NEWS

Molecular mechanisms: Rett, Angelman genes work together

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Fly eyes: An excess of the Rett syndrome gene disrupts the structure of fly eyes (middle), which look normal in flies that also lack one copy of the Angelman syndrome gene (right).

The genes involved in **Rett** and **Angelman syndromes** may collaborate to regulate the expression of other proteins, according to a study published 19 July in *Biochemical and Biophysical Research Communications*[1]. This may explain the overlap in symptoms between the two disorders, the researchers say.

Rett and Angelman syndromes both share features with autism and lead to developmental delay, intellectual disability and social deficits. Each can be traced to a single causative gene that controls the levels of many others.

The Rett syndrome gene is **MeCP2**, which **regulates the expression** of thousands of other genes. Mutations and deletions of **UBE3A**, which helps dispose of unwanted proteins, lead to Angelman syndrome.

Using fruit flies, mice and mammalian cells, researchers in the new study explored whether overlap in these secondary targets can explain the disorders' shared symptoms.

The results in flies suggest that MeCP2 and UBE3A function in the same pathway: Excess MeCP2 disrupts normal eye structure, but deleting one copy of UBE3A fixes this deficit.

In mice, neither protein regulates levels of the other, however. Mice lacking UBE3A have typical levels of MeCP2 and *vice versa*. Instead, researchers found that a subset of proteins are sensitive to levels of both UBE3A and MeCP2.

For example, mice with excess MeCP2 have elevated levels of somatostatin, a known target of MeCP2. Somatostatin levels are dampened in mice lacking UBE3A. And knocking out UBE3A in mice with excess MeCP2 normalizes somatostatin levels.

UBE3A levels did not affect the expression of CREB1, another MeCP2 target, however. This suggests that UBE3A and MeCP2 have only a subset of targets in common. Of a random selection of 60 proteins whose levels are elevated in mice with excess MeCP2, 6 are dampened and 13 are boosted in mice lacking UBE3A. The remaining are unaffected.

When researchers used antibodies to pull out MeCP2 from mammalian cells, they found that the UBE3A protein comes along with it. This suggests that UBE3A may bind directly to MeCP2 to regulate its function, they say.

References:

1: Kim S. *et al. Biochem. Biophys. Res. Commun.* **437**, 67-73 (2013) **Pubmed**