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Interview with Huda Zoghbi

Huda Zoghbi MD

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**Texas Medical Center
Women's History Project**

Huda Zoghbi

Interviewed by: Darra McMullen
Date: February 9, 2016
Transcription: Darra McMullen
Location: Huda Zoghbi's Office Suite

DM: O.K. We are in the offices of Dr. Zoghbi; today is Feb. 9, 2016, and this is an interview about Dr. Zoghbi's life and many successes.

First question – where were you born, raised, and do you have siblings?

HZ: Yes, I was born, raised in Beirut, Lebanon, and I started my high school schooling there and early university there, and I do have siblings; I am one of five. The oldest one passed away two years ago, but I have a sister and two brothers now.

DM: All right, and how much of your life did you spend in Lebanon?

HZ: I was in Lebanon until I was about 21, all of my childhood, teenage years, early young adulthood.

DM: O.K., and what did your parents do for employment?

HZ: So, my father worked with olive oil extraction, quality olive oil, and making soap from olive oil, so all foreign based products from soaps to oil, and he was a business man working in this arena, and my mother was a stay-at-home mom who took care of us.

DM: O.K. All right. Did your parents or any other relatives in your family influence your decision to go into a medical field?

HZ: Actually, yes. Both of my parents have always pushed us to learn a lot and pursue scholarship. My dad is a historian by interest, very well read. So, they both pushed us to

pursue learning, and when I planned to enter college, I was determined to do English literature; that was my passion, but my mom insisted I should do medicine; so, there was a little tug-of-war between us. I wanted to do literature; she insisted I was good at biology, and I should do medicine, and that English literature and writing could be my hobby. So, after a lot of back and forth, I finally yielded to her and took some pre-med classes and entered medical school. So, I would say my mom was a big influence.

DM: I'm glad you followed your mom's advice.

HZ: Thank you!

DM: O.K. What is your personal earliest memory of thinking you might want to go into a medical field? Did you ever think about it at all yourself, or were you so set on literature that you really didn't?

HZ: I actually, as I was growing up, medicine was not on my radar screen; I was just learning – I mean I loved biology; I liked math; I loved philosophy, but literature was my passion; literature and English literature [especially]; I loved both very much; I loved poetry, but I gravitated more toward English literature as I got to read more in high school, and that was what I was interested in, and I must say in college, even though I yielded to my mother to do pre-med, I took, of course, all the typical art education at the American University at Beirut. I took all the cultural studies courses, and I would say it was my grades in literature and cultural studies that got me into medical school!

DM: Into medical school! [Laughter from both]

HZ: All the pre-meds had high grades in biology anyway; that was not distinguishing; what got me in was my grades in humanities.

DM: Humanities! [Laughter] That's interesting! O.K. Can you think of any other

childhood influences or experiences of any sort that helped lead you into a medical career? Anything that happened either in childhood, or as a teen even?

HZ: Again, it really – because medicine was an afterthought yielding to my mother, I can not say there were any other people that influenced me. As far as childhood influences, probably in my dad, who pushed us to always study and do the best we can do all the time, and my Mom, who always gave us the time – every time I would go into the kitchen to be with her, she would shoo me out. “You go read; you go study.” [her mother would say]. It was really that sort of environment that probably influenced me to pursue scholarship, but medicine again was not on my radar screen until I was 21 or 20.

DM: O.K. Tell me a little bit about your educational background, and why you chose the schools and programs that you did.

HZ: Right. So, in Lebanon, I went to a private school, which was one of the grade schools in the city, and in that school you learned Arabic, English, and French, mostly Arabic and English because I started English from kindergarten, but you take French after middle school. It was a great school, and I am still very close friends with my classmates from that school, and there are many of them [that] are in this country and are successful.

DM: Great!

HZ: We had small high school classes. Like my high school class was 13 or 15. They divide you into mathematics, literature, sciences. After that, you have to make a decision for university. There is the French university, there is the American University of Beirut, and the [inaudible word or two] university, and we chose the American University of Beirut. My dream was to go there because it is the oldest and the best, really, in the region, and it continues to be that. It is 150 years old this year. It was started by

American missionaries, who started it in 1866. It really functions as an American university with an emphasis on liberal arts education, and really building the whole person through education. So, that was my dream was to get into AUB, for short. So when I got there I was thrilled! So that was really the choice of schooling that I had, and I entered as a sophomore because I had taken AP classes in high school, so I did not have to do the freshman year. I did the sophomore and junior year, and usually, if you take all the proper courses and you're accepted into medical schools, then you can start medical school. So, basically, I spent two years in college, and started in medical school at AUB. Our class was 63 students at the time, and it was a great class, and we were loving and learning – loving the experience until half-way in that class year the civil war erupted in Lebanon, and it became – things escalated, and the city had bombs falling everywhere; it was really dangerous to stay in the school and commute.

DM: I can imagine.

HZ: So we had to make a decision with our faculty, as students, if we want to continue the school year or everybody goes home.

DM: Right.

HZ: And the decision between the students and faculty was we will continue; we want to finish the school year, but with that decision came the second decision. All the students have to live on campus; nobody can commute anymore. If you step out of the campus, and bullets will fall on you. The reason the campus was spared was because it had the hospital.

DM: Nobody wanted to blow that up!

HZ: Right. The militias needed the hospital for both sides, so they left us alone. So

that really determined that we would finish the school [year], but we would all live on campus and had to find rooms that were safe. The safe rooms within the dorm were filled, so we really needed to be in double walled rooms to avoid stray bullets and such from the surrounding streets, and we made the decision to do so, and each of us tried to find the right room, and I found a tiny little room that was about maybe 2 ½ meters by 2 ½ meters that was inside the ladies room. It was a double walled room. I just put a little sleeping bag on the floor, and stayed there for the six months.

DM: Oh, no!

HZ: It was a room without windows, which was the whole idea. In some ways, it was convenient to be inside the ladies room because everything was right there! The sink and everything was right there! And then, some of my classmates stayed in one of the lecture rooms. Others made a – [would] shift a closet [and] turn [it] into a bedroom at night. We really all had to stay in the basement to be in a safe place. So, we stayed between the basement and the first floor but double walled, and at night, we would, after classes, we would sit together, and some of our classmates would play guitar. We were good at entertaining ourselves. I was good at making desserts, so I would make desserts in the laboratory using the Bunsen burner.

DM: O.K.! [Laughter]

HZ: They were simple desserts. You have no outlets. Imagine for six months, you have nowhere to go. You are studying during the day, and you absolutely have nowhere to go at night. So, that's why the class bonded, and our only entertainment was talking, singing songs, and making desserts, and studying.

DM: Wow! That's an incredible story!

HZ: Thank you!

DM: O.K. After you came to the U.S., then at that point, I know you came here for awhile, for a summer just to get away from the war, visit family, that sort of thing, and then when it became apparent that you were not going to be able to go back, at that point, then what did you do? Did you sort of go, “How am I going to get into another school?”

HZ: So, the school year ended, and now, of course, we have to go home because the students can not stay on campus when there are no classes in the summer, and the school year ended in June, so each person tried to find a way home, and I lived close by so my home was about three miles from the university, so I went home, and my parents said, “We want you to go with your two younger brothers and join your sister in America for the summer. We’re very concerned that the war is really rough, and your younger brother was hurt with the shrapnel, so we don’t want to take a risk. Just go back for the summer, and you’ll be back.” You couldn’t leave via the airport because the airport was closed, so they said, “We’ll arrange for a car to take you to Syria, and you fly from Syria and meet an uncle in Switzerland and from there, go to the United States.”

And so, I was apprehensive because my brothers were younger than me; I was 21, and they were younger too – one was 11, and one was 16 at the time. And so, I complied. I really did not want to go because after six months of living on campus, you bond with your classmates. You make friends.

DM: You don’t want to leave.

HZ: It was very sad leaving, right. You’re not thinking about war; you’re living in your own little world, but I think they convinced me it was only to be for the summer. I could return in October when the school started again, so I complied and went with my

siblings via by car to Syria. It was a little bit rough there, because being young and female with two younger boys wasn't as well received or supported. People would make fun of you. Political correctness was not in place.

DM: Not in place! Right. [Laughter]

HZ: So it was pretty challenging; I couldn't wait to get out of there. Once I got to Switzerland and could stay with my uncle and family for a while, that was a nice distraction and then managed to come to the States.

My sister, at the time, was on summer break, and she was living at Austin, and I arrived to the United States in July and to Austin on July 4, 1976, and if you know the history, that was the Bicentennial [of the U.S.]. I had no idea. July Fourth did mean nothing to me [at that point in her life]. So we're driving into the city at 8:00 p.m., and I start hearing explosions, and I started screaming because they sounded very much like the ones in Beirut.

DM: Oh, no! Oh, how awful to scare you like that!

HZ: Right. So I had no idea that this was fire works for the Fourth of July, and it was a very big celebration.

DM: Right.

HZ: So, it took me a while [to adjust], but I think now, in retrospect, doing what I do, I realize now what I had then was PTSD, Post Traumatic Stress Disorder. Because I think any logical person here involved in America, [if] something sounded, they would say, "Oh! What's going on? A firework!" Me, I burst into tears and started screaming, thinking this is bombs. That's the PTSD component. So, really, I did not know. Back then, we did not know about PTSD, but in hindsight [that's what it was]. So, anyway, we

got there, and it was nice to be together and so on, but I missed home, missed my parents. It was the first time I leave home, period. Besides living on campus, I had never lived outside home. And then, we kept watching and monitoring the situation. August came and went. September came and went, and we're thinking maybe now by the end of September things will change, and I could go back, but instead, things got worse, and the situation escalated, and you couldn't anymore return because now Syria was bombing Beirut.

DM: Oh, no!

HZ: So you couldn't go back via car, because you're at war with Syria at that point in time – because the war changed who is against whom hundreds of times.

DM: Oh, my gosh!

HZ: So, now I'm in a situation where the airport is closed, and I can't go via Syria, and I'm stuck. I really could not go back, and I was pretty devastated about that, so I had to figure out a way, what to do, and the younger ones were easier because my brother could start college, and the youngest one was put in middle school, but I had – I was just 20 and had a year of medical school behind me; I needed to find a medical school; in Austin, there was no medical school. In October, what do you do? Some people started saying, "Well, why don't you do a PhD in Pharmacology? That's the closest thing to medical school in UT Austin." "No, I really don't want to do that. I really want to finish medical school," [Huda replied].

DM: Right.

HZ: So, I started really being upset, and feeling very despondent about my situation, and a friend of the family who lived in Nashville – he was calling to check on me - he

and his wife, and he knew I was really down in the pits, and I was crying. He said, “Why don’t you come visit us for a weekend, just to have a change?” So, I went and visited them, very nice couple, Gaspar and Annie, and they said, “You know we’re going to take you here and see if we can find another school that will take you.” [Gaspar adds] “I work in a building where Hospital Corporation of America has its headquarters. I’m going to go ask them to guide and see if they can help us.”

I said, “Fine.” I knew nothing really; it was all news to me. So, he took me up there, and the guy says, “Yes, there’s a great medical school in Nashville; Vanderbilt is a great school. You should really go visit them.” So, Gaspar took it upon himself to schedule an appointment, and we went to Vanderbilt, and I told them my story, and they said, “Well, it is October; school started in August; we don’t take transfer students in the first place, and we don’t take them if they’re two months late. So, we’re really sorry we can’t take you, but there’s another medical school here you might consider looking into.” And I said, “What is it?”, and they said, “It’s called Meharry Medical College.” And I said, “That’s great!”

So, we went there, and we told them the same story; I had a printout of my grades that my family was able to send me by Tell-ex. Back then, there was no fax, but there was Tell-ex. So, they sent me that, and showed them the grades, and the administrators and the admission physician from Meharry said, “Oh, your grades are good, and I know you are two months late, but we will be happy to take you.”

DM: Great!

HZ: So, I was thrilled that they took me. And they said, “You can start tomorrow,” and I did, and I found out that the day after were the first quarter exams.

DM: “Oh, no!” [Laughter]

HZ: So it was quick that I had to find an apartment. Found an apartment in the same complex where the friends lived. And then, really, buy books. And rapidly now learn how to adjust all on my own.

DM: Again.

HZ: Again, right. But I managed to do that and started school. Felt very sad and isolated because I was in a new place away from family. War was still raging back home. Couldn't call home. If you wanted to call Beirut back then, you would have to do it through an operator, and you could stay on the line for hours to get through. The lines, because of the war, were limited, and the operators would tell you to try again later after you talked to them. So you have to talk to a person on line from here to see if they can get you through, so it was really hard; so, it was a very tough situation.

DM: I guess so! How long did it last, the war that is?

HZ: Fifteen years.

DM: Fifteen years – oh, my gosh!

HZ: Fifteen years – it was very brutal. So, after that, I just immersed myself into studying. I did not know much; I really knew nothing about minorities in this country. So it did not register to me that Meharry is a minority medical school. I just said it was an American medical school, and then, I learned its history, and I learned it was a minority medical school. So, I was a minority in a minority medical school.

DM: Right.

HZ: And to me, I would have been – everything would have been new to me no matter where I landed, and [when] they ask us to poll [evaluate] American culture, sports, dating

– all of that was so different. So, I was there standing – totally different I would say, but they were very welcoming, very kind to me; everyday, they would ask me if I want to go out, and everyday, I would say, “No, I really want to go and study,” because I was so behind and so lonely and so homesick.

So, I would go home after school and try hard as I can to see if I could connect by phone and so on. I cried a lot that year. I really remember it being very sad, all alone, worried about family. And having just to get by and study and make do with what I have to do; I was grateful I was in medical school; it was not an easy thing, and so, I finished the year, and I was determined to go back.

You could not go back; I don’t remember; I think I went via airport. The airport opened momentarily, and so I packed all my things and went back, planning to stay, and I was so excited to be back home and to see everybody, and my professors, and they were wonderful, and they all said, “We would love to have you. You can come back here anytime, but you would be better off graduating from an American medical school, and we think you should just go back,” and I was just devastated, but they all advised me to come back, and so I returned.

DM: Good!

HZ: But there was a silver lining. So, in the first year of medical school, halfway, when the war has erupted, I met William Zoghbi, and we dated for a few months before the war separated us, and dating was walking on campus. You can’t go out anywhere. It was a beautiful period. We got to know each other, and know each other well. And then I left, and that was really hard, meeting and then leaving somebody I really liked, and so then, when I went back a year later, he said, I think I want to leave too. So, he applied to

Meharry, and he got accepted.

DM: Oh! How wonderful!

HZ: So, he came to Meharry a year later. So, then we finished medical school at Meharry, and the fourth year, we spent time at Baylor, and I did Stanford and Emory, and he did Johns Hopkins and Emory. We were trying to find where we would want to be for residency, and I must say, both of us, because we had a “checkered” medical history, part of it at AUB, part of it at Meharry; you didn’t go to one medical school. Although we were both AOA, and top student, it was a challenge to find residency, but we were both fortunate to end up at Texas, and eventually, at Baylor College of Medicine. So, we’ve been here since ’79. Came to Baylor for residency, and I’ve never left. William came here in 1980. He did one year at UTMB, and we both have been here.

DM: And what was your first job? Was that at Texas Children’s?

HZ: My first job was at Baylor College of Medicine as an intern in pediatrics, which of course, you see the patients at Texas Children’s [Hospital], and here, really, I would say, it was Ralph Feigin who I would give credit for, for my being here because as I mentioned to you, when I interviewed around the country, many top universities – I had top grades; William and I both had very, very high grades, top 5% of the class, and had good national grades and were AOA, but almost everybody would not want to have anything to do with us because they feel you went to a minority medical school, and you are not a minority. We don’t really want to deal with you because we don’t know why you did that. Even if you try to explain, it didn’t really matter. And for me, Dr, Feigin here was the turning point in my life. He was a 36-year-old, really young, Chairman, had just been here a year, and I’m here doing an elective, and I got called into his office, and

he said, “What can I do to get you here?” And I looked at him, and I said, “Are you serious? You’re not kidding me?”

DM: [Laughter]

HZ: “I’m very serious.” [Dr. Feigin replied.] And I said, “I would love to come here, and end up matching here.” He took me under his wing, both William and I, particularly me. I consider him my American father because he truly mentored me in anything. If I needed anything, if we wanted to get married, and we didn’t know how to find a judge, I went to Ralph. He really became a great supporter, and he was a great mentor. I learned clinical scholarship from him. He was an amazing teacher, an amazing physician. He was a true role model in compassion and scholarship. So, I feel the most fortunate at being reared by him academically. He was my first mentor, and I don’t think I would be here, nor would I have the same successes, were it not for Ralph Feigin.

DM: O.K. Great. Please tell me a little bit about, sort of a little history, from when you had your residency at Texas Children’s and how that ultimately led you to these discoveries about Rett syndrome.

HZ: I mentioned to you I was in pediatrics here, and I quickly discovered while it is an interesting specialty, it is not enough for me; I needed something more stimulating; I was actually contemplating cardiology very seriously, and that’s the elective I did here when I came as a medical student, so everybody thought I was going to be a cardiologist, but then I had rotated with Marvin Fishman, who was then the new chief of Neurology, and he really was a great teacher, and I became interested in the brain, having spent a month with him, learning on rounds about neurological patients and decided to do neurology, child neurology, and so I did that, and during my first year of child neurology, it became

clear to me that it is really a vast specialty. You see the children with very bad disorders, and most of them are genetic, and you know this could happen 1 in 4 or 1 in 2, but you don't know the cause, and you can't help the parents, so you tell the parents, "This is what we think they have, and we think this could happen again in your family, so you have to be careful," and it was very sad. I felt it was a tough specialty, and I did encounter patient with Rett syndrome, at that time of October of 1983. Her name was Ashley, and I was really fascinated by her clinical picture, whereby she was normal until about two years of age, and then started losing her ability to communicate, started losing social interaction, and started losing the use of hands and started wringing her hands and becoming really more isolated, and [having] balance issues, and progressed.

Her father was a professor at A&M, and so, he brought her here to be evaluated, and I had seen her, and the symptoms [of the disease] had just been described by Andreas Rett, and I was fascinated by this disorder and saw her at Texas Children's at that time. But you see one child, and you see one case, and that's really an isolated [incident].

The week after, I saw a child at the Bluebird Circle Clinic, which is a volunteer clinic, and we get to pick the diagnosis [that the doctor wants to work with]. I pick cerebral palsy, and this young lady walks in wringing her hands, and looking exactly like the first child. So, I went through the paper again, and lo and behold, she had all the features of Rett syndrome, so now we have two Rett syndrome girls, and back then, the syndrome was not really described in the States. It was only described by 35 cases in Europe in one article, so I became fascinated, and I asked the Bluebird Circle volunteers if they would [help]. I gave them the list of symptoms, and said any child that has these symptoms, pull that chart for me. So, they were so wonderful; they pulled 35 charts.

DM: Wow!

HZ: So, they started going through these charts, and I was able to find more girls that I thought had Rett syndrome, and so I brought these girls in and started examining them, and was able to find another five or six in that group, and now I have several patients with Rett syndrome, and I became really fascinated with the disorder and worked on that and published a paper in the *New England Journal of Medicine*, and that resulted in a lot more Rett patients coming here, and so today, we have the largest Rett's clinic in the country, with about a thousand girls [that] are followed in the clinic. But it is because we were among the first to, here in 1985, with these girls and [to] make a report on them, and I decided since they're all girls, and it's a unique disorder, where you're born normal, lose milestones, but you don't regenerate, I'm really going to try to figure it out, and I'm going to try to figure it out by finding the genomes. And since it's genetic - although we really didn't have the data that says so - because it is only one case in every family, so you don't have that many affected people in a family, it is isolated, sporadic if you will, and I decided that to do that I have to do research, and I don't know how to do research.

I have to find a mentor who will teach me how to do research, so I was fortunate to find Dr. Arthur Beaudet, who was that faculty [person] - back then, there was no Department of Genetics; there was a division; and so, I told him how long I had studied molecular genetics and research, and would he train me, and he was very excited. He said, "I'll be happy to train you. What do you want to work on?" I told him Rett syndrome. He said, "Show me the family." I showed him. "Oh no, these are very tough. It's a sporadic case," [Dr. Beaudet replied]. Back then, there was no technology to do that. "Pick another problem."

DM: Right.

HZ: So, he and I talk back and forth, back and forth. So, he settled on a dominant, inherited alternative disease called spinocerebellar ataxia, where there was a big family in Montgomery, Texas that he was aware of, and he referred me to that family, and that was a family with 200 people in it.

DM: Wow!

HZ: So, you could map a gene and go after it, so we decided I will work on that. Because there's no way I could, even if I had 200 samples from Rett, there's no way I could find a gene with technology [available] back then.

DM: Right.

HZ: So, between '85 and '88, I then trained with him to do that. Then in '88, I started my own lab. I've always worked on the side with Rett syndrome. I never gave it up, and I continue to pursue it, and as I moved in to my own lab, I pursued an indication of the ataxia gene, and [we] were successful in doing that through a collaboration with Harry Orr in 1993, and continued to work on Rett. We were always coming up empty-handed.

It was like coming to Houston and finding Huda Zoghbi with no Internet and no home address, or anything. You just know she lives in Houston, and you have to find her. You don't have a map and no addresses. It was really that kind of thing. So, I think if you came to Houston, and you go randomly from place to place, and you don't know anything about me, it will take you 16 years to find me.

DM: At least! [Laughter]

HZ: And that's why it took me 16 years to find the Rett syndrome gene. But we found it in 1999.

DM: Wow! That's incredible, and very impressive I might add.

HZ: Thank you!

DM: O.K. You sort of answered this question I think already – about your decision to move into the genetics research – and the influence of your work with the Rett's patients on your decision to pursue the genetics. After you started in the genetics, what about it did you really like, and what inspired you to just keep moving forward – that gave you more and more enthusiasm?

HZ: I think I like genetics because it is black and white. It is my favorite thing. And you can see I wanted to do literature; I did medicine; I wanted to do pediatric cardiology; the only thing I stuck with is research, particularly using genetics to push the research forward. And the reason I like that is because it is the closest thing to black and white to answer some specific questions as you can get.

DM: Because the genetics is – it's either on or it's off.

HZ: You either have a mutation, or you don't have a mutation; there's no other in-between, but at the time, I liked it because it told me, yes, Rett syndrome is a genetic disorder. It made it very clear.

DM: Right.

HZ: It took out all the ambiguity. So, I decided to continue to pursue the genetics to understand the disease better [and] create animal models for the disease and for the other, spinocerebellar ataxia disease, and figuring out what goes wrong in the brains in these animal models and figuring out how can we manipulate things to perhaps change the course of the disease. So this is where we have been working, and if you fast-forward to today, we have actually found a pathway where we could develop a therapeutic tool for

spinocerebellar ataxia, and we're finding new ways to perhaps modulate the course of the diseases caused by mutations in the Rett gene.

DM: That is really impressive.

HZ: So, I really think that's why I really stuck with it; I feel it is solid. It is at the root of what happens that leads to abnormal function.

DM: Function. O.K. All right. Can you give me sort of a brief – I know this would be really hard to do because all of these are such complicated topics – but can you give me a brief rundown of the highlights of your discoveries, of what you found, some of the major ones?

HZ: Sure. The first discovery we had was finding the gene for the spinocerebellar ataxia. I did that work collaboratively with Harry Orr. We had families; I had families; it is a rare disease; we pooled our resources, and we were both fortunate to find the gene on the same day.

DM: What are the symptoms of the disease? I'm not familiar with it.

HZ: Yes, I'm going to tell you that. It is a degenerative disease, where one is born healthy, but as they get older, they would lose balance and coordination. Slowly, they will become more and more incapacitated. First, they will walk unbalanced. Then they will be unable to walk; they will need a walker; they will go to a wheelchair; their hands will shake; if they were to drink a cup of water, they will spill that. Then, their ability to speak and swallow will become uncoordinated, and eventually, they'll die because of the choking. So, it is a lethal disease.

DM: Does this happen early in life, or when they become aged?

HZ: Usually, it happens when they're in their forties or fifties.

DM: In their forties.

HZ: But sometimes, it hits early because of the mutation's kind. So, we find the mutation is three base pairs of DNA, that in you and me, [there] are about 30 of them in our DNA, but in the patient are about 40 typically, and the longer it repeats, like if the patient has 50 repeats, they will have disease when they are 40 years old, but if the patient has 80 repeats, then they will have it as a child.

DM: Really?

HZ: So, you can sometimes see it in children, and it is inherited, so if somebody has the mutation, it will pass to their children. So that was the first discovery I made, and since then, created an animal mouse model for that, and have collaborated with colleagues here to make fly models. Juan Botas at Baylor has done that, and then we understood exactly why the protein becomes toxic. We found the protein with longer repeats lives longer in the cell and is degraded less efficiently, and having a little bit more of that protein is enough to hurt the neurons.

So, in a more recent discovery we made, we found if we can just a little bit reduce the protein, by 20%, we can help the disease, and that's where we're finding ways to do that, and we're using that to develop therapeutics. So, this is what I would call major discoveries in that finding the gene for the ataxia, understanding, creating an animal model, understanding that the disease is driven by the protein, and understanding that this protein is really doing nothing more than it normally does, but a little bit more, and too much of a good thing is not good. So, that concept of too much protein being toxic was the first discovery we made in neurodegenerative disease, and that is, I would say, sort of a game changer because there are many adult neurodegenerative diseases that are driven

by a little bit too much of a protein. So, that's one area.

Then there's the area of Rett syndrome, and the importance of that discovery, of course, first finding the Rett gene will help with early diagnosis and better management and better physical therapy early on and so on, and take away the guilt of the parent that they didn't do anything. So, there are many benefits, like sparing the child from so many diagnostic tests and so on. So, that's one.

The second really important thing, back in 1999, we did not know that sporadic autism could be caused by a genetic defect. Back then, people thought autism was just due to a behavioral issue, or issues with the parent or something. Nobody knew. But when we found out that here's a sporadic disease, one case in a family, and it can be caused by a gene mutation, a new gene mutation, then people started looking at other problems of autism, and it became clear that the majority of autism is similarly different genes that also have a sporadic mutation. So, the work has impacted the field of autism, and here again we found that dosage matters. If you don't have the right gene, functioning well, you get Rett syndrome. If you double the Rett gene, you get another syndrome, also another childhood progressive neurologic disease – back to this idea that you've got to have certain proteins at the right level; too much of a protein is not good; too little of a protein is not good.

So, we've done all that work, and most recently, we're able to show, using a new, small molecule, that if we reduce the doubled protein in an animal model, we can actually reverse the symptoms of the disease. So, we've done a lot of work on how to modulate the course of both Rett syndrome, as well as this duplication syndrome in mouse models. And this is now pushing us to keep moving forward to keep exploring these diseases.

DM: That's incredible!

HZ: These are what I call my disease-oriented discoveries. Then, I had a fun area of study that was not disease oriented. It started from a conversation with a colleague here, Hugo [last name not clearly audible], where I asked him to tell me about a cool gene in the fruit fly that's really important in the fruit fly. So, he told me about this gene that's called "Atonal" because it's important for hearing and for the fly to feel its wings and arms in space. So, I said, "Good. I'm going to find the equivalent of that gene in mice and humans and see what we will learn," and when we did, it's been – work over the last 20 years or so – it's been one discovery after another. To cut a long story short, we found that this gene made the little hair cells in the cochlea in the vestibular system that are very important for hearing.

DM: Right.

HZ: So, if you damage hair cells – the tiny, tiny sensory receptors in hair cells – one will become deaf. And from that, studies have shown that if you use this gene in gene therapy, you can restore these hair cells and restore hearing. So, companies are now working with this as a gene therapy tool for treatment of age-related deafness. We also discovered that this gene is important for neurons in the cerebellum, the back of the brain that is for balance and for perception. We found that it is important for many, many, many neuronal maps critical for you learning your position in space, just like it does in the fruit fly, the same function concern.

And we learned it is important for the primary receptors in your fingertips, so when you play the piano, you can tell the white key from the black key, or you touch fabric, those sensory cells depend on this gene, and it's important for neurons critical for

breathing in newborn babies, and it's critical for cells in our [possibly the word "gut"; recording is briefly unclear], important for secreting endocrine hormones, secreting mucous, and secreting anti-microbial peptides. It is a very essential gene.

DM: Sounds like!

HZ: This is another area I've worked with. The gene we call the MATH – 1, and we've worked on it ever since.

DM: That's very impressive.

HZ: Thank you!

Interviewer's Note: Having covered Dr. Zoghbi's early life, education, influences, mentors, and lifelong career highlights, this interview comes to an end. The remaining few lines of discussion on the audiotape are Darra McMullen and Huda Zoghbi discussing how to meet up again to discuss other topics of interest to Darra McMullen.