FINANCIAL DISCLOSURE:
No relationships to disclose

UNLABELED / UNAPPROVED USES DISCLOSURE:
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Bbs1 gene deletion from the leptin receptor neurons causes obesity and hypertension in mice

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Bardet-Biedl Syndrome (BBS)

- Obesity
- Hypertension
- Retinopathy
- Polydactyly
- Learning disabilities
- Hypogonadalism
- Renal abnormalities
BBS knockout mice are obese

BBS proteins

Nachury et al., *Cell* 2010

BBSome (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, BBS18)

BBS Chaperonins (BBS6, BBS10, BBS12)
BBS1 physically interacts with LRb and is necessary for membrane localization of the LRb in cultured HEK 293 cells.

These results suggest that the Bbs1 gene is critical for LRb trafficking and signaling.
To investigate whether loss of the \textit{Bbs1} gene in LRb expressing cells affects body weight and blood pressure

- Use of Cre-LoxP system to ablate the \textit{Bbs1} gene from LRb expressing cells
Deletion of the *Bbs1* gene in LRb expressing cells using Cre-LoxP system
Question?

Are mice lacking the *Bbs1* gene in LRb expressing cells obese?
Growth curve of LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl} mice

Body weight (g)

Time (weeks)

LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl}

WT

n = 22-29, *p < 0.05 vs. WT
Increased fat mass in LRb<sub>cre</sub>/Bbs1<sup>fl/fl</sup> mice measured by magnetic resonance imaging

MRI images

WT     LRb<sub>cre</sub>/Bbs1<sup>fl/fl</sup>

Fat mass (g)

WT     LRb<sub>cre</sub>/Bbs1<sup>fl/fl</sup>

* <p < 0.05 vs. WT
Increased food intake in LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl} mice

\[ *p < 0.05 \text{ vs. WT} \]
Pair fed LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl} mice are obese

\*\(p < 0.05\) vs. WT

\[\blacklozenge\] \(p < 0.05\) vs. WT and LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl}

- Body weight (g)
- Fat pad weight (g)

Subcutaneous fat
Reduced energy expenditure in LRb$^{cre}$/Bbs1$^{fl/fl}$ mice

* p< 0.05 vs. WT
Reduced core body temperature in LRb^{cre}/Bbs1^{fl/fl} mice

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*p < 0.05 VS. WT

Body temperature (°C)

Time (days)

38

37

36

WT

LRb^{cre}/Bbs1^{fl/fl}

*p < 0.05 VS. WT
Question?

Are mice lacking the *Bbs1* gene in LRb expressing cells hypertensive?
Radiotelemetry arterial pressure

WT
LRbcre/Bbs1fl/fl

Systolic BP
Diastolic BP
Mean BP

* p < 0.01 vs. WT
Increased renal sympathetic nerve activity in LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl} mice

WT

LR\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl}

Renal SNA (spike/sec)

*p < 0.01 vs. WT
Exaggerated depressor response to ganglionic blockage (hexamethonium) in \( \text{LRb}^{\text{cre}}/\text{Bbs1}^{\text{fl/fl}} \) mice

\[ \Delta \text{MAP (mmHg)} \]

\[ \begin{align*}
\text{WT} & \quad \text{LRb}^{\text{cre}}/\text{Bbs1}^{\text{fl/fl}} \quad \ast
\end{align*} \]

* \( p < 0.05 \) vs. WT
Mice lacking the \textit{Bbs1} gene in LRb expressing cells are obese. Both increased food intake and reduced energy expenditure contribute to obesity in LRb\textsuperscript{cre}/Bbs1\textsuperscript{fl/fl} mice.

Mice lacking the \textit{Bbs1} gene in LRb expressing cells are also hypertensive. Increased sympathetic nerve activity contributes to the development of hypertension.
Conclusion

- *Bbs1* gene in LRb expressing cells is critical for the regulation of energy homeostasis and arterial pressure
Clinical relevance and perspective

1. BBS is a rare genetic disorder, but its clinical features including obesity and hypertension are common.

2. Bbs genes in LRb expressing cells are critical for metabolic and cardiovascular regulation.
Cre-dependent reporter mouse (tdTomato^{fl/fl})
Specificity in Cre expression in \( LRb^{cre}/td-Tomato^{fl} \) mice
Fat imaging using MRI

WT                Bbs2\(^{-/-}\)                Bbs4\(^{-/-}\)

\begin{itemize}
  \item Subcutaneous fat
  \item Visceral fat
\end{itemize}


BBS knockout mice are obese