Conference given by Dr Jamal Ghoumid
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Plateforme des Maladies Rares
96, rue Didot 75014 Paris

Introduction by the association board:

The MED13L Association is very young, since 8 months ago it did not exist yet. That's how it happened: I am Françoise, the mother of 29-year-old Elise and 19-year-old Louis, both diagnosed MED13L in April 2016 at The Pitié-Salpétrière Hospital in Paris by Dr. Delphine Heron and her team. 25 years of medical wandering. I imagine you know what that means since you've all been there. Once diagnosed, I wanted to meet other families, but it was not easy. Facebook was not part of my environment until then, but I decided to create a Facebook page like a bottle at the pier to search for families. I quickly met American families; then Sabrina, French and mom of Noam and then Philippe, dad of Céleste and we decided to create an association which was born in March 2018. At the same time, a US MED13L Foundation has been launched, thanks to a mom who also has two MED13L children. I am the president of the MED13L Association, Sabrina is the vice-president, Philippe the treasurer and Cedric, Noam's dad, the secretary. We are now an active small team and are impressed and happy to welcome you today.

We are honored and pleased to welcome Dr. Ghoumid today. He comes from the Regional Hospital Center of Lille, France. He knows very well our MED13L issues and he also knows some families here. Let's him speak now. He will talk about his work and studies and then we will do a questions/answers session. The video is live on FB as we want to share information and allow families and anyone interested to watch and listen to the conference.

(Noam, our new speaker wants to speak)

Speech of Dr Ghoumid:

Hello, I am impressed by the audience. I am Jamal Ghoumid. I am a clinical geneticist at the Lille Hospital Center. I was interested in the syndrome because I had patients who had mutations of the MED13L gene. We wondered about this pathology and we asked other colleagues in France and elsewhere if they had other patients with MED13L mutations. When I received families, I was not able to answer many questions given the bibliography. Rare diseases are complicated. You know it better than others.

Let's make a few reminders about what MED13L is and what has been identified with colleagues. I'm going to talk to you about the research techniques started a year and a half ago, and I'm going to talk about the research themes that we are launching with other colleagues. We do not really have any results yet, but these are the targets that interest us and that I want to share with you today.

Genetics is complicated, we can increase the level of complexity to infinity or almost. There are things that go far beyond us, and I wanted to make a simple presentation. Do not hesitate to ask anything to make it clear.

We all consist of cells, they are small bricks that assemble us. In these cells are nuclei that contain DNA, molecules that encode our physical characteristics.

(Noam wants to take the microphone to give us a course in genetics)

The DNA is in the form of chromosomes, these little sticks that work in pairs. each pair carries a chromosome transmitted by the mother and a chromosome transmitted by the father. The DNA is in the form of a helical double strand. By scrolling it, we come to a level where we realize that the DNA is formed in pairs of 4 letters ATCG.

The assembly of all these letters ATCG forms a structure called the gene which is the brick of the genetic information. Each gene controls a characteristic.

When you saw the geneticist, who gave you the diagnosis, he told you about mutation or deletion.

Just a substitution, for example the letter T becomes a letter G, and that is enough to make the gene inactive or give it an unusual function.

The mutation is responsible for the difficulties encountered by the patients. This is for most patients but for other patients, the gene is missing.

A missing gene is a deleted gene with a missing portion: there is a deletion at the time of synthesis

A gene is responsible for encoding a character but more precisely it allows to code a protein. The real things that work in a cell are not the gene but the protein. Genes are not effective in themselves. This is the source code decoded by the cell and it will allow the production of the protein. Proteins are the important stuff, not the gene itself. The gene produces the protein that will be activated to perform the task for which it is encoded. MED13L has a complex function and we are far from knowing everything.

A deletion or a mutation has an impact on the coding, the cell does not know how to decrypt the code and one can describe two types of variation:

For a truncating mutation: the cell does not know how to make the protein, so the MED13L protein is not produced.

For a missense mutation: the cell makes the MED13L protein, but it works abnormally which implies a consequence of specificities leading to the syndrome.

For a deletion: the protein is not produced

Mutations or deletions have pathological consequences related to the absence or abnormality of the protein. Then a cascade of things that we do not really know yet that come to explain the difficulties encountered in patients.

In 2003, a team of cardiologists showed that this gene is responsible for pathologies. In fact, one patient had complex heart disease and developmental difficulties. When the karyotype was done, they saw in the region of the long arm of chromosome 12, a breakpoint. The gene was broken. They concluded that this was the cause. Gradually, other teams began to study a number of genes either by exome or by sequencing gene panel. They found other MED13L patients but without heart disease. We realized that MED13L is not therefore responsible for cardiac malformation, as we thought at the beginning, but rather for delay of speech, walking etc. Two years ago there were about twenty cases with truncating mutations. Collaboration was sought from other colleagues, and 36 new patients with truncating and missense mutations were found. Missense mutations occur in one third of cases but not anywhere, and two thirds are truncating mutations. 2 missense mutations showed more severe pathologies than in other patients and gave different signs of classical mutations, such as loss of walking, epilepsy. But we do not understand these things well and we will move forward with the families. There was a MED13L publication at the human medical Genetics Congress last February in Nantes presented by Dr. Thomas Smol.

GENida is a platform developed by Professor Mandel of the IGBMC Strasbourg, in which families can put information from everyday life. This platform with accurate questionnaires allows to identify more specific details that are not found during a medical consultation. We, the doctors do not know how the child is from day-to-day because do just see the patient half an hour in consultation. Parents are more expert than doctors. The head of GENida sent us the first results MED13L. We realize that the number of responses has increased after January 2018 thanks to the Medical Genetics Congress of February 2018 and thanks to the association. Twenty families participated, which is a lot for a rare pathology. Origin: 50% France, 25% France and 25% Europe. France is promoter for MED13L. Families have pointed out peculiarities. One of the first signs that emerges is the intellectual difficulty, but also vision problems such as strabismus, hyperopia, no sign of retinopathy. Behavioral disorders, sometimes signs of aggressiveness or self-aggressiveness, may be noted, while other families describe jovial and very mild children. Food difficulties and hearing problems that were not reported in the literature are also detected. Heart problems are not in the foreground. Epilepsy either. There are problems with foot malformation at birth and foot Varus, which was not previously described as important. There are also signs of autism and autism spectrum disorders, but this is not the major proportion. This is not associated with any type of mutation. The two signs may be related in varying proportions to each other on other syndromes.

Q: We always hear that autism is a symptom of a set of genetic abnormalities.

A: Yes that’s exactly the point. We are made up of 20,000 genes and the genes interact with each other. If we have a mutation MED13L, it causes difficulties, but the effect of other genes can also affect or not the variability of signs and today we cannot understand, it's too complex. Some families pointed out behavioral and neuro-development problems, 3 families pointed to restricted interests, obsessions or things like that. We do not know the exact proportion. The difficulties that one finds

are attacks of the neuro development whereas other malformities are not in the foreground (except deformation of the feet)

It was therefore the clinical part. We will now talk about the basic biological part.

At the biological level, we will try to understand why the MED13L mutations lead to the difficulties that we see in patients.

(Noam wants to take the microphone for a lesson in genetics)

MED13L produces a protein, which interacts with thirty other proteins to form the « MEDIATOR COMPLEX», a very large protein complex that plays a major role in controlling gene expression. In fact, we are made up of 20,000 genes that cannot be expressed anytime and anywhere. The must have a direction, a guidance from the cell to tell a gene when it has to express itself or not to express itself. This is very important especially at the embryonic level and there are very special sequences of gene expression for development.

MEDIATOR COMPLEX is there to discipline the expression of genes and ensure that each gene is expressed when it is needed. The revelation of gene expression is a very broad and complex research topic. For the gene to be expressed, it is necessary that the cell gives it the authorization to express itself and to give it the authorization to express itself, it is necessary that several protein complexes come to associate with two regions: the regulating region and the promoter region. At first, you have the complex 1 which is fixed on the regulating region and the complex 2 which is fixed on the promoter. As long as the two regions are not linked, the gene will not be expressed. The mediator must come to mediate between the regulating region and the promoter region so that the gene is allowed to express itself.

On the next slide, you see that the mediator comes between the two complexes to allow the expression of the gene. When one has a MED13L mutation, one thinks but without being able to explain it, that the MED13L mutations come to interfere in all this cascade, and these interactions between the different regions. It is thought that the mutation hampers all these interactions and that some genes will not express themselves or speak at the wrong time or in the wrong place. We try to move forward in this very great complexity with several mechanisms coming to regulate MED13L. It is necessary to dissect all this, we are not helped by the bibliography. So far, we do not have lot of data. Many things are coming out of the mediator complex but there is still a lot of shade

At first, we want to know why these missense mutations that make this abnormal protein will come to cause the difficulties we see in children. The second thing is to discover the essential genes regulated by MED13L. We would also like to know if the same genes are deregulated with a truncating mutation and with a missense mutation to better understand why there are differences between patients.

Do you have any questions? especially on the exomes, the panels

When we meet families in consultation, there are syndromes we know and for which we can make the diagnosis without genetic analysis, but for MED13L there are not enough distinctive signs that

make it possible. Now, we have fairly broad molecular biology tools that deal with many genes at the same time which allow us to identify specific mutation.

For our research, we use cell models, we make express the MED13L genes with mutations and we try to understand what is happening.

It is necessary to use skin biopsies to study fibroblasts because it allows the diagnosis; and we would like to start from these skin biopsies for our next research protocols.

Q: How do you work? do you have a team around you? and how does the research fit in time? six months, one year, two years?

A: It fits in the long time. In Lille, we have a young team. Last year, I had a Master student in biology who worked on missense mutations and set up techniques that we will use to study other mutations. We put in place the tools that will allow us to move forward.

It was complicated, but she progressed well. Now, we begin to get a better idea of the performing tools to answer our questions. We welcome in our team other students in biology. Dr. Thomas Smol works on the different axes/targets of MED13L. My job is rather to identify the genes regulated by MED13L

I want to continue working on ME13L. I'm leaving for a year in the US in a scientific laboratory working on gene processing. I will use their laboratory, their technology and move with them on MED13L.

We want to tackle MED13L in our research team. We are becoming experts and other medical teams do not hesitate to contact us to improve or refine a diagnosis because we can identify variations.

Q: Is there a professional cohesion? Yes, there is a great cohesion, we know our geneticists very well, we are not a lot and colleagues contact us easily on MED13L cases. We have regular meetings with sectors as "DEFISCIENCES" and "anDDI-rare" *(National rare diseases institutions)*

Q: What worries me a lot is the damage of neurologic speech center, because children are impacted at this level.

A: There is variable damages, but what stands out is that the oral expressive language is complicated. We do not know why.

It seems that the understanding is good though. Some families use tools such as pictograms, Makaton or sign language. These are tools that should not be neglected because it helps and accompanies families.

Q: Finally, is this speech damage a neurological damage or not?

A: I admit that I do not have the answer. Research protocols for speech centers should be created for that. We do not know what is happening in the brain. MRI does not show any malformation. The communication between neurons might impact the expressive language.

END OF TRANSLATION