

Distinguishing Pediatric Transverse Myelitis from ADEM and CIDP: Clinical and Genetic Aspects

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Overview

- What is Pediatric Transverse Myelitis?
- Clinical Characteristics of Pediatric ADEM
- How can we distinguish Pediatric TM vs ADEM?
- Clinical Characteristics of Pediatric CIDP
- How can we distinguish Pediatric TM vs CIDP?
- Why does a particular child develop demyelinating disease?

How Frequent is CNS Demyelination in Children?

- Yann Mikaeloff MD et al in Journal of Pediatrics 2004
- Included Children under 16 yrs between 1985-1991 admitted to 12 Pediatric Neurology Centers in France
- Exclusion criteria include preceding neurologic abnormality, metabolic cause, infectious cause, systemic immunologic disorder



Journal of Pediatrics Article

- Follow up period 2.9 +/- 3 yrs with 20% < 5yrs
- 296 patients (>80% White)
- Age of Onset first attack 9.9 yrs
- MS 12 yrs
- Monophasic ADEM 7 yrs
- Single focal episode 9 yrs



Journal of Pediatrics Article

- Other distinguishing characteristics
- Infection during preceding month (ADEM/Focal episode 51-55% vs MS 16%)
- TM was high (63%) with a single focal episode (low in MS 8% or ADEM 2%)
- Optic Neuritis was more common in MS (35%) vs ADEM (7%)
- Brainstem dysfunction was common in ADEM (55%) vs MS (36%)
- Severe mental status changes are more common in ADEM (75%) vs MS (13%)



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- Initial MRI findings
- In group with final Dx-ADEM, 100% suggestive of ADEM and 15% suggestive of MS
- In group with final dx- MS, 57% suggestive of MS and 0% suggestive of ADEM

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- **Distribution of Initial MRI lesions**
 - Subtentorial lesions – MS (72%) and ADEM (86%)
 - Thalamus/BG- MS(8%) vs ADEM (40%)
 - Optic Nerve lesion- MS (6%) vs ADEM (0%)
 - Spinal Cord lesion- MS (19%) vs ADEM (11%)
 - Tumor like lesion- MS (12%) vs ADEM (18%)
 - Gadolinium enhancement- MS (28%) vs ADEM (11%)



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- CSF Findings
- >10 WBC cells- MS (37%) vs ADEM (51%)
- >0.5 gm/dl protein- MS (18%) vs ADEM (36%)
- Oligoclonal bands- MS (40%) vs ADEM (5%)

Message from This Article- Identified thru Multivariate Cox Analysis

- Predictive factors of second attack of demyelination
- Age at onset
- Presence of myelitis or optic nerve lesions
- MRI at onset suggestive of MS
- Protective factors of second attack of demyelination
- MRI at onset suggestive of ADEM



Pediatric Transverse Myelitis

- We have heard from Frank Pidcock about the JHU Pediatric Transverse Myelitis data

Pediatric Acute Transverse Myelitis

- Incidence: 1:100,000
- Defreese et al, Journal of Child Neurology 2003
- 24 patients
- Defined as acute onset of bilateral spinal cord dysfunction
- Exclusion criteria: Prior neurologic illness, evidence of trauma, irradiation, or spinal cord compression

Pediatric Acute Transverse Myelitis

- Mean age of onset- 8 years
- M:F- 1:1
- 58% had illness in setting of infection (URI)
- 50% of cases in the winter season
- Fever was a present in 60% patients
- In the initial phase (5 days), severe symmetric pain was present in 88% patients over one or more spinal segments

Pediatric Acute Transverse Myelitis

- Sudden of severe motor dysfunction over 12 hours or respiratory insufficiency in 30% of patients
- Mean duration of plateau phase is 6 days
- 75% had back pain, most commonly in the neck
- 23/24 patients developed a symmetric flaccid paralysis of LE with sphincter dysfunction

Pediatric TM

- One or more DTRs were abolished in 83% patients
- 42% of patients had moderate UE weakness
- Abnormalities (82%) in sensation were present, being asymmetric (83%). The levels were thoracic in 88% and cervical in 12% of patients
- Sphincter dysfunction (83%) was severe in 50% of patients, requiring catheterization for a mean of 12 days

Pediatric Acute Transverse Myelitis

- All patients were treated with IV solumedrol
- Mean duration of follow up 7 yrs
- Mean time to independent walking 56 days
- 50% had a normal recovery
- 13% had mild motor sequelae
- 24% had moderate motor sequelae
- 13% had severe motor sequelae



Outcome Factors

- Unfavorable outcome: 1) complete paraplegia or 2) time to maximum deficit < 24 hrs
- Favorable outcome: 1) plateau < 8 days or 2) time to independent walking < 30 days
- No patients had a re-occurrence of their TM or other neurologic deficits
- None developed MS

Labs

- CSF had abnormalities in 62%
- Most common elevated WBCs (mean 210 cells with range 0-1800)
- 3/24 had slightly elevated protein (up to 120 mg/dl)
- 5/24 patients (20%) had serologic evidence of recent viral infection (HSV, EBV, Varicella, Measles)
- None had oligoclonal bands
- MRI spine- with swelling and increased T2 signal in cervico-thoracic regions
- Increased T2 signal is located centrally in spinal cord

Acute Disseminated Encephalomyelitis (ADEM)



- Inflammatory demyelinating disease of the CNS after viral infection or vaccine with age of onset 5.3 +/- 3.9 yrs
- Typically monophasic illness 90%; Multiphasic illness 10%
- A clear infectious event or vaccination precedes (1-4 weeks) the onset of neurologic symptoms in 75% of patients
- Typical interval between febrile prodrome and onset of neurologic symptoms is 12-14 days

ADEM : Prodromal Events

- Tenembaum et al, Neurology 2002
- 84 consecutive patients in Argentina
- Nonspecific URI 35%
- No defined prodrome 26%
- Vaccine 12%
- GI illness 11%
- Varicella 5%
- HSV encephalitis 2%, Mumps 1%, Rubella 1%

ADEM: Presenting Features

- Long tract signs 85%
- With acute hemiparesis 76%
- Changes in sensorium 69%
- Cerebellar ataxia 50%
- Seizures 35%
- CN palsy 44%
- Meningeal Involvement 43%
- Headache/vomiting 24%



ADEM: Presenting Features

- Visual loss 23%
- Aphasia 21%
- Extrapyrarnidal syndrome 12%
- Hemiparasthesia 2%

Radiologic Features: 4 groups

- Small lesions (<5 mm) in GM and WM : scattered and asymmetric 62% (Group A)
- Confluent asymmetric and tumor like white matter lesions 24% (Group B)
- Bilateral symmetric basal ganglia or thalamic lesions with either small or large cerebral WM lesions 12% (Group C)
- Large demyelinating lesion with hemorrhage (acute hemorrhagic encephalomyelitis) 2% (Group D)

ADEM: CSF findings

- 28% patients < 180 cells/mm³
- 38% patients > 1 gm/dl protein
- 96% patients negative for oligoclonal bands
- 13% patients elevated CSF IgG
- 17% patients antibody or PCR evidence of recent infection
- 11% patients elevated MBP



ADEM: Treatment

- 20 mg/kg solumedrol or steroids- 80%
- AEDs 35%
- Acyclovir 69%
- PICU patient 43%
- Ventilation 16%

ADEM: Outcome

- IV solumedrol or dexamethasone followed by PO steroid taper over 4-6 weeks
- Mean follow up 6.6 +/- 3.8 yrs
- Disability- ranked by MRIs scan
- Group A 96% normal or nearly normal
- Group B 80%
- Group C 80%
- Group D (AHEM) 50%

Residual Deficits & Neurologic Syndromes

- Mild to severe hemiparesis 8%
- Symptomatic partial epilepsy 6%
- Visual acuity reduction 6%
- Mild paraparesis 4%
- Mental handicap 4%

Bi- or Multiphasic ADEM

- 2-10%
- Age of onset 4.6 +/-3.7 yrs
- 1-2 relapses
- Mean interval between relapses 2.9 yrs
- No patients with oligoclonal bands in CSF
- Follow up period mean 8 yrs

Pediatric Chronic Inflammatory Demyelinating Polyneuropathy

- Incidence 0.5-1 in 100,000 children
- Subacute onset of progressive proximal and distal weakness over at least 2 months
- Research criteria: 1) progressive or relapsing motor and sensory dysfunction of more than one limb & 2) hyporeflexia or areflexia of all four limbs
- M: F- 1:1 with age of onset 11 yrs old



CIDP

- Two groups
- 1) progressive loss of ambulation over 1-3 months, improved by treatment, & tends to have monophasic course 13%
- 2) 30% of one series presented looking similar to Gullian Barre syndrome (1 to 4 weeks)



CIDP

- 83% have progressive loss of ambulation over 3 months and tends to have a relapsing course (5 episodes)
- Fatigue and sensory symptoms, including dysesthesia and sensory loss, are common
- Large fiber sensory loss is more common than small fiber sensory loss
- Small % need ventilation for any episodes 10-15%



CIDP

- Electrophysiology can be helpful
- CIDP- conduction velocity has non-uniform slowing with conduction block (common), MDL-non-uniformed & prolonged, F waves- non-uniformed & absent/prolonged, Sensory conduction-focal & non-uniformed slowing

Mimics of CIDP

- Transverse myelitis- more acute onset
- Hereditary motor sensory neuropathies- are usually more distal motor loss and sensory loss is more severe than CIDP
- Often times has a dominant inheritance
- Conduction velocity- marked slowing, conduction block is uncommon, MDL- uniformly prolonged, F waves- uniformly slowed, sensory conduction- uniformly slow/absent



Mimics of CIDP

- Acquired myopathies- dermatomyositis may mimic CIDP when rash is not present
- CK is usually elevated with acquired myopathies
- Autosomal recessive neuropathies- metachromatic leukodystrophy or Krabbe's disease may mimic CIDP
- Peripheral nervous system involvement may precede CNS symptoms
- MRI brain can be helpful in this situation



Treatment of CIDP

- Pathogenesis- humoral immune response...some patients have elevated intrathecal IgG synthesis
- Autoantibodies against gangliosides, sulfatides, PMP-22, beta-tubulin, acidic glycolipids, and Schwann cells
- Corticosteroids 57/63 (93% response rate)
- IVIG 14/20 (70% response rate)
- Plasma exchange 11/12 (92% response rate)



CIDP: Prognosis

- Monophasic illness group- tends to have full recovery
- Relapsing group- average 4-5 relapses
- Duration of illness- 7 years
- Short term studies- 12-60 months off therapy suggest most children have little or no motor disability
- However the true long term prognosis is unknown. Thought to be excellent.



Why Did My Child Develop a Demyelinating Disease?

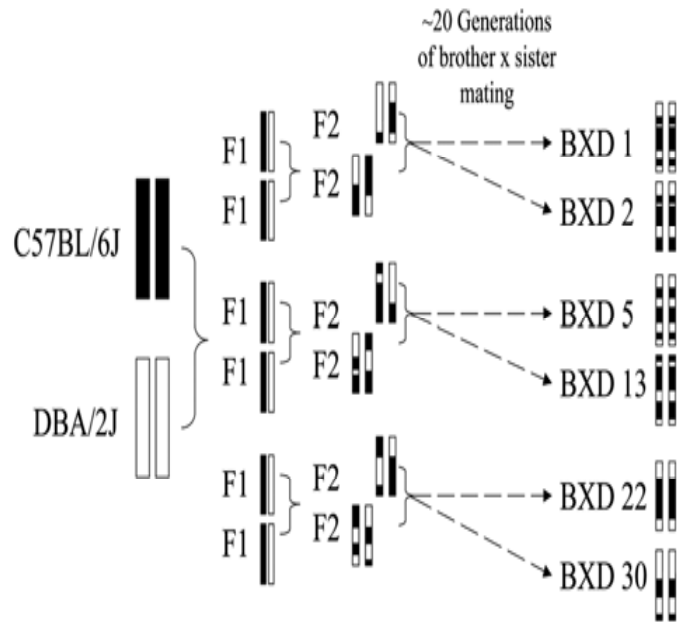
Future of Molecular Diagnostics



- The concept of “genetical genomics” is the combination of genetic linkage and genetic association studies with unbiased gene expression analyses/microarray studies.
- Genetical genomics treats variation of gene expression within a population as a quantitative trait (essentially a QTL).
- Quantitative trait loci (QTL) are the locations of segregating genetic polymorphisms or genes and are the foundation to the understanding of individual differences.

Use of a Genetic Reference Population

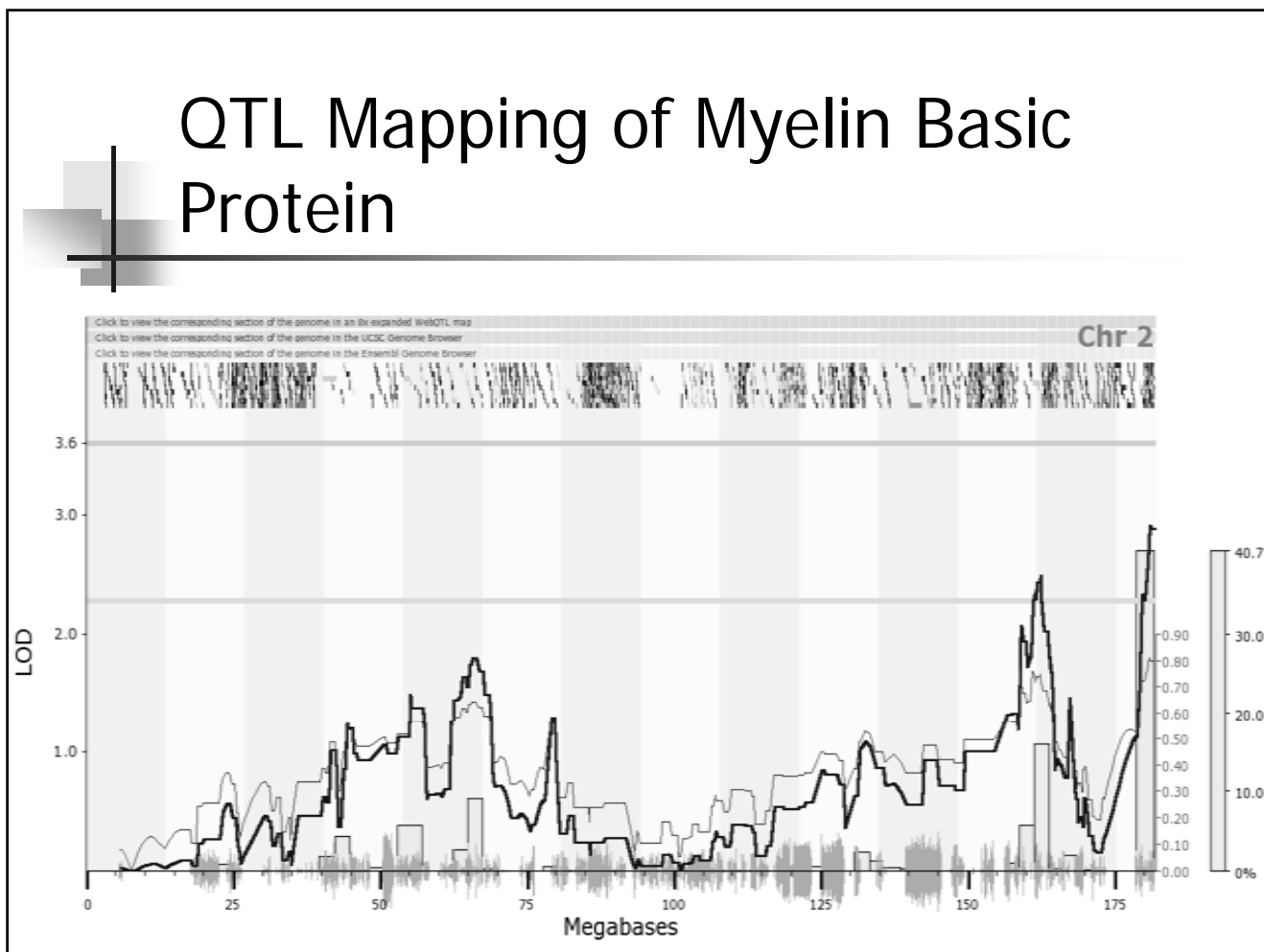
- BXD RI mice generated from two independent advanced intercrosses between C57BL/6J (B) and DBA/2J (D) progenitor strains.
- The advantage of using the 80 BXD RI strains is that both progenitor strains B and D have been sequenced, and their sequences differ at ~1.8 million single nucleotide polymorphisms (SNPs) and 756 microsatellite markers.



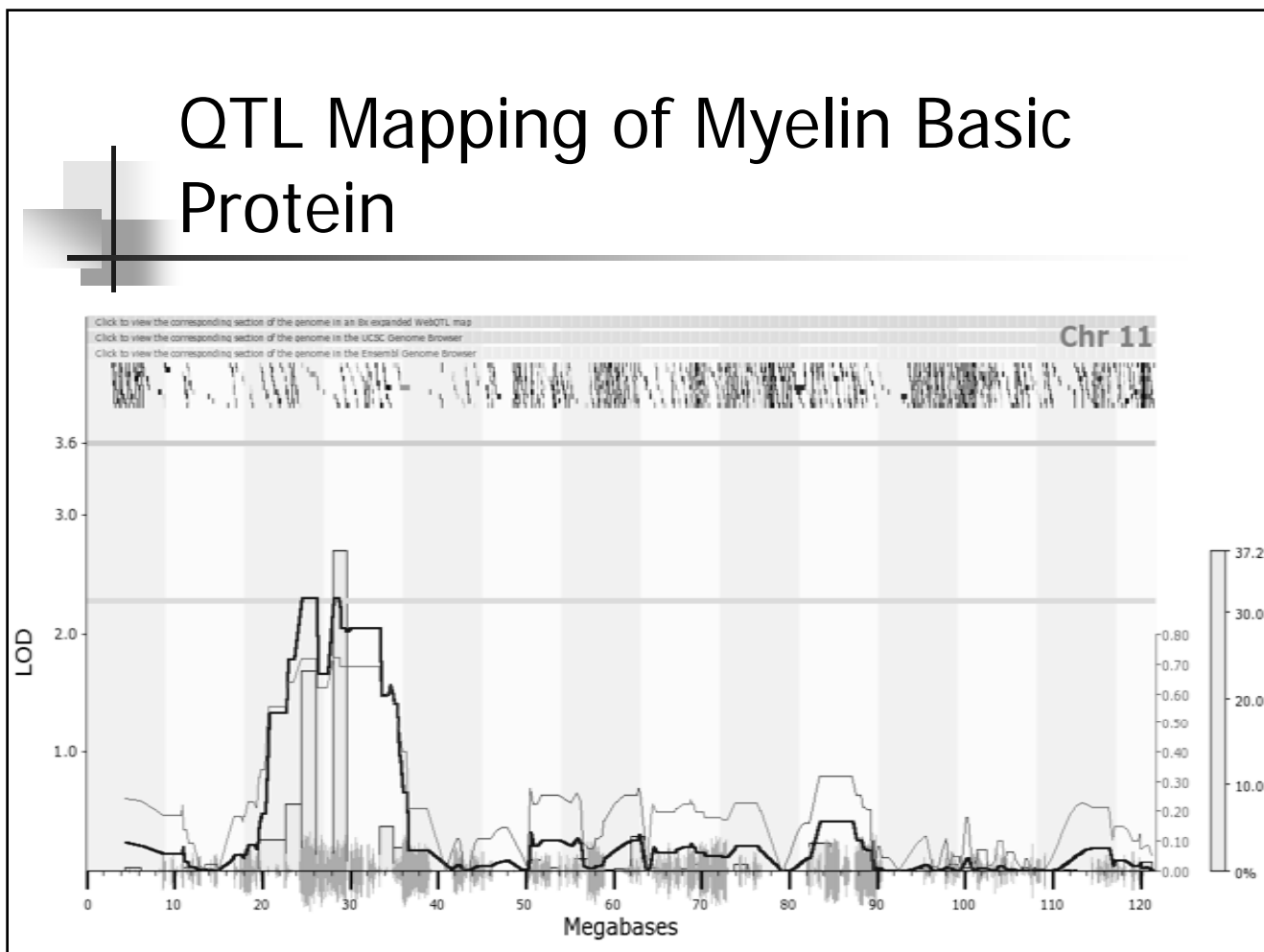
Why Map a QTL within a Genetic Reference Population?

- The mapping of QTLs is the typical approach used for identification of naturally occurring polymorphisms that influence complex phenotypes.
- Genotypic values at markers of known genomic location are associated with phenotypic values measured in a segregating population.
- Simply put, at the QTL, genotype is a strong predictor of phenotype. Away from the QTL, genotype does not predict phenotype.

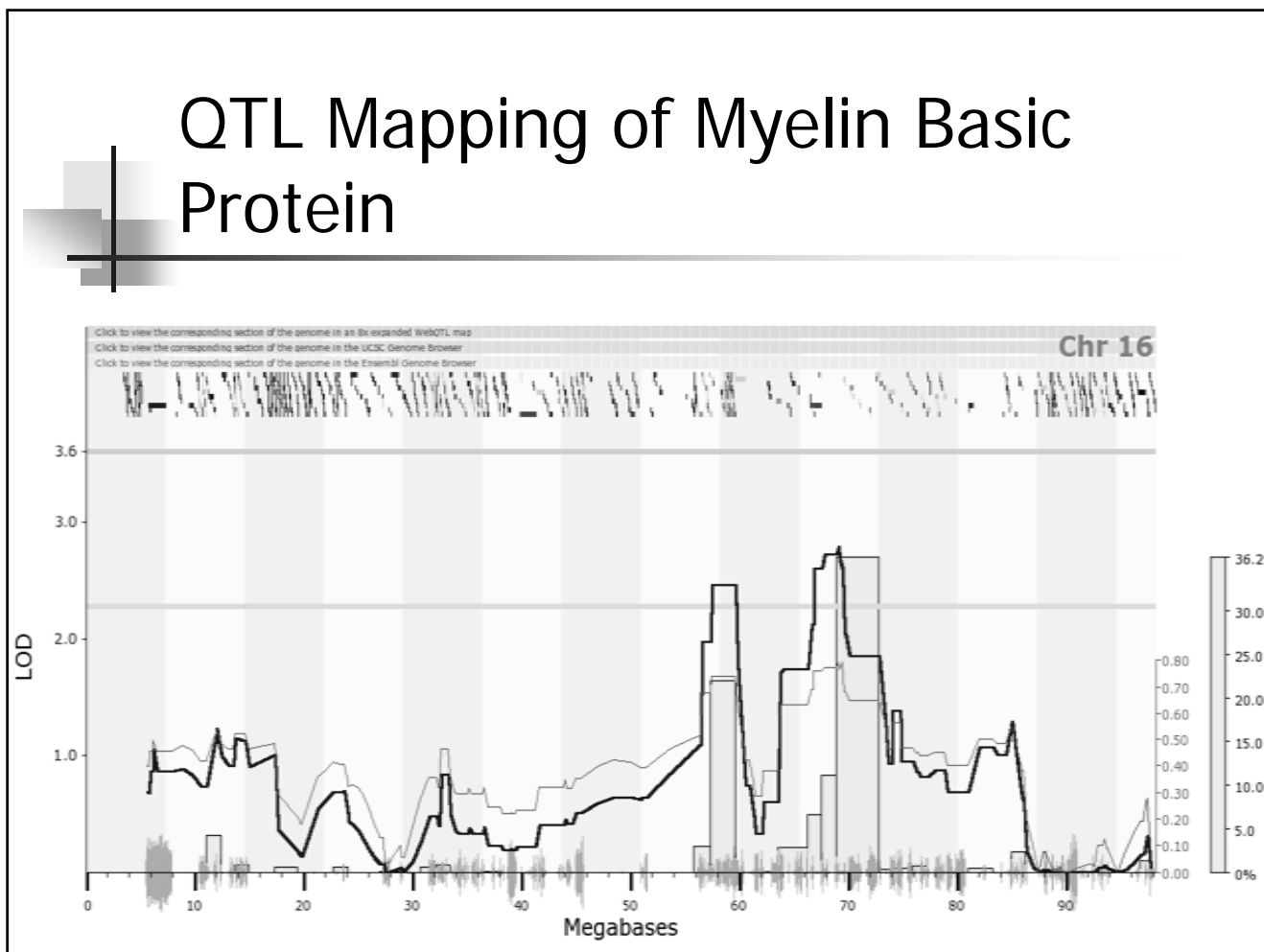
QTL Mapping of Myelin Basic Protein



QTL Mapping of Myelin Basic Protein



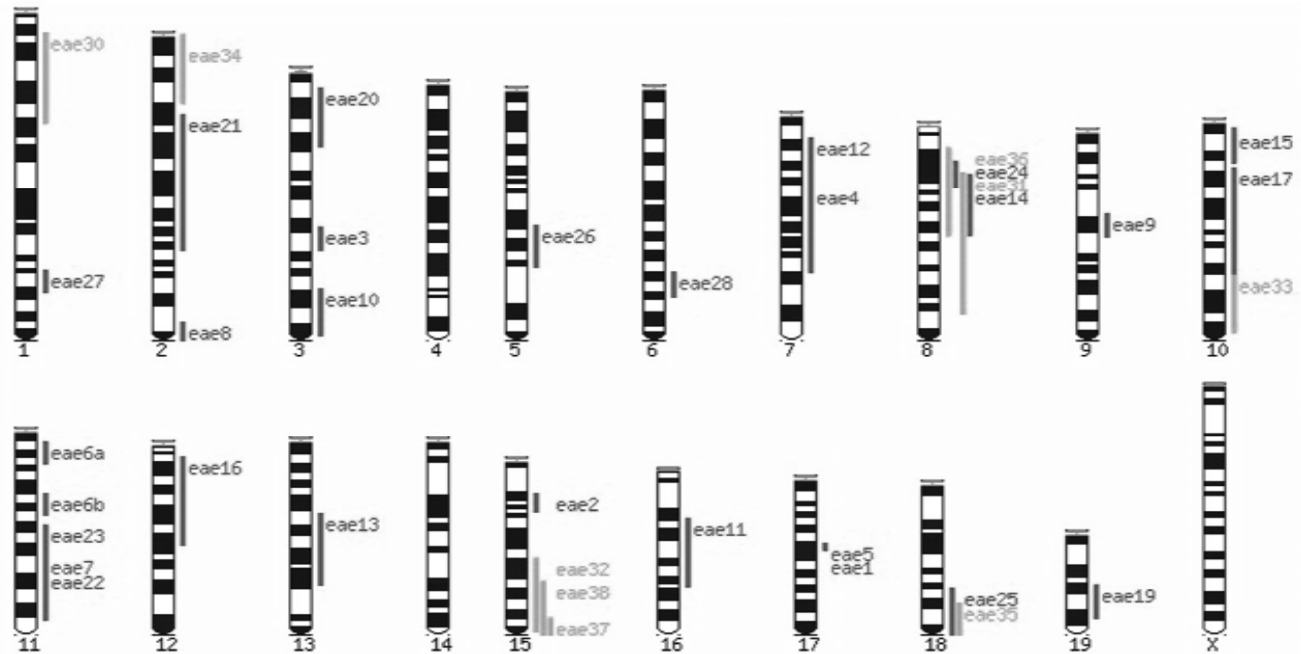
QTL Mapping of Myelin Basic Protein



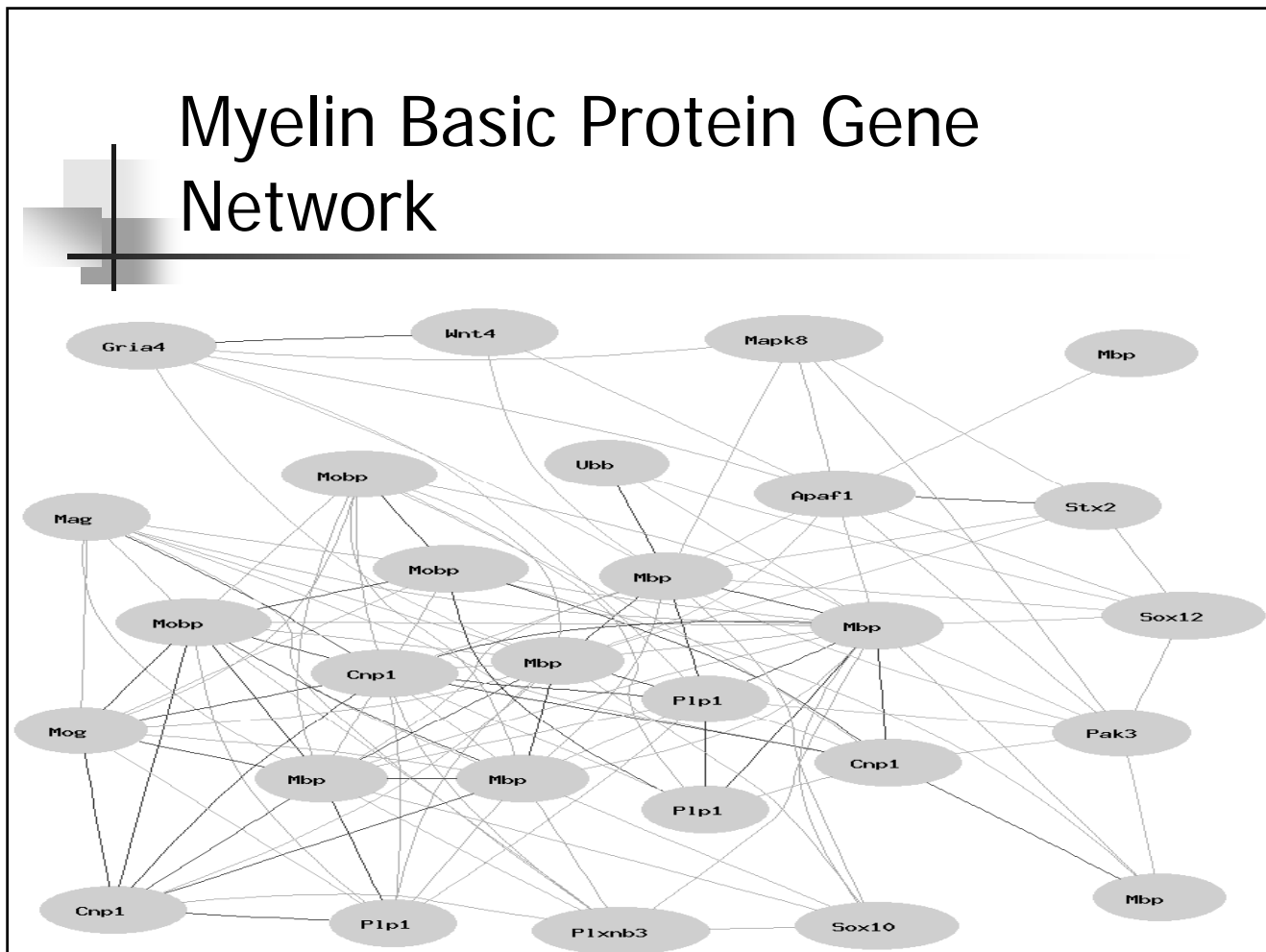
QTL Mapping Reveals Interesting Putative Regulators

- Chromosome 2 QTL- adenosine deaminase, Wisp2, Ubc 2E, Cadherin 22
- Chromosome 11 QTL- vaccinia related kinase 2, polyribonucleotide nucleotidyl transferase 1, Smek2 –suppressor of MEK1
- Chromosome 16 QTL- Pit 1/Pou1f1

How Do BXD RI derived QTLs compared to Known EAE QTLs?



Myelin Basic Protein Gene Network





Summary of Genomics Data

- These data provides a comparison of potential gene regulatory pathways controlling MBP expression in relation to EAE in mice.
- It is important to keep in mind, particularly when dealing with molecules such as MBP that are so heavily implicated in neurodevelopment, that indirect compensatory responses by the biological system or genetic modifiers may also contribute importantly to findings in EAE.



Conclusions

- Investigation of gene networks and genetic loci within a heterogeneous but genetically defined population such as the BXD RI mice in part may explain the pleotropic effects of a given allele and delineate previously unknown physiologic processes of the gene in EAE.
- These data from murine models may identify genetic modifiers which may be important in human disease such as Pediatric TM.