The MC4R pathway serves as the principal regulator of mammalian energy balance by modulating energy intake and expenditure.

Defects in genes associated with the MC4R pathway can result in rare genetic diseases of obesity.

Genetic testing is needed to aid in the diagnosis of individuals with such diseases, which can lead to specialized management strategies or identification of eligibility for clinical studies.

Clinical data in patients with genetic defects in the MC4R pathway indicate that setmelanotide can effectively reduce weight and hunger scores in scientifically rationalized subpopulations with obesity in which MC4R pathway deficit is a factor contributing to obesity.

Gene candidate selection process

Rhythm utilizes a core set of nonclinical (experimental) and clinical (human genetics) evidence to evaluate the functional association of genes to the MC4R pathway (human genetics) evidence to evaluate the functional association of genes to the MC4R pathway.

Experimental evidence assesses a gene’s involvement in the function of the MC4R pathway

This approach is adapted from the National Institutes of Health ClinGen gene-disease clinical validity framework, which is the evolving standard for the identification of disease-associated genes (Table 2).

Genetic evidence helps define a gene’s contribution to human obesity and can rescue an obesity phenotype in preclinical models with gain-of-function mutations in a known pathway gene or loss-of-function mutations in a gene with a functional connection to the MC4R pathway (Table 2).

A list of MC4R pathway–relevant “Very Strong” and “Strong” genes with biological evidence of functional connection to the MC4R pathway is provided (Table 3).

Clinically meaningful reductions in weight and hunger score reductions following setmelanotide treatment in patients with obesity due to variants in 6 genes, all initially classified as “Very Strong” or “Strong.”

The DAYBREAK trial is a Phase 2 clinical trial that will evaluate setmelanotide in patients with specific variants in 1 of these 31 genes.

Table 1. Evidence for assessing MC4R pathway relevance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Molecular/Cellular function</th>
<th>Physiological function</th>
<th>Functional rescue</th>
<th>Gene expression</th>
<th>Neuronal activity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Strong</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Is the gene involved in energy balance and body weight regulation in preclinical models?</td>
</tr>
<tr>
<td>Strong</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Is the gene involved in energy balance and body weight regulation in preclinical models?</td>
</tr>
<tr>
<td>Moderate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Is the gene involved in energy balance and body weight regulation in preclinical models?</td>
</tr>
<tr>
<td>Weak</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Is the gene involved in energy balance and body weight regulation in preclinical models?</td>
</tr>
</tbody>
</table>

Table 2. MC4R pathway–relevant gene set for “Very Strong” and “Strong” genes

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</thead>
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</tr>
<tr>
<td>Weak</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Is the gene involved in energy balance and body weight regulation in preclinical models?</td>
</tr>
</tbody>
</table>

The cumulative weight of evidence informs a semiquantitative score that enables rank ordering of genes into 4 strength-based tiers: “Very Strong,” “Strong,” “Moderate,” and “Weak.”

Table 3. MC4R pathway–relevant gene set for “Very Strong” and “Strong” genes

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<td>✓</td>
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The evidence-based framework presented here is supported by clinical data that demonstrate significant weight and hunger score reductions following setmelanotide treatment in patients with obesity due to variants in 6 genes, all initially classified as “Very Strong” or “Strong.”

The DAYBREAK trial is a Phase 2 clinical trial that will evaluate setmelanotide in patients with specific variants in 1 of these 31 genes.

The nature, quantity, and quality of evidence required for each tier builds upon that of the previous tier, with higher ranked genes being most likely to define patient populations potentially responsive to long-term setmelanotide treatment.

The clinical data in patients with genetic defects in the MC4R pathway indicate that setmelanotide can effectively reduce weight and hunger scores in scientifically rationalized subpopulations with obesity in which MC4R pathway deficit is a factor contributing to obesity.

To identify genetically defined patient populations most likely to benefit from long-term setmelanotide therapy using an evidence-based framework that was designed to assess the relevance of genes to the MC4R pathway.

Methods

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