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Background

Since Rett syndrome was first described, there has been much commentary about the range of expression of symptoms in Rett syndrome, including atypical forms of the condition. In 1999, mutations in the *MECP2* gene were first associated with Rett syndrome. Since then, there has been considerable research examining the relationship between the expression of symptoms and type of *MECP2* mutation.

Common types of mutations include missense mutations or truncating mutations. A gene can be pictured as a string of beads. A missense mutation is when a blue bead is put in place of a yellow bead. A truncating mutation is when the string of beads is cut short, resulting in a reduced number of beads (e.g 15 instead of 20). There are two types of mutations that can cause a truncation – nonsense mutations and frameshift mutations.

A nonsense mutation, is when the a bead is replaced by a "stop", similar to having a knot in a string of beads, and the string of beads is cut short. A frameshift mutation is where the beads follow a particular pattern and a bead is added in or taken out, causing a change in the pattern. Sometimes, this pattern change can also lead to a "stop" pattern, resulting in the string of beads being cut short.

All of these mutations in the gene can result in a protein that does not function the way it normally does, which can in turn, lead to a disease or illness. We investigated the differences in severity of symptoms between those with different *MECP2* mutations.

What we did

We used information provided by families participating in the Australian Rett Syndrome Database and coded this according to four severity scales. This allowed us to compare the severity of symptoms of girls and women in different groups.

We then grouped the girls and women according to the type of mutation they had and the location of their mutation. We also specifically examined the characteristics of those with the seven common mutations – p.R133C, p.T158M, p.R168X, p.R255X, p.R270X, p.R294X and p.R306C, compared to those with other mutations.

What we found

Overall, we found that those with truncating mutations had more severe symptoms and developed hand stereotypies at a younger age compared to those with other mutations. However those who had truncating mutations within the C-terminal region (located at the end of the gene) had much less severe symptoms when compared to those with similar mutations in other regions. We also found that mutations located in different functional domains of the *MECP2* gene can result in different levels of symptom severity. This relates to the function of each domain in the MECP2 protein, with some domains appearing to have more functional importance then others.

When comparing specific mutations, we found that those with a p.R133C, p.R294X or a p.R306C mutation had the milder symptoms. On the other hand, those with a p.R270X mutation had more severe symptoms compared to those with other mutations. Those with a p.R168X mutation lost communication ability at an earlier age.

What does it mean

Those with certain mutations tended to have milder symptoms overall, whilst those with other mutations had more severe symptoms. It is important to understand the relationship between mutation type and the associated clinical features so doctors and families can prepare for the future needs of the child.

Related information

You may also be interested in:

- Investigating genotype-phenotype relationships in Rett syndrome - see

  http://rett.claritycommunications.com.au/our-research/research-snapshots/bebbington-genotype-phenotype.aspx

- Updating the profile of C-terminal MECP2 deletions in Rett syndrome – see

  http://rett.claritycommunications.com.au/our-research/research-snapshots/bebbington-c-terminal.aspx