Cytogenetic evaluation and identification of MeCP2 gene mutations in Rett syndrome patients in a south Indian population

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Introduction: Rett syndrome (RTT) is a postnatal neurological disorder caused by mutations in methyl-CpG binding protein 2 (MeCP2) gene. The aim of this study was to investigate this MeCP2 mutations associated with the risk of RTT in south Indian population. A total of 20 Patients (18 females/2 males) were evaluated based on the DSM IV questionnaire.

Methods: The study was approved by the Institutional ethics board. Clinical profiles of the patients were recorded. PCR amplification of MeCP2 gene coding exons was performed using primers and automated sequencing was done on the DNA sequencer. The Karyotype results of 20 subjects were carried out by Trypsin G- banding and their results were confirmed by FISH.

Results: Higher degree of chromosomal alterations were observed in X- chromosome includes 46,XX,t(X;22) (p11.2;p11), 46,XX,del(X) (Xp20.4-20.5), 46,XX,del(13) (13q12.1-q21.2)). MeCP2 mutations were observed in 10 of 20 (50%) cases. Of these 8 of them were classical sporadic and 2 were familial. Significantly milder disease was noted in patients carrying mis-sense mutations as compared with those with truncating mutations, that mutations in MeCP2 cause RTT and other neurodevelopmental disorders has called attention to the importance of epigenetic modifications in neuronal function.

Conclusion: As MeCP2 is only one member of family genes that play a role in DNA methylation-dependent transcriptional repression, it will be interesting to find, whether mutations in other genes cause developmental disorders (like autism) which share some features with RTT. Our results support the previously described role of MeCP2 mutations and will require detailed and larger analysis.

Disclosure: Nothing to disclose

Fatal familial insomnia presenting with diverse age of onset in a Chinese-Canadian family

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Background: Fatal Familial Insomnia (FFI) is a genetic prion disease characterized by insomnia, motor symptoms and dysautonomia due to mutation of codon 178 (D178N) of the Prion Protein (PRNP) gene. The presence of methionine (M) or Valine (V) at codon 129 determines whether phenotype is FFI or familial Creutzfeldt-Jacob disease (fCJD). A Chinese-Canadian family presenting with FFI at variable ages are described below.

Methods/case descriptions: Patient 1 presented in 1989 at age 29 with insomnia, fever and hallucinations. She died 14 months after onset. Autopsy showed thalamo-olivary degeneration without spongiosis. Patient 2, brother of Patient 1, presented in late 2012 at age 53 with insomnia, weight loss and hallucinations. Progressive decline continued with gait ataxia, myoclonus and mutism. Investigations were negative. Genetic testing revealed D178N and codon 129 MM. He died 11 months after onset. Patient 3, mother of Patients 1 and 2, presented in October 2013 at age 73 with insomnia, gait ataxia and hallucinations. Genetic testing revealed D178N and codon 129 MM.

Results/discussion: The majority of genetic prion disease in Caucasian populations are fCJD. The MM polymorphism accounts for 40% of Caucasians but over 93% of Han Chinese. The penetrance of PRNP mutations is 0.5-1.0 and increases with age.

Conclusion: The prevalence of codon 129 MM in Han Chinese makes FFI more likely in this population. A Chinese-Canadian family presented with FFI with variable onset highlighting the increasing penetrance of FFI with age.

Disclosure: Nothing to disclose
Epilepsy, optic atrophy, axonal neuropathy, sensory-neural deafness and cerebellar ataxia: extending the phenotype in argininosuccinic aciduria

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Introduction: Argininosuccinic Aciduria (AA) is a urea cycle disorder caused by defects of Argininosuccinate Lyase (ASL). A severe neonatal form is characterized by hyperammonemia, and a late-onset form is characterized by neuro-cognitive deficiencies, seizures, hepatitis, hypertension and trichorrhexis nodosa. We present two brothers with AA and a complex clinical phenotype.

Methods: Both probands, 21 and 14 years old, presented with AA due to homozygous c.532G>A mutation in the ASL gene. They were diagnosed at age 11 and 4 respectively, based on a history of cognitive deficit and epilepsy, and put on a low-protein diet and arginine supplementation. The second brother experienced also subacute vision loss, deafness and ataxia at 7, 11 and 12 years, respectively. Both underwent neurologic examination (NE), venous serum lactate assessment after standardized exercise, electroencephalogram (EEG), nerve conduction study (NCS), visual evoked potentials (VEPs), optical chence tomography (OCT), audiometry, neuropsychologic evaluation, brain MR and complete sequencing of mitochondrial DNA (mtDNA).

Results: NE revealed signs of peripheral neuropathy and cerebellar involvement; lactate after exercise was abnormally elevated; EEG showed generalized epileptiform activity and NCV a severe axonal neuropathy. VEPs were reduced in amplitude and OCT revealed thinning of the temporal retinal nerve fiber layer. Audiometry showed severe sensorineural deafness in the second brother. Neuropsychological testing detected cognitive deficit in both. Brain MRI and complete sequencing of mtDNA were unremarkable.

Conclusions: ASL deficiency may manifest with a complex phenotype and mitochondrial dysfunction, not due to mtDNA abnormalities. The underlying mechanism is under investigation.

Disclosure: Nothing to disclose

Association of the PSMA3 gene polymorphisms with multiple sclerosis

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Introduction: The cause of Multiple sclerosis (MS) is still poorly understood and different metabolic pathways seem to play a role in disease development. Failure of ubiquitine proteasome system (UPS) efficiency had been recently implicated to MS pathogenesis.

Methods: The rs2348071 SNP of the PSMA3 gene (c.543+138G>A) has been genotyped in 281 MS patients (201 women) being diagnosed on relapsing - remitting (188 subjects) or secondary progressive (93 subjects) course of the disease, versus 191 control subjects (117 women) without inflammatory and any autoimmune disorders.

Results: In controls the rs2348071 locus showed allele and genotype presentation similar to other Europeans with minor allele frequency (MAF) about 30% and genotype GG being most frequent (53%). In both female and male cohorts of MS patients the minor allele A was observed slightly more frequent than in controls (p<0.05), frequency of both GG and AA homozygotes was decreased (about 30% and 5% respectively) in favour of heterozygote GA genotypes (from 61% to 71% in patients of relapsing - remitting and secondary progressive course of disease respectively)that was significantly higher than in controls (p<0.0001; OR=3.539 [95% CI 2.409 - 5.198] according to co-dominant model).

Conclusion: The rs2348071 heterozygous genotype appears to be the MS risk factor in Latvian population.

Disclosure: Nothing to disclose
**PP4194**

**The eNOS gene polymorphisms (exon 894 G/T, promoter -786T/C, and intron G10T) in migraine cases of a Turkish population**

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**Introduction:** Migraine is a neurovascular and common primary headache disorder characterised by recurrent headaches. We investigated the frequency of three endothelial nitric oxide synthases (eNOS) gene polymorphisms (894 G/T, -786T/C, and G10T) in migraine and control groups.

**Methods:** A total 137 individuals (84 migraine cases and 53 control) were included in this study. The eNOS gene polymorphisms were detected using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

**Results:** The intron G10T polymorphism was not significantly different in migraine (58 GG, 26 GT) and control (38 GG, 15 GT) group (p:0.742). For exon 894 G/T polymorphism, this difference was meaningful in migraine (20 GG, 55 GT and 9 TT) and control (24 GG, 27 GT and 2 TT) group (p: 0.06). Although the promoter -786T/C gene polymorphism was not significantly higher in migraine (23 TT, 49 TC and 12 CC) than control (27 TT, 16 TC and 10 CC) group, it was nearly meaningful (p: 0.070).

**Conclusions:** The exon 894 G/T polymorphism is seen as related with migraine disease. Although this relation is not meaningful for intron G10T but it was nearly meaningful for promoter -786T/C gene polymorphism. eNOS polymorphisms may be useful markers for assessment of migraine risk and clinical diagnosis. Thus additional studies including more individuals should be performed to more exact understanding of these relations in migraine disease.

**Disclosure:** Nothing to disclose

**PP4195**

**Late-onset Huntington’s disease: diagnostic and prognostic considerations**

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**Introduction:** We sought to address diagnostic and prognostic issues in patients with late-onset Huntington’s disease (HD).

**Methods:** We analyzed a cohort of 41 late-onset (≥60 years) HD patients and compared them to 39 late-onset patients referred for HD testing that were negative for the HD-expansion and to 290 HD patients with onset in the usual age range (usual-onset, 20-59 years). Disease severity was assessed by the Total Functional Capacity Scale.

**Results:** Late-onset HD comprised 11.5% of our HD cohort. In total, 70.7% of late-onset HD patients had positive family history compared to 15.4% of late-onset expansion-negative patients (p=0.000). Clinical features at onset or presentation could not usefully distinguish between late-onset expansion-positive and negative patients, excepting hemichorea, which was absent from the HD group (p=0.024). Chorea was the first clinical feature in 53.7% and a presenting feature in 90.2% of late-onset HD. The mutation hit rate for late-onset patients was 51.3%, lower than in usual-onset patients (p=0.04). Frequencies of chorea, cognitive impairment and psychiatric manifestations at onset or presentation were not significantly different between late-onset and usual-onset HD patients. Gait unsteadiness however was more common at presentation in late-onset HD (p=0.007). Late-onset HD patients reached a severe stage of illness on average 2.8 years earlier than usual-onset HD patients (p=0.046).

**Conclusions:** A positive family history suggestive of HD, although absent in a third of patients, remains a helpful clue in diagnosing late-onset HD. Prognosis of late-onset HD in terms of Total Functional Capacity appears somewhat less favorable than usual-onset HD.

**Disclosure:** Nothing to disclose
PP4196

Coexistence of autosomal recessive spastic ataxia of Charlevoix Saguenay and spondyloepiphyseal dysplasia in a Turkish patient

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Introduction: Here, we present a female patient from consanguineous parents whose genetic analysis revealed the coexistence of Autosomal Recessive Spastic Ataxia of Charlevoix Saguenay (SACS) and Spondyloepiphyseal dysplasia (SED).

Methods: A 47-year-old woman with short stature presented with gait disturbance and paresthesia. She was complaining of gradually increasing ataxia since her early childhood. Neurologically, her speech was cerebellar dysarthric, she had symmetrical weakness, lower limbs were spastic, she had tenar, hypotenar, interosseal, tibialis anterior and intrinsic foot muscle atrophy. Hypoesthesia was detected in feet and hands. Deep tendon reflexes were decreased, plantar responses extensor. Patient had pronounced ataxic gait. Similar complaints were present in her two sisters.

Results: MRI revealed cerebellar atrophy, radiographically there were prominent end plate irregularities and sclerosis of the vertebral bodies, spondylosis and kyphosis. Nerve conduction study was consistent with demyelinating sensory-motor neuropathy. GAA expansion in the frataxin gene was negative. Patient was subjected to exomic sequencing due to her pronounced family history. Exome analysis revealed two homozygous novel mutations in the SACS gene (exon10:c.G8315C:p.G2772A; exon9:c.2093+1G>A). Additionally two homozygous novel mutations were present in the ACAN gene (exon12:c.C3635T:p.T1212I; exon12:c.C3638T:p.A1213V). These mutations have to be validated in the affected sisters and also in the heterozygous parents.

Conclusions: One of the two mutations in the SACS gene would explain the above-described ataxic features of the patient, firmly excluding other causes of ataxia. Furthermore, either both or one of the homozygous mutations in the ACAN gene is expected to explain her skeletal deformities.

*Kurt and Kartal joint first authorship

Disclosure: Nothing to disclose

PP4197

RYR1 gene: three mutations c.10097G>A, c.11798A>G, c.115G>A in a patient with central core myopathy

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Introduction: Ryanodine receptor gene (RYR1) mutations have been associated with central core disease (CCD), multiminicore/minicore/multicore disease (MmD), and susceptibility to malignant hyperthermia (MH). Determining the pathogenicity and mode of inheritance of each mutation is essential for prognosis, genetic counseling and also prevention of potentially life threatening reactions to general anesthesia.

Clinical case: Woman, 35 years old, clinically diagnosed with congenital myopathy with proximal limb weakness since early childhood. She has very mild clinical impairment being able to accomplish most daily tasks. No relevant family history was known. Her CK was slightly elevated and a muscle biopsy was compatible with CCD. RYR1 gene was screened and three mutations were found: c.10097G>A (p.Arg3366His), c.11798A>G (p.Tyr3933Cys), already described with recessive trait; c.115G>A (p.Glu39Lys) not described and of unknown significance. Her asymptomatic non-consanguineous parents were screened in order to establish the allelism in the patient and mode of inheritance of these mutations. The mother carried c.10097G>A and c.11798A>G in cis and the father carried c.115G>A.

Conclusions: Based on the literature and the findings in our case, we can conclude that these three mutations are pathogenic and all have a recessive trait. Its clinical significance is paramount for genetic counseling since the parents and all her children will be asymptomatic carriers for CCD or MmD but will be at risk for MH. Other at risk relatives may also benefit from genetic screening.

Disclosure: Nothing to disclose
**PP4198**  
**Novel LRRK2 6165C>G mutation in a patient with Parkinson’s disease-dementia: a case report**  
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**Introduction:** LRRK2-related Parkinson’s disease (PD) is characterized by motor and non-motor symptoms consistent with idiopathic PD. Asymmetrical, tremor-predominant parkinsonism with bradykinesia and rigidity is a core feature. Disease severity, rate of progression, occurrence of falls, dyskinesia, affection of cognition and olfaction are considered more benign than those of idiopathic PD (1). Onset is late, generally after 50 years, with an autosomal-dominant mechanism of inheritance.  

**Objective:** We describe a novel LRRK2 heterozygous mutation 6165C>G (P2036R) in a patient with PD and dementia and a positive familial history (a sister and mother with PD).  

**Methods:** Full clinical assessment of the patient at the age of 66 years. Genetic testing: Direct Sanger sequencing of DNA, extracted from peripheral leucocytes.  

**Results:** The disease onset was at 60 years with asymmetrical bradykinetic-rigid parkinsonism, with bilateral involvement over the next three years. Mild postural tremor of the limbs appeared at age of 65, together with postural instability and on/off phenomenon. During the disease course an impaired olfaction, sialorrhea, sleep disturbances, unpleasant sensations in the legs, apathy, depression, obstipation and dementia were added. The DNA tests revealed a heterozygous nucleotide exchange cDNA.6165C>G in the exon 41(a highly conservative region) of LRRK2. The programs for prediction suggested high pathogenicity of the mutation.  

**Conclusions:** We present a patient with the putative mutation 6165C>G in heterozygous state, affecting the kinase domain of LRRK2 and predominantly bradykinetic-rigid form of PD and dementia.  

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**PP4199**  
**LRRK2 mutation c.4536+3A>G in a patient with multiple system atrophy: a case report**  
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**Introduction:** The mutation c.4536+3A>G (IVS31+3A>G) in the LRRK2 gene (PARK8) is previously described in three genetic studies of Parkinson’s disease (PD), however its pathogenicity is not firmly established yet. Zabetian et al. (2005) identified it in a sporadic PD patient out of 371 tested patients and 281 controls. Shojaee et al. (2009), found this mutation in a family consisting of affected and unaffected individuals. Importantly, this variant was identified in healthy family members, but not in the affected sister of the proband. The third study, conducted by Anfossi et al. (2013) and based on 88 unrelated PD patients, identified the mutation in a patient with PD and dementia and a positive familial history.  

**Objective:** To identify a genetic reason for parkinsonism in a cohort consisting of 137 patients with PD or atypical parkinsonism.  

**Methods:** Full clinical assessment of the patients. Direct Sanger sequencing of LRRK2 in proband’s DNA, extracted from peripheral leucocytes.  

**Results:** The DNA tests revealed the heterozygous mutation c.4536+3A>G in the LRRK2 gene in a patient with clinical features consisting with the diagnosis MSA-C (probable). The disease onset was at 62 years with asymmetric bradykinetic-rigid parkinsonism. Over the next years the patient developed urinary incontinence, static and locomotor ataxia, blurred speech and mild cognitive impairment. At age of 66, the patient is wheel-chair bound.  

**Conclusions:** We present a MSA-C patient with the LRRK2 mutation c.4536+3A>G in heterozygous state and suggest its putative effect in a case of atypical parkinsonism.  

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PP4200
Usefulness of corpus callosum splenium versus middle cerebellar peduncle hyperintensity in FXTAS
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Introduction: FXTAS corresponds to FMR1 premutation, ataxia, action tremor and middle cerebellar peduncles (MCP) hyperintensity, which is the only major radiological criterion for definite FXTAS. The importance of corpus callosum splenium (CSS) hyperintensity was recently reported in FXTAS, but its interest in comparison to MCP is unknown.

Methods: Twenty-two until yet unreported patients (17 men; 5 women) with suspected FXTAS, because of the combination of FMR1 premutation and suggestive neurological signs, were included from 6 neurology centres from April 2012 to July 2013. Clinical and radiological study of these premutated patients with neurological signs has been performed.

Results: Among the 22 patients, 13 were diagnosed with definite FXTAS. Considering CSS hyperintensity as a new major radiological criterion allowed to diagnose definite FXTAS in 4 additional patients. CSS was as frequent as MCP hyperintensity (64 % versus 64%), 23% of patients had CSS but not MCP hyperintensity. MCP hyperintensity was less frequent in women than in men. MCP hyperintensity was correlated to inaugural action tremor.

Conclusions: We confirm the usefulness of CCS hypersignal in FXTAS, supporting its inclusion in the diagnostic criteria as a new major radiological criterion.

Disclosure: Nothing to disclose

PP4201
Transient central nervous system involvement as initial “stroke-like” presentation of X-linked Charcot-Marie-Tooth type 1 (CMTX1) with a novel GJB1 mutation
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Introduction: X-linked Charcot-Marie-Tooth type 1 (CMTX1) is the second most common CMT type and is associated with mutations in the GJB1 (gap-junction B1) gene, which encodes connexin-32. More than 400 GJB1 mutations have been described to date. Most hemizygous affected males have subclinical central nervous system (CNS) involvement, a few show mild CNS clinical signs, whereas only rarely overt though transient CNS dysfunction occurs.

Case report: We observed a 29-year-old man with CMTX1 who at age 16 years showed short-lived CNS symptoms with transitory white matter abnormalities on cerebral MRI as first clinical presentation of a novel GJB1 mutation (Gln99_His100 ins CAA). He had three consecutive episodes of right hemiparesis, together with sensory loss in the paretic limbs and expressive aphasia, all lasting a few hours, over a two-day period, with concurrent white matter hyperintensity on MRI. These “stroke-like” episodes occurred just after arriving at sea level, coming from home at 700 m of altitude. Only a few years later did signs and symptoms of peripheral neuropathy appear. Discussion and conclusion: This is another case of CMTX1 where the neuropathy is overlooked at presentation and the initial manifestations are acute transient CNS symptoms and signs with widespread white matter changes at MRI, suggesting strokes, metabolic or inflammatory disorders. Cx32 expression in the oligodendrocytes explains CNS features which appear only in particular conditions and are entirely reversible. Precipitating factors include fever, intercurrent illness or, as in this case, travels with rapid changes in altitude.

Disclosure: Nothing to disclose
PP4202

Report of 3 unusual cases of DMD/BMD patients with very large deletion within DMD gene

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Introduction: Duchenne/Becker muscular dystrophy is X-linked recessive, progressive muscle-wasting disease affecting 1 in 3500 boys, caused by mutations within DMD gene. The prediction that Duchenne muscular dystrophy patients have out-of-frame deletions and Becker muscular dystrophy patients have in-frame deletions of the dystrophin gene hold well in the vast majority of cases. We aimed to describe unusual cases with large deletions of the actin-binding and rod-shaped domains of the dystrophin gene associated with severe clinical phenotype.

Methods: The patients were diagnosed using standard clinical diagnostic criteria, including: EMG, serum creatine kinase (CK) levels. Screening for dystrophin gene deletion was performed on genomic DNA by using multiplex polymerase chain reaction and primer sets designed by Ashton.

Results: All the patients showed a raised serum CK level than normal. It has been established in-frame deletions of 3 to 44 exons in one patient and deletions of 1 to 45 exons in two patients. Due to deletion of exon 1, there is probably no mRNA and protein produced. All these mutations are not reported in Leiden Muscular Dystrophy data base.

Conclusions: We have identified 3 unusual cases: 1 case of BMD and 2 of DMD patients, with large deletions of the actin-binding and rod-shaped domains, that has not been described below. Additionally, this observation emphasizes the uncertainty in predicting the phenotype based only on laboratory evaluation and that the clinical picture should be considered.

Disclosure: Nothing to disclose

PP4203

SPG11 knockout in mice mimics the phenotype observed in patients

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Introduction: Hereditary spastic paraplegias (HSPs) are inherited neurological disorders characterized by lower limbs progressive spasticity and weakness. This clinical picture can be complicated by additional neurological signs in some forms. Autosomal recessive HSP with thin corpus callosum and mental impairment is a common and clinically distinct form of familial spastic paraplegia that is associated with mutations in the SPG11 gene on chromosome 15q in most affected families (40-80% according to their geographical origin). SPG11 mutations are either nonsense or indels leading to a frameshift, in agreement with a loss of function mechanism. SPG11 encodes a 2,443 amino acid protein of unknown function named spatacsin.

Methods: To identify cellular impairments underlying SPG11 HSP form, we invalidated the causative gene in a mouse model.

Results: These mice breed normally, their offspring appear normal at birth and their survival does not differ from control littersmates. Based on the complex clinical picture observed in patients with SPG11 mutations, we analyzed both cognitive and motor deficit in Spg11-/- mice using a series of behavioural tests at different ages. They showed a possible cognitive impairment and motor dysfunction starting from 4 months of age and worsening with time. This phenotype is associated with a progressive neurodegeneration affecting various cerebral structures.

Conclusion: This knock-out model mimics the SPG11 pathology with a relatively early onset of cognitive and motor alterations and will help decipher the physiopathology of this disabling disease.

Disclosure: Nothing to disclose
Role of rs333 polymorphism of the CCR5 gene in multiple sclerosis patients in Csongrád County in Hungary and the North-Bácska region in Serbia

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Introduction: Multiple sclerosis (MS) is a degenerative disease of the central nervous system characterized by the inflammatory process of demyelination. Genetic and environmental factors have been implicated in the aetiology. Examinations of the Δ32bp allele of the chemokine receptor V (CCR5) gene in MS have yielded conflicting results. In a few studies, the allele was confirmed as a risk factor, in others ones it was a protective factor, and some results indicated that the deletion is neither a risk nor a protective factor in MS. In the present work, the role of Δ32bp deletion of the CCR5 gene was investigated in the MS population in Csongrad County and the North Bácska.

Methods: Examinations were performed on 428 unrelated patients with the relapsing/remitting or secondary progressive form of MS and on age-sex matched 831 healthy persons as controls. Fluorescent labelled Taqman probes were used for allele detection. For data evaluation, SPSS software version 20.0 was performed.

Results: No significant differences were found in the genotype (OR=1.092 95% CI=0.807-1.478 p=0.568 for wt/wt vs wt/delta32, delta32/delta32) or in the allele frequency (OR=0.914 95% CI=0.692-1.207 p=0.525). Neither the deletion nor the wild allele affected the age at onset or the Expanded Disability Status Scale score.

Conclusions: These results indicate the lack of an association between the CCR5 Δ32 allele and MS, in confirmation of the literature data: the CCR5 delta 32 allele is neither a risk factor nor a protective factor of multiple sclerosis.

Disclosure: Nothing to disclose
PP4210
Giant angiofibroma associated with tuberous sclerosis
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PP4211
Fabry disease presenting with lymphoedema
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PP4212
Correlation of prothrombotic coagulation parameters with genetic markers of thrombosis in ischaemic stroke
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PP4213
Hereditary spastic paraplegia: clinical, laboratory, electroneuromiographic and magnetic resonance image of eight recessive cases
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PP4214
Is inherited thrombophilia in pregnancy a risk factor for familial stroke?
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PP4215
HNPP case with CIDP like clinic
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PP4216
Polymorphisms of methylenetetrahydrofolate reductase (MTHFR-677 and MTHFR-1298) genetic in an Albanian population
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PP4217
Neonatal manipulation of sex hormones in rats and its effect on MWM performance and expression of ten memory related genes in hippocampus
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PP4218
Uncommon features in a Turkish family affected with Friedreich's ataxia
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Extrapyramidal symptoms unrelated to Huntington's disease in a member of a large family with Huntington's disease
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