NEWS

# Duplication of Rett syndrome gene triggers immune problems

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Children with multiple copies of **MeCP2**, the gene linked to Rett syndrome, have an immune deficiency in addition to intellectual disabilities, impaired motor skills and seizures. The findings, published 5 December in *Science Translational Medicine,* may explain why these individuals suffer from frequent bouts of severe respiratory infections and pneumonia[1].

MeCP2 resides on the X chromosome and underlies a pair of rare sex-linked disorders — one caused by too little functioning MeCP2 protein, the other by too much.

Children with mutations in the gene, who are almost always girls, have Rett syndrome. Those with extra copies of MeCP2, who are almost always boys, have a constellation of symptoms called MeCP2 duplication syndrome. Both disorders have features of autism.

MeCP2 regulates the expression of **thousands of genes**, but its precise targets aren't yet clear. The new research implicates the immune system.

Mice that have extra copies of MeCP2 and children with MeCP2 duplication syndrome produce abnormally low levels of an immune molecule called interferon-gamma, a key part of the immune system's response to infection, the study found.

Many children with the duplication syndrome are confined to wheelchairs, and often have high rates of respiratory illness because their lungs are not well developed. The new work indicates that these boys have an added disadvantage, says **Melissa Ramocki**, medical director of the neurogenetics clinic at Baylor College of Medicine in Houston, Texas, and lead psychologist on the study.

## Lone player:

The findings suggest new avenues for preventing infections and for exploring MeCP2's function.

They also show that MeCP2 — rather than nearby X chromosome genes that are also often duplicated in the syndrome — can explain much of the impaired immune response. Mice that have a duplication of only MeCP2 have issues similar to those of children with the duplication syndrome.

"This helps pinpoint the immune defects in this syndrome to MeCP2 itself," says **Janine LaSalle**, professor of medical microbiology and immunology at the University of California, Davis, who was not involved in the study. "It's interesting that a gene that is mostly thought to be involved in the nervous system also has roles in the immune system."

To test whether too much MeCP2 affects mice's ability to fight disease, the team infected mice that carry three copies of the human MeCP2 with two different microbes: the protozoan *Leishmania major* and the fungus *Aspergillus niger*.

The immune system fights off each pathogen with different tools: the former with T helper 1 ($T_H1$) cells and the latter with T helper 2 ($T_H2$) cells. Each of these cell types, which develop from immature cells when the body senses an infection, produces its own signature molecules that further the body's response to pathogens.

The mice fight off *A. niger* handily, but they cannot seem to kick *L. major* infection. Examining cells taken from the animals' lymph nodes revealed that mice with the duplication have fewer $T_H1$ cells, and those cells produce less interferon-gamma, compared with controls. When the *L. major*-infected mice are given an injection of control $T_H1$ cells, they recover from the infection.

The team next examined blood samples taken from 27 otherwise healthy boys with MeCP2 duplication syndrome and 26of their unaffected siblings. The researchers did this work at a 2011

international conference of families with the syndrome, hosted by Baylor.

Although the anomalies are sometimes slight and do not always hold across different age groups, blood samples from the boys with the duplication show some signs of immune irregularities.

Notably, they have low levels of mature memory T and B cells, which develop after an infection and allow the body to remember a pathogen. What's more, immature $T_H1$ cells in their blood produce less interferon-gamma than cells from the unaffected siblings, and develop at only a third of the rate of the siblings' cells.

Now that the problem has been identified, researchers can investigate ways to alleviate it, says lead scientist **David Corry**, chief of immunology, allergy and rheumatology at Baylor.

Corry outlines two potential therapies, both of which carry severe side effects: bone marrow transplants, which would replace all the children's immune cells with better-functioning ones, and interferon-gamma replacement therapy, which is already given to children with other immune defects, but which has its own problems.

"It's very toxic," Corry says. "It causes a great deal of side effects, including liver toxicity."

Another potential therapy, further in the future, might consist of removing some T cells from the children, engineering them to lower MeCP2 levels, and reinjecting them into the children. But that's just an idea at the moment, he says.

It's not yet clear whether MeCP2's immune effects are linked to the neurological symptoms of MeCP2 duplication syndrome. Even if they are, treating the immune defect is unlikely to eliminate the neurological problems.

"The first thing is, can we help these boys stay alive and stay healthy and decrease their morbidity and mortality from the infections themselves?" says Ramocki. "Is there going to be a secondary effect of neurological function? I think nobody knows."

## References:

**1: Yang T.** *et al. Sci. Transl. Med.* **4**, 163ra158 (2012) **PubMed**