This a Speech-to-Text service for deaf and hard of hearing people.

Ladies and gentleman, my name is Sam, I'm Director of Museums and archives here, it gives me enormous pleasure to welcome you here today to the event, "A tall story", which starts with a wonderful public talk by Professor Korbonits and Mr Holland and goes into, for those involved in the FIPA patients' group, will continue with the event here and other members of the audience you are very welcome to stroll upstairs to the library where our archive and library colleagues have put out a related display from our rich, historical archives.

Our aim here is to use the historic human remains we have in the museum to improve quality of life for living communities today, there is no better illustration of that aim than the work that Martin will speak about today.

A couple of points of housekeeping: if there is a fire alarm the exits are here and here. You turn either right or left. There will be a comfort break at about 2, when we will go our separate ways and if before that conveniences are across the corridor.

You will note there are cameras here, Ronan is filming on behalf of the FIPA patient group that can't be here today and also for the medical, British medical journal they will only be filming the presentations not the audience, we hope to have about ten minutes for questions and answers at the end, I'll come back up to Chair that.

Without further ado ladies and Jen welcome I hand you over to Professor Korbonits.

MARTA: Thank you very much for coming today to listen to our story about the Irish giant.

So I'm an endocrinologist, it's a science of the hormones, we're dealing with the thyroid gland in the neck, or the pituitary gland, or the testis or the ovaries, or the pituitary gland. Where is the pituitary gland? It's right in the middle of the head and you can see this drawing here showing the

pituitary gland it's a rather small organ behind our eyes and behind the sinus, the nasal sinus here, it's shown on this MRI picture, in the area here, this white bright gland is the pituitary gland.

So where is the pituitary gland sitting? This skull from above and this area here in the bone is like a little bony pocket, this is called the pituitary fossa. This is where the pituitary gland sits. You see this little sticking out bit from the pituitary gland, this is the one which connects it with the rest of the brain in an organ called the hypothalamus sitting above the pituitary gland, it regulates the function of the pituitary gland and the information is coming from the brain.

If we look at the pituitary gland location on this picture, this is the pituitary gland, this is the stalk connects it to the rest of the brain sitting above here, the yellow structure this optic nerves crossing, if something goes wrong with the pituitary gland, the optic nerve can easily be damaged due to this.

You also see these red circles here, these are the carotid artery

, the artery that supplies the brain with blood, important organs, this grey area is the lining of the brain called the Ura, we have venous blood ordinarily, these there are structures, the nerves that supply the eyes and part of the face, again very important areas, if something wrong with the pituitary gland, again these could be damaged.

How do we see that in the patients? This is an MRI scan from the patients, this area you can see here, again it's the pituitary gland, this little bit in the middle is the pituitary stalk and right above it this optic crossing, what we call the Latin {*Latin*}, normally it's quite far-away the pituitary gland and this is how it should be.

So what is the pituitary gland doing? The pituitary gland has two parts, the one towards the face is called the front part and there is the back part. The front part is the one which is a glandular tissue and the back part is more like {*inaudible*} tissue. The front part makes 6 different hormones, one

is growth hormone, we will talk more about growth hormone, another one regulates the thyroid gland two hormones regulate the function of the testis or the ovaries,, there is yet another one to control milk production in women that are breast feeding, also important for immune function. Then the last one is controlling the adrenal gland, part of the kidneys.

We can see if something goes wrong with the pituitary gland, clearly it's not just one but several, or even all the hormones could be affected by the disease.

So I said we would talk a lot more today about growth hormone. So what happens if we do not have enough growth hormone, this needs to be quite seriously not enough growth hormone. If you don't have enough growth hormone you might develop short stature, this is of course when it happens in childhood. I'll show you a picture here of two gentleman who suffer from genetic condition, this gentleman next to them is a healthy adult, a bit shorter than me, you can see these 24-year old gentleman are about half of his size.

So how about when we have too much growth hormone. In that case, if it occurs in childhood we will see a patient with gigantism, if it occurs in adulthood we will see acromegaly, it's more or less the same disease caused by too much growth hormone, but if it occurs in childhood there is a slightly different consequences.

So the word 'Acromegaly', comes from two, two words in Greek, ‘acro’ means the end of the body, the hands and feet, ‘megaly’ means enlargement, this is a really good name given that end of the 19th century.

What is acromegaly, it's usually a pituitary tumour. Now I show you yet another MRI , cutting the head, this nose, this is where the pituitary gland is, it's quite large you can see it on the schematic drawing, there is the pituitary gland, I made it very obvious with some colouring, so this is now a lot bigger than you see it on the first slide, it should be just a small gland.

So what are the signs of acromegaly? One of the most typical signs that often leads to the diagnosis is changes in the hands. This is a hadn't of a patient, you see that it's quite a wide hand, because the disease develops usually throughout several years, often 5 to 10 years by the time the patients are diagnosed there are lots of consequences. For example the tissue in the wrist can be also growing in an abnormal way that it gives a patient pins and needles. If it goes on for a long time it can even damage the nerves in the hand and give them a disease we call carpal tunnel syndrome which some patients suffer from. You see the dimple in the muscle here in this hand, this is actually due to this.

How we can measure if somebody's hand is bigger we use these rings, you see between this hand and acromegaly hand there are 16 ring sizes, if we treat the patient they improve and the ring sizes can move down.

Just to show that it's not just male, females can have disease as well, this is a female hand next to a patient with acromegaly.

Another important sign we can see is that the jaw typically grow really enlarged, especially this part of the lower jaw, so it makes the lower jaw a lot longer. If it's more longer one of the effects would be that the teeth come more forward. You see that the lower teeth are actually biting the front of the upper teeth, a front byte. Some people have this naturally without disease, it's part of an inherited condition to have this structure of the mouth, if it occurs later in life there is usually a pathological process going on.

Very often the diagnosis maybe just based on the patient's face. I show you here couple of patients with acromegaly, they have characteristic changes to the face, widening of the nose, flashy features and also quite course facial features. In the second row you see patients with probably a bit more serious disease a lot more typical facial features for acromegaly. Then I show you a couple of patients who have really severe deformities of their faces due to the disease.

Again if we treat the patients many of these changes regress and improve, not necessarily go back to where exactly they were, but we shouldn't forget that the disease develops through several years, so the processes are slow and sometimes difficult to note them.

So acromegaly is quite a rare disease. We see about one patient in every 10,000 inhabitants. So if we calculated for greater London with about 7.7m inhabitants we see that there should be about 770 patients if we would count all of them in all the hospitals.

So I told you that if the disease starts in childhood then it will have a different, slightly different effect, it could make the patient go really, really tall. This patient is one of the tallest patients in England with the disease. So gigantism develops when the growth hormone secretion in humans starts in childhood before the bones stop growing. Normally the bones stop growing due to puberty in response to sex hormones. So it's very important that we have normal regulation of the sex hormones to have the bones actually stop growing.

Patients with a large pituitary tumour may have low levels of the two hormones which regulate puberty and regulate the sex hormones, the two I showed you, therefore, patients with gigantism have really two reasons why they are abnormally tall, one reason is that they have too much growth hormone coming out of the pituitary tumour which make too much growth hormone, but there is another reason as well that their bones do not stop growing. In childhood, before puberty everybody still growing, if the patient has higher growth hormone they will grow quicker. In all the subjects for example in teenagers when they should slow down their growing, usually boys stop growing by the age of 18, girls stop growing even before that, patients with gigantism usually have a delayed development of their puberty and therefore a lengthening time while the extra amount of growth hormone can have its effect on the lengthening of their bones.

So, have you ever heard of a giant? Well, we all heard of Goliath and we know beautiful paintings of him and David. With this picture I would

just like to suggest a hypothesis which many other doctors suggested before, that maybe Goliath wasn't able to see properly David approaching him, if he indeed had a pituitary tumour and that was pressing on the optic crossing as I showed you on the earlier picture, that it would have caused the giant to be able to see right where he's seeing, but he would be able to see the periphery of his vision, so wouldn't have seen the danger, but this is pure hypothesis.

So another giant, you probably all know 007 films and there was an actor in these films who is a patient who suffers from gigantism, he's very open about it. If you look it up on the Internet it's clear. Again if you look at his features it's very clear that he suffers from this disease.

Giants are sometimes just showed as villains, but of course we know from our patients that giants have certain inoculants, this is a French patient, Maurice Tillet, he was a rest already, people say that the cartoon character Shrek was probably based on him.

So we are coming to this picture, this picture was taken that beginning of a 20th century of a French family, 7 siblings here, five of them normal height and two of them suffering from gigantism. I think this is one of the first photographs showing a family with gigantism and that is actually quite important for our topic today.

A gene has been identified to cause familial acromegaly and especially familial childhood on site acromegaly, it's the AIP gene, it was found in 2006 by some Finnish scientists. Previously we didn't really think of acromegaly as a congenital disease, while we realise that the fast number of patients with acromegaly don't have a genetic disease some of them, especially the ones that start in childhood have a higher chance to actually carry the gene causing the disease.

So a new disease has been established in the last few years called familial isolated pituitary adenoma. FIPA. The word 'Isolated' here is important, there are two other diseases where you can see this, in this

disease the only thing we see is the pituitary adenoma, so to identify they put the word isolated in.

If you look at all the families you have 20% of the new patients with this gene, the AIP gene, while the majority of the patients we do not know what is the cause of it, we think there is a gene, we are desperately looking to find this gene or even genes, there may be more than one. At this point the only gene causing FIPA is the AIP gene.

We need to under stand what Deoxyribonucleric Acid is, this in the nucleus of the cell is where DNA is present. If we want to look at DNA we first look at chrome zones, the human chromosome, we have two pairs, one from your father and one from your mother. If we concentrate on this chromosome, number 11, this is the one that has an area in this 11th chromosome enlarged here showing you lots of markers. Between these two markers the location of the gene has been suggested, a couple of years ago, in 2006 the Finnish scientist identified exactly at the same position the AIP gene, so now we know that this gene is actually, is here on the 11th chromosome.

So chromosome is really just a very tightly packed long chain of DNA. If you look at this drawing you will see that the DNA is really like a twisted ladder of two sugar kind of sides, the purple colour. Between the two sugar chains we see these cross bars and the cross bars are the bases. We have four bases, guanine, cytosine, thymine, the sites of these bases give you the genetic curve.

If you look at this picture you see again the double helix of the bases. You we'll see the three bases, for example here CGA, can identify an amino acid. Amino acids are the building blocks of all the proteins. So three base pair identifies one amino acid, this identifies argenine, this is read by the cell and then creates the protein.

What happens if there is a mistake in the DNA? For example, this, "C", here, at the beginning of this trip let or co don, it can change to a, "T', if it changes to a t, it changes, the code for an amino acid, can code to another

message to the machinery, the TGA is the stop message, it tells the cell that the protein should stop here, that's the end of the protein.

This mutation will cause a protein which actually is shorter than it really should be. This is exactly what we see with one of the mutations that we see in the AIP protein, this green molecule is a model of the AIP protein, you see kind of straight in the bits and you see this beautiful helix. This change what I would like to talk about is located close to the end of the molecule here and actually this, it should be an argenine here, it changes to a stop protein, this very end of the molecule is missing, we know that the end of the molecule is quite important for the function of the molecule. So, a patient who has this protein but missing the end is, probably will have a damage to the function of the molecule.

I show you here again the AIP gene with the X on, they code for the protein, this is the process, when at the 304 position change's to a stop codon, this is not the only mutation we identified, we identified in our patients a lot more different mutations and we have patients in the audience with some of these mutations, for example we probably have a patient with this one and another patient with this change, different changes in the AIP gene in different families.

Today we will concentrate - so I'll just show you the map, in our cohort there are quite a lot of patients from various parts of the world, not just England, because it's a rare disease only a few labs work with it.

Coming back to this mutation the three or four stop mutation. In 2008 a patient came to our clinic at the age of 20 and he said that he was - so by the time he actually came to our clinic it was already diagnosed as acromegaly and he was operated, he said he has a first Cousin, his father's brother's son, his first Cousin who at the age of 13 was diagnosed with acromegaly and a pituitary tumour and was actually very, very tall. So we have a first Cousin with young onset acromegaly is very typical of a familial disease, so we asked the lab to sequence the DNA of these patients. We found there is a mutation in their DNA and this mutation is the argenine 304

stop mutation. I realised that this family was coming from Northern Ireland. I knew that there was a patient from Northern Ireland, suffer ring from young onset acromegaly, it was a giant in the 18th century whose skeleton is in the building where we are today.

I thought that he was also coming from Ireland and could there be a link between this very, very rare disease, where coming from, the same part of the world.

Harvey Cushing, an American neurosurgeon, he was interested in pituitary disease, operating on patients with pituitary disease, at the beginning of the 20th century, in 1909 he came to London to see the skeleton of the giant, already in this museum for 100 years by then. It was exactly at the time when doctors started to realise that acromegaly and giantism was caused by a pituitary tumour when he was alive this was not known. He asked the museum to open up the skull, this cut in the skull we can see here was done by Harvey Cushing about 110 years after the patient died.

So he saw inside the skull what we will see in a minute. We took the skull to the natural history museum where there is machine called computer topograph, it can make very detailed images. I may need to press the mouse for this to start to work, but we made these images from the skull using this machine. You see the characteristic features of the very thick bones, the very long jaw bone here and the quite prominent eyebrows and the huge frontal sinus here, all this area I'm showing you here is the frontal sinus of the patient, very typical with acromegaly, here you can see the bony fossa where the pituitary tumour was sitting and it's quite large. So this is what Harvey Cushing was seeing when he opened up the skull and could actually identify that the patient had gigantism due to a large pituitary tumour.

So another feature I would like to talk about is the hand. You can see how the hand is drawn here with the wrist here and two bones of the lower arm. This is an x-ray of a real adult patient's hand here, you can see again this area. I show you here now an x-ray of a child's wrist. Of course it's a bit smaller, it's a child's one but there is a another very important difference

between the two. You can see that the bone is a nice piece of bone here, but what you see here, the same area, that this top bit is actually separate from the other bit. That is because this child is still growing and this is the area where the bone is actually lengthening. This is a normal x-ray of a child, nothing wrong with this child, the child is still growing, you can see the end of the bones are separate from the main part of the bone, this is where the bone is actually growing, every child's wrist looks like this while they are growing. The reason why I explain this, this is the x-ray of the hand of Charles Byrne, the skeleton we see in the museum, he died at the age of 22 years, of course this radio graph was made about 200 years after he died, but what we can see here is that they have to use extra pieces of metal, little nails to fix this part of the bone, the reason is not easy to see, this nails are actually shadowing the view, you can see there is a distance between this part of the bone and this part of the bone, the fact that they needed to use extra nails to fix it together, suggests that this part of the bone and this part of the bone was probably separate, that's because at the age of 22 he was still growing. That is because he probably had a delayed puberty, a normal healthy man would stop growing around the age of 18, so somebody still growing at the age of 22, something is abnormal there. Clearly that is also an explanation why he was so tall, he had lots of growth hormone, he was growing and growing, his bones did not fuse at the normal time.

So I wrote to a letter to the museum thinking that this might be a connection between that family I showed you and this patient from Northern Ireland a lot of years ago. Of course museums take their time, so while they were thinking {*laughter*}, we found a few more families also from Northern Ireland and also exactly the same mutation, argenine304 changing to a stop codon this family here, this is actually Mr Holland's family, this is here Mr Holland, there is another family here and a fourth family here and some of the members of this family sitting in the audience. From this fourth family we can see a patient diagnosed by my professor, Professor Besser also in the audience. You can see that here is the pituitary fossa, at the time there was no MRI when this patient was diagnosed, they only did x-ray of the skull, you can see enlarged fossa and an x-ray of the hand showing he had acromegaly.

He also said that his father and brother, there is a picture of his father, brother, the patient's uncle at the age of 18, standing next to a lady, this is an adult lady, you see the huge difference between the size of gentleman and the young woman. This is the same gentleman a number of years later, it's probably quite easy to make a diagnosis, that this patient is acromegaly, he had an uncle who had gigantism.

They also had the same mutation what we, what we found in the other families as well.

So we thought could these four Irish families be related to each other? If we look at the mutation here on chromosome 11, what we did with my colleagues in Exeter is to look at a couple of markers of the DNA around the gene and what we found that these four families, quite a large chunk of chromosome 11 is exactly the same in the four families, they have the same mutation in the middle and quite a large piece of the DNA is exactly the same. The only possibility for this to happen if these families had a common ancestor, somewhere in the past they had a common ancestor and they are related to each other. They don't know each other but we know from this genetic study that they actually related to each other.

At the same time, file we were waiting for the museum to reply, I also found this picture, this picture is in the national portrait gallery, it was drawn by a gentleman called John Kay who did a lot of painting of people in the society, more or less a cartoonist at the time, this one is Charles Byrne in the middle and according to the, to the museum the two gentleman standing next to him are some distant cousins. Of course we can see that these distant cousins are twin brothers and they also have gigantism. So here we have three family members who have all three of them a very, very rare disease. So this suggests that there must be a congenital condition behind this.

Then there was a third clue to the story and this was when I, was with my friend Ronan who is filming here today, started to learn about northern Irish geography. I learned that one of our families lives in this village

and another family lives in this village and a third family is originally from this village here. Then I realised that the birth place of Charles Byrne was here, then the twin brothers on the previous etching was actually here. So we have these five families with the same very rare disease coming from quite a small area, somewhere in Northern Ireland.

So I came to the museum and a colleague, a Professor mark Thomas advised us if we want DNA from the skeleton we should take a tooth sample, so we removed a tooth here and another one from the other side of the lower jaw, these are the teeth that were removed. These are very precious samples so I wanted the DNA to be extracted in a specialist laboratory, so I contacted a laboratory specialising in ancient DNA in Germany. They extracted the DNA and were able to do, to look at the sequence of the AIP gene. What we found was that the DNA from the Irish giant contained exactly the same mutation as the other four families that I showed you. Further on we looked at the, looked at the micro satellite, the markers round the gene and we found that the giant also shared the same sort of region as the four families. Suggesting it's not just the four of them are related to each other but also the Irish giant is related to them.

We started with the hypothesis that challenges Byrne as FIPA, due to a mutation in the AIP gene manifesting as gigantism due to a growth hormone secreting adenoma.

We think he did, an enlarged pituitary fossa, tall structure, thickening of the bones, enlarged jaw bone, enlarged frontal sinus, all typical in adenoma. Delayed puberty allowing continuous growth, his growth plates were not fused at the age of 22, his bone age was actually delayed by five years or so. We identified a mutation in his DNA from actually two different samples and he had a family history of gigantism, we have the etching with the twins. We also have current families from the same geographical area and we also showed that there are matching markers round the gene that match these other patients with the same disease.

So I came to the museum with one of the patients, Holland, who was treated by Professor Besser in the 70's. I would like to ask him to give you his view on this disease. Brendan.

BRENDAN: Thank you Marta. {Irish Language} My name is Brendan Holland, that is the first language of Charles Byrne and that was Irish.

When I was first diagnosed with gigantism by Professor Mike Besser, he assured me that my tumour was not life threatening and that I would have a life worth living. I realised that that life I could fulfil my dreams and ambitions and aspirations. I also realised immediately that it was up to me as to how I dealt with this hitherto unexplained illness.

I address these remarks to my fellow patients and, in some cases, to my distant cousins. When diagnosed all of us who suffer the effects of this condition have a choice to make, a choice to so eloquently expressed in Shawshank Redemption, by one life prisoner to another when having a discussion about hope. One guy said, "Well, hope is a good thing. You have got to get busy living or get busy dying." So we have all got to get busy living.

We have a choice to make to deal with the illness in our body and deal with it also in our minds. I know that patients are different human beings but, mostly, I believe we essentially face the same set of problems, patients with this condition.

As a patient I'm only too aware of the pain in the mind and that the effects of the condition can be immensely personal. Personal to us and sometimes difficult to talk about. I also agree with the old maxim, "A problem shared is a problem halved." Do talk about it to your partner or your family, immediate family.

Until today those of us diagnosed with this particular form of the disease have not had a forum to discuss the condition and it's effects with other patients. I give thanks to the initiative of my very good friend Professor

Marta, we now have that forum I would advise patients here, however hard you have found to share your experiences, talking about it is great therapy.

As an impressionable and immature young man, I'm taking that from very good authority, none other than the Professor, I did not find it easy at first to come to terms with my diagnosis, but I was pleased with a wonderful family support mechanism and we all need that.

I also want to emphasise that the wonderful staff and team of medics assembled by Professor Mike Besser in St Bartholomew's metabolic unit in 1972 and under his guidance were so sensitive to the psychological needs of patients that such an intensely, immensely personal range of endocrine problem, which Marta just explained. Taking the time to sit down and explain what the condition is all about, to explain why we have the symptoms we experience and their associated problems and how they were going to treat the condition, gave me a confidence in them and in myself and for that I will always be grateful.

I also speak for a great number of patients here today who feel exactly the same way. I would also like to take this opportunity to pay tribute to the work that Professor Mike Besser and his team over the last 40 years have done in this field. It is an outstanding display of commitment to his patients and an outstanding display of commitment to his profession and an outstanding display of hunger to find out what this condition was all about.

As someone who was more fortunate than Charles Byrne, I'm alive here today 40 years later to tell you about my experience. So I give you a very, very sincere thank you to the Bartholomew's team.

Our understanding of this genetic condition has only recently be heightened due to the groundbreaking research by Professor Kobonits and her team, this work has helped us all to see we have been numbered among our ancestors as suffers and carriers of the rogue gene, it's not our fault, nothing to do with life style, diet, environmental issues *et cetera*, this is an

inherited condition and it's part of who we are we must all learn to deal with that unassailable fact and, as I said earlier, move on.

Personally I find the revelation that the condition is genetic a source of great comfort, in a strange way. I had always been intrigued as to why I had been selected, the only one of a family of eight siblings, so why not my brothers or sisters, my friends of my acquaintances.

This condition is so rare, but also so obvious, fellow patients if you excuse the pun, so 'In your face', one cannot be intrigued because it's so much part of you and your identity. I grew up in a rural setting where society is much more parochial than say a large conurbation like London. Often people think they know me. They say they know me, but more often they think they know me but certainly most know of me because of my stature.

It does take a little while to accept that fact, but as I said, move on, because of the results of the Professor's work, her work, only recent in my lifetime, the revelation has hitherto answered the unanswered question: why me?

Please do not beat yourself up with feelings of low self-worth or low self-esteem, essentially you are still the wonderfully unique person you are and you have always been.

We may look and appear a little different but you are still you.
I have, for a long time, believed that the person and the personality are more important than the image and I do realise that we live in a very image conscious world and that we are more than we sometimes care to admit, pressurised by that otherwise advertising would not be the huge industry that it is.

From personal experience the majority of the most interesting and sociable human beings that I have met, do not give a bit for their image, I became friends with a little polish man about 15 years ago, when I was in for a check up in St Bartholomew's on a general ward. I spent a week in his

company, which I found to be enriching and a privilege he had survived a German execution squad in his native polish village at the age of 16, and with his 16-year old friend they escaped, travelling on foot through occupied Europe to neutral Switzerland and eventually to this country his name was Viktor Tiede, a 72-year old man in failing health. He had life had taught him to see the inner person in everyone he met, regardless of age, shape, social status or wealth. The person within defines everyone, not their latest fashion label, not their house, nor the car. Viktor taught me to accept the real person within us, including are imperfections. That's what makes us different and I would urge you to accept that as a first step in accepting and understanding who you really are, that you be happy in your own skin. If other people have a problem with that, then they deserve our sympathy and our understanding for their ignorance.

I would also like to conclude just on something that the Professor touched on in her presentation. Those of you who do not know the Professor, I can assure you she is the most engaging, interesting, stimulating person with whom I have ever had any sort of social relationship with. She asked me to look into this area of Northern Ireland which is now become known as a genetic hot spot for this and during my research I called on a good friend, a curator of a local museum, he directed me towards some books. In 1834 - I discovered in one of these books - that the royal engineers of their day had conducted a survey of the very area in which George Byrne had lived, in Northern Ireland. In this description or this survey, it's called an ordinance survey, in this they described having talked to four gentleman that in the late 1700s there was a quarry of white limestone, most unusual in Northern Ireland, pure white chalk limestone, this quarry had been opened I presume, for decorative reasons for decorative stone. As the quarry was being mind the face of it regressed towards a cemetery. Eventually commerce being what it was in those days it overtook human considerations, so they under cut the cemetery and lo and behold out poured bones and skeletons, some of which were of huge stature, so big that one of the skulls - this very much described in detail in the ordinance survey - so big that the local gentleman who was the tallest man in the area picked up one of the skulls and put it on

top of his wig and it fitted him. There were also detailed descriptions of the long bones of the body and this, ladies and gentleman, was in a graveyard within 3 to 4 miles of where Charles Byrne grown out and where the Knipe Twins also grew up, in fact the graveyard is within two minute walking distance of where the Knipe Twins were born. So that little story, I suppose in many ways, encapsulates the genetic aspect of this condition and the age of this condition. This graveyard was one of the first to be recorded as being consecrated by Rome, so we know around 1200 this graveyard was consecrated by Rome as a place where humans could be buried. So we had no access to those bones today of course, although I have had an archaeologist look at it and he thinks he may be able to find them, if he is successful in doing that we will share that information with you at a later date. Thank you for your time.

{*applause*}

I apologise, Marta I think you ought to handle this, just to give you some idea of my own personal history here. This is me aged 12 and a half years on the left with my brother two years older than me, as you can see I've already caught up in height with him, it's taken outside our home in Northern Ireland. One year later we are photographed I think coming from church outside our home and you can see my older brother, Aden, standing on the right hand side of this frame, here today, 6 foot tall, I'm starting to catch up on him, if you look at that closely you can see the beginnings of my condition in my facial features.

Here we are aged 14 years and that's me second from the left in the back row, again with my brother Aden, who is in the audience. At that stage I believe, since he's 6 foot and hasn't changed a bit in 40 odd years - he paid me to say that! {*laughter*} - I suppose I'm there about five foot 8 inches tall.

This is me 6 years later at the time of diagnosis in St Bartholomew's hospital, my photograph taken by Professor Besser's team. This is Professor Besser when he was still, well he still looks a young man,

but he looks even younger there, of course the very famous institution in the middle.

This is me at aged 38 years, so this is 18 years later and these are my hands compared to someone else, a normal person I guess, someone with normal stature. As you can see the difference in the features are quite marked. That's the regression which the Professor talked about earlier.

This is an interesting photograph, because this was taken with my hand inside the outline of an Irish giant whom come of you may have heard of, his name is Patrick cutter, he was of similar stature to Charles Byrne. To put some scale of that, my hand is fitting inside the outline of his hand and each of my digits are a full two inches shorter than his.

Again, that's a normal sized human hand inside Cutter's outline. Okay, thank you.

MARTA: Thank you Brendan. So we went on to think that when this common ancestor of all these patients were living, we call this the founder person, the person who probably first had this mutation. If we think of our four families which we found as thee four blobs here in the purple and this is the current generation, if we go to the previous generation, their parents and then the previous generation, the grandparents and then back one by one with each line being one generation, we can come to the common ancestor somewhere here. So if you draw this line more simplistically, he looks quite simple how to put this. We can put some complicated mathematical complications into this to calculate then, when about how many generations ago this might have happened. This was done by our colleagues in the university college and they came up with this number. So, based on the genetic map of the human genome, called the HapMap, we calculated that this common ancestor lived about 66 generations ago. If we calculate one generation is about 25 years, then we can see that it's about 1500 years ago when this person lived. You see that there are huge ranges here, as usual with statistical calculations you can't give an exact answer, but still this is the mean number that they came up with.

Then I asked them another question, if this mutation occurred that many years ago, how many subjects would live today. Of course there are a lot of factors in here, if indeed this was in Ireland and there was lots of worse, potato famine, lots of things difficult to take into account. They took up with a number of maybe three generations alive today would be 270, but the range again is very large. We already know that we have a lot more patients than 15 and the highest number they suggest is around 1500 subjects living with this particular mutation coming from this particular founder person 66 generations ago.

So, if this is the case there should be a lot more giants in this area. This is indeed the case. This is Cornelius McGrath who lived about fifty years before Charles Byrne and is skeleton is in the Dublin Trinity college, a beautiful painting of him when he was touring in Italy. Unfortunately, also, as all these untreated patients died very young, he was 24 when he died.

This is a patient whose outline of his hands you have seen, Patrick Cutter, a contemporary to Charles Byrne and he was actually taller than Charles Byrne. This is a skull, his skull, the photograph by Professor Jeremy Musgrave also in the audience, he wrote the wonder book, "The Irish giant", he was also from Ireland, although not the northern Irish area.

There was a German Kaiser who was keen to have a tall soldier army, the research found some letters in Belfast library where a soldier who is already in this army suggesting to his brother that he should join him because it's nice to be in that regiment. This Langen Kerls still exist today and I contacted them and asked the leader today what were the criteria that somebody could be in this area and there are set criteria how tall you need to be and so clearly a lot of patients, a lot of male subjects went into this army, some of them, some of those probably had gigantism, especially the one maybe from Northern Ireland.

This is a giant from the 19th century, called Patrick Murphy, that's another one from the beginning of the 20th century, Hugh Murphy, then the

famous Irish King, who was said to be a giant, he lived around 1,000, so in the time range to be related.

So we went on to look for further families with this particular mutations, we found quite a few families with this, some live in the UK, some is close to Northern Ireland but living in southern Ireland, we found some more families in Northern Ireland. For example this gentleman who lives not too far from Brendon, although they didn't know each other they were both diagnosed in their late teenage years and suffered from the same condition, just to compare their height with a healthy person here.

So why is this research important? Just a couple of examples why is that. So I would like to talk about this little girl, who at the age of 6 was taller than anybody else in her class and had some headaches, suddenly in 2008 she had a very severe sudden onset of headache, felt sick and was vomiting, it was noted in the hospital she could not open the right eye, remember in the first slides I pointed out the yellow bits, actually the nerves that move the eye. Her MRI showed this picture here, you see this is a human tumour, a 6-year old child and this tumour takes almost a third of the width of her head, it's clearly pushing on those nerves and that's why she can't open the eye on that side.

So she suffered of what we call pituitary apoplexy, she was operated, she came out of this situation quite well and she's obviously treated now.

But what is said about her, this is her here with tall stature and gigantism at such a young age. Her mother was operated for a pituitary adenoma when she was 16. Her grandfather's brother was also diagnosed with a pituitary adenoma. Her grandfather's other brother was actually a giant, this giant also had a daughter who was diagnosed at acromegaly in the late 20's. Here we have a patient at the age of 6 who actually had four living relatives with pituitary adenoma, with the disease. All these patients were diagnosed in the past well before we realised the AIP gene is the one causing the disease. Of course we found the AIP gene being mutated in this family.

So coming back to the very first family I showed you with the patient at the age of 20 and the other one at the age of 13 with the disease. This family was now more lucky than the previous one, because we found the mutation, identified the people who carried the gene, as you see there are a lot of people who carry the gene and are not ill, it's quite typical of this condition, not everyone with the keen will not develop the disease, at this point we don't know why some people develop the disease and others don't.

Out off all the patients, all the patients you see in yellow have been screened either by our department here in London or at the Belfast endocrinology department, Professor Atkinson's department, all of them had MRI s and blood test taken and been clear of the disease accept the ones who were actually were found to have the disease, the only reason we found the disease they went to the doctor due to their genetic status, both of these patients have pituitary adenoma, both operated on, they were probably diagnosed earlier than they other was would have been due to the screening, we hope that screening the other families we will avoid the children to avoid growing to be a giant, that's probably the most important outcome of all this research.

So families can be screened for the mutation and the carriers can have clinical follow-up that can lead to early diagnosis of the disease inevitably it will be a better outcome although we won't be able to see that just in a few years.

Because this disease I is so rare and you don't find much about it in the text books, we set up a website to inform patients and the doctors about the disease, if anybody is interested, you can look up the website.

That's leaves me with the last slide, to thank the people who help us to find all this data, Ronan and Brendon of course very important in all this and my colleagues Professor Besser, Professor Grossman and my young colleague, Harvey who was part of this story, very importantly, geneticist, this is the most prominent genetic lab in the country, led by Dr Allard’s very enthusiastic team, Richie is a colleague in the Natural History Museum and

did the beautiful turning skull pictures, Mac Thomas, again here today, who did the genetic calculations.

I would like to thank all the patients and their families who were happy to be talked about and took part in our studies, of course also my colleagues who are referring the patients, colleagues from the museum, Martin was actually one of the dentists who removed the teeth from the skull and also Philip and Debbie for some of the drawings which I showed you today. Thank you very much for your time.

{*applause*}

If we take five or ten minutes for questions, ladies and gentleman, if you raise your hand my colleague Jane will do some running up and down with the microphone, there is a question right at the front here to kick us off. So if you can be patient while we bring you the microphone, that will be very helpful.

FROM THE FLOOR: When I was a schoolboy, in the early 60's, when I was a teenager, young teenager, we had a child in our class, I can remember... {*mic not switched on*} I'll start again. When I was a young teenager the school we had a giant in our class, Keith, and he was bigger than all of us – just, it took ten of us to keep him on the ground, his height at 14 was 6 foot 1, I'm wondering what your height would have been at 14. He went on and took part in the Olympics and got a bronze metal for Judo. That's all I can remember about him afterwards. I don't know where he is, but I remember 6 foot 1 at 14. Does that ring a bell.

BRENDAN: At 14, I was about five foot eight and it certainly didn't take ten men to hold me down! {*Laughter*} I would suggest that perhaps this chap just matured physically quite early and that's all. If he went on to win a bronze metal, I doubt there was anything of a metabolic nature wrong with him, I might be wrong.

MARTA: Just to be tall doesn't mean that you have an illness, there are a lot of healthy tall people, one of the signs of acromegaly they would have muscle

weakness, it's unlikely that very good sportsmen would have acromegaly or the person needs to be examined.

NEW SPEAKER: May I make it clear, here at the college we don't advocate anybody holding anybody else down! {*Laughter*} Another question, yes.

FROM THE FLOOR: Hello, it's really interesting talk today and I've learned a lot, an interesting topic, I do have a question. You're talking about the pituitary gland, have you done any research into this of transplanting the pituitary gland?

MARTA: Oh, well, you couldn't have asked a more timely question than this one, as just last week a new paper came out where Japanese scientists actually created stem, from stem cells they were actually able to create a pituitary gland. This is absolutely stunning achievement because the pituitary gland is so complicated, it has the hormones I told you, I didn't have time to explain that the interaction between the different cells is so important. So I don't know if this ever will be used for clinical purposes, but this was just published last week. This obviously would be important for patients who lack pituitary hormones, so for example they were operated or they have a genetic condition and their own pituitary gland is not working. I don't see it being very useful for patients with acromegaly, but certainly a very important and new achievement in science.

FROM THE FLOOR: Thank you for the excellent - thank you for the excellent presentation, both scientifically and philosophically there. I have a question, could you comment on types of treatment and success rates. Is it limited to surgery and medical treatments, what is the overall success rate and at what age is the patients surviving.

MARTA: This is a very complex question, we can sit here for another two hours just to discuss that. Just in short we give three types of therapy, one would be operation, the other would be medical treatment and the third would be radiotherapy.

So if we come back to the medical treatment, we can give actually three types of therapy. There is a tablet treatment which we sometimes try and if it works it's fine, but most of time we need to go on to the second treatment which is an injection treatment at this point which drugs an logs and there is another hormone that inhibits the growth hormone and inhibits the growth of the tumour, we can actually shrink the size of the tumour, that is useful in a very large number of patients and there is a new drug, available in all the last few years, which is actually an, antagonist of the growth hormone and stops the growth hormone working, it won't have an effect on the tumour itself but it will have an effect on the hormone effect. This is important in those patients where we can't remove the tumour, you show you the anatomy of the situation, the neurosurgeon doesn't have the luxury to remove all the tissue, because of important structures such as the carotid artery, quite often after the operation if the tumour is large we need to go on for other therapies the long-term radio therapy is effective and that's, for example, the therapy which Brendon received at the time when he was diagnosed surgery wasn't so successful as today and also the other drugs, the medical treatment wasn't available at all. So at the time radio therapy was one of the main sources of the treatment.

In terms of success rate, well it's, it's a very complicated question. If we it depends on how big the tumour is and we come back to the importance of this research. If we can pick a tumour when it's only a couple of millimetres, then the success rate of the operation is high. If we pick a tumour which is grown over 1 cm, or much larger, you see in this little girl already her tumour was over 3 cm, it's a rule that the surgeons won't be able to remove all the tissue, there is always tissue left, then we need to think of some other treatment in the future. So the success rate very much depends on what stage you pick the disease. It's so important in these families we pick the disease early. There is an issue that I didn't go into, tumours in families with acromegaly are more rapidly growing than patients with ordinary tumours, it's more difficult to treat them, they also don't {*inaudible*} they have several disadvantages, we should diagnose early so we can interfere.

NEW SPEAKER: Probably our two last questions, gentleman here had a question and then the lady beside him, the mic is just there.

FROM THE FLOOR: Retired clinical chemist and patient, you {*inaudible*}.

MARTA: That's an excellent, very interesting question, if you think of the pituitary gland as it develops in the embryo the cells are evolving in to the cells making 6 different hormones, one of the cell types as it develops, the growth and the cells grow together and at the very end they divide into growth hormones producing cells, you can see these cell types are similar to each other for example during pregnancy when you need Prolactin afterwards, half of the healthy females cell can turn into a Prolactin cell, after pregnancy it turns back to a growth hormone cell, the reason why it's interesting for the family cases, what we see in the families about 80% to 90% of the patients have growth hormone secreting tumours some of them purely growth hormone, others a mixed tumour type, which, the tumour makes both hormones, about 10% of the familial cases in the AIP, I'm talking about the AIP families have pure Prolactin, they don't have high hormone levels related to growth hormone, only high Prolactin, so that is part of the disease and that's one of the reasons it's not appropriate to call the {*inaudible*} the vast majority of them as acromegaly, it's more appropriate to call it familial...

NEW SPEAKER: A final question please.

FROM THE FLOOR: Acromegaly patients, looking at the photograph, it's amazing the whole subject, I'm concerned, should I be, with my Cousin back in Israel, you can hear the foreign accent, I'm aware that my condition started in my early 20's, looking back at history, now he's in his late 30's, in metres 1m 90 something, in the early 90's, very tall, having to bend down all the time. So if my condition started later, maybe he's got it and it's stopped, will it wake up later on if he has it, should - the question is, should I make him concerned and ask him to maybe check up, asked to be checked, blood tests what ever?

.

MARTA: Okay, so that is also a very, very good question. FIPA is rare but it does exist I can't rule it out just based on what you said. If he doesn't have symptoms now and he never had symptoms related to acromegaly, probably he's just a tall gentleman, if you look at the height generally in this family, that would help you decide if he's just normally similarly tall to the rest of the family or he might be a lot taller than everybody else in his family, that's an important point. The other point you alluded to, maybe he was ill before and now he's not ill. We see that rarely that patients suffer, something what that little girl suffered, pituitary apoplexy, then the tumour has an infarct, the tumour days, people have acromegaly in the passed and without medical treatment after an event, what we call pituitary apoplexy, they cure themselves, it's rare and it's been well described and it's possible. All these options can be thought of in this situation, of course I can't give you a proper medical answer.

NEW SPEAKER: Ladies and gentleman, I'm sure there are many, many more questions and this is the symptom of an extremely interesting paper that we are still bursting with questions. I feel we should give you a breather, first thanks to those that have spoken and given their time. We would like to thank the society for endocrinology for the support of this event, there is lots of information about that at the back. I would like to thank my colleagues Jane and Hayley who did the hard work of organising the event and our colleagues at StageText. Now, if you found the information provided by StageText useful, please put the little card on your chair in the green tray, if you didn't find it useful, please put it in the red tray. You will also see our evaluation sheets on the chairs as per usual.

Our next event in this series around disability, it's on the 1st December on disability in the role of the military, military medicine, 1st December at 7 o'clock.

Those of you who are staying for the FIPA patients' event, you know who you are, if you would care to remain in this room those of you who aren't for the FIPA patients we would encourage you to look at the display we laid out in the library and Jen and Hayley who are waving now would be happy to direct you towards that, towards the library.

In the meantime, finely, one more time I would like to thank Marta and Brendon for a fascinating talk. Thank you.

{*applause*}