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The Diagnostic Odyssey for Individuals With Rare Diseases: Achondroplasia and Other Causes of Disproportionate Short Stature

October 27, 2022

Gary A. Bellus, PhD, MD

Hello everybody, and thank you for having me, inviting me to give this lecture. I'm really excited to talk about human skeletal dysplasias. This is a field that I've been interested in since I was a fellow doing my genetics training, and I think it's been a very fascinating and fast-moving field and hopefully, I can kind of give you some idea of what's happened and what's going on now.

So if we're going to talk about, you know, skeletal dysplasias, we have to talk about the skeleton. The skeleton is derived from the Greek word skeletos, meaning dried up, which is what was left of human beings after they died and, you know, one sees the skeletons.

Being that it's near Halloween, I think it's very appropriate. One sees lots of examples, you know, around one's neighborhoods these days.

Anyway, the human skeleton has about 200 bones and it is a component of the musculoskeletal syndrome, so it operates, you know, in concert with cartilage, tendons, ligaments and muscles.

The skeleton has many functions. It's responsible for linear growth, mechanical support, it enables us to move. It's also a reservoir for minerals and where our blood cells are made, and it also serves as a protective system for vital organs.

So where does the skeleton come from? Well, you know, when the skeleton develops a lot prenatally and the components are all derived from mesenchymal precursor cells. And where one gets various condensations of mesenchyme it places where bones will be. Eventually you form a cartilage structure and then through, you know, early development, the cartilage expands, osteoblasts come in, and, you know, bone is formed.

When a child is born, you know, most of the bones are formed but they have quite a bit of growing to go, and this happens at the growth plates of the long bones which are at the ends.

There are sort of two ways that, you know, bones grow and are mineralized. The most common is endochondral ossification; this is what happens in the long bones, and then membranous ossification is a different form of bone formation that occurs in the skull bones and other various bones, you know, in the body.

So just to know a little bit about long bone developmental anatomy because this is, you know, important in the nomenclature of describing skeletal dysplasias. So this is just sort of a prototypical long bone. You have a growth plate here which is called the physis, and then the bone above the growth plate is the epiphysis, and then directly beneath it is the metaphysis, and then the, you know, sort of the middle part of the bone is referred to as the diaphysis. And all of these can be affected in various skeletal dysplasias, so one needs to know that terminology.

Okay, so a little bit about endochondral ossification. So if you were to, you know, look at a magnified view of the growth plate, one would see that, you know, at one end there are these kind of, at the top, this resting zone, where there are, you know, chondrocytes, neocartilage cells that aren't really doing much. As you move down, you know, you start to see that these chondrocytes proliferate, and then they go through a process of differentiation where they actually expand into what we call hypertrophic chondrocytes. Those, you know, die by apoptosis, programmed cell death, and then one has osteoblasts come in to fill in the bone.

I would say that, you know, my other interest is skin, and this is kind of if you flipped over the epidermis it would look like this, where you have the, you know, the resting zone would be the basal layer and then you'd have the, you know, various other layers of skin, ending with the cornice. In skin your cells are shed off, in bone the osteoblasts come in and, you know, lay down the minerals.

So this is tightly regulated, so, you know, there's lots of different things that go on to control this process during development. And, you know, if we think of, you know, bones as being kind of calcium salts that are fixed on a protein matrix, most of the proteins are collagens. We have about 20 different types of collagens in our body. These occur, you know, in different areas, and many of them are associated with skeletal dysplasias.

So, you know, on this calcium salts fixed on a protein matrix, one has lots of sort of remodeling going on, so we have two populations of cells, one called osteoclasts, which break down bone, and another called osteoblasts, which form bone. And there's kind of a dance that goes on between these to sort of regulate bone growth.

So our bones are not static organisms or structures, they're always changing, and osteoclasts and osteoblasts are always working, even when a bone is fully mature.

So I mentioned, too, that there are lots of molecular pathways that go on with this, so what causes bone growth, why do resting cells become proliferative. Why do proliferative cells, you know, undergo differentiation in programmed cell death. You know, how is all this controlled. And a lot of these pathways have been elucidated from studies of the genetics of skeletal dysplasias.

You know, that's the great thing about genetics and positional cloning is you don't have to know the function of a gene, you know, to figure out that it's associated with a disease. You can map it; that's what we did in the old days. And we learned a lot from that process and kind of are filling in the jigsaw puzzle of how this all works in real time.

So skeletal dysplasias, they're defined by just a generalized abnormality in the skeleton. Individually they're pretty rare but collectively they're about 1 in 5,000. So, again, I think most people in their lifetime are going to come across a few people with a skeletal dysplasia. And

they range, quite a big range in phenotype, from just having sort of premature arthritis with average stature, to severe skeletal dysplasias that die in utero or shortly thereafter.

In addition to the skeleton, the orthopedic problems that go along with these, there's a host of other medical conditions that can occur in various skeletal dysplasias that you have to take account of. And most of these, as I mentioned to you, you know, have a genetic etiology. So they're either passed on in families or they occur sporadically.

So when you think about dwarfism, it goes back in history. People that were excavating tombs in Egypt, you know, there were depictions of people with dwarfism that go back there, in ancient Africa. So dwarfism has been around as long as human beings have been around.

Dwarfs have had sort of various roles in society. In ancient Egypt, in the bottom panel, you can see kind of people working at little tables. There was actually sort of a guild of goldsmiths that were all dwarfs. So, you know, medieval miners were dwarfs when one sees because they could fit into small places and they were, you know, physically functional.

So, you know, those memes that changed and they varied from being sort of esteemed and worshiped to, you know, kind of being disparaged. And that's been one of the challenges of this condition of skeletal dysplasias is that, in addition to the medical issues, there are sort of societal stereotypes and things like that that people have to deal with.

So, like I said, some forms are not compatible. If you have a skeletal dysplasia, what does that mean other than being short? So, again, some forms are not compatible with survival, children die in utero or very shortly thereafter. There are many with limited physical capabilities, so not only are they short, but, you know, they don't have full use extension of their arms or various limitations.

Pain and arthritis is a very common issue. We know when bones aren't formed normally, you know, it's kind of like sort of parts in a car that are misformed, you know they're going to wear out more quickly and cause problems. And then we talked a little bit about the social stigma and the memes that go along with these.

So what is short stature? By definition you're below the fifth percentile for height for age, and so we're talking mostly about children here, and that's when it comes up, when people see pediatricians and they're concerned because their child isn't growing.

And the two things we sort of look at is their normal growth velocity? So don't get too excited, you know, if a child has normal growth velocity and they're short. This could be familial short stature, you know, stature height is a multifactorial phenomena, so they're probably polygenic, you know, multiple genes. Some families have constitutional growth delay. I call this the ten-year reunion phenomena, where you go to your high school reunion, your tenth high school reunion and realize that there are people that were much shorter than you when you graduated that are taller than you now. So some people just have a prolonged period of growth.

But we get concerned in medicine when we see growth failure or decreased growth velocity This can be due to many different, you know, issues; endocrinology, people that have chronic illnesses, as well as genetic factors and factors that we don't understand.

So when do you, if you see a child with short stature, with growth failure, when do you start to think about, could this be a skeletal dysplasia? So, first, a big clue is a disproportionate body habitus, and we'll see some examples of this. So where they just kind of appear out of proportion to a normal child that age.

And then, also, there can be sort of unusual features, too. So sometimes there's things in the face, you know, how limbs are shaped. And usually other signs are going to tip you off to whether there's a skeletal dysplasia present or not.

So how do we classify skeletal dysplasia? And it's really come a longways, you know, since the 20th century. Before about 1960, people kind of looked at skeletal dysplasias as being sort of two types. And if you ever watched the Wizard of Oz, there are lots of little people actors in that, and you can see some of them look very, you know, just like sort of condensed people. They're perfectly proportionate, and other people have different proportions.

So proportionate short stature was always thought to be due to pituitary problems, whereas you had achondroplasia if you had short limbs and were thought to have Morquio syndrome if you had a short spine.

So, in the late 1960s and 1970s, as people started looking at more radiographs, you know, there were many more skeletal dysplasias that were categorized, and it was realized that there were many more than two forms. And these initial categories were basically based on radiographic findings. So a lot of radiologists became prominent. It was a kind of a popular field to go into to, you know, you would describe a skeletal dysplasia, get your name put on it, hopefully. But there was just this sort of explosion of information about these conditions that happened there.

So, if we talk about how people, when people started to classify them more because this became pretty unwieldly, and you couldn't possibly remember all of the different conditions because there might have been only one or two articles published about them. So the radiologists started classifying them about where the abnormalities were, and then going back to that bone anatomy with the epiphysis, the metaphysis, and diaphysis.

So there were certain skeletal dysplasias where the epiphysis seemed to be affected more. There were ones where the metaphysis, you know, underneath the growth plate was formed, some with the diaphysis, so the middle part of the bone was deformed. And then another category spondylo, so in some cases the spine had sort of more noticeable changes. And these can occur in different combinations, so you can have epi, metaphyseal spondylo, you know, dysplasia, and sort of all the combinations.

In 1970, people started getting together to create a nomenclature, and this has been revised many times. And I think a big breakthrough came through the efforts of a German radiologist, Jurgen Spranger who, among others, noted that a lot of these skeletal dysplasias shared similarities. So, for instance, achondroplasia is very common. There were forms that were sort of milder but looked like achondroplasia, and then there was a neonatal lethal form, thanatophoric dysplasia, that had many similar radiographic features.

So he sort of proposed grouping skeletal dysplasias into families, and this proved to be very prophetic as a lot of the genetics of these conditions, you know, it was the same gene with different changes throughout the families. So I think people give a lot of credit to Dr. Spranger for kind of starting us thinking in that direction.

So this is where we are currently. We know that this nosology has been published by a group of people that are interested in the field from all over the world. And as of 2019, when the last one was completed, there were 461 conditions. When I started in fellowship, it was estimated to be around 200 conditions, so it's more than doubled in that time. And these conditions are split up into 42 different groups, again some of those families that Dr. Spranger had mentioned. And the genetics has been very successful with this.

So, as you all know, the Human Genome project was completed in 2000, and there's been a wave of new genetic discoveries related to medical conditions since that time. And as of 2019,

you know, there were 437 genes that were implicated in 425 of these disorders, so that's a hit rate of about 92%.

So recognition of skeletal dysplasias used to require a knowledgeable radiologist, which was always kind of subject to debate. Nowadays it's more straightforward because genetic testing can sort out, can give you a diagnosis in many cases.

So this is just a – these nosologies are essentially one big table that lists the different families of skeletal dysplasia. So here at the top there's the FGFR3 chondrodysplasia group, they're all autosomal dominant. They give you the OMIM numbers so that you can look things up, get more information, the protein that's produced. And you can see that there are many entries.

So getting these articles is good because it sort of gives you sort of a list to go through with references to kind of pursue things further.

So this is just kind of for more formal sake, that skeletal dysplasias are kind of grouped into two groups. One group is called osteochondrodysplasias, where there's abnormalities that are intrinsic to bone and cartilage. These clinical changes, the phenotypes evolve through life, so there's different things going on in childhood versus later on in life. There's usually multiple bones affected, and these are divided into dysplasias where there's kind of abnormal bone or cartilage growth, again, going back to that endochondral ossification. And then there's the osteodystrophies which involve sort of abnormal bone or cartilage texture or structure.

That is in comparison to the dysostosis which are much less common. These tend to be focal skeletal dysplasias that primarily involve the face or the hands, different areas of the bodies. These are thought to be due to abnormalities that occur earlier in embryogenesis. But the osteodystrophies are a much more common group.

So how do you diagnose a skeletal dysplasia? Somebody comes into your clinic with short stature, they look a little disproportionate or other people in the family have short stature. So it's like any other diagnosis, you know, having a medical history and a physical exam is important. Again, some conditions have other medical issues that go hand-in-hand, so that can kind of give you a clue of what you're looking at. Like I said, body proportion, dysmorphic features.

It's still recommended to get a radiographic skeletal survey when you suspect a skeletal dysplasia. That can, in some cases, provide the diagnosis right away. I think most radiologists now are pretty comfortable diagnosing achondroplasia and some of the more common ones. But the mainstay now, I think, is the molecular genetic testing which can give you an answer, and there are many next generation sequencing panels that are quite comprehensive, and a lot of times that can be the easiest way to get a diagnosis.

So I think we go on, like a lot in genetics, from relying probably primarily on the the phenotype and trying to find a genotype, to now we're just surveying the possible genotypes, and a lot of times that will give us the answer we're looking for.

So, if you're ordering a skeletal dysplasia radiographic series, we usually call it genetic skeletal survey, you want various views of the skull. These are all kind of standardized because there are features that are sort of seen in each one. So most radiology departments, this is already sort of built into the ordering process.

Okay, so for the rest of time, I wanted to go through just some of the more common forms of skeletal dysplasia, and we'll start with the FGFR3 group. And this is the group that I got to contribute to, and we were involved in the mapping of achondroplasia back in the early 1990s. I thought this was going to be a long drawn out process, but it moved fairly quickly in terms that 4p16.3's where Huntington's disease was, there weren't many genetic markers around the genome at that point but the people who found the gene for Huntington's disease had kind of

put down all of the street signs, so to speak, so it didn't take long to find linkage to achondroplasia.

And from Dr. Spranger's work we knew that achondroplasia was part of a family. At the time, we knew about a hypochondroplasia which is kind of less severe, and then thanatophoric dysplasia, which is more severe. You know subsequent genetic studies have picked out other members of this group as well, and we'll go through these briefly.

So achondroplasia is the most common form of human short limb dwarfism, probably maybe 70-80% of the membership of Little People of America organization are people who have achondroplasia.

It's really a misnomer, achondroplasia means you're missing, you're not growing cartilage. Individuals with achondroplasia have cartilage in their bones, it just develops abnormally. It's autosomal dominant so it's not uncommon to see families where a parent is affected, has an affected child, and that can go through many generations. But 80% of the cases are spontaneous, so ____ the parents, and they'll have a child with achondroplasia.

This has a strong association with advanced paternal age and there's some evidence that as men get older, if your germ cells, your spermatogonia accumulate an FGFR3 mutation, they will have some growth advantage, so you have a higher percentage of sperm that carry the achondroplasia or other FGFR3 mutations as one gets older. This is the case with thanatophoric dysplasia as well.

Incidence has been debated. I think most people think it's around 1 in 20,000, which is kind of, you know, it's rare. It's not super rare but it's not as common as like Turner syndrome or Down syndrome or something like that.

So I'm getting a little more clinical here, you know, what are the clinical features of achondroplasia? So they have rhizomelia which means shortening of the proximal limbs, so the humeri and the femurs tend to be shorter. They tend to have what we call a trident hand, so that there's kind of some altered deviation of the little finger. You can see this little girl that's standing up, you know, it looks like she's kind of giving a Spock sign, but that's kind of what her hand does when she's at rest.

People with achondroplasia have large heads but it's actually what we call megalencephaly, it's large for the age of the child, not just in proportion to the body status. They tend to have a little bit of limitation of elbow extension, and then this characteristic facial appearance with frontal bossing, where the forehead sticks out a bit, and with midface hypoplasia, so the eyes set back a bit more.

They also have the exaggerated lumbar lordosis, so you can see that their butts kind of stick out a little bit more. And then also having issues with the knees, genu varum being the most common.

So we throw around these names, genu varum, genu valgum. I had a hard time remembering what they were, so just a little refresher. So genu valgum is when you're sort of knock kneed, and genu varum is when you're sort of bowlegged. A friend of mine said that you always remember genu valgum because it was like gum, so you figured that there was some gum sticking your knees together. So whatever – in medicine you learn all sorts of little tricks to try to remember stuff, so.

Okay, so the radiographic features of achondroplasia are fairly well recognized. Again, most radiologists can pick up this. There's certain spine abnormalities that one sees, there is kind of little bit of narrowing of the vertebral bodies, there's sort of – usually the spinal canal widens as you go down the lumbar spine. In achondroplasia it actually tends to narrow or stay the same.

And then you can see in the pelvis that there's little sort of dark areas on both sides. Those are the sciatic notches and those tend to be very narrow as well.

So, again, I wouldn't be too concerned about trying to recognize it yourself but, again, most radiologists are able to figure that out.

So one of the clinical issues that we worry about in achondroplasia is that the foramen magnum, so the hole in the skull where your spinal cord comes out, can be quite smaller than it is in average people. And this can lead in some cases, you know, maybe 2 to 3% of babies with achondroplasia will develop spinal cord stenosis in the cervical region. That can lead to hydrocephalous in the spinal cord compression because it occurs right at the medulla, can resort in suppression of breathing. So having central apnea is a concern and it's one of the things that we screen for in babies with achondroplasia.

There's other medical issues, mostly orthopedic with tibial bowing and kyphosis. As adults they develop spinal stenosis, again those narrow interpedicular distances can compress spinal nerves, so people are not able to walk as far as normal because they kind of accumulate some edema in the lower spinal which presses on the nerves. It's very common, I should say, for individuals with achondroplasia to undergo a laminectomy usually later in life to try to treat that.

Also, otitis media because of the midface hypoplasia tends to be more common. So it's very common to have ventilation tubes put in ears to kind of prevent hearing loss.

So, you know, there's a lot of new data about taking care of individuals with achondroplasia. These are two recent reports that came out, one in *Pediatrics* in 2020 from the American Academy of Pediatrics, and then there was recently in *Nature Reviews in Endocrinology*, there's an international consensus statement for lifelong care of individuals with achondroplasia.

Not as much evidence-based medicine as we would really like. As is the case for all rare diseases, it's hard to put together kind of large cohorts of these to kind of study things. But people, the orthopedic community has been involved with skull dysplasias for quite some time, and it's nice now that I think there is more of a worldwide consensus. Even in the United States there was quite a controversy about how significant the foramen magnum stenosis was and whether people needed surgery. The West Coast people thought you never saw it, East Coast people said you saw it really often, and you should worry about it a lot. As usual, the answer, the correct answer is somewhere in between on those.

But, anyway, these are two good references to kind of learn about what's currently recommended for care, and I don't have time to kind of go into that today.

So the genetics of achondroplasia was really kind of fascinating. Again, you know, I think the mapping studies, which we were involved, there were three laboratories that sort of published pretty much simultaneously about this. And, again, it was facilitated by the fact that, you know, people had spent a lot of time and effort looking for the Huntington disease gene.

So it turns out achondroplasia is related to the fibroblast growth factor receptor 3 gene which did not really have a function before that. But, remarkably, for a condition where most cases are sporadic, I think it was really quite remarkable that everybody pretty much had the same mutation. So this was a G to A change at position 380, excuse me, at position 1138, G to A in the messenger RNA, and that results in an arginine for glycine substitution.

And, at the time, we had a large series, it was about 150 individuals with achondroplasias, everybody had one of those two mutations. They both result in the same amino acid substitution. It seemed to be the single most highly mutable nucleotide in the human genome.

I think we realized now that it's not so much that it's a highly mutable site, but there's just sort of selective fresher endurance for mitogenesis. Just about all sporadic cases are derived from the paternal chromosome and, again, this is a phenotype that is recognized pretty easily. So if you're born with achondroplasia and you see a doctor, you know somebody's going to make note of it.

So just one of those little sort of interesting side effects with achondroplasia that everybody pretty much has the exact nucleotide change, same nucleotide change.

Okay, so hypochondroplasia is the sort of the milder form of achondroplasia. A lot of times this goes undiagnosed because people are near the normal spectrum of height, they have less facial dysmorphism, and they tend to blend in with the general population.

Hypochondroplasia was over diagnosed before. If somebody was mildly short and it looked a little like achondroplasia, you got that diagnosis. We realize now that there are specific features that are kind of more common in FGFR3 related hypochondroplasia.

Again, there seemed to be fewer medical complications in terms of the spinal stenosis, although it can occur. Anything that occurs in achondroplasia can occur in hypochondroplasia, so you can't exclude it. The interesting thing is though that there seems to be a higher incidence of developmental disabilities.

We have really not great evidence on this. There's not been any large studies. Hypochondroplasia is less common than achondroplasia, but that's something that, hopefully, will be looked at in the future.

Thanatophoric dysplasia is on the opposite end. It's a lethal skeletal dysplasia. All cases are sporadic. It's, again, has a similar incidence as achondroplasia. Two forms are recognized, Type 1 and Type 2. Type 1 has sort of severe shortening of the limbs. They have these really

wafer thin vertebral bodies and these individuals usually die at birth or shortly after birth. There have been reported cases where people have been kept alive on ventilators for an extended period of time, but it has a pretty dismal outcome.

And then there's thanatophoric dysplasia Type 2 which has sort of less skeletal problems with long bones. You can see in Type 1, they used to call these telephone receiver femurs, they're kind of bent, whereas in the Type 2, the femurs tend to be shorter. The unique feature about thanatophoric dysplasia Type 2 is that they have cloverleaf skull anomaly, so there's pretty significant skull abnormalities. And this is a lethal skeletal dysplasia as well. There's no reports of any children surviving with this disorder.

A new one that we described, there were individuals who had severe achondroplasia, they had developmental delay, and they had what at the time we called acanthosis nigricans. You can see on the individual at the top, he has that kind of brownish tinge to his skin. That's typically seen in diabetes or people with obesity. And this ended up being a unique FGFR3 change.

So if we look at kind of where the mutations occur in the FGFR3 gene, this is a kind of schematic of the protein. This is a receptor that sits in a membrane, so there's a transmembranous region. That's where the achondroplasia mutations occur. It's a tyrosine kinase with a split tyrosine kinase domain. Some mutations hypochondroplasia, thanatophoric dysplasia Type 2 occur there. And then there's the extracellular binding domain, they're the sort of three immunoglobulin like domains that are responsible for binding the fibroblast growth factor - factors I should say - and there are different mutations that can occur there as well.

So one of the remarkable things is that the different phenotypes can occur at the exact same position in the FGFR3 gene. So if you look at position 650 in exon 15, there's normally a lysine there. If you switch the first A to a G, that converts the lysine to glutamic acid that gives you thanatophoric dysplasia Type 2 mutation. SADDAN is a change at the middle position, gives

you methionine. And then hypochondroplasia, so mild forms of hypochondroplasia, can also occur there. So it's kind of like mother nature does the site directed mutagenesis and we were able to kind of sort out what the phenotypes were.

So how do FGFR3 mutations result in the various types of skeletal dysplasias, the various severities? Well, about the time that the work was being done, so this was in the mid-1990s, there was a knockout mouse for FGFR3 that actually ended up being a very big mouse, so it had overgrowth of the bones and it had, on the right side you can see growth plates where they're quite expanded in the mutant mice. Whereas in people with achondroplasia the growth plate is actually shrunken quite a bit. So it was kind of known that FGFR3 seems to be a negative regulator of bone growth.

And then work that we had done a few years later showed for the exon 650 that the severity of the phenotype kind of correlated with the activity. So these mutations were actually turning on the gene inappropriately to varying intensities with the most intense; this is a kinase assay where the mutant, the FGFR3 construct is immunoprecipitated and then incubated with radioactive phosphorous, so that the thanatophoric dysplasia Type 2 and SADDAN mutations give you very large activation of the receptor.

So we know that, again, so this has to do with the pathways that FGFR3 acts with. It seems like this is kind of driving your car with the emergency brake on is going to eliminate or slow down growth.

Now the nice thing about knowing what the pathway is, what the gene is, and what pathway it's in, is one can start thinking about how can one treat this? And we know that activation of FGFR3 leads to various different intracellular pathways. And back a number of years ago, it was found that there's the C natriuretic peptide actually kind of down regulates one of the pathways that FGFR3 activates. And that was the basis for BioMarin to develop its drug called BMN11,

which is now called vosoritide and was approved by the FDA last year. So there is now a treatment out for achondroplasia that does appear to increase growth velocity, and there are other drugs kind of in the pipeline as well to look at this.

So this was, I guess, really something I wasn't expecting at the time, but the field moves onward and a lot of genetic diseases now, we're coming up with rational treatments for.

Okay, so I spent most of the time there. I'm going to kind of go rapidly through some of the other skeletal (AUDIO GOES OUT – STATIC) and just with a few interesting facts.

So Type 2 collagen, it's one of the major proteins found in bone, that protein matrix that the minerals are deposited on. There's a wide range of skeletal dysplasias that go with that. These are fairly common, and a good percentage of the LPA population has, or people with these conditions.

Again, this was a family that Dr. Spranger had first proposed, going from neonatal lethal up to mildly affected. This is Kniest dysplasia. It's sort of people are pretty short, usually in the range of under 5 feet tall. Key features of all of the Type 2 collagenopathies, we call then, they can have C spine instability, they can have flat facies, severe myopia, cleft palate, and hearing loss. So those are things that are additional medical management issues when you're dealing with children with this condition.

Kniest is pretty easy to recognize. They have really large distal femoral metaphyses and epiphyses as well as the other radiographic signs. Again, I'm not going to spend a lot of time on this.

SED congeita is also very common. This is a set of identical twins with SED congenita. They were very successful real estate people in Florida and shown at an LPA convention with their Segways. Again, hearing loss, myopia, cleft palate, cervical instability are issues that we're

concerned about. Again, tend to have retarded ossification, so when you look at an x-ray of a baby, not all the bones are ossified, and certain bones come in at certain times. Usually, that's a key feature that you're dealing with a Type 2 collagenopathies that things aren't ossified when they're supposed to be during infancy. They do get ossified; it just takes them a bit longer.

So coxa vara is part of that and, again, just cox vara just has to do with the angle of the femoral epiphysis and the femur. If it's kind of shortened or at a more acute angle, that leads to loss of height versus coxa vagal where it's tilted the other way. That can lead to hip dysplasia and hip replacement, joint replacements are pretty common in Type 2 collagenopathies.

Stickler syndrome is usually normal stature. This is haploinsufficiency for Col 2A1, so people have one copy that's functional and one that's not. Again, cleft palate, flat facies, myopia, hearing loss. The main feature with Stickler is, other than the myopia and hearing loss, is arthritis. They tend to have premature onset of arthritis.

Stickler syndrome is genetically heterogeneous so there are other collagens that can be implicated as well with that condition.

And then the lethal forms, achondrogenesis and hypochondrogenesis. Achondrogenesis is kind of an appropriate name; if you look at the vertebral bodies, they have not ossified at all in these conditions, or they can be just severely retarded in hypochondrogenesis.

And then the Col 2A1 mutations can occur at various parts. These are all dominant conditions and, generally, collagen has a GLI X PRO repeat that's very important for collagens form a triple helix so that then it's kind of like cables on a bridge. You have wires that are twisted together that have been twisted into cables. Things that disrupt the internal integrity of the protein are going to have a destabilizing effect on the collagen fibrils that are formed, where other areas they have less of an effect.

A little bit about sulphation group. This is associated with predominantly diastrophic dysplasia and also some more severe forms, achondrogenesis 1B and atelosteogenesis. This is an autosomal recessive condition described back in the 1960s. The name comes from geological formations where there is kind of undulating rocks, and the bones in diastrophic dysplasia are usually quite dysplastic. Common in Finland, again, probably from a genetic bottleneck effect, and there are some neonatal problems, but life span is otherwise fairly normal, and people have normal intelligence.

A couple of things to look out for in children, I mean a lot of kids present with dwarfism right after birth. They develop this kind of cystic mass on the oracle that's kind of unusual, but that's one of those kind of pathognomonic signs that kind of tips you in that direction. And they also kind of have unusual thumb location, called a hitchhiker's thumb, so the thumb comes out at a sort of more obtuse angle from the hand.

So talipes equinovarus is very common in diastrophic dysplasia and just talipes is kind of condensed from two words, one from the ankle talus and foot pedis. That's where the word comes from. And so foot peds are usually seen in diastrophic. They are more difficult to repair as well. The bone consistency, as we'll see later, when I get to the genetic etiology, is a bit different. So that's been a challenge to fix club feet in individuals with diastrophic dysplasia.

Again, one can see that the bones are pretty abnormal looking with shortening and different undulations on them. Again, I think some radiologists would pick this out, some would not have a real good idea. Again, this is not a real common one.

And then just some of the other clinical information. There is a diastrophic dysplasia support group. That's the thing about the LPA, it's kind of like a confederation of lots of different skeletal dysplasias that all come under the umbrella of being little people, so they have kind of their own

support organizations and ways to disseminate information. And then there are also the lethal skeletal dysplasias so, again, these a lot of times are picked up in utero now.

So diastrophic dysplasia is due to a sulfate transporter, so this is a gene that transports sulfur across membranes. Sulfur is important in the extracellular matrix for certain types of proteoglycans. Again, when you make bone, you've got those hypertrophic chondrocytes there breeding an extracellular matrix. That serves as the scaffolding for putting bone onto, and if that's abnormal, that can lead to bone that is weaker and has abnormal consistency.

So then there are the metaphyseal dysplasias. I'm going to kind of fly here because we're getting kind of close to end of time. Schmid metaphyseal dysplasia, relatively mild, has coxa vera as well. These are Col 10A1 genes, so a different kind of collagen that's really unique to the hypertrophic chondrocytes itself.

Cartilage-hair hypoplasia – the founder of the Little People America, Billy Barty, was a dwarf actor back in the 1930s, was in a lot of movies, and that's what he has. This is severe short stature. They can have sparse hair and that's where it kind of got its name. It used to be called McKusick type metaphyseal dysplasia. The main feature of these is that they could have immunodeficiencies, hypoplastic anemia, and an increased risk of lymphomas, so there are other issues that go along with this. This is a recessive condition, but it tends to pop up quite commonly. Again there's a higher incidence in Finland.

This is an interesting gene, this is an RMPR gene. It's an RNA component of mitochondrial RNA processing endonuclease, endoribonuclease; that's a big mouthful. Kind of unusual because mitochondrial disorders usually don't result in short stature, but I guess the exact mechanism of this, why things go wrong, is still not known to my knowledge.

Then the multi-epiphyseal dysplasias, so pseudoachondroplasia being one of the most recognizable. Again, it was called pseudoachondroplasia because it kind of looked like achondroplasia but not really. Back when people weren't looking that hard, people got lumped together.

This is postnatal onset, so people usually start out normal stature and then develop disproportionate short stature later on, and also can have usually extreme joint hypermobility. It's quite remarkable when you see these people, how flexible they are. It kind of gets confused with some of the Ehlers Danlos syndrome and other connective tissue disorders but has the feature of short stature. Normal facies, no facial dysmorphisms to speak of.

Interesting fact, the Ovitz family; this was a group of Eastern European musicians and actors that were Jewish, were imprisoned, put in concentration camp during World War II when the Nazi's took over or just before. Dr. Mengele, who was sort of infamous Nazi German physician with poor ethics, was very interested in this family and sort of kept them alive because he was interested in studying them. So a lot of other dwarfs were sort of summarily eliminated during those kind of political times, but they were a large family of people that had pseudoachondroplasia.

Again, pretty typical radiographic features, bones look very ragged. This is due to a change in a gene called collagen oligomatrix proteins or COMP. And what happens is it actually gets stuck inside the cells. This is a normal component of extracellular matrix. And it's not so much that its missing from the extracellular matrix, is that it clogs up the chondrocytes and kills them, so eventually you get dropout of the growth plates, the intraarticular cartilage or growth plate cartilage as time goes on.

Okay, and then there are also multiple epiphyseal dysplasias that COMP can be part of, but there's also collagen genes, so there's quite a bit of genetic heterogeneity there.

I'm moving really fast here, sorry. So they're lysosomal storage diseases, so Morquio, as I mentioned earlier, was the short limb form of dwarfism, and many different lysosomal storage diseases can present with skeletal findings typically characterized by dysostosis multiplex which, again, most radiologists can recognize. So it has to do with specific abnormalities in the spine and the hands. So when you see dysostosis multiplex you should be thinking of a lysosomal storage disease.

So Morquio, the name did stick to two, Types 4A and 4B. Again, these are lysosomal enzymes. Again, these children tend to be normal at birth but then by age 1 to 3 years, one starts to see the growth failure and then the coarsening features over time.

And then, finally, osteogenesis imperfecta, many different types. We used to think of just the three types, and then there was four. Those were all Type 1 collagen genes, but now the list is quite extensive and there are many different genes that have been implicated.

Type 1 is compatible with survival, variable frequency. Some people have fractures in infancy and then not so much afterwards, whereas there's the lethal Type 2 which, usually, it's not compatible with survival or requires a lot of support at birth. There are medicines to treat this now. If you inhibit osteoclasts, that can sort of improve the bone structure in the different forms of OI.

And then OI Type 3 is sort of in between, it's sort of chronic deforming. This has had a very good response to pamidronate and other osteoclast inhibitors. So they still have problems but they're doing a lot better now than they were 20-30 years ago.

So I mentioned the LPA. It's a great organization that's unlike any other support group. People here aren't trying to cure dwarfism; they're just trying to adapt to being little people. As a physician, that takes a little sort of mind bending to get around that. But they're real people and

they're just trying to make it through life like the rest of us, and they have to kind of do it with the arthritis and the orthopedic problems they have, as well as the social stigma that they have to sort of fight against.

So I think, in closing, we've come a long way since we've looked at dwarfism. This was from a movie called "Freaks," that came out in the 1930s. The producer was the same person who produced the Dracula movies with Bella Lugosi. I think people with genetic differences were kind of looked at oddities and something for entertainment. And nowadays with - these are the Roloff's, and they had their own television show, "Little People Big World." So I think we look at little people now as just being part of the great diversity of society that we are that gives us lifelong richness than everybody being the same.

So a few just general references that I'll put up there, and that is it. So I kind of took up the whole hour but if there are questions, I can stay a bit longer.

Speaker: Thank you, Dr. Bellus, for an excellent presentation. At this time we would like to take a few questions from the audience. Questions may be asked via the Instant Message box located at the bottom left-hand side of webcast player.

We do have some questions that came in already. One of them asks, "Are there any orthopedic treatments for achondroplasia, human growth hormone?"

Dr. Bellus: So human growth hormone does not seem to work. That was tried a long time ago. There's some evidence that it actually makes the disproportion worse over time. It's been controversial whether human growth hormone works for hypochondroplasia or not, although I think most people don't think that if you have FGFR3-related hypochondroplasia, that it works.

I think everybody is very excited about the vosoritide, the new compound that's come out, and that's just getting started. We're not going to see the final effects of that until probably several years from now when people have converted their growth cycle.

Orthopedic issues are, if you have achondroplasia, you should probably get to know an orthopedist. Again, spinal stenosis is very common, especially in adults, especially in individuals that put on extra weight and are more sedentary. So having a laminectomy to treat that is fairly common, as well as tibial bowing can be an issue, especially if there's increased ligament laxity in the knees. So sometimes doing an osteotomy to try to straighten out legs can be helpful.

Speaker: And one final question since we are short on time, at what point during the diagnostic pathway do you rule out endocrinologic causes of short stature, for example, GHD, ISS, SGA? Is there a role for growth hormone in patients with achondroplasia?

Dr. Bellus: Yeah, again, achondroplasia not so much Growth hormone wouldn't be the right way to go. We overlap with short stature and growth failure. Usually, we work hand-in-hand with endocrinology. If somebody comes to us with short stature first and we're not finding a skeletal dysplasia in terms of radiographs, we'll have them do an endocrine evaluation, and then endocrinology sends us many individuals as well.

I think since growth hormone became more available, and there was a time when it was isolated from human cadavers and there was a big safety risk with Jakob-Creutzfeldt disease that went along with that, but now it's produced from recombinant genetic techniques. And it is, it's used in Turner syndrome now, it's used, obviously, in growth hormone deficiency, and I think it has a pretty good safety track record, so people are willing to try it.

The problem with growth hormone therapy is that you kind of buy into a long-term course of daily injections and some people find that objectionable, so.

END OF PRESENTATION