Updates on VCP Inclusion Body Myopathy Paget disease, FTD and ALS (IBMPFD)

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OBJECTIVES

1. Discuss clinical features of VCP disease

2. Learn about mouse model and its use in developing treatments

3. New study trials available and on the horizon
1st Family from Central Illinois 1998
Localisation of Inclusion body myopathy, Paget’s disease of bone and fronto-temporal dementia (IBMPFD) to 9p21 in four families.

Kovach et al/Mol Genet Metab 2001

[Diagram showing genetic markers and loci on chromosome 9, with distances in cM and Mb.]

AR IBM2 locus (GNE)
Limb-girdle-Bone-fragility (MTAP)
ALS-FTD locus (C9ORF72)
Mutations in the VCP gene causes the disease


Region involved in Ubiquitin binding
Inclusion body myopathy seen in 90% individuals. CPK muscle enzyme may be normal to slightly elevated.

Muscle weakness mean age onset: 35 y.
Biopsy showed variation in fiber size, rimmed vacuoles, and inclusions.
Approx. 50%- Paget disease of Bone - overactive osteoclasts  Localized painful enlargement of bone

Early onset- mean age of 41 years (Range 31-61 y.)

Alkaline phosphatase is elevated with PDB (mean 290 U/L, range 58-2105 U/L; normal range 30-130 U/L)

High urine pyridinoline, deoxypyridinoline

PDB of Hip and Pelvis- 55 y old male

EM Osteoclast- PHF in nucleus
Frontotemporal Dementia (FTD)

- 30% of individuals at a mean age of 56 y
- Degenerative condition of the frontal and anterior temporal lobes
- Reasoning, personality, social graces, language and preservation of memory.
- Many genes associated with FTD.
  - Tau, C9ORF72, Progranulin, TDP 43, VCP
10% subjects recruited diagnosed as ALS

- **Female 48 y. with R155C and ALS**
- Rapid deterioration over 2-3 years to full-blown ALS
- Cranial nerve muscles and lower extremities: Upper motor & lower motor neuron involvement
- Upper extremities: Lower motor neuron involvement
- Severe bulbar dysfunction
- Severe respiratory dysfunction with severe diaphragmatic insufficiency-13% lung capacity.
- EMG - severe motor neuropathy with widespread fibrillations, fasciculation, & neurogenic potentials. No myopathic potentials

Autopsy confirmed ALS.
Parkinsons in 4% in VCP disease

- 5 families with PD and VCP disease

**Case - 54 y. male with R159C**
- 44 y decreased driving ability in L arm golfing
- Progression over 1 y to rigidity, reduced dexterity and resting tremor
- Responsive to dopaminergics
- Scapular winging 53 y.
- Muscle Bx- rare rimmed vacuoles
- Parkin negative
- Cousin recently Dx with PD

Other phenotypes

• Cardiomyopathy
• Anal incompetence
• Charcot Marie Tooth 2
Frequencies of phenotypes in 187 individuals

- IBM only: 37%
- PDB only: 5%
- FTD only: 3%
- IBM & PDB: 27%
- PDB & FTD: 1%
- IBM & FTD: 16%
- IBMPFD: 10%

FTD only: 3%
IBM only: 37%
PDB only: 5%
Lifetable Analysis of survival:

A. Survival of Affected

B. Survival Time from Onset of Myopathy

C. Survival Time from Onset of Paget

D. Survival Time from Onset of Dementia
Frequency of VCP genotypes in UC Irvine cohort

- R93C, 2, 1%
- R95G, 5, 3%
- L198W, 7, 4%
- R159H, 5, 3%
- R159C, 10, 5%
- R191Q, 5, 3%
- R155P, 9, 4%
- R155C, 31, 16%
- A232E, 3, 2%
- N387H, 2, 1%
- G97E, 5, 3%
- A160P*, 3, 2%
- G128A*, 2, 1%
- M158I*, 1, 1%
- R155H, 97, 51%
### Genotype-phenotype correlations

**Clinical and biochemical data for symptomatic individuals in different mutation groups**

<table>
<thead>
<tr>
<th>Family ID</th>
<th>Mutation group</th>
<th>N symptomatic</th>
<th>Age of onset IBM (yrs)</th>
<th>Age of onset PDB (yrs)</th>
<th>Age of onset FTD (yrs)</th>
<th>CPK (U/L)</th>
<th>ALP (IU/L)</th>
<th>ALS Phenotype</th>
<th>PD</th>
<th>AD</th>
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<tbody>
<tr>
<td>1, 3, 4, 7, 10, 15, 16, 19b, 22, 25, 52, 56, 57</td>
<td>1 (R155H)</td>
<td>97</td>
<td>86</td>
<td>43</td>
<td>44</td>
<td>43</td>
<td>24</td>
<td>55</td>
<td>136</td>
<td>230</td>
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<td>2, 5, 14, 19a, 26, 34, 54</td>
<td>2 (R155C)</td>
<td>31</td>
<td>30</td>
<td>38</td>
<td>14</td>
<td>36</td>
<td>10</td>
<td>53</td>
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<td>282</td>
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<tr>
<td>11, 40</td>
<td>3 (R155P)</td>
<td>9</td>
<td>7</td>
<td>43</td>
<td>7</td>
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<td>13, 33</td>
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<td>5</td>
<td>47</td>
<td>2</td>
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<td>2</td>
<td>61</td>
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<td>24, 48**</td>
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<td>15 (M158I)*</td>
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<td>187</td>
<td>168</td>
<td>43</td>
<td>80</td>
<td>41</td>
<td>55</td>
<td>56</td>
<td>183</td>
<td>290</td>
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</table>

IBM present in 89%, PDB in 43%, FTD 29%, ALS in 8.5% and Parkinsons in 3.7%

CPK creatine phosphokinase (NL 22 to 198 U/L), ALP alkaline phosphatase (44 to 147 IU/L)* indicates novel mutations
Analysis: Any APOE4 haplotype vs Dx

<table>
<thead>
<tr>
<th>Condition</th>
<th>ChiSquare</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Myopathy</td>
<td>0.09</td>
<td>0.77</td>
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<tr>
<td>Paget's</td>
<td>0.06</td>
<td>0.81</td>
</tr>
<tr>
<td>Dementia</td>
<td>9.20</td>
<td>0.002</td>
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</table>
### Baseline Natural History Study

**Characterization of Familial Myopathy, Paget Disease of Bone**

IRB 2007-5832

<table>
<thead>
<tr>
<th>Table 1 of tests (schedule subject to change if needed)</th>
<th>Repeat testing at 1 or 2 year intervals</th>
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<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
</tr>
<tr>
<td>Measure/ Procedure</td>
<td></td>
</tr>
<tr>
<td>Medical History (30 min)</td>
<td>X</td>
</tr>
<tr>
<td>Medication Use/Updates (5-10 minutes)</td>
<td>X</td>
</tr>
<tr>
<td>Blood: CPK (10 min)</td>
<td>X</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>X</td>
</tr>
<tr>
<td>Urine deoxy/pyridinolines</td>
<td>X</td>
</tr>
<tr>
<td>MRI/MRS Measurements (one hour with prep)</td>
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<tr>
<td>Muscle volumetric analysis</td>
<td>X</td>
</tr>
<tr>
<td>Intramuscular Lipid (%)</td>
<td>X</td>
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<tr>
<td>Muscle T2</td>
<td>X</td>
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<tr>
<td>IBM rating Scale (15 min)</td>
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<tr>
<td>ASA24 Diet Questionnaire</td>
<td>X</td>
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<tr>
<td>Quality of Life scale (20 min)</td>
<td>X</td>
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<tr>
<td>6 minute walk test (20 min with prep time)</td>
<td>X</td>
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<tr>
<td>Biodex dynamometry testing (30 min)</td>
<td>X</td>
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<tr>
<td>Echocardiogram and Electrocardiogram (30 min)</td>
<td>X</td>
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<tr>
<td>Electromyography/Nerve Conduction Velocity (60 min)</td>
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<tr>
<td>Diffuse Optical Spectroscopy (DOS) (30 min)</td>
<td>X</td>
</tr>
</tbody>
</table>

**TOTAL TIME DAY 1 = APPROX. 7 HOURS**

| **Day 2**                                             |                                        |
| Neuropsychological testing (1 hr)                     | X                                      |
| Functional Measures                                   |                                        |
| Muscle strength-MRC (20-30 min)                       | X                                      |
| Hand held Dynamometry (30 min)                        | X                                      |
| Skin biopsy (10 min)                                  | X                                      |
| Muscle biopsy (20 min)                                | X                                      |
| Pulmonary Function Studies (Spirometry, MEP, MIP) (15 min) | X                                      |
| DEXA scan (20 min)                                    | X                                      |
| Bone Scan (30 min + 3 hrs wait)                       | X                                      |
| XRAYs (20 min)                                        | X                                      |

**TOTAL TIME DAY 2 = APPROX. 3-8 HOURS**
MRI of thighs and Biodex measurements from twins discordant for the VCP disease

Pixel-intensity histograms of the segmented muscle group in T2-weighted histograms of (A) Control twin and (B) Affected twin. (C) Biodex measurements of twins

Summary

- VCP inclusion body disease is under-recognized
- Currently > 40 mutations, R155H most common
- Progressive Myopathy in 89%, presents as IBM, LGMD, FSH
- Paget is present in 43%
- FTD in 29%
- ALS in approx. 8.5%
- Parkinson’s in 3.7%
- Genotype-phenotype correlations difficult because of heterogeneity
- We need natural history studies to attract clinical trials
Preclinical Studies in VCP Disease Using Mouse Models
Giles Watts & Kimonis designed Knock-in mouse model for IBMPFD.
Progression of muscle weakness in knock-in Neo+ R155H mice.

Grip Strength

Rotarod testing
Histological analysis of the VCP^{R155H/+} mouse quadriceps muscles.
Survival Curve of Homozygote $\text{VCP}^{\text{R155H/R155H}}$ VCP IBMPFD Mouse Model. Animals do not survive after 21 days.
Translational Studies with the R155H mouse
Targeted Excision of VCP R155H mutation by Cre-LoxP Technology as a Promising Therapeutic Strategy for Inclusion Body Myopathy

Targeted Excision of VCP R155H mutation by Cre-LoxP Technology improves myopathy

**Graph:**
- **Weight in grams:**
  - WT corn oil control
  - WT Tamoxifen
  - CRE-ERTM-VCP R155H/+ VCP R155H/+ Corn oil Control

**Graph:**
- **Grip Strength**
  - WT Corn oil control
  - WT Tamoxifen
  - VCP R155H/+ Tamoxifen
  - VCP R155H/+ Corn oil Control

**Images:**
- Wild Type
- Oil
- VCP R155H/+ Tamoxifen
- CRE-ERTM-VCP R155H/+
VALOSIN CONTAINING PROTEIN

- Nuclear Envelope Reconstruction
- Ubiquitin Dependent Protein Degradation
- Membrane Fusion (NSFL1C)
- Endoplasmic Reticulum Associated Degradation
- Transcription Activation
- Cell Cycle Control
- Apoptosis
- Autophagy
Rapamycin-induced autophagy aggravates pathology and weakness in a mouse model of VCP-associated myopathy.


- Mice treated every other day for 21 days
- Mice developed weakness, increase CPK, increase in vacuolated and atrophic fibers
- Inhibition of mTOR with rapamycin resulting in autophagosome biogenesis worsens muscle degeneration
Survival curve for the untreated and treated homozygous VCP$^{R155H/R155H}$ IBMPFD mouse model. VCP$^{R155H/R155H}$ animals fed an increased fat diet several survive >3 months.

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>Percentage difference 2020x (normal) VS 2019 (higher-fat) diet</th>
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</thead>
<tbody>
<tr>
<td>C16:0 Palmitic</td>
<td>0.3% increase</td>
</tr>
<tr>
<td>C18:0 Stearic</td>
<td>0.1% increase</td>
</tr>
<tr>
<td>C18:1ω9 Oleic</td>
<td>0.6% increase</td>
</tr>
<tr>
<td>C18:2ω6 Linoleic</td>
<td>1.3% increase</td>
</tr>
<tr>
<td>C18:3ω3 Linolenic</td>
<td>0.1% increase</td>
</tr>
<tr>
<td>Total saturated</td>
<td>0.4% increase</td>
</tr>
<tr>
<td>Total monounsaturated</td>
<td>0.6% increase</td>
</tr>
<tr>
<td>Total polysaturated</td>
<td>1.5% increase</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Amino Acids</th>
<th>Percentage difference 2020x (normal) VS 2019 (higher-fat) diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td>0.1% increase</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>0.1% increase</td>
</tr>
<tr>
<td>Proline</td>
<td>0.1% decrease</td>
</tr>
</tbody>
</table>
Measurements, and histological analyses of WT and VCP\textsuperscript{R155H/R155H} mice on normal and HFDs.
Lipid analyses of quadriceps and livers from VCP^{R155H/R155H} and WT animals on normal and lipid-enriched diets.

**Graphs:**

- **Panel A:** Palmitic acid (nmol/g tissue) for WT and HZ animals on ND and LED diets.
- **Panel B:** d18:1/16:0 Ceramide (nmol/g tissue) for WT and HZ animals on ND and LED diets.
- **Panel C:** Palmitic acid (nmol/g tissue) for WT and HZ animals on ND and LED diets.
- **Panel D:** d18:1/16:0 Ceramide (nmol/g tissue) for WT and HZ animals on ND and LED diets.
Summary of animal studies

- VCP \(^{R155H}\) mice are excellent models of human disease for translational studies

- Uphill exercise improved grip strength/Rotarod

- Cre excision of VCP mutation improved pathology. Exon skipping or allele silencing may be a promising strategy in patients

- Autophagy modifying drugs as therapy.

- High fat diet (soy bean oil) improves survival and pathology in homozygotes with translational potential
Promising treatments for VCP disease

- Arimoclomol
- Mitochondrial modifiers
- Flavinoids
REATA RTA 408 Capsules in Patients With Mitochondrial Myopathy - MOTOR

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Mitochondrial Myopathy (MOTOR)

- Mitochondrial myopathies are caused by mtDNA mutations and/or nuclear mutations of the electron transport chain leads to a reduced ability to produce cellular adenosine triphosphate (ATP), often resulting in muscle weakness, exercise intolerance, and fatigue.

- RTA 408 is a potent activator of Nrf2 and inhibitor of NF κB (nuclear factor kappa-light-chain-enhancer of activated B cells), and thus induces an antioxidant and anti-inflammatory phenotype.

- Several lines of evidence suggest that Nrf2 activation can increase mitochondrial respiration and biogenesis.

A Multicenter, Dose Ranging Safety and Pharmacokinetics Study of Arimoclomol in Amyotrophic Lateral Sclerosis (ALS)

- The primary purpose of this study is to evaluate the safety and tolerability of arimoclomol in ALS patients following 90 days of dosing. In addition, the amount of arimoclomol in blood and cerebrospinal fluid will be measured.

- Arimoclomol is a small molecule that upregulates "molecular chaperones" in cells under stress. Arimoclomol extends survival by five weeks when given both pre-symptomatically and at disease onset in a mutant superoxide dismutase (SOD1) transgenic mouse model of ALS. Furthermore, it has been demonstrated to have neuroprotective and neuroregenerative effects in other rat models of nerve damage. Molecular chaperone proteins are critical in the cellular response to stress and protein misfolding. Recent data suggest that the SOD1 mutation responsible for ALS in some patients with familial disease reduces the availability of a variety of molecular chaperones, and thus weakens their ability to respond to cellular stress. Protein misfolding and consequent aggregation may play a role in the pathogenesis of both the familial and sporadic forms of ALS. Therapeutic agents such as arimoclomol that improve cellular chaperone response to protein misfolding may be helpful in ALS.
Study of Arimoclomol in Inclusion Body Myositis (IBM)

- This study is not yet open for participant recruitment.
- **Sponsor:** University of Kansas Medical Center
- **Mazen Dimachkie, MD, University of Kansas Medical Center**
- **Contact:** Laura Herbelin  (913) 588-5095
  LHERBELIN@kumc.edu
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