Epidemiology and Genetics of MS in Non-Caucasian Populations

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Disclosures

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Objectives

- Identify differences in the clinical phenotypes between African American and white MS patients
- Understand that the phenotypic differences between these groups is in part due to genetic variation

Why Study African American MS?

- Multiple Sclerosis is rare in Africa
  - Only a handful of case reports
- African Americans are less susceptible for developing MS than whites
  - 40-64% relative risk 1, 2
- African Americans
  - Are an admixed population with some contribution from Northern European chromosomes3
  - Have different genetic alleles compared to Northern European descended populations potentially of fine genetic mapping studies difficult to perform in 4

Are the clinical characteristics of MS similar in African Americans and whites?

African American MS Project

702 African Americans from 33 States

718 whites from 37 States

### Demographics

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>whites</th>
<th>AA</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F:M</td>
<td>3.5:1</td>
<td>4.1:1</td>
<td>P=0.195</td>
</tr>
<tr>
<td>Mean Age at Onset (years)</td>
<td>29.9</td>
<td>32.8</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Mean Disease Duration (years)</td>
<td>9.9</td>
<td>9.7</td>
<td>P=0.62</td>
</tr>
<tr>
<td>Mean Years Onset to Dx (Median)</td>
<td>3.40 (1)</td>
<td>3.15 (1)</td>
<td>P=0.325</td>
</tr>
</tbody>
</table>


### Race and Disease Course

![Race and Disease Course Graph](image)

Time to Secondary Progressive MS*

- WA, N=663
- AA, N=587

*Excluding CIS, PP, PR, and Unclear disease courses


Global Disability: Multiple Sclerosis Severity Scale

P<0.001

MSSS

**Time to Cane Dependency**

- P<0.0001
- WA, N=714
- AA, N=685

**Time to Wheelchair Dependency**

- P=0.0006
- WA, N=714
- AA, N=685

25-Hydroxyvitamin D levels are lower in African Americans with multiple sclerosis than controls.

African American Phenotype Summary

- African Americans are more likely to have:
  - an older age of onset
  - multi-symptom onset
  - transverse myelitis
  - opticospinal MS
  - secondary progressive MS
  - ambulatory impairment
  - Lower vitamin D levels

Gelfand J. Neurology 2011;76:1824-1830
What are the imaging characteristics of African American MS?

Magnetization transfer ratios (MTR) of African American patients (green bars) versus whites (white bars) in lesions, normal-appearing gray matter (NAGM), and normal-appearing white matter (NAWM).

Weinstock-Guttman B. Neurology 2010;74:538-544
CSF Humoral Response

Rinker JR. Neurology. 2007;69:68-72

Relationship Between B-cell Humoral Response and Gray Matter Volume

Khan O. 2008 WCTRIMS P347 presented 9/18/08
B-cell Mediated Effector Mechanisms of Tissue Injury and Gray Matter Loss

- Brain atrophy in African-American MS patients is driven by disproportionately higher gray matter atrophy compared to white matter atrophy in Caucasians
- The higher the CSF IgG Index, the greater the gray matter atrophy. No significant correlation with white matter atrophy

Imaging and CSF Correlations

- Compared to whites, African-Americans with MS have
  - higher T2 lesion load and gadolinium enhancing lesions
  - lower NAA values
  - lower brain MTR
  - higher CSF IgG Index that correlates with myelin injury (MTR)
- B-cell driven humoral auto-immunity may underlie aggressive disease
Can genetics explain some of these differences?

**Single gene disorder**
- Mutation
- Gene A

Dominant inheritance pattern

Impact of mutations on disease

Genetic risk in different families

100%

Family 1  Family 2  Family 3

**Complex disorder**
- Polymorphisms
- Gene A
- Gene B
- Gene C
- Gene D

Complex inheritance pattern

Impact of polymorphisms on disease

Genetic risk in different families

30%

Family 1  Family 2  Family 3

**Genome Wide Association Study**

Case-control design compare single nucleotide polymorphisms (SNPs) in two populations

Non-affected individuals (controls)
- 50% of controls carry the GTG genotype
- 50% of controls carry the GAG genotype

Affected individuals (cases)
- 75% of cases carry the GTG genotype
- 25% of cases carry the GAG genotype

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**Genome Wide Association Studies Definitively Implicate the MHC with MS Susceptibility**

IMSCG, NEJM. 2007;357;1-12
The majority of MS risk SNPs identified involve genes implicated in regulating immune function.

The most recent meta-analysis identified ~200 regions across the genome that each fractionally influence MS risk.

The most strong influence derives from the MHC region, especially around HLA-DRB1.
**DRB1 and Antigen Presentation**

- HLA-DRB1*15 (DR2b), HLA-DRB5*01 (DR2a) and HLA-DQB1*06 (DQw6) form heterodimers with HLA-DRA that can present myelin antigens to T cells.
- These genes are tightly linked in Northern European descended populations.
- Together they function as a "master switch" for immune regulation.


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**Do genes influence MS phenotypes?**
**DRB1*15 dosage effects on onset age**

![Bar chart showing the effect of DRB1*15 dosage on onset age with P corr = 0.034 and P NS = 0.154.](image)

- **Onset age in years**
  - Negative 1 copy: 33.6 (N=427), 31.6 (N=233), 29.9 (N=27)
  - **P corr = 0.034**
  - **P = NS**

**DRB1*15 is not associated with opticospinal MS**

- **Bar chart showing the percentage of DRB1*15 among different groups.**
  - White American Typical MS: 40%
  - African American Typical MS: 35%
  - African American Opticospinal MS: 30%
  - White American Healthy Controls: 20%
  - African American Healthy Controls: 10%
  - **P = 0.002**

Cree B. Archiv Neurol 2009; 66:226-33
Global Disability: Multiple Sclerosis Severity Scale

Proportion of European Ancestry correlates with Vitamin D level

Cree B. Archiv Neurol 2009; 66:226-33

Gelfand J. Neurology 2011;76:1824-1830
Genotype-Phenotype Correlations in African Americans

- Both \( DRB1^{*}1501 \) and \( DRB1^{*}1503 \) alleles were associated with
  - a younger age of onset (statistically significant only for \( DRB1^{*}1503 \), \( P=0.02 \))
  - opticospinal disease course (\( P=0.002 \))
- African origin at HLA was associated with a more severe disease course
  - Genes within the MHC influence disease severity
  - This effect accounts for 49% of the difference in MSSS score between African Americans and whites (95% CI 33.6%-63.7%)

Cree B. Archiv Neurol 2009; 66:226-33

MHC SNPs in African American MS

- MHC SNP associations in African Americans MS are less pronounced than in European descended populations.
- Suggests that MHC places a less prominent role in African American MS susceptibility.
- European defined SNPs may not adequately map African origin alleles

**DRB1 and DRB5 Frequencies in African American Cohort**

<table>
<thead>
<tr>
<th>DRB1 Allele</th>
<th>DRB5 Allele</th>
<th>Case Chromosomes</th>
<th>Control Chromosomes</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1501</td>
<td>0101</td>
<td>98</td>
<td>47</td>
<td>2.35</td>
<td>1.62-3.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1503</td>
<td>0101</td>
<td>205</td>
<td>183</td>
<td>1.26</td>
<td>1.01-1.57</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>1503</td>
<td>∆</td>
<td>18</td>
<td>7</td>
<td>2.89</td>
<td>1.15-8.22</td>
<td>0.015</td>
</tr>
<tr>
<td>X</td>
<td>∆</td>
<td>1190</td>
<td>1339</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- DRB5 is only on chromosomes containing DRB1*1501
- drb5∆ occur spontaneously in African Americans with DRB1*1503
- African Americans with drb5∆ can still develop MS excluding DRB5 as a major susceptibility factor and emphasizing the role of DRB1
- drb5∆ may have a more rapidly progressive course


**DRB1*1501/DRB5*0101**

- MS Susceptibility
- OR = 2.35
- P < 0.0001
- 95% C.I. = 1.63 – 3.43

**DRB1*1503/drb5∆**

- MS Susceptibility
- OR = 2.89
- P = 0.015
- 95% C.I. = 1.15 – 8.22

African American MS Summary

- HLA-DRB1 alleles and not HLA-DQB1 alleles contribute to MS susceptibility in African Americans and are associated with a lower age of onset.

- African Americans more frequently have optico-spinal MS which is immunogenetically different from typical MS because it is not associated with DRB1 alleles.

- African Americans have a more rapid disease course and African ancestry at HLA, independent of DRB1 alleles, accounts for ~50% of this difference.

- Humoral auto-immunity plays a prominent role in African American MS.

Next Steps

- GWAS in Northern European descended populations identified >200 genes involved in MS risk, all with small individual O.R.s.

- Replication studies are ongoing in AA MS:
  - Many, but not all, MS SNPs identified from European descended populations are risk factors in AA MS patients.

- Large-scale phenotype-genotype correlation studies are being planned.

- Identify genes involved in radiographic phenotypes.

- Whole genome sequencing to identify rare risk alleles, especially in AA MS.
UCSF MS Center

International Multiple Sclerosis Genetics Consortium (IMSGC, https://www.imsgc.org/)
Is the therapeutic response different in African Americans?
African American Multiple Sclerosis and Interferon

- Do African Americans respond to Interferon beta equally well as Caucasian Americans?
- 616 Caucasian Americans were compared to 36 African Americans participating in the EVIDENCE RCT (thrice weekly sub cutaneous VS once weekly intramuscular interferon beta-1a)
- Baseline characteristics were comparable (EDSS, relapse rate, age, gender)

Cree B. Archiv Neurol 2005;62:1681-3

Number of Relapses with Interferon Treatment

<table>
<thead>
<tr>
<th></th>
<th>whites 24 Weeks</th>
<th>AA</th>
<th>p</th>
<th>whites 48 Weeks</th>
<th>AA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Number of exacerbations</td>
<td>0.33</td>
<td>0.47</td>
<td>0.06</td>
<td>0.57</td>
<td>0.73</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Cree B. Archiv Neurol 2005;62:1681-3
Despite the small numbers of AAs in the EVIDENCE study, AAs appeared to not respond as well as whites to treatment with IFN in all clinical and MRI outcomes at both 24 and 48 weeks. This is not explained by differences between the groups at baseline. Statistically significant only for T2 lesion count at 48 weeks but trends for all other outcomes. Suggests that the response to IFN in AAs is different from whites.
African American Multiple Sclerosis and Natalizumab

- Do African Americans respond to natalizumab?
- Post-hoc analysis of pooled subjects from the SENTINEL (IFN plus natalizumab VS IFN plus placebo) and AFFIRM (natalizumab VS placebo) clinical trials
- 10 black subjects in AFFIRM (6 Pl, 4 Nat)
- 39 black subjects SENTINEL (22 Pl, 17 Nat)

Cree B. Arch Neurol. 2011;68:464-468

**Annualized Relapse Rate: Adjusted for Baseline Covariates**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Natalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted RR</td>
<td>0.528</td>
<td>0.209</td>
</tr>
<tr>
<td>Adjusted n</td>
<td>28</td>
<td>21</td>
</tr>
</tbody>
</table>

RR: 0.395
p = 0.0232
60% reduction

Adjusted for: # relapses 1 year prior to study entry, baseline EDSS (≤3.5 vs. >3.5), presence of Gd+ lesions at baseline, and age (<40 vs. ≥40) s

Cree B. Arch Neurol. 2011;68:464-468
### Mean Number of New or Enlarging T2 Lesions over 2 years

![Graph showing the mean number of new or enlarging T2 lesions over 2 years for Placebo and Natalizumab groups.](image_url)

- **Placebo**
  - n=21
  - Mean Number of NET2 Lesions: 8.52

- **Natalizumab**
  - n=16
  - Mean Number of NET2 Lesions: 0.88

*p = 0.0081

Adjusted for: baseline # of T2 lesions (<9 vs. ≥9)

**Cree B. Arch Neurol. 2011;68:464-468**

### African American MS and Natalizumab Conclusions

- African Americans appear to respond to treatment with natalizumab with statistically significant reductions in relapses, time to next relapse, contrast enhancing lesions, new lesions on T2 imaging and burden of disease on T1 or T2 weighted imaging.

- Suggests that immune suppression may be an effective, possibly preferable, strategy in this patient subgroup.
African American Additional Phenotypes

Non-recurrent Myelitis

- Percent

Recurrent Myelitis

- Percent

Opticospinal MS

- Percent

Multi-symptom Onset

- Percent


MRI Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>African-Americans</th>
<th>n</th>
<th>whites</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2W Lesion Load (ml)</td>
<td>92</td>
<td>18.41 ± 11.33</td>
<td>104</td>
<td>12.88 ± 7.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean No of Gad Enhancing Lesions per pt</td>
<td>92</td>
<td>2.21 ± 3.54 (range: 0-19)</td>
<td>104</td>
<td>1.03 ± 2.18 (range: 0-19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with Gadolinium Enhancing Lesions (%)</td>
<td>92</td>
<td>56.5%</td>
<td>104</td>
<td>43.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Whole Brain MTR (%)</td>
<td>92</td>
<td>39.86 ± 3.26</td>
<td>104</td>
<td>43.35 ± 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NAA/Cr (NAWM; SVS)</td>
<td>92</td>
<td>1.88 ± 0.12</td>
<td>104</td>
<td>2.12 ± 0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cervical Spinal Cord Volume at C2 (mm²)</td>
<td>59</td>
<td>75.58 ± 6.88</td>
<td>70</td>
<td>81.45 ± 5.72</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CSF Humoral Response

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>African-Americans</th>
<th>n</th>
<th>whites</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF IgG Index</td>
<td>150</td>
<td>1.50 ± 0.86</td>
<td>150</td>
<td>1.08 ± 0.88</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Khan O. 2008 WCTRIMS P347 presented 9/18/08
*drb5*Δ MS patients appear to be at greater risk for SPMS

Kaplan-Meier Survival Estimates for Time to SPMS

Analysis Time in Years

P=0.036