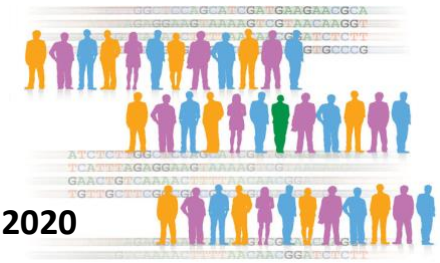

Newsletter RP17 **October 2020**

In the past, you or one of your family members has donated blood or DNA material in order to help finding the genetic defect that is responsible for Retinitis Pigmentosa (in short, RP) within your family. Recently, important progress was made in the field of genetics research, which led to the successful identification of this genetic defect. This genetic defect is called "RP17". With this newsletter, we would like to explain to you how this defect was found, what RP17 is and what this finding means for you and your family members.

Background of the RP17 study

The human DNA consists of 3.200 million DNA building blocks. These building blocks are divided over 23 chromosome pairs, of which 22 are numbered based on size: chromosome 1 is the largest; chromosome 22 is the smallest. Additionally, there are the sex chromosomes which are called chromosome X and chromosome Y (**Box 1**).

In order to find the genetic defect that is responsible for RP in your family, a method called 'whole genome sequencing' was used. With this method, the exact order of all 3.200 million DNA building blocks can be determined in a precise manner. This revealed a duplication of a set of DNA building blocks that is located on chromosome 17. This, or similar, DNA duplications were found in 22 different families worldwide. Within these families, more than 300 persons are diagnosed with a dominant form of RP. With this information, we concluded that the identified DNA duplication on chromosome 17 is also the genetic defect that causes RP within your family.

In **box 2** we will explain the identified DNA duplication in more detail. In **boxes 3, 4 and 5** we will try to explain in a stepwise manner, the consequences of these DNA duplications and how this could potentially lead to a retina defect in RP.

Box 1: Heritability

The human body consists of billions of cells. Almost all cells have a cell nucleus. This cell nucleus contains our hereditary material, the DNA, which is made up by 23 pairs of chromosomes (**Figure 1**). Of these chromosome pairs, 22 are identical between males and females, one pair, the sex chromosomes X and Y, is different. A male carries the chromosomes X and Y; a female carries two X chromosomes. Children inherit their chromosomes from their parents. Of each chromosome pair, one chromosome is inherited from the mother, and one chromosome is inherited from the father. Each chromosome is built up by DNA and contains a large number of genes. When mistakes are present in the DNA building blocks of a gene, this can cause an inherited disorder.

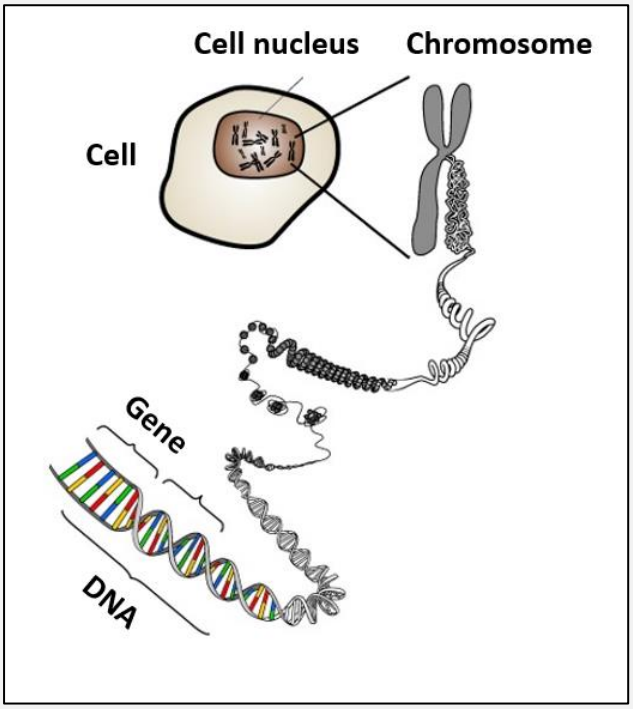

Figure 1: Hereditary material

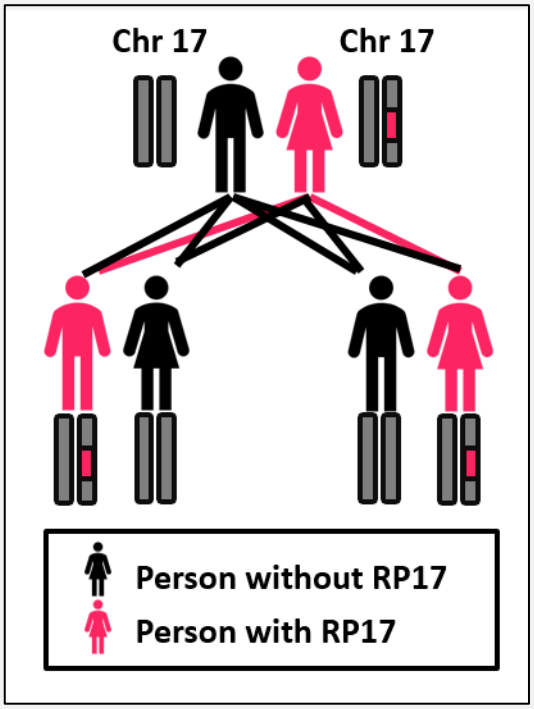

Figure 2: Dominant inheritance

In a person with a dominantly inherited condition, such as RP17, a DNA mistake is present on one chromosome of the 22 chromosome pairs. Therefore, this person has one normal and one disease-causing copy of the gene or genes that contain the DNA mistake.

Every child of a person with RP17 has 50% chance to inherit the DNA mistake and to develop the condition. For RP17, the DNA mistake is located on chromosome 17 (Chr 17) (**Figure 2**).

Box 2: The DNA duplication in more detail

The DNA duplication found on chromosome 17 contains the genetic code for four different genes, here referred to as genes A, B, C and D. In **Figure 3**, the different genes are illustrated by the boxes in green. In a healthy person, each chromosome 17 contains one copy of each gene. One chromosome is received from parent 1 (father or mother), and the second chromosome is received from parent 2 (father or mother). In persons that have RP17 within your family, one correct chromosome is received from parent 1. Additionally, a second chromosome is received from parent 2 that contains the duplication of DNA building blocks. This duplication contains the genetic code for genes A, B, C and D. The DNA building blocks that are duplicated on chromosome 17 are illustrated by the boxes in pink.

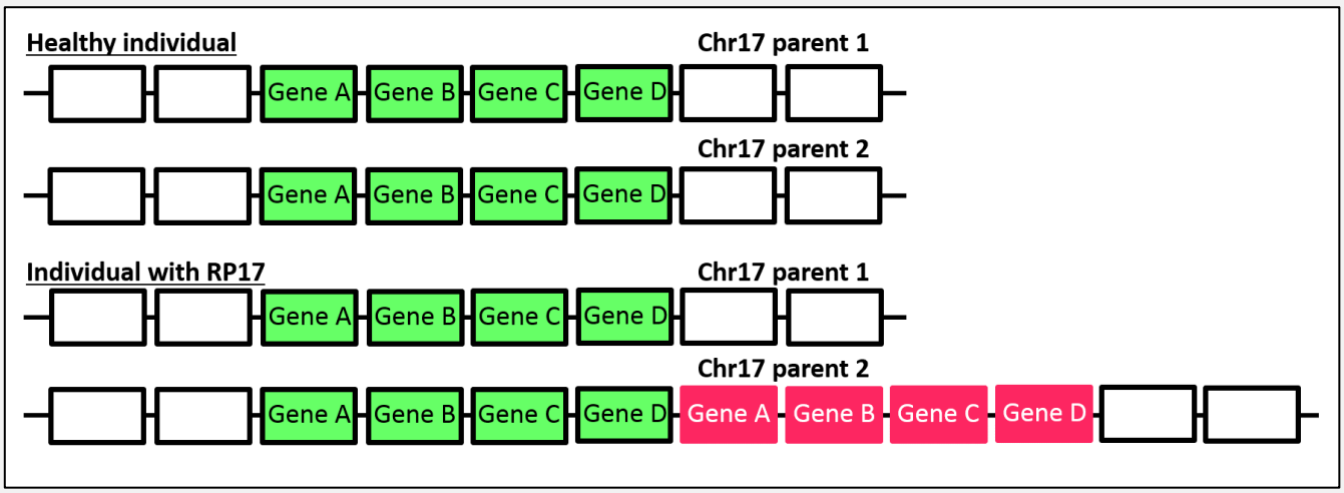

Figure 3: A DNA-duplication located on chromosome 17 in persons with RP17

Each gene has a unique function in the human body. This function can be related to multiple organs in the body, or can be a specific function that is related related to only one organ. Some genes have a clear function in the eye (gene determines eye color), other genes have a less clear function in the eye, but are still very important (gene is in control of the gene that determines eye color). There is no clear function known for genes A, B, C or D in the eye. However, this set of genes can still be important for normal function of the eye. Missing a copy of any of these genes or the addition of an extra copy of these genes can still have serious consequences for the function of the eye or specifically the retina. In the next boxes, we will try to explain the possible consequences of the inclusion of an extra set of these genes on chromosome 17 of individuals with RP17.

Box 3: DNA junctions and a retina-switch

Figure 4 provides again a schematic illustration of chromosome 17 including the RP17 defect. Researchers have focused on mapping this region of chromosome 17 in more detail, in order to learn more about the DNA duplications that cause RP17. Firstly, they found that a 'retina-switch' is located between genes C and D. This switch is illustrated by the circle symbol with the eye. These switch is responsible for 'activating' the genes that have an essential function in the eye. In this way, the required gene will be activated and consequently the gene will produce functional protein.

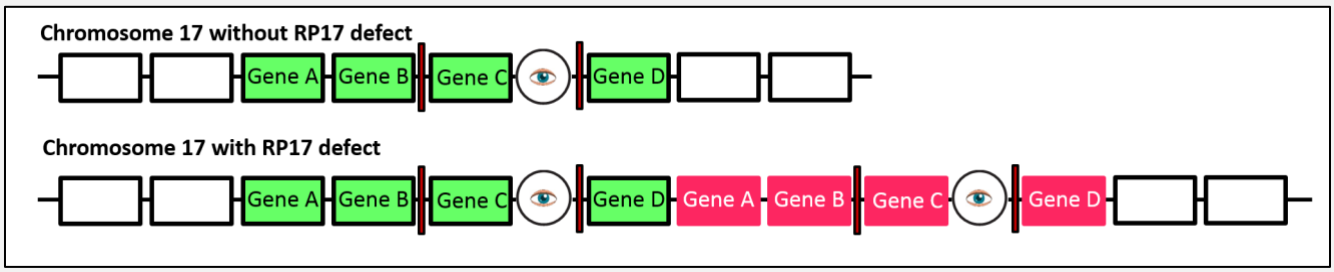

Figure 4: Schematic illustration of the organization of chromosome 17

Secondly, researchers have mapped the DNA junctions that are present on this specific part of chromosome 17. The human DNA is about 2 meters in length. The DNA junctions are necessary to fold all DNA efficiently in such a way that all the DNA chromosomes can fit in a single cell nucleus. Every time and in every cell nucleus, the DNA will be folded in exactly the same manner due to these DNA junction points.

In the figure, the DNA junctions are illustrated by the vertical red bars. In a normal copy of chromosome 17 without the RP17 defect, the DNA junctions are located between genes B and C and between genes C and D. On chromosome 17 with the RP17 defect, an extra set of DNA junctions is visible between the pink duplicated versions of genes B and C, and the pink duplicated versions of genes C and D.

Box 4: Loop formation of the DNA

When the DNA is folded correctly, the junction points will join together and connect. In **Figure 5**, the looping of a normal copy of chromosome 17 is illustrated. The two red bars connect and a loop will be formed of the DNA segment that is located between the two bars. The retina-switch is now in close proximity to gene C. This means that in this situation, gene C can be switched on and consequently protein will be produced. Because of the loop, genes B and D are out of reach for the retina-switch and will not be activated.

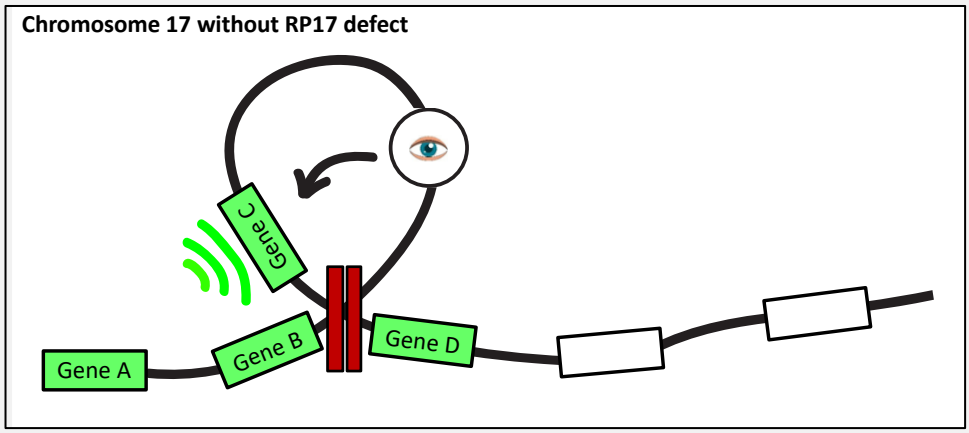

Figure 5: Schematic representation of 3D looping of the normal chromosomal 17 region

Box 5: Incorrect activation of gene C

In **Figure 6** you can observe a schematic illustration of chromosome 17 that includes the RP17 defect. Because of the DNA duplication, an extra loop is formed. Besides gene C, the extra loop contains gene B (blue). Normally, gene B is non-active in the retina. However, as gene B is now included in the loop, it in close proximity of the retina switch. As a result gene B can also be activated. Incorrectly, protein will be produced from gene B. Extra production of this protein could be toxic or damaging in the eye. Over the years, the production of toxic protein B builds up and will ultimately lead to the development of RP.

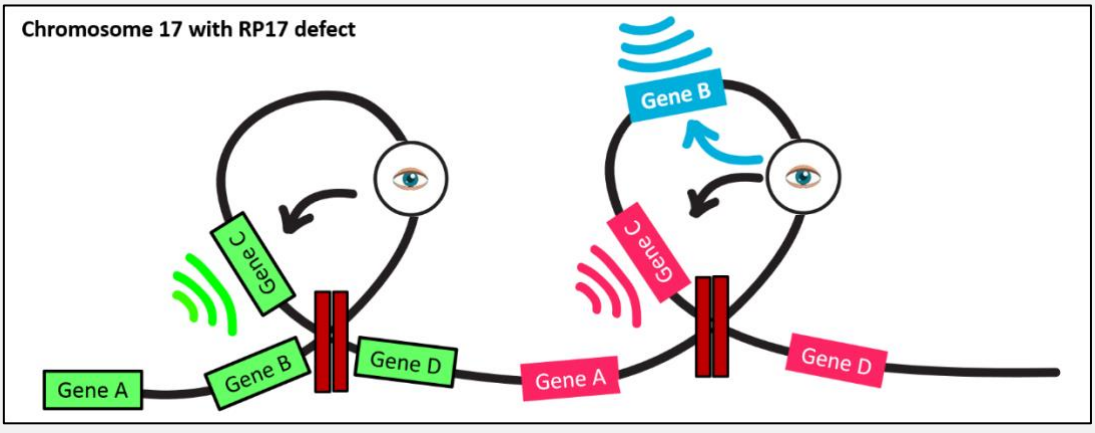

Figure 6: Schematic representation of 3D looping of the duplicated RP17 region

What do these results mean for you?

As mentioned above, the DNA-duplications found on the chromosome 17 that cause RP17 have been found in 22 different families worldwide with more than 300 people diagnosed with RP17. In total, 8 different DNA-duplications (with different combinations of genes A, B, C or D) have been found. All 8 DNA-duplications will lead to the formation of extra DNA loops and the activation of gene B. Therefore, we are confident to conclude that these changes in the DNA leads to the development of RP17.

The finding of the genetic defect of RP17 will be published in the American Journal of Human Genetics in the issue of November 2020 and is already published online from October 5th 2020.

What does it mean that the genetic cause of RP17 is identified?

The breakthrough of this research practically means the following:

- If one of your parents diagnosed with RP17 and you do not have any symptoms, and you would like to know whether you are at risk to develop RP17 as well, please contact your ophthalmologist or clinical geneticist.
- If you have RP and have a child wish, you can get information about the possibilities for preventing passing on the RP17 defect to your offspring's. Depending on the national regulations in your country you may apply for pre-implantation genetic diagnostic. For more information on this, please contact your ophthalmologist or clinical geneticist.

When you have questions on genetic testing we would like to refer your clinical geneticist. For this, you can bring this newsletter along for their information.

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