GENETIC AND GENOMIC TESTING (RNA)

Looking at the RNA for answers

IN SUMMARY

- RNA stands for **r**ibo**n**ucleic **a**cid
- RNA is similar to DNA (**d**eoxyribo**n**ucleic **a**cid), it also contains long chains of chemicals called bases connected by a sugar 'backbone'
- There are many types of RNA, which are all contained in our cells
- The most well-known type of RNA is the RNA blueprint or 'recipe' for proteins that make our body function
- RNA testing is most often done after someone has a DNA test with unclear or no findings
- Genetic conditions can occur when there is a problem in the way the RNA recipe is cut and pasted together, known as splicing.
- RNA testing is usually done on a few different types of cells (e.g. blood, urine, skin or another tissue sample)
- Testing is done in a specialised laboratory and may take months to complete.

WHAT IS RNA?

To understand RNA, we first need to understand DNA Our complete set of DNA is like our own personalised recipe book and our genes are like the recipes. Often these recipes are for proteins, which are very important as they are chemicals that do most of the work in our cells.

There are different types of **RNA**, which are all contained in our cells and help many important processes, including making proteins. Like DNA, RNA contains long chains of chemicals called bases, connected by a sugar backbone. RNA's bases are **a**denine, **g**uanine, **c**ytosine and **u**racil (**A**, **C**, **G**, **U**) while DNA is slightly different in that it does not have **u**racil and instead has **t**hymine (**A**, **C**, **G**, **T**). Another important difference is that RNA has only one strand, while DNA has two.

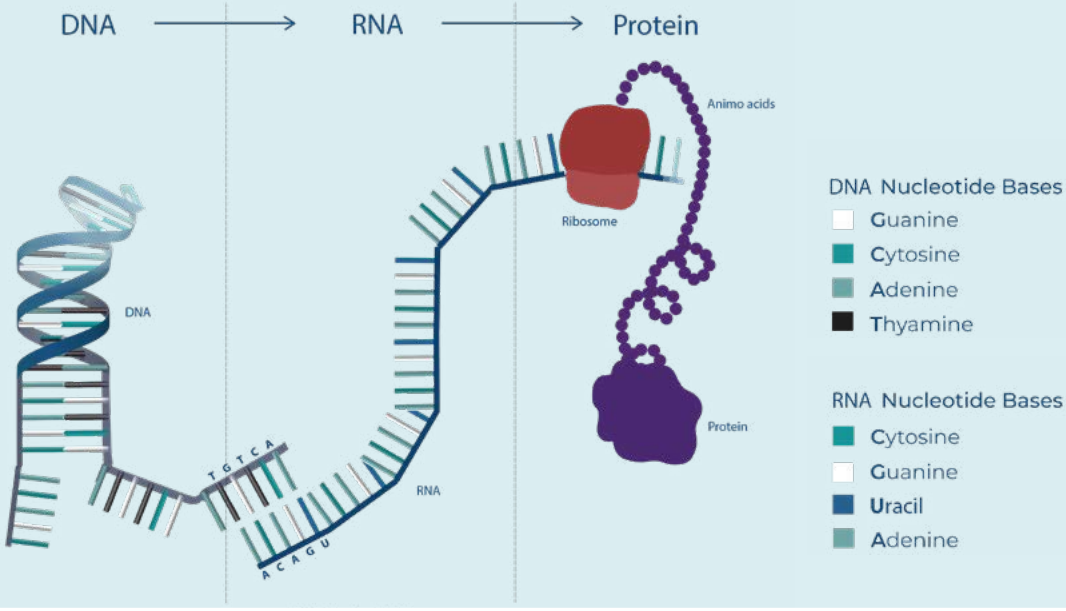


Figure 1: The DNA is copied into RNA, which is used to make proteins.

Content updated November 2021
SHPN: (HETI) 240965

RNA testing mainly looks at messenger RNA (**mRNA**) and pre-messenger RNA (**precursor-mRNA**). They have 'messenger' in their name because they are the 'message' or blueprint that is taken to the protein-building machinery in our cells to make proteins.

PRE-mRNA

'Pre' stands for 'precursor' which means 'before', so pre-mRNA gets its name because it is made before the messenger RNA. Making the pre-mRNA from the DNA is the first step in making a protein (transcription), where each base in the DNA that makes up a gene is copied into a matching pre-mRNA base (see *Figure 1*). This is done because our cells cannot make a protein straight from the DNA recipe. It needs to be copied into RNA first.

The RNA is made up of exons and introns (see *Figure 2*). Both the exons and introns have useful information, however, only the exons are needed for the rest of the steps in protein-making. The exons can be thought of as the ingredients listed in a recipe, whereas the introns are like the introduction and other extra information in a recipe. For example, everything you need to know about installing an oven or stove, how to set the temperature and timer to cook the item in the recipe.

mRNA

Because not all the information in the pre-mRNA copy is needed to make a protein, in the next step (**splicing**), the exons are joined together by cutting out the introns to make mRNA. It is a bit like just leaving the ingredients in a recipe by cutting out the introduction and other extra information. Splicing is explained in more detail in the Splicing Variant Result Fact Sheet.

Finally, in the last step called **translation** a protein making machine called a ribosome attaches to the mRNA (*Figure 1*). The ribosome connects a matching amino acid to each group of three mRNA bases. Amino acids are like the ingredients in this recipe. The ribosome forms them into a long chain that folds into a protein.

WHAT IS RNA TESTING?

RNA testing looks at the order of a person's RNA bases to see if there has been a change in splicing of the mRNA recipe that might explain their symptoms, for example by contributing to a genetic condition.

Often, a few different types of samples are needed to get enough RNA for the test. These might include blood, urine, skin, or a biopsy of another type of tissue.

RNA testing uses similar techniques to DNA testing. Laboratories mainly look at how the pre-mRNA is spliced to make the mRNA recipe. Sometimes they cross-check results by re-testing someone's DNA.

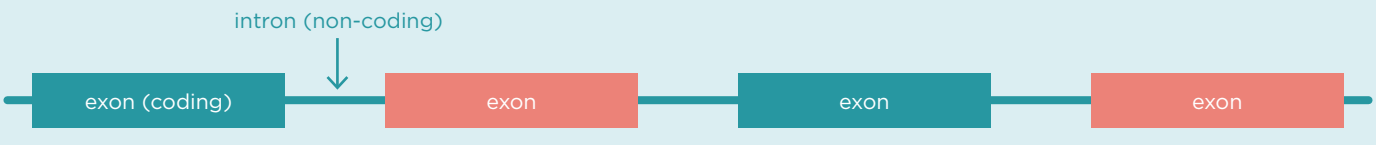
Testing may take several months and may need to be done as part of a research study in a specialised laboratory.

REASONS WHY AN RNA TEST MAY BE DONE

Often an RNA test is done after a DNA test has not provided a clear result. As RNA is a different step in the process of making proteins, it can hold answers that we can't find in DNA. There are two main situations when RNA testing can be helpful:

- A DNA test has found a change in someone's DNA (a variant) that might affect splicing and explain their condition, but we aren't sure. This is

Figure 2:
Pre-mRNA has exons and introns.



called a variant of uncertain significance (VUS), a change that isn't yet confirmed to be damaging or benign.

- A DNA test has not found any variants that explain someone's condition, but we still think they likely have a genetic condition. This is called an uninformative or negative result. A variant leading to their condition might be found in their RNA.

POSSIBLE RESULTS OF AN RNA TEST

- RNA testing finds new information, for example finds a variant or helps re-classify a VUS.

OR

- RNA testing does not result in more clarity or answers. What this means and what might be the next steps can be discussed with a genetic counsellor or clinical geneticist. It could be that no further testing is available at this stage. However, it might be worth re-investigating in the future as our genetic technology and understanding continue improving.