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Case Series

Co-occurrence of Phelan-McDermid syndrome and metachromatic leukodystrophy

Snehal Mallakmir[1]*, Anbukayalvizhi Chandrasekaran[2], Kety Phelan[3], Rashid Merchant[1], Shekhar Patil[4]

[1]Apollo Genomics Institutes, Apollo Hospitals, Navi Mumbai, Maharashtra, India
[2]Medgenome laboratory Pvt Ltd, Bengaluru, Karnataka, India
[3]Genetics Laboratory Florida Cancer Specialists & Research Institute, 2848 Center Pointe Drive, Fort Myers, USA
[4]Apollo Hospitals, Navi Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Snehal Mallakmir,
E-mail: drsnehalm@gmail.com

ABSTRACT

Very few cases have been described so far with co-occurrence of Phelan-McDermid syndrome (PMS) and metachromatic leukodystrophy (MLD). Those patients harbour a chromosome (chr) 22q13deletion encompassing at least the SHANK3 and ARSA genes and a pathogenic variant in the arylsulfatase A (ARSA) gene residing on the other allele. The deletion in chr22q13 results in PMS phenotype and the presence of pathogenic variation on the other intact copy of ARSA gene, leads to MLD phenotype due to biallelic loss of ARSA function. We describe a male infant, born to a third-degree consanguineous couple, who exhibited neuroregression at the age of 8 months, presented with developmental delay, hypotonia which rapidly progressed to feeding difficulties, axial hypotonia, ptosis, sleep disturbance, dystonia, spasticity, and abnormal eye movements. Brain MRI showed T2 hyperintensities consistent with MLD. Biochemical workup showed deficiency of ARSA enzyme activity. Genetic investigations revealed heterozygous deletion of size 2.5 Mb on chr 22q13.3 encompassing the entire ARSA gene and a pathogenic variant in the other copy of ARSA gene. Parents and sibling were tested and informed about the disease management and genetic testing in extended family members to understand the risk and preventive measures. Few case reports have proposed screening for urine sulfatides levels at the time of PMS diagnosis to identify pre-symptomatic or asymptomatic MLD patients to facilitate management and our case supports this proposal.

Keywords: Phelan-McDermid syndrome, Metachromatic leukodystrophy, SHANK3, Arylsulfatase A

INTRODUCTION

Phelan-McDermid syndrome (PMS) is caused either by a heterozygous pathogenic variant in the SHANK3 gene or by a heterozygous contiguous deletion on chr 22q13.[3] often involving all or part of the SHANK3 gene.[1] The 22q13 loss may arise due to a simple deletion, unbalanced translocation, ring chromosome formation or, less frequently due to a structural rearrangement at the terminal long arm of chromosome 22.[2,3] The prominent clinical features of PMS include neonatal hypotonia, delayed fine motor abilities, mild to profound speech delay, intellectual disability, autistic traits and modest facial dysmorphism. Clinical variability is possible and is mainly influenced by genomic aberration patterns.

The inheritance of other haplo-insufficient genes together with SHANK3 gene, in the deleted 22q13 region contributes to variability in cases of substantial genomic loss.[4,5] Individuals with a ring chromosome 22r (22) are at risk of developing tumours in the nervous system due to neurofibromatosis type 2 (NF2). Occasionally, the

patient additionally inherits a pathogenic variant from the other intact copy of chromosome 22. This would cause PMS plus the related recessive disease to co-occur. ARSA, CHKB, ODF3B, SCO2, SBF1, TUBGCP6, MLC1, ALG12, TBC1D22A, ATXN10 are the notable recessive genes located at chromosome 22q13 loci.[6] A recognised example of this co-occurrence condition is PMS with MLD.[7]

The establishment of molecular diagnosis in patients suspected with PMS plays a critical role in understanding the disease progression and management. Chromosomal microarray analysis (CMA) is the recommended first line of testing for a suspected diagnosis of PMS. Point mutations in SHANK3 or in other overlapping recessive genes can be screened via whole exome (WES) or whole genome sequencing (WGS).

Karyotyping, FISH or MLPA are recommended in individuals with terminal deletions of 22q13 to rule out ring chromosome 22. Low-level mosaic changes in PMS are at times underdiagnosed or misdiagnosed.[3]

MLD is caused by homozygous or compound heterozygous pathogenic variation in ARSA gene and is located on chromosome 22q13 region of human genome. The disorder has different clinical subtypes such as severe infantile, moderate juvenile, and mild adult-onset forms.

Severe infantile form may begin at any age before 2 years with the weakness, hypotonia, frequent falls, dysarthria, regression of cognitive and motor skills and symptoms worsening with spasticity, seizures and decerebrate posture. The disease course is comparatively milder for juvenile and adult onset. The severity of MLD disease depends on the impact of genomic aberration on ARSA enzyme levels and activity. The patient with infantile onset typically has homozygous or compound heterozygous for I-type alleles (alleles that encode ARSA protein with <1% enzyme activity). R-type alleles, on the other hand, code for an ARSA enzyme that exhibits some residual activity.

I-type and R-type alleles are frequently inherited in trans in the MLD patients with juvenile onset. While adult-onset patients are found to harbour R-type alleles in homozygous or compound heterozygous state.

Magnetic resonance imaging (MRI) of the affected individuals shows diffuse symmetric abnormalities of periventricular myelin with hyperintensities on T2-weighted images.

To date, very few cases have been described with co-occurrence of PMS and MLD. Rapid neurological decline may be anticipated if infantile onset severe MLD is coinherited with PMS.[7-10] To provide a precise diagnosis, prompt disease management, and appropriate therapy choices, suspected PMS cases must undergo genetic screening in addition to other investigative procedures.

CASE SERIES

Whole exome sequencing analysis of the patient identified a hemizygous pathogenic mutation in the ARSA gene (NM 000487.5:c.979+1G>A) and terminal copy number loss in chromosome 22 (2.5 Mb length), which contains 31 OMIM genes including the ARSA and SHANK3 genes (Figure 1, 2 and Table 1).

Both parents and the elder brother's CMA testing revealed no abnormality at the same locus. Thus, the CMA results were suggestive of de novo origin of CNV loss in proband. The targeted ARSA gene sequencing revealed that he inherited the essential splice site variation from his mother. His father carries the wildtype allele and his elder sibling has the pathogenic variation in the heterozygous state as in mother (Figure 3). Father, mother and the elder male sibling are asymptomatic. Enzyme studies of proband and his sibling-Arylsulphatase A level in blood leucocytes. Enzyme study of Affected proband showed following results. Enzyme study of asymptomatic elder sibling having heterozygous variant in ARSA gene and normal chromosomal microarray showed following results.

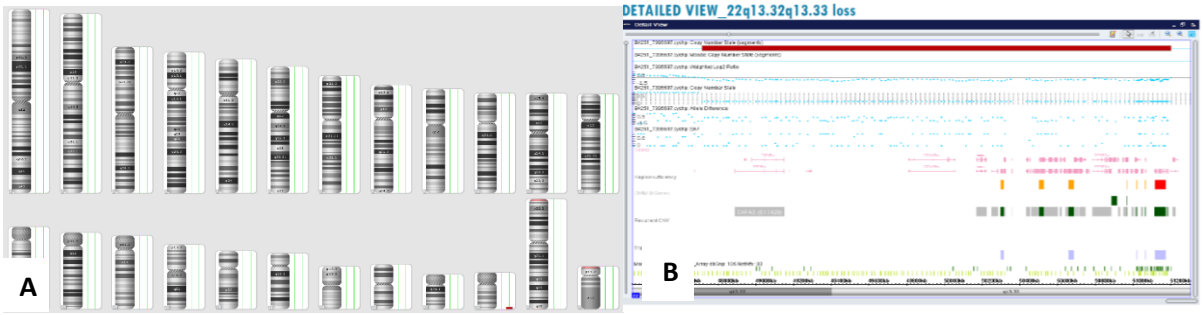

Figure 1 (A and B): Chromosomal microarray using the Affymetrix Cytoscan 350K array (Thermo Fisher Scientific, Waltham, MA, USA) revealed an approximately 2.5 Mb deletion (arr(GRCh37) 22q13.32q13.33 (48710480_51197838)x1) on the long arm of chromosome 22 encompassing 31 OMIM genes. The result is indicative of Phelan-McDermid syndrome. A similar 2.3 Mb deletion has been documented priorly in ClinVar database.

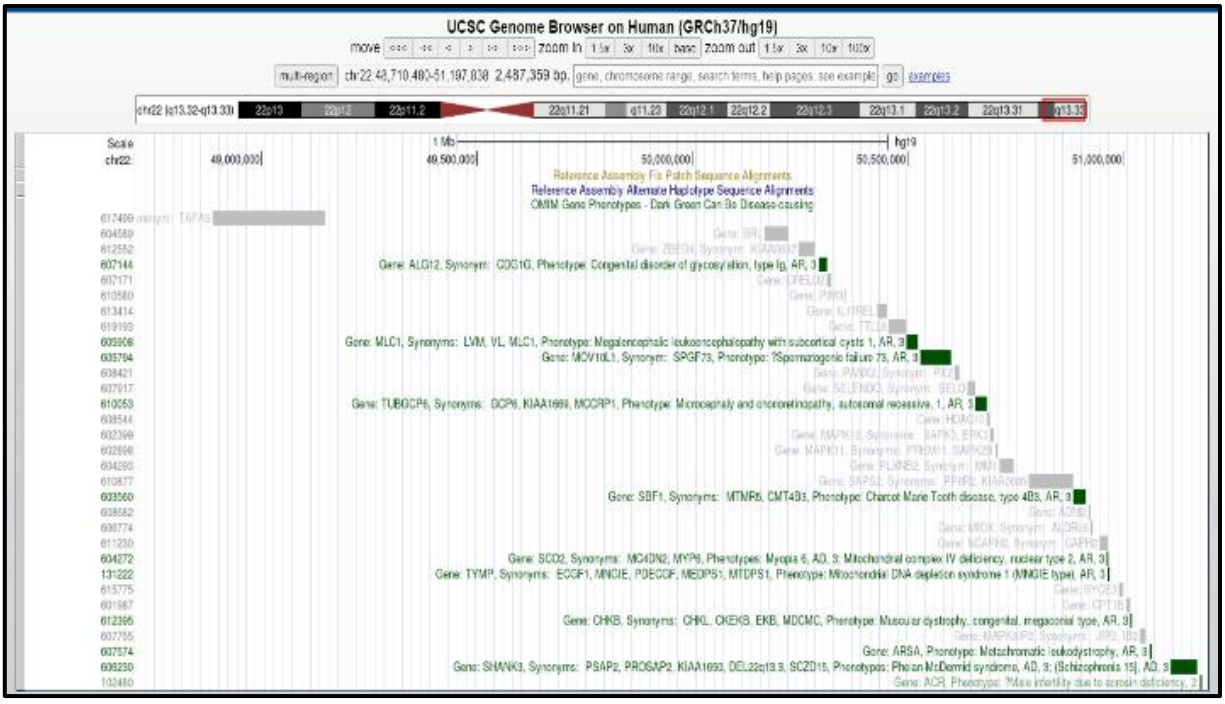

Figure 2: UCSC genome browser view highlighting the deleted chromosome 22q13.3 region identified in the patient and depicting the genes and associated OMIM phenotype.

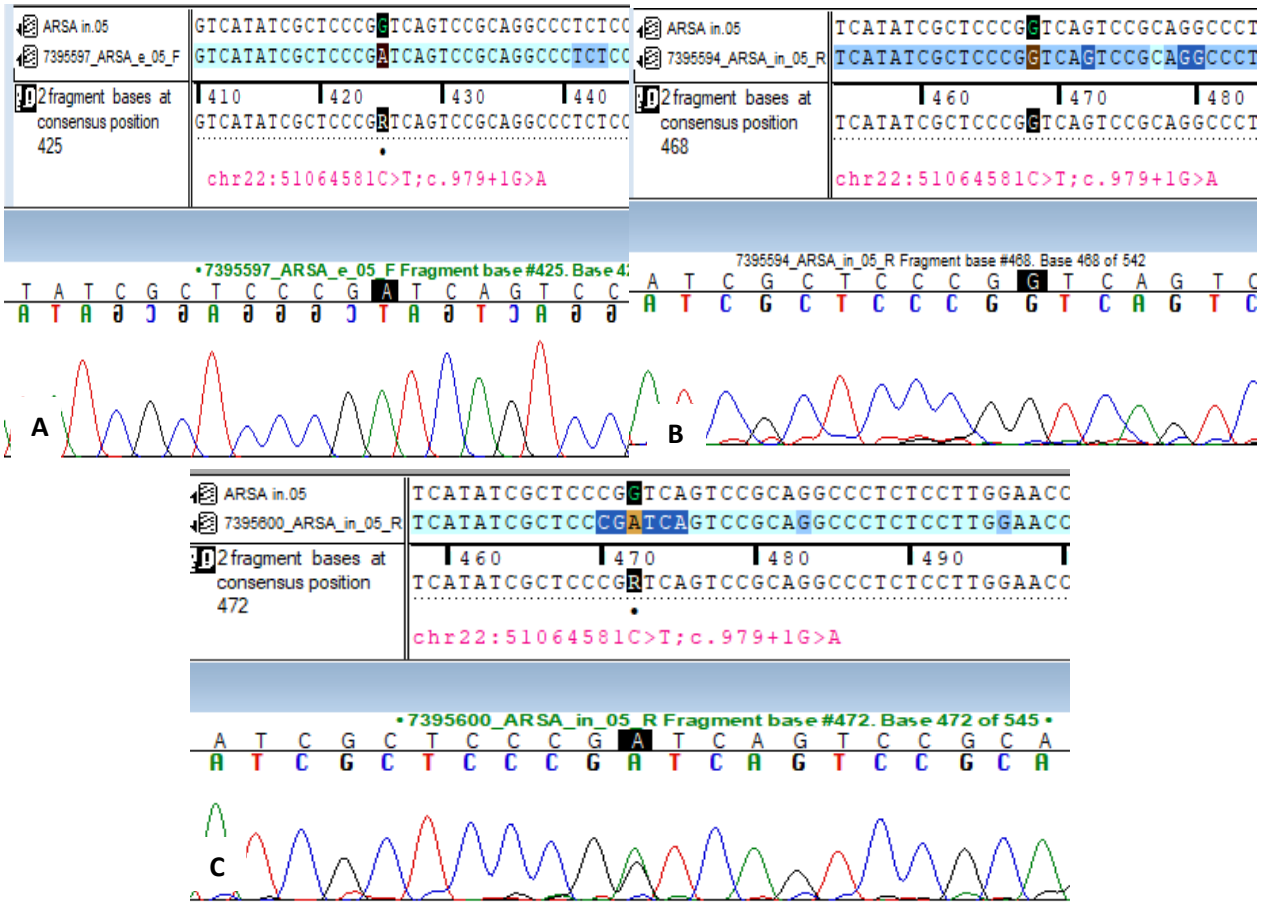

Figure 3: Sanger sequencing ARSA gene (NM 000487.5:c.979+1G>A) in family members. The proband has this mutation in hemizygous state. Mother and older sibling have this mutation in heterozygous state, while the father carries the wildtype allele. (A) Proband; (B) Father & (C) Elder brother.

Table 1: List of OMIM genes present in chr22q13.3 deletion region.

Molecular karyotype	Primary genes (OMIM)
ARR[GRCH37) 22Q13.32Q13.33 (48710480_51197838) X1	TAFA5 (617499), BRD1 (604589), ZBED4 (612552), ALG12 (607144), CRELD2 (607171), PIM3 (610580), IL17REL (613414), TTLL8 (619193), MLC1 (605908), MOV10L1 (605794), PANX2 (608421), SELENOO (607917), TUBGCP6 (610053), HDAC10 (608544), MAPK12 (602399), MAPK11 (602898), PLXNB2 (604293), PPP6R2 (610877), SBF1 (603560), ADM2 (608682), MIOX (606774), NCAPH2 (611230), SCO2*(604272), TYMP (131222), SYCE3 (615775), CPT1B (601987), CHKB (612395), MAPK8IP2 (607755), ARSA (607574), SHANK3* (606230), ACR (102480)

*marked genes are haplo-insufficient genes.

Table 2: Enzyme study of affected proband.

Test (units)	Disorder	Result	Biological reference interval (mean±SD)	Status
Aryl sulphatase A (nmol/17hr/mg)	Metachromatic leukodystrophy	6.4	67-396 (187.5±63.9)	Low (3.4 % mean normal)
β- galactosidase (nmol/hr/mg)	GM1- gangliosidosis	96.0	70-324 (148.1±35.7)	Normal

Table 3: Enzyme study of asymptomatic elder sibling having heterozygous variant in ARSA gene and normal chromosomal microarray.

Test (units)	Disorder	Result	Biological reference interval (mean±SD)	Status
Aryl sulphatase A (nmol/17hr/mg)	Metachromatic leukodystrophy	13.9	67-396 (187.5±63.9)	Low (7.4 % mean normal)
β- galactosidase (nmol/hr/mg)	GM1- gangliosidosis	169.3	70-324 (148.1±35.7)	Normal

Table 4: Enzyme studies of proband and his sibling: Arylsulphatase A and β- galactosidase levels in blood leucocytes.

	Test (units)	Result	Biological reference interval (mean±SD)	Status
Proband	Arylsulphatase A (nmol/17hr/mg)	6.4	67-396 (187.5±63.9)	Low (3.4 % mean normal)
	β- galactosidase (nmol/hr/mg)	96.0	70-324 (148.1±35.7)	Normal
Sibling	Arylsulphatase A (nmol/17hr/mg)	13.9	67-396 (187.5±63.9)	Low (7.4 % mean normal)
	β- galactosidase (nmol/hr/mg)	169.3	70-324 (148.1±35.7)	Normal

DISCUSSION

There are only few case studies with co-inheritance of PMS and MLD phenotype reported so far in literature, but PMS has been well studied.[7-10] The severity of the MLD phenotype in those co-inherited patients is determined by the inheritance of I-type or R-type variant in ARSA gene, whereas the severity of the PMS phenotype determined by the substantial loss of haplo-insufficient genes on chromosome 22. Here in our case study, the child had I-type allele with infantile onset MLD. His MLD phenotype was predominating over the PMS phenotype. His whole exome analysis aided in revealing the presence of ARSA mutation in trans with chromosome 22 deletion.

The diagnosis may be missed if CMA alone is done at the time of initial presentation of developmental delay, and MRI brain is normal. It could have been a challenge for a treating clinician to suspect other coinheriting disorder.

MLD suspicion in PMS patients must be considered in those patients showing rapid neurological deterioration. Further investigation studies like MRI and ARSA activity might remain as clue to delineate the diagnosis. Mingbungerjerdsuk et al, suggested screening all individuals with deletion 22q13 for urine sulfatides to detect pre-symptomatic and early cases of MLD. This would allow for counselling to discuss treatment options, prognosis, medical surveillance, and management.

CONCLUSION

It is quite challenging to decide on the diagnostic tool to identify the mutation of underlying disorder. The acceptable first line of testing for PMS is CMA. The prevalence of co-inheritance of PMS with MLD may have previously been underestimated, due to the limited exploration of PMS phenotype by CMA/MLPA/ Karyotype/FISH. The choice of TRIO whole exome sequencing accompanied with CMA may be a more promising approach for familial studies. Molecular diagnosis plays an inevitable role on PMS patients for understanding clinical progression, treatment strategies and disease management.

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