Autosomal Recessive Spastic Tetraplegia Caused by \textit{AP4M1} and \textit{AP4B1} Gene Mutation: Expansion of the Facial and Neuroimaging Features

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Adaptor protein complex-4 (AP4) is a component of intracellular transportation of proteins, which is thought to have a unique role in neurons. Recently, mutations affecting all four subunits of AP4 (\textit{AP4M1}, \textit{AP4E1}, \textit{AP4S1}, and \textit{AP4B1}) have been found to cause similar autosomal recessive phenotype consisting of tetraplegic cerebral palsy and intellectual disability. The aim of this study was analyzing AP4 genes in three new families with this phenotype, and discussing their clinical findings with an emphasis on neuroimaging and facial features. Using homozygosity mapping followed by whole-exome sequencing, we identified two novel homozygous mutations in \textit{AP4M1} and a homozygous deletion in \textit{AP4B1} in three pairs of siblings. Spastic tetraplegia, microcephaly, severe intellectual disability, limited speech, and stereotypic laughter were common findings in our patients. All patients also had similar facial features consisting of coarse and hypotonic face, bitemporal narrowing, bulbous nose with broad nasal ridge, and short philtrum which were not described in patients with \textit{AP4M1} and \textit{AP4B1} mutations previously. The patients presented here and previously with \textit{AP4M1}, \textit{AP4B1}, and \textit{AP4E1} mutations shared brain abnormalities including asymmetrical ventriculomegaly, thin splenium of the corpus callosum, and reduced white matter volume. In conclusion, disorders due to mutations in AP4 complex have similar neurological, facial, and cranial imaging features. Thus, these four genes encoding AP4 subunits should be screened in patients with autosomal recessive spastic tetraplegic cerebral palsy, severe intellectual disability, and stereotypic laughter, especially with the described facial and cranial MRI features.

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INTRODUCTION

Adaptor protein (AP4) is a heterotetramer, composed of two large chains, beta (\textit{AP4B1}) and epsilon (\textit{AP4E1}), a medium chain (\textit{AP4M1}), and a small chain (\textit{AP4S1}) [Matsuda and Yuzaki, 2008, 2009]. Five types of AP complexes have been identified [Hirst et al., 2011]. Each type has different function and localization in intracellular trafficking between the organelles. AP4 has been shown to traffic the amyloid precursor protein from the transgolgi network to endosomes [Boehm and Bonifacino, 2001]. Matsuda et al. [2008] also demonstrated that AP4 plays a unique role in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking in neurons. AP4 regulates proper somatodendritic distribution of its cargo proteins, including AMPA receptor and the autophagic pathway in neurons. AMPA receptors are highly expressed in migrating interneurons and in immature oligodendrocytes at the time when they initiate myelination.

Conflict of interest: The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

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Verkerk et al. [2009], were the first to describe association with AP4-complex, where they identified mutation in AP4M1 gene in five patients from a consanguineous Moroccan family with autosomal recessive type of tetraplegic cerebral palsy and intellectual disability (SPG50, formerly CPSQ3; OMIM 612936). These patients also had infantile hypotonia, progressive spasticity of all limbs with generalized hypertonia, lack of independent walking, microcephaly, severe intellectual disability, stereotypic laughter, ventriculomegaly, white matter abnormalities, and variable cerebellar atrophy.

Recently, Moreno-De-Luca et al. [2011], Abou Jamra et al. [2011], and Bauer et al. [2012] described similar patients (SPG51, formerly CPSQ4, OMIM 613744; SPG47, formerly CPSQ5, OMIM 614066; SPG52, formerly CPSQ6, OMIM 614067) associated with homozygous mutations in AP4E1, AP4B1, and AP4S1 genes. The overlapping clinical phenotypes with mutations in any of the four AP4 subunits prompted the term “AP4 deficiency syndrome” [Moreno-De-Luca et al., 2011]. Here we report on three pairs of Turkish siblings, two carrying mutations in AP4M1 and one pair in AP4B1 genes. Similarities with the reported cases are discussed; neuroimaging and facial dysmorphic features are emphasized.

**MATERIALS AND METHODS**

**Patients**

The study group was composed of three Turkish families each having two children with spastic tetraplegic cerebral palsy and intellectual disability (Fig. 1). Family-1 had two daughters (Patients 1 and 2) with spastic tetraplegic cerebral palsy and intellectual disability. The parents were first cousins once removed. In the Family-2, mother and father were double first cousins. Their first and third children (Patients 3 and 4) were affected whereas, the second child was healthy. Family-3 also had two daughters (Patients 5 and 6) who were affected. The parents were not related but were from the same small village.

The study was approved by ethics board of Istanbul university. Written informed patient and parent consents were obtained for additional genetic investigations.

**Whole Genome Genotyping**

Whole-genome genotyping was performed in six patients from three families using Illumina 610K SNP chips following the manufacturer’s protocol and as described previously [Kolb

![Figure 1](image-url)
et al., 2010]. The image data were normalized and the genotypes were called using data analysis software (Genome Studio, Illumina).

**Exome Capture and Sequencing**

Whole-exome capture and enrichment were performed using Nimblegen v1 solid (Patients 1 and 4) and v2 liquid phase whole-exome capture oligo pool (Patients 3 and 5) [Choi et al., 2009]. The enriched libraries were sequenced Illumina Genome Analyzer Ix (Patients 1, 3, and 4) and HiSeq2000 (Patient-5) with single-read (Patients 1 and 4), and paired-end chemistries (Patients 3 and 5) [Bilguvar et al., 2010]. Analysis of the sequencing data was performed using the previously described data-analysis pipeline. Briefly, the sequencing reads were aligned to the human genome (NCBI36/hg18) by Maq and BWA software [Li et al., 2008]. Coverage and error rates were detected using perl scripts. Both single nucleotide variations and indels were identified with SAMtools and annotated for novelty as compared to the dbSNP build 131, nine personal genomes published, and 1000 Genomes database (August 4, 2010 release). In addition, data from a large cohort of exome-sequencing experiments performed were used to check for the novelty status of the identified variants. The variants were analyzed for their impact on the encoded protein. Conservation of the affected residues was evaluated across vertebrate and Caenorhabditis elegans, and Drosophila melanogaster orthologs [Li and Durbin, 2009; Li et al., 2009].

**RESULTS**

**Clinical Findings**

**Family-1.** Patient-1, 17-year-old female, was the first child of the family. She had head control at 4 months, sat unsupported at 10 months, walked with support at age 3 years, and lost the ability to walk around 4 years of age. She started having tonic-clonic and atonic seizures once a month at age 6 months which stopped at age 8 years under the therapy with phenobarbital and valproate. Patient-2, her 11-year-old sister who had identical motor and language development. She had head control at 4 months, sat unsupported at 12 months, walked with support at age two and a half years, and lost the ability to walk around 4 years of age. She had tonic-clonic seizures precipitated by fever between 6 months and 8 years of age. Later, she also had astatic seizures treated with valproate. Their EEG did not reveal epileptiform discharges (Fig. 1a, Table I).

They could only say “mother” and “father”. Their craniofacial and neurological features are summarized in Table I. Similarities of the facial features are shown in Fig. 1d. The ophthalmologic examinations and metabolic screening for organic acids, amino acids, and fatty acid disorders were normal. Karyotype analysis also was normal.

**Family-2.** Patient-3, 10½-year-old girl, was the first child. Head control was gained at 2 years of age. She sat unsupported with a drooping posture but could not walk. She could not say any words and had difficulty chewing and swallowing. She had tonic-clonic seizures precipitated by fever which started at age 11 months, which were controlled with phenobarbital. She also had adducted thumbs and club foot. Patient-4, 2½-year-old boy, was the third child of Family-2. He sat unsupported at 18 months. He could not walk but crawl and say three words at 3 years of age. He had tonic seizures precipitated by fever or trauma which started at the age of 10 months and recurred three times. The facial features are illustrated in Fig. 1e. While the eye examination was normal in Patient-3, strabismus convergens was present in Patient-4. The sibs had normal karyotype analysis and metabolic screening for urine organic acid as well as serum amino acids. Their EEG was normal (Fig. 1b, Table I).

**Family-3.** Patient-5, 12½-year-old female (Fig. 1c, Table I), was the first child of the family. She had head control at 8 months, sat unsupported at 12 months, walked with support at 4 years of age. She started having rare seizures, some febrile, at age 9 months which stopped at age 8 years. The seizures manifested some focal features but generalized, some leading to status epilepticus. She responded to valproate therapy. She could not walk independently and she could say 10–15 words. Patient-6, 10.5 year old sister, had head control at 6 months, sat unsupported at 10 months, walked without support at age 3 years of age. She lost the ability to walk around 5 years of age. She could only say four words. Her seizures started at the age of 6 months as febrile convulsions, responding therapy with phenobarbital. Around 4 years of age, she developed complex partial seizures with scared appearance, unresponsiveness, and right-sided stiffening occurring weekly. These responded partially to valproate which led to liver failure. Later, seizures were controlled with levetiracetam at the age of 8 years. She also had occasional status epilepticus. Both siblings had rare multifocal sharp waves on EEG. She had similar facial features as her sister (Table I, Fig. 1f). Their karyotype analysis and screening for urine organic acid as well as serum amino acids were normal.

**Cranial MRI Features**

The cranial MRI findings of all patients are summarized in Table I and illustrated in Figures 2–4. They shared asymmetrical ventriculomegaly, thin splenium of the corpus callosum, abnormal white matter changes, and hippocampus globoid formation (Figs. 2–4). In addition, Patient-1 and 2 had a flat and thin hippocampus on the right side (Fig. 2). Patient-3 had cerebral atrophy and enlargement of subarachnoid cisterns; Patient-4 had T2 hiperintensities of the sub cortical white matter (indicating late maturation) in right temporal lobe at the age of 3 years (Fig. 3); Patient-5 and 6 had a flat and thin hippocampus bilaterally and Patient-5 also had gliotic signal changes in the subcortical frontal lobes asymmetrically; Patient-6 had bilateral hyperintensity of the denteate nucleus and enlargement of the basal cisterns (Fig. 4).

**Molecular Studies**

In Family-1, homozygosity mapping identified a total of six shared segments between the affected individuals on chromosomes 7, 10, and 11, which composed of 63.49 CM. In Patient-1, the only novel homozygous coding variant detected within the shared homozygosity intervals by exome sequencing was in APH4M1 (c.1012C>T; p. Arg338Ter) on chromosome 7 position 99,541,837 (NCBI36/hg18). This variant is predicted to create a premature stop-codon (R338X) and early truncation of the encoded protein. The other affected sibling also harbored this mutation in homozygous state while both parents were heterozygous for the mutation (Fig. 1a).
<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>AP4M1 mutation</th>
<th>AP4B1 mutation</th>
<th>AP4E1 mutation</th>
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<td></td>
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<td>11</td>
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<td>−3 SD</td>
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<td>−2 SD</td>
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<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
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<td>+</td>
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<td>+</td>
<td>NA</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<tr>
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<td>2.5</td>
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<td>−</td>
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<td>Ambulation</td>
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<td>−</td>
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<td>Seizures</td>
<td>+</td>
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<td>Drooling</td>
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<td>−</td>
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<td>−</td>
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<td>Club feet</td>
<td>−</td>
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<td>−</td>
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<td>Adducted thumbs</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>Broad nasal ridge</td>
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<td>+</td>
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<td>+</td>
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<td>Bulbous nose</td>
<td>+</td>
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<td>Short philtrum</td>
<td>+</td>
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<td>Thin splenium of CC</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<td>White matter loss</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cerebral atrophy</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Hippocampal globoid formation</td>
<td>Left</td>
<td>Left</td>
<td>Right</td>
<td>Right</td>
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**TABLE I. Clinical Features of the Present and Previously Reported Patients with Mutations in AP4M1, AP4B1, AP4E1, and AP4S1 Genes**
In Family-2, homozygosity mapping revealed a total of 11 shared segments on chromosomes, 1, 3, 5, 6, 7, 8, 12, 14, and 20 which composed of 183.65 cM. In the affected siblings (Patients-3 and 4), exome sequencing identified two novel homozygous mutations within shared homozygosity intervals. One of these variants was a nonsense mutation located in AP4M1 on chromosome 7 at position 99,541,540 (NCBI36/hg18), while the other was a missense mutation in M6PR on chromosome 12 at position 8,987,677 (NCBI36/hg18). The nonsense variant (c.952C>T) leads to a premature stop-codon (p.Arg318Ter), which predicts early truncation of the protein. Sanger sequencing confirmed that the parents as well as the unaffected sibling were heterozygous for the mutation (Fig. 1b).

Both nonsense mutations identified in AP4M1 were located in the mu homology domain of the protein and they were not previously reported in public databases and absent in control chromosomes.

In Family-3, we identified a total of three shared segments on chromosome 1 which composed of 17 cM. Whole-exome sequencing of the first sibling revealed a single novel homozygous deletion in AP4B1 (c.869delC; p.L221fs) on chromosome 1 at position 114,244,498 within the shared homozygosity intervals. This variant was confirmed to be homozygous in the affected sister and heterozygous in mother. Variant was confirmed to be homozygous in affected subjects and heterozygous in parents (Fig. 1c). This variant was not previously reported in public databases and absent in control chromosomes.

Whole-exome sequencing provided sufficient coverage across the targeted bases with low error rates and high sensitivity and specificity to detect homozygous variants. For Patient-1, with over 92% of the exomic bases being covered at least four times. For Patient-3, 96.26% of the exomic bases within the shared homozygosity intervals were covered at least four times. For Patient-4, 4× coverage was observed for 93.8% of the homozygosity intervals. In Patient-5, 97.46% of all targeted bases which were read more than four times.

**DISCUSSION**

The three pairs of siblings reported here have constellation of rather nonspecific symptoms. These include developmental delay in motor and cognitive areas, seizures, mild dysmorphic features, and subtle imaging abnormalities. With the application of whole-exome sequencing, we were able to identify mutations in concordance with the results of homozygosity mapping. We describe in two pairs of siblings two different nonsense mutations of AP4M1, in exons-12 [c.952C>T (p.Arg318Ter)] and exon-13 [c.1012C>T (p.Arg338Ter)], leading to premature stop-codons (R318X and R338X). All four patients had spastic tetraplegia, severe intellectual disability, stereotypic laughter, limited or absent speech, microcephaly, and seizures (Table 1). Verkerk et al. [2009] reported a donor splice site pathogenic mutation in intron-14 of the AP4M1 gene (c.1137+1G>T) in five patients with autosomal recessive type of tetraplegic cerebral palsy. A missense mutation in the AP4M1 gene also was identified by Najmabadi et al. [2011] in children of first-cousin parents who had severe intellectual disability, microcephaly, and spastic paraplegia. When we compared the clinical findings of our patients with those in the Verkerk et al. article, severe
intellectual disability, limited or absent speech, and stereotypic laughter are common (Table I). Seizures were not seen in the Verkerk et al. patients. Our patients also carried some facial features such as coarse and hypotonic face, bitemporal narrowing, bulbous nose with wide nasal ridge, short philtrum with everted upper vermillion, and wide mouth which were not reported in the Verkerk et al. patients.

The third family reported here carries a mutation in AP4B1 gene. Mutations in the same gene were previously identified by Bauer et al. [2012] and Abou Jamra et al. [2011]. Two affected siblings in the Bauer et al. article, previously published [Blumkin et al., 2011], had slowly progressive spastic paraparesis, intellectual disability, seizures, microcephaly, periventricular white matter changes, and thin corpus callosum. Here, we describe a novel homozygous deletion (c.869delC; p.L221fs) which was predicted to lead to frame shift and premature stop-codon. Neurological findings of these sisters were similar to the other patients reported here and in the past either with AP4M1 or AP4B1 mutations (Table I). In addition, these patients with mutations in AP4B1 gene had facial dysmorphic features consisting of coarse and hypotonic face, bitemporal narrowing, bulbous nose with wide nasal ridge, short philtrum with everted upper vermillion, and wide mouth which were not described by Blumkin et al. [2011].

We also compared the clinical findings of the patients with those of the reported patients who had AP4E1 and AP4S1 mutations in Table I. Although the dismorphic facial features in our patients were not described in previously published cases with AP4M1 and AP4B1 mutations, similar features were present in patients with AP4E1 or AP4S1 mutations [Abou Jamra et al., 2011; Moreno-De-Luca et al., 2011].

The neurological findings such as spastic tetraplegia, severe intellectual disability, stereotypical laughter, limited or absent speech, and microcephaly were characteristic findings in all patients presented here and reported patients. Seizures appear to be a variable feature in patients with AP4 mutations as seen in the Table I.

Even though spasticity and tetraplegia are the uniformly evolving pattern of the patients with AP4 mutations, their initial presentation is with hypotonic developmental delay. After delayed achievement of even walking ability, regression develops with spasticity and probably related foot deformities also reported by others [Verkerk’s et al., 2009; Abou Jamra et al., 2011; Moreno-De-Luca et al., 2011].

The cranial MRI of our patients with AP4M1 revealed asymmetric ventriculomegaly with thin splenium of the corpus callosum and abnormal white matter (Figs. 2 and 3), which were also reported before. However, there was no cerebellar atrophy which differs from

FIG. 2. Patient-1: Cranial MRI at 8 years of age [a] and 18 years of age [b,c] reveal ventriculomegaly which is prominent on the left side, left hippocampal globoid formation, flat and thin hippocampus on the right, and thin splenium of corpus callosum. There is no difference between the images of the patients obtained at different ages. Patient-2: Cranial MRI at 4 years [d] and 13 years of age [e,f] were similar to the older sister.
the Moroccan family reported with AP4M1 gene mutation [Verkerk et al., 2009]. Variable white matter changes with normal signal intensity and cerebellar atrophy on imaging studies were accepted as indications of axonal disarray and loss of myelin integrity [Verkerk et al., 2009]. The cranial MR angiography of the Moroccan patients also showed intra- and extracranial tortuosity of the large vessels, but this is due to the additionally found mutation in SLC10A2, associated with arterial tortuosity syndrome (ATS, OMIM 208050). The cranial MRI of the patients with AP4E1 mutations reported by Moreno-De-Luca et al. [2011] and with AP4B1 mutations reported by Blumkin et al. [2011] also showed similar findings such as ventriculomegaly, thin corpus callosum, white matter loss, and cerebral atrophy, which was present in our patients with AP4B1 mutations (Fig. 4). In addition, the patients presented here both with AP4M1 and AP4B1 had globoid formation, thinning and flattening of the hippocampus.

The finding of a thin corpus callosum can be a distinguishing feature in hereditary spastic paraplegias particularly for SPG11 and SPG15. Thinning of the corpus callosum is often accompanied by white matter changes, cortical atrophy, and cognitive impairment. Additional findings such as asymmetrical ventriculomegaly and particular involvement of the splenium should bring AP4 deficiency syndromes, thus, SPG47, 50, 51, and 52, in the differential diagnosis. Interestingly, both SPG11 and SPG15 have recently been linked to the newly indentified AP5 [Schüle and Schöls, 2011].

Verkerk et al. [2009] considered this disease entity as a genetic model for cerebral palsy occurring through glutamate receptor abnormality and neuroaxonal damage. The clinical pattern of initial hypotonia later evolving to spasticity can also support this. However, given the rather broad spectrum of hypoxic-ischemic injury patterns, this could only partly explain the pathological mechanisms in cerebral palsy. In mouse embryos, Verkerk et al. [2009] also demonstrated AP4M1 expression in all ventricular zones at different stages, suggesting a role in cerebral and cerebellar development. The localization corresponded to brain areas characterized by neuroglial progenitor proliferation, suggesting that an AP4M1 mutation might affect neurons as well as oligodendrocytes. Widespread expression of AP4B1, AP4E1, and AP4S1 transcripts were observed in fetal and adult brain structures [Abou Jamra et al., 2011].

In conclusion, “AP4-deficiency syndrome” due to mutations in the subunits of AP4 complex has very similar neurological, facial, and imaging findings. None of the clinical features are specific or
distinguishes involvement of different AP4 subunits. However, constellation of autosomal recessive spastic tetraplegia, severe intellectual disability, stereotypical laughter, limited or absent speech, microcephaly as well as mentioned facial and cranial MRI features should prompt screening for homozygous mutations in any of the four subunits leading to “AP-4 deficiency syndrome.”

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