Rett Syndrome and Genetics- Questions Parents Ask

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Updated by Dr. Hayley Archer and Prof. Angus Clarke, January 2008

1. What are genes and what do they do?

We have thousands of different genes. Genes are coded instructions which tell the body how to make different proteins. Proteins form the structure and control the shape and function of all parts of the body. Rett syndrome usually occurs when a mistake arises in a specific gene which tells the body how to make a protein called MeCP2 (methyl CpG binding protein 2). This protein is important for controlling how the brain develops and how we all learn.

2. Why do mistakes arise in genes? Was it something we did?

When eggs form in the ovaries and sperm form in the testes, all the genes have to make copies of themselves. Now and again, a gene does not copy itself correctly and a mistake arises. We cannot prevent these mistakes happening and no-one is to blame for them. All we can do to make them less likely is to avoid unnecessary exposure to radiation and hazardous chemicals.

3. Do all children with Rett syndrome have mistakes in the MECP2 gene?

No. When girls with a definite diagnosis of classical Rett syndrome are tested, mistakes in the MECP2 gene are found in more than 90% (9 out of 10). Children with atypical Rett syndrome have some but not all features of Rett syndrome. A smaller percentage of children with atypical Rett syndrome have alterations in MECP2. More recently, another gene called CDKL5 has been identified. Girls with mistakes in CDKL5 usually have seizures as babies and may go on to develop some of the features of Rett syndrome. The illness caused by changes in the CDKL5 gene is currently known as “CDKL5”. Some children given a diagnosis of Rett syndrome may have their condition caused by changes in this gene, especially if they have the Hagberg variant of Rett syndrome with early seizures. There is real overlap between the problems caused by changes in MECP2 and CDKL5 and, indeed, the two proteins do interact and work together. Researchers are working to understand further just how the MECP2 and CDKL5 genes work and to identify other genes in which alterations can cause Rett syndrome.

4. Does my child definitely have Rett syndrome?

To make a diagnosis of Rett syndrome, your paediatrician will look for a number of different features in your child. If your child has all these features she (or he) has classical Rett syndrome. If your child has only some features your paediatrician might say she (or he) has possible Rett syndrome. Finding a mistake in the MECP2 gene confirms the diagnosis of classical Rett syndrome and can help make a diagnosis of Rett syndrome if there is doubt.

5. Could we have another child with Rett syndrome? How can that happen?

If you have had one child with Rett syndrome, there is a small chance of having another affected child. The chance is around 1 in 100 (i.e. around 1%). It can happen in two different ways - but both of these situations are rare.

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5A. The first way is when a mistake occurs when genes are copying themselves in either the testis or the ovary. It is possible that more than one egg cell or more than one sperm cell will receive an altered copy of the gene. This means that a proportion of the eggs or sperm contain the altered copy of the gene and the remainder the normal copy. If one of the eggs or sperm with the altered gene forms an embryo, then the baby would be affected. If an egg or sperm with a normal copy of the gene forms an embryo, the baby would not be affected.

5B. The second possibility is extremely rare and occurs because the MECP2 gene is located on the X chromosome. Women have two X chromosomes and men have only one, as well as the Y chromosome which makes him male. Each cell of the body only needs one X chromosome. In women, one of the two X chromosomes is switched off in every cell. This is done randomly so about half the cells in the body will usually have one X chromosome switched off and about half will usually have the other X switched off. If a woman has a mistake in her MECP2 gene on one X chromosome, and if that X chromosome is switched off (by random chance) in most of her cells, she might have only very mild learning problems or no problems at all. In this very rare situation, each time this woman had a child there would be a 1 in 2 (or 50%) chance of passing on the gene with the mistake and having an affected child; equally, there is a 1 in 2 chance of passing on the gene without the mistake and having an unaffected child. CDKL5 is also located on the X chromosome but no child has yet been found to have inherited a mistake in CDKL5 from their mother in this way.

6. Mum: "Should I have a gene test?"

If a mistake has been found in the MECP2 or CDKL5 gene in your child it would be possible to look for the same gene mistake in you to rule out the very small possibility that you carry the same gene alteration because the gene is switched off in all your cells. (See paragraph 5B. above).

7. Dad: "Should I have a gene test?"

No, it is probably not necessary. If you had a mistake in the MECP2 or CDKL5 gene, because a man has only one X chromosome and one copy of the gene, you would almost certainly have severe problems associated with Rett syndrome. If you did carry the gene alteration on just some of your cells, which happens very rarely, then it would be unlikely to be shown up with an ordinary genetic test on your blood.

8. Can we have a test in our next pregnancy?

The chance of having a second affected child is small. If a mistake in the MECP2 or CDKL5 gene has been found in your child, it would be possible to test a future pregnancy. Tests in pregnancy can cause miscarriage and therefore before deciding about testing, we suggest couples think very carefully about what they would do if the test gave an unfavourable result. A test done in the first third of pregnancy has a risk of miscarriage of around 2% (1 in 50). Amniocentesis, which is performed in the middle third of pregnancy, carries a risk of miscarriage of around ½ % (around 1 in 200). The precise risks vary between centres and operators.

9. Should anyone else in the family be concerned about the chance of having an affected child?

The chance of anyone else in the family having an affected child is very low.

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If an individual is known to have a mistake in their MECP2 or CDKL5 gene, it would be possible to test their mother and their unaffected sisters, to reassure them that they do not carry the same gene mistake without showing signs of it.

10. Can boys have Rett syndrome?

Yes, but it is very rare. Boys usually have only one X chromosome and one copy of the gene, whereas girls have two copies, one with a mistake and one without. It is likely that most boys with mistakes in their MECP2 gene cannot survive because they do not have any intact copies of the gene to compensate. However, some boys have Rett syndrome because:

EITHER they have two X chromosomes as well as the Y chromosome that makes them male, and one of the two X chromosomes has an altered MECP2 gene,

OR they have the genetic mistake in only some of the cells of their bodies, while other cells have an intact MECP2 gene, without a mistake.

Some boys have a more severe set of problems than the usual Rett syndrome since their altered copy of the MECP2 gene is functioning in every cell in their body. This usually causes severe problems from the newborn period. We also now realise that some mistakes in the MECP2 gene do not have such a severe effect on how the MeCP2 protein works. These boys tend to have less severe, learning disabilities than are usual in individuals affected by classic Rett syndrome and they are usually non progressive.

11. Whom can we speak to about genetic tests and about the chance of having another affected child?

There are Clinical Genetics departments in all the regions of the United Kingdom. You can ask your general practitioner or paediatrician to refer you.

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