers of marker loci and is not suitable for multipoint analyses.

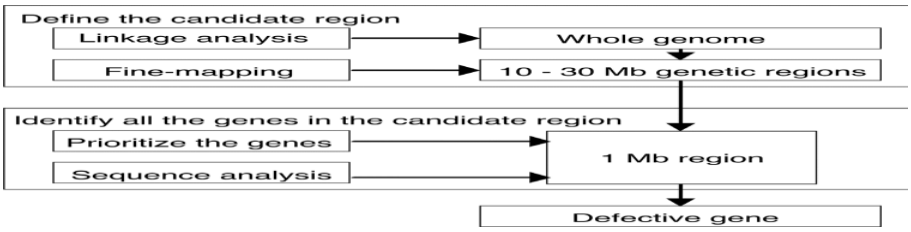

Figure 4: Disease gene identification through positional candidate gene analysis. The first step is to assign the disease locus to a chromosomal region using linkage analysis. Next, the candidate region is narrowed further by fine-mapping. Positional candidate genes are prioritized and evaluated for mutations cosegregating with the disease phenotype.

Gene hunter allows more effective multipoint analyses, but pedigrees need to be of moderate size (Nyholt 2002). However, model based analysis is usually not optimal for complex, nonmendelian diseases, in which nonparametric linkage analysis may be the method of choice. Although straightforward, a positional cloning project may also have some pitfalls. It requires suitable family material, and is sensitive to misdiagnosis. Locus heterogeneity within individual families can be avoided using large families in autosomal dominant disorders and homozygosity mapping in autosomal recessive diseases, if possible. Microsatellite markers distributed across the genome at intervals of 10 cM may fail to identify a disease locus, but this problem could be overcome by using a denser set of SNP markers (Chiang et al. 2006).

3.4 Chromosomal abnormalities:

In some cases it is possible to localize the disease gene with the help of associated cytogenetic abnormalities. For severe dominant diseases, in which the genetic cause is d e n o v o , chromosome aberrations are especially helpful while linkage analysis is not applicable (Breuning et al. 1993). In balanced translocations or inversions, the breakpoints may directly pinpoint the defective gene. For larger, cytogenetically visible deletions and microdeletions detected with high-resolution comparative genomic hybridization analysis, the whole deleted area rather than a specific breakpoint becomes the candidate region and focus of the search.

Gene identification: Before the complete human genome sequence became available, the isolation and examination of all the genes contained in the candidate locus was a major effort. Now, the entire human sequence is available in electronic format except for some gaps in difficult areas (The International Human Genome Sequencing Consortium 2004) and the identification of genes in the region of interest is much easier.

Mutation screening: The final step in identifying a disease gene is to detect disease-associated mutations in patient samples. There are several mutation detection methods with varying sensitivities and costs including direct sequencing, Southern blotting, as well as PCR-based mutation scanning methods such as singlestrand conformational polymorphism analysis. Sequencing is nowadays used as a primary method because of its decreased costs. However, sequencing of only

the coding regions of a gene is not an optimal method if the mutation lies in an intronic region. Alternative methods, such as MLPA (multiplex ligation-dependent probe amplification), quantitative PCR, or Southern blotting, are also required to detect larger chromosomal aberration e.g. deletions, insertions or duplications.

Molecular chaperones: Molecular chaperones have an important task in assisting the proper folding and assembly of other proteins hence preventing inappropriate interactions between polypeptides and the accumulation of misfolded proteins. Chaperones also regulate several other cellular processes, including protein targeting, transport, recognition of misfolded proteins and targeting to degradation, and signal transduction (Ellgaard et al. 2003; Muchowski et al. 2005). Conditions of cellular stress increase the synthesis of certain molecular chaperones, the heat shock proteins (HSPs), as a response to increases in the amount of misfolded proteins. HSPs are classified into six main families on the basis of their molecular mass: HSP100, HSP90, HSP70, HSP60, HSP40, and small heat-shock proteins (sHSPs) (Muchowski et al. 2005). Different family members function in different subcellular compartments, for example stress-70 protein (GRP75) in mitochondria, heat shock cognate 71 kDa protein (HSP7C) in cytosol, and 78 kDa glucose-regulated protein (GRP78) in the ER. **Diseases associated with defective chaperones:** Some inherited diseases, many of which are described in more detail below, are caused by mutations in general chaperone proteins. In addition, mutations in a few substrate-specific chaperones have been identified (Barral et al. 2004; Muchowski et al. 2005). **The GRP 7 8 chaperone system / Cochaperone SIL 1:** Human SIL1 (also known as BAP for BiPassociated protein) is a ~54 kDa Nglycosylated protein with N-terminal ER targeting and C-terminal ER retrieval sequences (Chung et al. 2002). It acts as an adenine nucleotide exchange factor for GRP78 and promotes the exchange of bound nucleotides by stimulating the dissociation of ADP and the subsequent uptake of ATP.

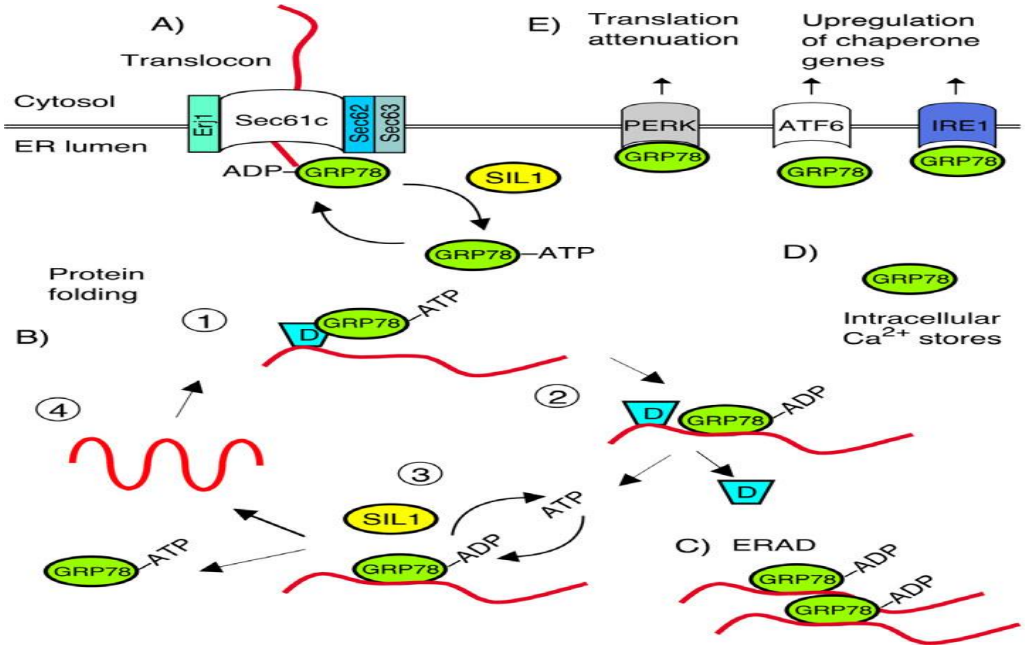

FIGURE 5: Functions of the ER localized chaperone GRP78. A) Nascent proteins are co-translationally translocated across the ER-membrane, where GRP78 has been shown to participate in sealing the translocon to maintain the permeability barrier between the ER and cytosol. GRP78 may require its ATPase activity during protein translocation (Zimmermann et al. 2006). B) The ATPase cycle of GRP78 regulates its binding and release from nascent protein chains: 1) Chaperone DJB11 binds to the unfolded region of a nascent protein and recruits ATP-bound GRP78 to the substrate. 2) DJB11 stimulates the ATPase activity of GRP78: ATP is hydrolyzed to ADP locking the ADP-bound GRP78 onto the unfolded substrate. 3) Nucleotide exchange factor, such as SIL1, catalyzes the release of ADP allowing the rebinding of ATP to GRP78. 4) The ATP-bound GRP78 is released from the substrate, which is ready for another round of assembly until the folding process is completed. C) GRP78 recognizes proteins that fail to fold properly and targets them to ER-associated degradation (ERAD). D) GRP78 has a role in maintaining ER calcium stores. E) GRP78 also participates in ER stress signaling, as in normal physiological conditions GRP78 is bound to ER transmembrane proteins IRE1, PERK, and ATF6 keeping them inactive. Modified from (Hendershot 2004), in the regulation of signal transduction pathway called the unfolded protein response (UPR). In physiological conditions GRP78 binds to stress-sensing proteins located in the ER membrane and keeps them in an inactive state. If unfolded proteins

accumulate in the ER, GRP78 is released from the stress-sensing proteins to interact with unfolded proteins (Figure 5e). Like all HSP70 family members, GRP78 binds both adenosine triphosphate (ATP) and adenosine diphosphate (ADP), which regulate its chaperoning functions with the exception of calcium storage (shown in more detail in Figure 5b). The GRP78 ATPase cycle is controlled by two other chaperone groups: HSP40 chaperones catalyze the hydrolysis of ATP to ADP, which locks GRP78 to unfolded protein, and nucleotide exchange factors SIL1 and HYOU1 induce ADP release so that ATP can be substituted back (Tyson et al. 2000; Chung et al. 2002).

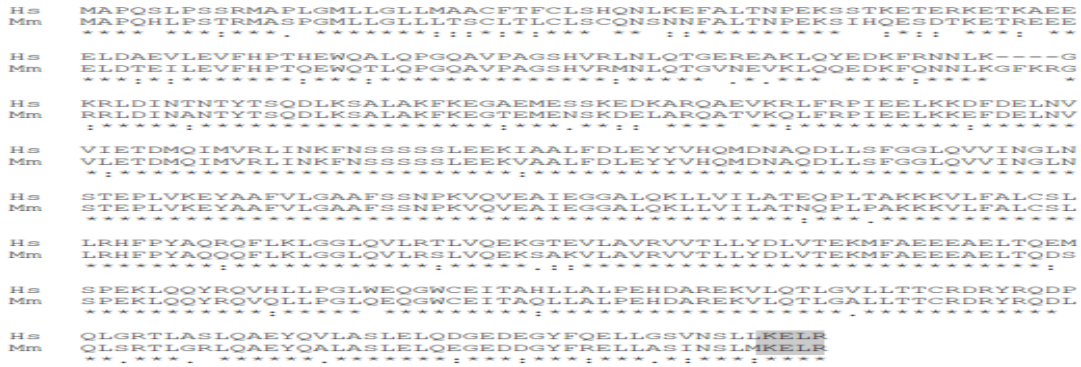

FIGURE 6: Conservation of SIL1 amino acid sequence in human (Hs) and mouse (Mm). Human SIL1 and the mouse ortholog show 85% identical amino acid sequence. The putative ER retention tetrapeptide in the C-terminus is highlighted in gray.

4. REVIEW OF THE LITERATURE

In the study of the 'Molecular basis of Marinesco-Sjögren syndrome` by Anna-Kaisa Anttonen, in Finland 2008, 8 Finnish families participated in this study. DNA samples were available from 14 patients with MSS and 15 family members. Two of the families, M1 and M5, had been earlier described (Herva et al. 1987). Through collaboration, totally 23 families contributed in this study from different European countries, the USA, Australia, and Japan and comprehensive data were collected. For the foreign families outside Finland, DNA samples were available from 34 patients with MSS and 42 family members. RNA samples were obtained from 6 patients and 4 parents. Different investigation methods (biological, molecular biological and others) were used. Genotyping and linkage analysis: Genomic DNA was isolated using standard methods. The segregation of the MSS phenotype with alleles of fluorescently labeled microsatellite markers was evaluated for two chromosomal loci. Six polymorphic markers covering the chromosome 18qter locus and ten markers covering the locus on 5q31 were studied. The marker order, intermarker distances, and primer sequences were obtained from the Marshfield genetic map (Broman et al. 1998), the deCODE genetic map (Kong et al. 2002), and NCBI sequence based STS.

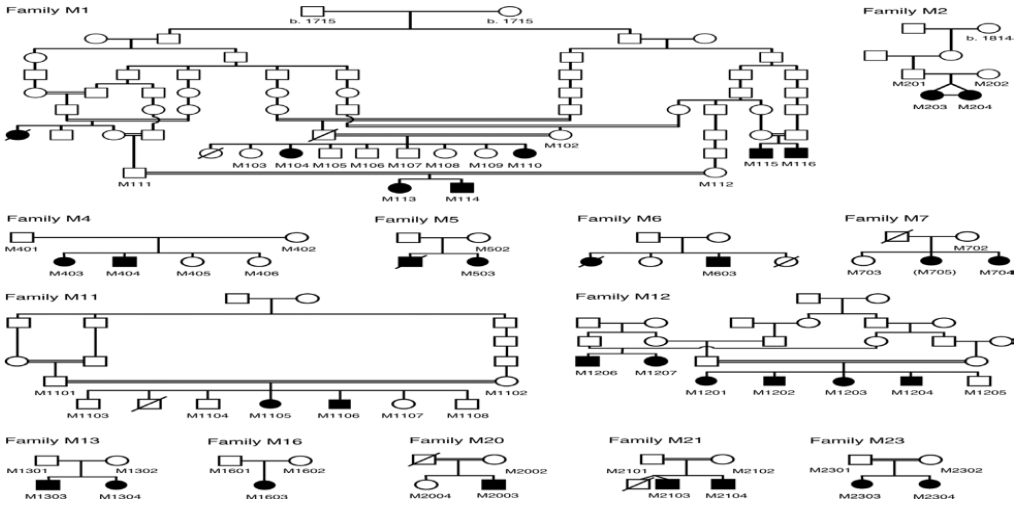

FIGURE 7: The MSS families with SI L 1 mutations. The affected individuals are indicated with filled symbols. For simplicity the individuals in the older generations in families M1, M2, M11, and M12 are not marked as deceased. Families M1, M4, M5, and M6 are from Finland. Family M2 lives in Sweden, but the paternal

grandmother was born in Finland. The three Norwegian families are M7, M12, and M13. M11 and M20 are of Turkish origin. Family M16 is French and families M21 and M23 are Japanese. The DNA samples and patient records (affected persons only) were available from numbered individuals. Patient records were available for one additional patient shown in parenthesis.

Mutation analysis: The gene content of the interval spanning D 5 S 4 7 9 and D 5 S 2 1 1 6 was examined with the NCBI Map Viewer, the Ensembl Human Genome Browser, and the UCSC Human Genome Browser. The exons and exon-intron boundaries of SI L 1 , the ten positional candidate genes on chromosome 5q31 (C T N N A 1 , E G R 1 , G F R A 3 , H B E G F , H S P A 9 B , K L H L 3 , M Y O T , N R G 2 , S P O C K 1 , and W N T 8 A), and the three functional candidate genes (A A R S , H S P A 5 , and H Y O U 1) were amplified from genomic DNA with intronic primers designed with Primer3 (Rozen et al. 2000) or ExonPrimer programs.

Gene expression studies: Commercial multiple tissue Northern blots (Human Fetal II, Human Brain II, and Human Brain V; BD Biosciences Clontech) were hybridized with a 1519 bp PCR-generated SI L 1 cDNA probe covering the whole coding region as well as with G A P D H (BD Biosciences Clontech). The probes were labeled with 32PdCTP using RediPrimeII kit (Amersham Pharmacia) and blocked with human placental (0.5 mg/ml) and salmon sperm (0.25 mg/ml) DNA before hybridization.

Immunohistochemisry: Frozen sections from muscle biopsies taken for diagnostic examinations from patients and controls were stained with a polyclonal goat anti-human SIL1 antibody (Abcam Ltd) detecting a C-terminal epitope. Sections were briefly fixed in –20°C acetone after which the protocol described below was followed with the exception that no antigen retrieval was used. Goat anti-human SIL1 antibody (Abcam Ltd) was used at a 1:200 dilution (stock 0.50 mg/ml). Paraffin-embedded sections of C57BL mouse tissues of embryonic day 12.5, 15.5, and 18.5, and of postnatal day 5, 14, 60, and 180 were deparaffinized, hydrated, and treated with 10 mmol/l citric acid in microwave oven for 5 min for endogenous antigen retrieval. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 5 min, and nonspecific binding was blocked with 1.5% normal serum in 0.1% Tween-phosphatebuffered saline (PBS) for 30–60 min.

TABLE 7: Results of two!point linkage analysis on chromosome 18qter.

theta / marker	0.000	0.001	0.010	0.050	0.100	0.200	0.300	0.400	cM (Marshfield[1])
D18S844	-inf	-3.599	-1.440	0.088	0.517	0.526	0.295	0.100	116.44
D18S462	-inf	-3.883	-1.622	-0.058	0.362	0.401	0.229	0.082	120.05
D18S461	-inf	-0.595	1.306	2.252	2.272	1.704	0.978	0.364	120.05
D18S1122	-inf	-1.148	0.882	2.071	2.179	1.627	0.879	0.287	122.61
D18S1095	-inf	-5.232	-2.753	-0.741	-0.037	0.305	0.230	0.073	124.11
D18S70	-inf	-6.595	-3.578	-1.070	-0.173	0.290	0.240	0.081	126.00

[1] (Broman *et al.* 1998)

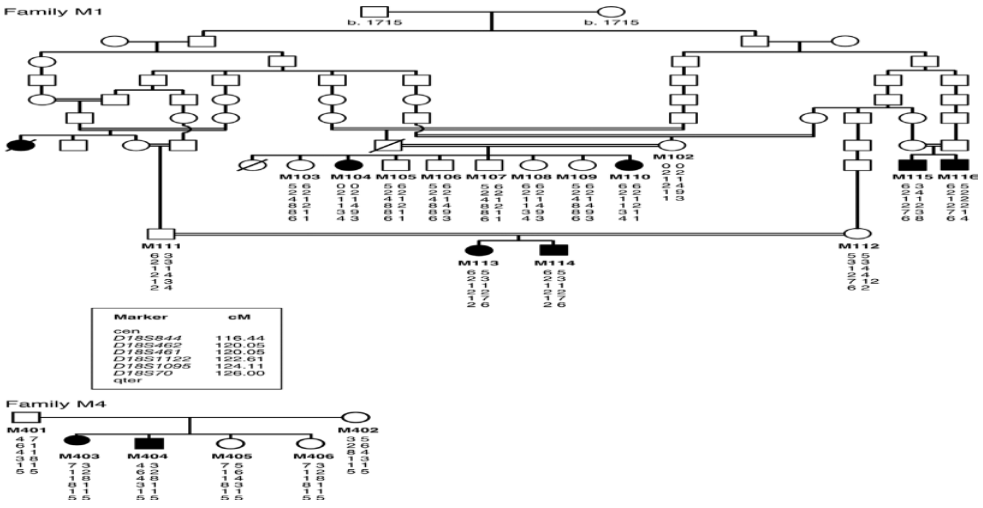

FIGURE 8: Haplotypes on chromosome 18qter. Marker order and location in cM are given according to the Marshfield genetic map (Broman et al. 1998). The affected individuals are indicated with filled symbols and for

simplicity the individuals in the older generations in family M1 are not marked as deceased. Only one affected pair of siblings, M113 and M114, share haplotypes over the region while other pairs of siblings are recombinant.

TABLE 8: Results of two!point linkage analysis on the M SS locus 5q31.

theta / marker	0.000	0.001	0.010	0.050	0.100	0.200	0.300	0.400	cM (Marshfield[1])	(deCODE[2])
D5S1995	-inf	-1.956	-0.045	0.962	1.090	0.825	0.456	0.156	137.95	135.81
D5S479	-inf	2.371	3.229	3.297	2.822	1.699	0.773	0.205	141.27	138.82
D5S1983	1.625	1.619	1.559	1.306	1.019	0.561	0.255	0.078	141.82	138.96
D5S414	7.095	7.078	6.917	6.200	5.294	3.505	1.888	0.669	141.82	-
D5S500	4.352	4.339	4.218	3.686	3.039	1.850	0.888	0.266	140.72	138.96
D5S476	2.913	2.902	2.809	2.404	1.926	1.104	0.503	0.140	140.72	139.38
D5S2009	1.134	1.129	1.086	0.902	0.670	0.383	0.174	0.051	142.92	139.38
D5S2116	1.157	1.177	1.296	1.374	1.218	0.783	0.398	0.130	142.92	139.91
D5S658	-inf	1.257	2.320	2.838	2.646	1.796	0.896	0.259	142.92	-
D5S1979	-inf	1.010	2.069	2.575	2.374	1.552	0.751	0.216	144.06	-

[1] (Broman *et al.* 1998), [2] (Kong *et al.* 2002)

D5S642	*D5S1995*	*D5S816*	*D5S479*	*D5S1983*	*D5S414*	*D5S500*	*D5S476*	*D5S2009*	*rs13385*	*D5S2116*	*D5S658*	*D5S2010*	*D5S1979*	No. of disease chromosomes	Patient no.
5	5	2	3	1	8	5	2	1	1	1	3	9	3	5	
1	5	2	3	1	8	5	2	1	1	4	2	5	5	5	
2	2	6	2	1	8	5	2	1	1	4	2	5	5	1	M104
1	5	2	3	1	8	5	2	1	2	1	5	6	6	1	M113
1	2	1	2	2	7	9	2	1	0	8	2	1	8	1	M203

FIGURE 9: Haplotypes across the M S S locus in families M1 and M2. In the M1 family four different haplotypes were present. The majority of the patients shared the two haplotypes depicted on the first two rows. Historical recombinations restricted the candidate region between markers D 5 S 6 4 2 and D 5 S 2 1 1 6 . Patient M104 had a meiotic recombination further narrowing the region to 3.52 Mb between markers D 5 S 4 7 9 and D 5 S 2 1 1 6 . A meiotic recombination present in patient M113 did not initially narrow the region until a heterozygous SNP rs13385 was detected while sequencing the H B E G F gene. The M S S locus was refined to between markers D 5 S 5 0 0 and r s 1 3 3 8 5 according to the "Finnish" disease chromosome present in patients M203 and M204.

Mutations in SIL 1 underlie M S S: The 11th gene selected for sequencing was SI L 1 , the ER-resident cochaperone of GRP78. Human S IL 1 is a 1923 bp transcript encoding a 461 amino acid protein. The main transcript has ten exons, of which nine are coding, and spans a 251.7-kb genomic region (Figure 8). One additional 5' noncoding exon (marked as exon 1a) is found at least in placental tissue. All Finnish patients were homozygous for a 4 nucleotide duplication in exon 6 compatible with the predicted founder effect. As expected, the Swedish patients M203 and M204 were compound heterozygotes for the Finnish founder mutation and another mutation changing the conserved donor splice site of intron 6. The analysis of further families with MSS from Norway, France, and Turkey revealed additional mutations, confirming that SI L 1 mutations underlie MSS. Refining the candidate region using the ancestral Finnish haplotype and identifying the founder mutation in S IL 1 is yet another example of exploiting the founder effect in disease gene identification. (Figures 7-11).

SIL 1 mutations in patients with MSS: A total of eight mutations were identified in the SIL 1 gene in 29 patients of different ethnic origins (Figures 8-11 and Tables 7-10). The mutations were distributed quite evenly throughout SI L 1 . Two mutations, c.331C>T and c.1367T>A, were nonsense changes creating PTCs: p.Arg111X and p.Leu456X, respectively. Three mutations were small duplications (c.212dupA, the Finnish founder mutation c.506_509dupAAGA, and c.936dupG) leading to frameshifts and PTCs (p.His71GlnfsX5, p.Asp170GlufsX4, and p.Leu313AlafsX39, respectively). (Tables 7-10).

Novelty Journals

ISSN 2394-966X

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

TABLE 9: Positional candidate genes in the 3.52!Mb MSS locus on chromosome 5q31

Symbol	Description
SPOCK1	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 1
KLHL3	kelch-like 3 (Drosophila)
HNRPA0	heterogeneous nuclear ribonucleoprotein A0
NPY6R	neuropeptide Y receptor Y6 (pseudogene)
MYOT	myotilin
PKD2L2	polycystic kidney disease 2-like 2
C5orf5	chromosome 5 open reading frame 5
WNT8A	wingless-type MMTV integration site family, member 8A
NME5	non-metastatic cells 5, protein expressed in (nucleoside-diphosphate kinase)
BRD8	bromodomain containing 8
KIF20A	kinesin family member 20A
CDC23	CDC23 (cell division cycle 23, yeast, homolog)
GFRA3	GDNF family receptor alpha 3
CDC25C	cell division cycle 25C
FAM53C	family with sequence similarity 53, member C - hypothetical protein *
JMJD1B	jumonji domain containing 1B - hypothetical protein *
REEP2	receptor accessory protein 2 - hypothetical protein *
EGR1	early growth response 1
ETF1	eukaryotic translation termination factor 1
HSPA9B	heat shock 70kDa protein 9B (mortalin-2)
LOC391836	similar to ribosomal protein L10a
CTNNA1	catenin (cadherin-associated protein), alpha 1, 102kDa
LOC401210	hypothetical gene supported by AK022326 - discontinued **
SIL1	**SIL1 homolog, endoplasmic reticulum chaperone (S. cerevisiae)**
MATR3	matrin 3
LOC441111	LOC441111 - discontinued **
PAIP2	poly(A) binding protein interacting protein 2
SLC23A1	solute carrier family 23 (nucleobase transporters), member 1
PACAP	proapoptotic caspase adaptor protein
LOC389333	LOC389333
LOC389334	LOC389334 - discontinued **
LOC202051	hypothetical protein LOC202051
DNAJC18	DnaJ (Hsp40) homolog, subfamily C, member 18 - hypothetical protein *
LOC340061	hypothetical protein LOC340061
LOC401211	similar to nuclear receptor coactivator 4
UBE2D2	ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast)
CXXC5	CXXC finger 5
PSD2	PSD2 pleckstrin and Sec7 domain containing 2 - hypothetical protein *
NRG2	neuregulin 2
PURA	purine-rich element binding protein A
C5orf32	chromosome 5 open reading frame 32
PFDN1	prefoldin 1
HBEGF	heparin-binding EGF-like growth factor
SLC4A9	solute carrier family 4, sodium bicarbonate cotransporter, member 9
ANKHD1	ANKHD1 ankyrin repeat and KH domain containing 1

The double line on the left indicates the final *MSS* locus refined by the shared haplotype between th e Swedish twins and Finnish patients as well as a meiotic recombination observed in patient M113.

* Current gene names are given to hypothetical genes that have been characterized since the release of NCBI Build 35.1 (August 2004).

** These genes have been discontinued since the release of NCBI Build 35.1.

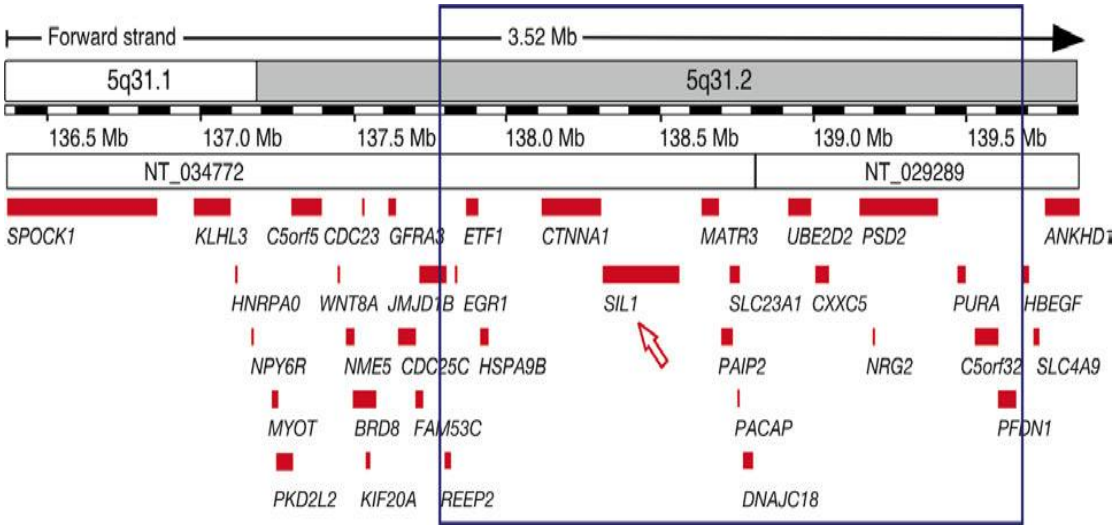

FIGURE 10:Genes in the 5q31 candidate region. The original 3.52-Mb candidate region is shown. The upper bar shows the chromosomal band and each gene is depicted as one solid bar. Blue box indicates the final candidate region between D 5 S 5 0 0 and rs13385. SI L 1 is marked with a red arrow. The picture was modified from the Ensembl genome browser view of the region.

International Journal of Novel Research in Life Sciences
Vol. 6, Issue 3, pp: (84-103), Month: May - June 2019, Available at: www.noveltyjournals.com

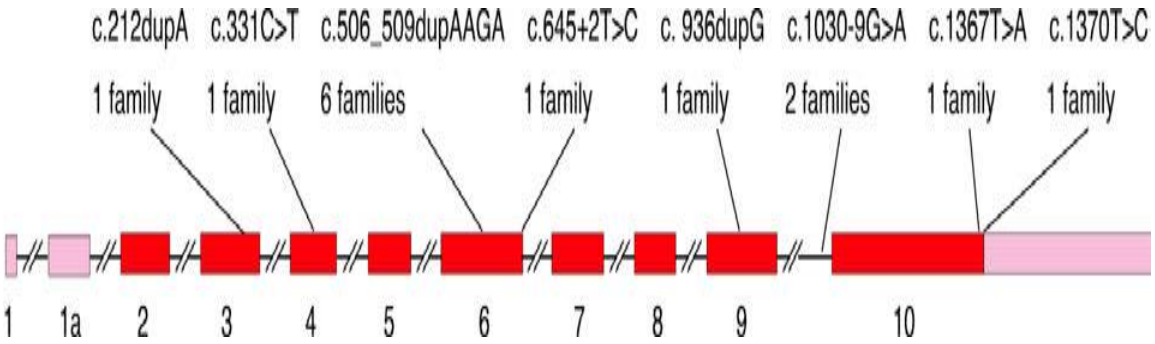

FIGURE 11: The structure of SI L 1 showing the MSS-associated mutations identified in this study. The main variant of SI L 1 is transcribed from ten exons. The boxes represent the exons. The coding region is in red while untranslated regions are in pink. The positions of the mutations are shown with lines.

TABLE 10: MSS-associated mutations in SIL1.

Location	Nucleotide change	Predicted consequence	Ethnic origin	Reference
Exon 3	c.212dupA	p.His71GlnfsX5	France	II
Exon 4	c.331C>T	p.Arg111X	Turkey Iran, Turkey Italy	II (Senderek *et al.* 2005) (Annesi *et al.* 2007)
Exon 6	c.506_509dupAAGA	p.Asp170GlufsX4	Finland, Sweden, Norway	II
Intron 6	c.645+2T>C	p.Val186_Gln215del p.Ala152_Gln215del	Sweden	II
Exon 9	c.936dupG	p.Leu313AlafsX39	Japan	III
Intron 9	c.1030-9G>A	p.Phe345AlafsX9	Norway	III
Exon 10	c.1367T>A	p.Leu456X	Turkey	III
Exon 10	c.1370T>C	p.Leu457Pro	Japan	III
Exon 3	c.178C>T	p.Glu60X	Vietnam	(Senderek *et al.* 2005)
Exon 4	c.346delG	p.Gly116fsX42	Vietnam	(Senderek *et al.* 2005)
Intron 6	c.645+1G>A	skipping of exon 6	Turkey	(Senderek *et al.* 2005)
Exon 9	c.947_948insT	p.Leu316fsX36	Germany, Russia	(Senderek *et al.* 2005)
Intron 9	c.1029+1G>A	skipping of exon 9	Bosnia	(Senderek *et al.* 2005)
Intron 9	c.1030-18G>A	p.Met344fsX13	Germany	(Senderek *et al.* 2005)
Exon 10	c.1249C>T	p.Gln417X	Mali	(Senderek *et al.* 2005)
Exon 10	c.1312C>T	p.Gln438X	Egypt	(Karim *et al.* 2006)
Exon 10	c.1366delT	p.Leu456fsX2	Russia	(Senderek *et al.* 2005)

5. CONCLUSION

MSS is an autosomal recessive disorder. Parents of an affected child have a 25% chance that any other child will have MSS. It is equally common in boys and girls. Mutations of the Sil1 gene are responsible for about 50% of all cases of MSS. There are milder variants with normal stature and minimal muscle weakness. The SIL 1 gene plays a role in normal protein folding.

MSS occurs in all ethnic groups. It is very rare except in a few genetically isolated groups.About 200 cases have been reported worldwide in the medical literature. There may be many more undiagnosed cases.

There is currently no treatment for MSS, but physical, occupational, and speech therapy are beneficial, along with special education services. Cataract surgery is required when vision becomes impaired. Hormone replacement is needed if hypogonadism is present. Some children wear braces on their feet to improve ankle and foot alignment. Most of the patients with MSS use a walker or crutches. Adults generally require some degree of support for daily living. Life expectancy is near-normal, but muscle weakness may increase with age.

The bilateral cataracts have been stated as congenital, but there are several reports on rapid postnatal development of lens opacities (Herva et al. 1987; Ishikawa et al. 1993; McLaughlin et al. 1996; Farah et al. 1997; Slavotinek et al. 2005). In only a few cases has the type of cataract been stated. In addition to variable single reports, posterior capsular opacities

have been reported (Ishikawa et al. 1993; Farah et al. 1997). The eyes are typically operated on in the first decade of life. Strabismus is a frequent finding and optic atrophy was present in three cases (Dotti et al. 1993). Radiography of the bones may help to determine the extent of skeletal involvement. In the literature, the most distinguishable skeletal features are shortening of metacarpals and metatarsals, shortening of phalanges, and deformation of the sternum. In addition, small posterior cranial fossa, scoliosis and kyphoscoliosis, scalloped vertebral bodies, gracile bones, pes planovalgus, and valgus deformities of elbows and hips are present (Brogdon et al. 1996; Reinker et al. 2002). Although atypical findings like optic atrophy, seizures, hearing loss, and peripheral neuropathy have been reported, it is unknown if these are rare manifestations of MSS or features of a distinct disorder (Williams et al. 1996; Lagier-Tourenne et al. 2003; Slavotinek et al. 2005). MSS patients are usually born after uncomplicated pregnancies. Muscular hypotonia is typically noted in early infancy. The most evident differences are that hypotonia, skeletal abnormalities, and hypergonadotropic hypogonadism are more frequent features of MSS than previously reported. At odds with some previous reports, the cataracts may present in early childhood rather than being congenital. This is important to notice when considering the differential diagnosis for other disorders resembling MSS.

REFERENCES

[1] Aguglia, U et al Vitamin E deficiency due to chylomicron retention disease in MSS. Ann. Neurol. 47: 260-264, 2000.

[2] Alter, M et al Cerebellar ataxia, congenital cataracts and retarded somatic and mental maturation: report of cases of Marinesco-Sjogren syndrome. Neurology 12: 836-847, 1962. [PubMed: 14012309]

[3] Anheim, M et al Epidemiological, clinical, paraclinical and molecular study of a cohort of 102 patients affected with autosomal recessive progressive cerebellar ataxia from Alsace, Eastern France: implications for clinical management. Neurogenetics 11: 1-12, 2010. [PubMed: 19440741]

[4] Annesi, G et al SIL1 and SARA2 mutations in MSS and chylomicron retention disease. Clin. Genet. 71: 288-289, 2007.

[5] Anttonen, A.-K. Personal Communication. 2006. Hensinki, Finland

[6] Anttonen, A et al The gene disrupted in MSS encodes SIL1, an HSPA5 cochaperone. Nat. Genet. 37: 1309-1311, 2005.

[7] Anttonen, A et al Novel SIL1 mutations and exclusion of functional genes in MSS. Eur J. Hum. Gen. 16: 961-969, 2008.

[8] Chudley, A. E. Genetic landmarks through philately: Georges Marinesco (1863-1938). Clin. Genet. 64: 297-299, 2003.

[9] Farah, S. et al A. Marinesco-Sjogren syndrome in a Bedouin family. Acta Neurol. Scand. 96: 387-391, 1997.

[10] Franceschetti, A., Klein, D., Wildi, E., Todorov, A. Le syndrome de Marinesco-Sjogren: premiere verification anatomique. Arch. Suisses Neur. Neurochir. Psychiat. 97: 234-240, 1966.

[11] Garland, H., Moorhouse, D. An extremely rare recessive hereditary syndrome including cerebellar ataxia, oligophrenia, cataract, and other features. J. Neurol. Neurosurg. Psychiat. 16: 110-116, 1953.

[12] Herva, R et al Disease with cataract, cerebellar atrophy, mental retardation & myopathy. Neuropediat. 18: 164-169, 1987.

[13] Jones, B et al Mut. in a Sar1 GTPase of COPII vesicles associated with LAD. Nature Genet. 34: 29-31, 2003.

[14] Komiyama, A et al Muscle pathology in Marinesco-Sjogren syndrome. J. Neurol. Sci. 89: 103-113, 1989.

[15] Lagier-Tourenne, C et al Linkage to 18qter differentiates two clinically overlapping syndromes: congenital cataracts-facial dysmorphism-neuropathy (CCFDN) syndrome and MSS. J. Med. Genet. 39: 838-843, 2002.

[16] Lagier-Tourenne, C et al. Homozygosity mapping of MSS to 5q31. Europ. J. Hum. Genet. 11: 770-778, 2003.

[17] Mahloudji, M et al Marinesco-Sjogren syndrome: report of an autopsy. Brain 95: 675-680, 1972.

[18] Marinesco, G., Draganesco, S., Vasiliu, D. Nouvelle maladie familiale caracterisee par une cataracte congenitale et un arret du development somato-neuro-psychique. Encephale 26: 97-109, 1931.

[19] Merlini, L et Genetic identity of MSS/myoglobinuria and CCFDN syndromes. Neurology 58: 231-236, 2002.

[20] Muller-Felber, W et al MSS with rhabdomyolysis: a new subtype of the disease. Neuropediatrics 29: 97-101, 1998.

[21] Sasaki, K et al Muscle pathology in MSS: a unique ultrastructural feature. Brain Dev. 18: 64-67, 1996.

[22] Senderek, J et alMutations in SIL1 cause Marinesco-Sjogren syndrome, a cerebellar ataxia with cataract and myopathy. Nature Genet. 37: 1312-1314, 2005.

[23] Sjogren, T. Hereditary congenital spinocerebellar ataxia accompanied by congenital cataract and oligophrenia: a genetic and clinical investigation. Confin. Neurol. 10: 293-308, 1950.

[24] Sjogren, T. Hereditary congenital spinocerebellar ataxia combined with congenital cataract and oligophrenia. Acta Psychiat. Neurol. Scand. 46 (suppl.): 286-289, 1947.

[25] Skre, H., Berg, K. Linkage studies on the Marinesco-Sjogren syndrome and hypergonadotropic hypogonadism. Clin. Genet. 11: 57-66, 1977. [PubMed: 830450]

[26] Slavotinek, A., Goldman, J., Weisiger, K., Kostiner, D., Golabi, M., Packman, S., Wilcox, W., Hoyme, H. E., Sherr, E. Marinesco-Sjogren syndrome in a male with mild dysmorphism. Am. J. Med. Genet. 133A: 197-201, 2005. [PubMed: 15633176]

[27] Superneau, D. W et al MSS described a quarter of a century before Marinesco. Am. J. Med. Genet. 22: 647-648, 1985.

[28] Superneau, D et al Myopathy in MMS syndrome. Europ. Neurol. 26: 8-16, 1987.

[29] Tachi, N et al Congenital muscular dystrophy in Marinesco-Sjogren syndrome. Pediat. Neurol. 7: 296-298, 1991.

[30] Takahata, T et al Novel muts in the SIL1 gene in a Japanese pedigree with the MSS J. Hum. Genet. 55: 142-146, 2010.

[31] Todorov, A. B. Le SMS: premiere etude anatomo-clinique. J. Genet. Hum. 14: 197-233, 1965.

[32] Varon, R et al Partial deficiency of the C-terminal-domain phosphatase of RNA polymerase II is associated with congenital cataracts facial dysmorphism neuropathy syndrome. Nature Genet. 35: 185-189, 2003.

[33] Walker, P. D et al MMS: evidence for a lysosomal storage disorder. Neurology 35: 415-419, 1985.

[34] Wertelecki, W. Personal Communication. 1986. Mobile, Alabama

[35] Zimmer, C et al Neuropathy with lysosomal changes in MSS: fine structural findings in skeletal muscle and conjunctiva. Neuropediatrics 23: 329-335, 1992.