Expanding phenotypic diversity of *PRUNE1 related disorders: an experience of four cases in a tertiary center*

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01 INTRODUCTION

PRUNE 1 gene on chromosome 1q21.3

- a member of the DHH*(Asp-His-His)* phosphoesterases family
- key role in cell migration, differentiation and proliferation[1]
- intensely expressed in early stages of normal cortical development
- ***NMIHBA****(OMIM#617481)* as the most common phenotype *(summarized in **Figure-1.**)*
- Homozygous or compound heterozygous mutations responsible for the disease, especially clustered in DHH domain[1]

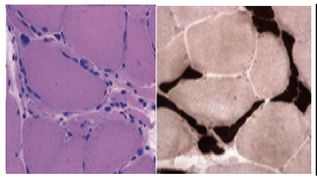
NMIHBA phenotype

Figure-1

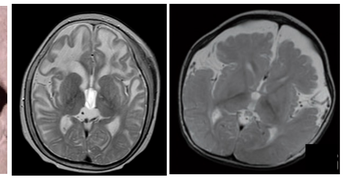
02 AIMS and METHODS

- Investigational enthusiasm by delineation of atypical presentations in recent reports[2,3]
- First aim to emphasize the phenotypic heterogenity and diversity of NMIHBA disease
- Secondly to reveal the most frequent variant of our series
- We describe the clinical characteristics of our patients underwent genetic analysis with whole exome/genome sequencing *(WES/WGS)*

Clinical phenotypes:
Patient images demonstrating facial dysmorphology, flask/spastic quadriparesis with generalized hypotonia and skeletal deformities



Muscle biopsy of *Case 3:*
clustered,distributed atrophic type 2 fibers



Neuroimaging of *Case 1 (L)* and *Case 4 (R)*
diffuse cerebral atrophy and white matter changes

Figure-2: Clinical phenotypes and some investigational tests of our cases with ***PRUNE1*** mutation (detailed information below in table)

Investigational Tests	Case 1	Case 2	Case 3	Case 4
EEG	Multifocal spike and sharp waves Slow background	Multifocal spike and sharp waves Slow background	Multifocal spike and sharp waves Slow background	N.A
Brain MRI	Diffuse brain atrophy WM changes Ventriculomegaly Thin Corpus Callosum	Diffuse brain atrophy Subdural collection Ventriculomegaly Thin Corpus Callosum Delayed myelination	Ventriculomegaly Posterior arachnoidal cysts	Diffuse brain atrophy Delayed myelination Inferior vermis hypoplasia
CK levels (IU/L)	347 IU/L	257 IU/L	1940 IU/L	N.A
Electromyography (EMG)	Unsuitable for assessment (severe contarctures)	N.A	Neurogenic	Neurogenic
Muscle Biopsy	Nonspesific	Not done	Type 2 fiber atrophy Type 1 predominance	Not done
Molecular Genetic Analysis	***PRUNE 1*** *Homozygous*	***PRUNE 1*** *Homozygous*	***PRUNE 1*** *Homozygous*	***PRUNE 1*** *Homozygous*
DNA level	c.316 G>A	c.316 G>A	c.316 G>A	c.874_875insA
Protein level	p.Asp106Asn	p.Asp106Asn	p.Asp106Asn	p.H292Qfs*3

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03 RESULTS of CASES

- ***Common features(all males ,with consanguinity):***
  profound neurodevelopmental delay,
  generalized muscle weakness and
  epilepsy with progressive disease course
- ***Most frequent seizure type:*** epileptic spasms

- ***Clue signs of neurological examination:***
  Primary progressive/secondary microcephaly *(except Case 2)*
  Facial dysmorphology with variable degree (*Figure-2*)
  Underlying atypical presentation of our case series:
  Early onset severe hypotonia suggesting neuromuscular disease
  in combination with hyperCKemia or neurogenic features on EMG

- **Major brain abnormalities** *(Figure-2):*
  diffuse brain atrophy ± ventriculomegaly
  delayed myelination and thin corpus callosum.

- **The most frequent variant in PRUNE1 gene**:
  homozygous c.316 G > A (p.Asp106Asn) variant

04 CONCLUSİON

- Stongly consideration of ***PRUNE1*** mutation if generalized hypotonia plus flask quadriparesis observed with objective findings suggesting spinal motor involvement
- ***p.Asp106Asn*** variant: a recurrent mutation in Middle East,Asian and some European (Italy) countries
- In line with our findings: might be a ***hotspot*** mutation and a suspicion of possibility for ***founder effect*** in Turkish population

All authors declare no conflict of interests.
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