The Gene Story
(Podcast 1 in 20000)

A - Avantika(Interviewer), D - Deepanjana(Interviewee)

Avantika- Welcome to the show Deepanjana, that is quite an impressive CV and I am very curious to know about your work and also the field of genetics in particular. So why genetics Deepanjana? What is the relation between genetics and rare diseases?

Deepanjana- So, when we let us break this questions down because there are probably three questions over here. One is what is rare diseases. S**o rare diseases are those diseases which are not commonly seen like it is not the common cold, cough or you know the normal appendicitis or whatever like you know the reasons why we crowd OPD rare diseases are those which are not often seen by a doctor in OPD or a hospital scenario and if we are looking at the numbers, these numbers anything which has an incidence of more than 1 in 2000, which we call as a rare disease. It means if we screen 2000 people 1% is going to get that and that is the lower limit of rare diseases.** Normally there rare diseases which are like 1 in 60000. Like if we screen 60000 individuals, 1 individual gets it. Most of these numbers are region specific so in a lay man's term the way I would describe it rare diseases are those diseases which are not commonly encountered by the doctor. Now as you can see that majority of these rare diseases like 80%, more than 80% of these rare diseases have a genetic background. That is why this link of genetics with rare diseases has been, the association has been so strong. When we talk of denovo it means when the egg meets the sperm it is a perfectly healthy egg and a perfectly healthy sperm. It forms an embryo and from this embryo which is almost a single cell, multi cellular organism or human being is formed. Anything can go wrong over here. **So if something goes wrong beyond the form of the embryo formation till the multi cellular organism is formed, this is something which we call as a denovo or spontaneously acquired change but sometimes in most of the cases there are cases where this is heritable which means it comes from the family, from the generations of the family. there maybe generations of the family, who do not have a clinical manifestation or do not have a clinical symptom of what we are seeing in the patient but still carry this genes in a hidden way.** If I again try to explain that it means that you know, all these genes are in pairs in humans because there are 46 chromosomes and these 46 chromosomes which sort of bear the genetic material or the blueprint of life are in pairs. So there are 23 pairs of these chromosomes and each of the 23, when the child is born 23 is received from the father and 23 comes from the mother. Now since the father and the mother have these genes in pairs, there may be one good copy and one copy which is a variant or you know sort of a bad or a mutant copy.

A- I am curious because you spoke about genetic counseling and genetic tests and how there is a perception among parents that these tests might be expensive so is that the case and are genetic tests available readily for parents to access what is the entire process like.

D- Genetic testing right now is available in India. Depending upon the type of test, the affordability comes in so our tests which are on the cheaper side and which covers a lot of diseases like the newborn screening or prenatal screening. **These tests right now are affordable and they are quite I will not say non expensive but on the lower side of the**

expense. Because if you are comparing this with a normal blood sugar test or a normal you know hemoglobin test , these are definitely more costly. But then there are tests when we are talking about the gene sequencing or a specific testing, these testings are obviously more costly or if we are talking about a chromosomal like you know chromosomal analysis. These testings are costly, sometimes many families are unable to afford it but then necessity is there to do all these testings. The good part is that most of these testings are right now being conducted in India itself and if it is being conducted here then it means that the prices would go down and that is what we have because we have to start somewhere at least the test which were not available even 5 years back are right now, all the tests are available over here and it is being done by companies which are doing all over the world , the quality of these testings are also as good as what you can get internationally. Regarding the affordability I would again say depends on the and sometimes we as genetic counselors or try to break down the test so that minimum tests are done but it is always not the case, sometimes three members in the family have to be tested so there financially it does become an impediment for these families to do that. **Also there is a social taboo, I have had families you know cases I would not say urban area but you know cities as well where they feel that if a family member is identified of a genetic disorder and confirmed then it is not good for them and their family in the society so there is a lot of psychological impediment.**

A- how long does it take usually because I think medicines take years to develop.

D- Yeah, when we are talking about medicines the thing is that there can be two kinds of you know therapy which is given. One is where when we are talking about gene variation we are talking about say an enzyme is missing because of the gene mutation or gene variations and we just supplement it so this is what happens in enzyme replacement theory as therapy as we see it in Gauchers or GM1 or even pompe's disease so you know this kind of thing exists and the enzymes first have to be tried as animal studies to see toxicity then they have to go through phase 1 trial where you administer it and very small number of human beings who you register for a trial, after seeing and following them up that there is no side effects then you go into phase 2 where you have more number of people in the trial and after that when there is no side effects who actually sort of, there might be a few side effects and you actually these benefits and if the benefits is more than this drug would be ultimately approved after a phase 3 trial which means, and the phase 3 trial huge lot of individuals would be registered and if the therapy works then it is accepted. This is for enzyme replacement therapies but this is also true for gene therapies as well. The problem with gene therapies is that it is very personalised because every person will not have the same kind of gene variations or gene mutations this means that a genetic diagnosis has to be made and whatever therapy has to be there has to be personalised for that particular person. Now in this scenario what happens is that as I said you know animal studies, toxicity studies becomes very difficult and this is the main impediment in disease research because the ethics comes in. Would you administer, even if you have the you know means in your hand you can not go and administer human being because you do not know what the side effects are. The cryspacas system is basically a self correcting system where if you introduce it, it will correct the gene variant and we are expecting that whatever damage has been done will remain but then it will not proceed. In this case what is happening right now is that though people are very hopeful about it people are also worried about off target effects means that if you introduce such a system, it will correct the system which you want but will it also not correct or will it also create other kinds

of problems? Will you have cancer because of this, will you have other toxicity because of this? Because of this would you, you know where you were given a life span of 10 years, would you just have a life span of 1 year. So these particular questions are now being answered as far as the research scenario is concerned, though we are very hopeful for a gene therapy for a personalised gene medicines to come up but I feel it will still take time this part was that what I wanted to say was that research is there we are very hopeful you know something will come out but there are ethical issues which need to be addressed and there are global bodies which are sort of looking at this, there are toxicity issues, there are also issues which are like off target, issues that it is correcting something right now but will it create more chaos in the person which we are not understanding at present. So the other part being that the rare disease, we do not have many patients for one particular disease so here the role of parent association groups also comes in where if you have such parent association you know the groups they can come in and they can actually raise these questions and help the scientists answer these questions in their own ways because then the ethical part or the other details get much easier.

A- It is quite overwhelming to hear about the complexities of the human body. Most of us grow up thinking that the human body is the same in the norm which means that basically all of us, almost will follow a certain trajectory but listening to you it is not the case at all.

D- That is it is a sad part because with cancer right now there is much clarity, **but with rare diseases the clarity is not there as far as the clinicians are concerned**. As far as the scientists are concerned the variability of the phenotype like which, by this what I mean is that a person can have same kind of genetic variations but the symptoms can be very different in two individuals having the same genetic variations. So in these cases right now they are saying there are modifiers, there are demodifiers **but you see the bottom line is that what we understand is very less and that is where the clarity is not there hence it is very complicated. Also as you very correctly pointed out through our discussions that a rare disease can happen anytime in life.** It is not necessary that it will be from the birth or it is not necessary that it will be form 5 years or 10 years, there are many cases where regression occurs like the child is all well but then the child comes down the wheelchair and almost lying, **so the trauma a family faces and what a family goes through is huge** so the researchers are working but then we also have issues I guess are right now being ironed out but still it is along way ahead, yes.

A- Indeed. Here I would just point our listeners to the last episode with Mr. Ziya who is a parent of a son with rare disease and he spoke exactly what you are pointing to that **rare disease are one of those things which are quite traumatic to families and coping with the rare disease as well as the medical angle which is the treatment going to doctors, knowing what it is about, being misdiagnosed than perhaps being diagnosed then continuing on with the treatment is one part,** the second part which in the conversation you did mention was the social part where a lot many families may not be open to a child with a rare condition and around them and as a genetic counselor I would be very interested to hear your perspective on how do you deal with such cases then. Here by cases I mean medical cases because humans can not ever be cases right? The medical part is one thing but a child's life, it is the question of a child's life or it is a question of a person's life. So how do you deal with cases

where families are not accepting off the diagnosis or not gonna accept going in for a genetic test?

D- So, yeah there are many families who are resistant to a genetic test you now let me put it that way. **And there are many families who have a genetic test but they are not ready to accept it that way. And let me tell you it is irrespective of the education status what I see**. So there if again I try to explain, there are many you know social obligations and social, ethical things which a genetic counselor has to face while counselling. These are one of them so here we more or less stress on the management part. So see it is a process of acceptance, it might not happen at one go. As a genetic counselor you have to be patient for these cases. In most of the cases when you understand that you know this might be the case but then the family is resistant you still ask the family to go for at least the management, maybe not the diagnosis part but the management part. Management over here involves multi disciplinary team, sometimes a cardiologist a pulmonologist, a pediatrician or maybe you know a neurologist so what your diagnosis is one part because sometimes families are very happy to find that closure. Sometimes families are resistant towards it but at the same time you will not you know stop the management or stop improving the quality. **Like I say there are many patients who come and say the drug is available but it is so expensive I can not give my child but then my question is why not by the time the drug becomes affordable why not increase the, you know why not give the child a good lifestyle by doing the standard of care protocols**. **There are many diseases where these standard of care protocols are available and if followed then the child's life quality increases greatly and actually reduces a bit of the suffering**. Also at the same time I always you now try and counsel patients who are psychological counselling this is very much needed for a family who has a diagnosis or has been suspected of rare disease. It is not easy, it is not at all easy. it is not easy on many levels, it is not easy to accept that my child has such a problem and might now survive after a point, it is not easy to accept that why me, It is not as a person to accept that my child has got this because I have something in me so these are not very easy things and these are not one day things so if a parent or if a family is resistant the first thing we stress is the management. The child needs a medical you know intervention. So interventions are what we try to provide first and once the interventions are going on the parents start having a communication with the doctors, the doctors also try to convince and let them understand that see if genetic diagnosis are done we can work more on the management part.
Sometimes in many cases families agree after a certain point of time because there is this 5 stages of grief which every family goes through and sometimes after that they sort of agree for genetic diagnosis. Sometimes it is financial, they say and we try to fund raise it but there is also a social issue to it. **There are many diseases which are X linked which means the mother of the child might be responsible for this disease because females have two XX's and they might not have the disease while the male child if receives that variant that bad X from mother would have it and these are social taboos because if you say that to families they will undergo a divorce or they will just put this mother back in her father's house and the whole family will break**. So these are very crucial cases while you can not withhold information, you also have to sensitise the family before delivering such information. So there are cases where the parent feels that if one of my child gets diagnosed of a genetic disorder then my other child I will not be able to place him in the society or my other child will not be able to have a married life or something. So there does not happen one day sometimes families irrespective of education status or irrespective of their you know profile, you need

convincing, you need a lot of talking for then to understand why it is necessary and many families do agree but yes initially there is a resistance and **sometimes families who get detected also they are very scared because of the social trauma so I guess as a society also if we are a bit open and a bit compassionate, you now if our mindset changes a bit that also helps these families who have been diagnosed.**

A- That is a very, very important point that in our daily course of life somehow we might not know that is a person is a rare disease patient or a person has a loved one who has a rare disease. Just I think because this is a medical podcast in the sense that we are talking about medical jargon. I'd just like to say that SMA is spinal muscular atrophy which affects muscular atrophy and it affects the muscular system which means that sometimes children or even adults who ever is diagnosed with SMA is not able to function properly in terms of their hands, their legs am I right?

D- **Muscular Atrophy is a problem with proximal muscle weaknesses. What happens is that the muscles which are closer to our trunk, you now closer to our torso gets affected and they cannot move these muscles** so they cannot raise their arms or raise their thighs. They can move down from theirs knees but cannot raise their thighs from the hips and they have severe spinal sort of bending which we call as scoliosis. The even have problem breathing because you know their lung capacity is not there because of the muscle weakness and also these people sometimes have problem with gastric system because of swallowing because that is also a muscle and that is also a muscle. So you can understand how difficult it is for these people like you know follow properly who cannot breathe properly, who cannot cry loudly so it is really heartbreaking to see even you know you are seeing sometimes this happens like sort of gradually in a child you know you see the symptoms around 7-8 years so you had a child who was absolutely healthy for 2 yrs, 3 yrs, 4 yrs and then suddenly you are seeing this kind of a muscle weakness. It is heartbreaking. but that is the sort of sad part where you cannot really help but here in these cases if you actually have management, if you actually go through all the types cardiologists and neurologists so it sort of **somewhere ensures your child has a better life quality than not being treated at all.** There are guidelines which can be followed and most of the times there guidelines are shared by the pediatrician to the parent and sometimes the parent association groups also have these kind of guidelines where they can train other mothers or the newly diagnosed families on this after the pediatrician has briefed them so that really helps because most of the parent association groups follow this and this actually increases the lifestyle a lot. Like it is really, really helpful in this case.

A- Right, my last question would be and I know that we covered the genetic part extensively as well as rare diseases in children but what about adults, I think in rare diseases a common statistic that we have is that 80% of rare diseases occur in children in childhood. So that is an estimate but what if an adult is diagnosed by a rare disease. What happens then? As a genetic counselor how do you counsel such people?

D- I will again tell you a story which sort of breaks my heart to say. So I had a patient who was in the mid 40s he was a computer scientist so he used to type a lot and the first thing felt was that he had muscle weaknesses and he could not type. Gradually he lost everything, all his motor functions and he was bound in a wheelchair. He had a life where he had his wife and

son. His wife got scared and she was unable to take this from him because he was the sole bread earner and she not to be judgmental but she couldn't handle this and she left him with the son. Now this parent, this adult who was supporting the whole family was looked after by octogenarian parents. Now the main problem over here comes to that you know these parents also cannot support the child, the adult. Because number one financially, number two the amount of care that needs to be taken for this particular adult is not physically possible for an octogenarian parents. So here as far as the diagnosis goes it is the same as what we do and as a child we go through the same kind of procedures, we go through. There are same kind of standard of managements there but see as a child it is easier because you have your parents and your parents are not octogenarian. They are also in their mid 20s, 30s, they are able to take care but here it is an adult and we sometimes really have no answers when they say that they have nobody to look after. That poses a lot of challenges. **Like in the west there are homes where you can out these child but unfortunately India does not have that, those kind of homes and this becomes a major challenge because financially they might be the bread earners and they have lost everything.** We can, as clinicians or as genetic counselors we can counsel them but we cannot go into the social support which they need. **Then I would repeat here NGOs and societies need to think about these people and also these people have a lot of mental trauma because they were leading a life which was suppose I will just quote, unquote normal.** "NORMAL". And suddenly they have to live with a particular thing which they cannot accept and here the acceptance is you know more difficult than in a child because normally the child as it is difficult for the parents to accept but the child is fine, the child does not understand. The child is ok because the child has it from birth. The child does not know or the child understands that okay I have a problem. Children are more open but as adults you are more closed so here the major issue is the mental health and also the social support which we in most cases are unable to provide if we are looking from the clinical side and that becomes an impediment also.

A- Indeed and which brings me to the question why are we not being able to support fellow humans as a society and I do not mean this as a moral judgement but I just mean in terms of the facts of the situation. Now this can happen to anybody at any point in their life so why is the discussion so limited. Thank you so much for a very very insightful conversation. It has been a delight talking to you and your inputs and your feedback from the field, **from day to day looking at patients and not just patients, that is just one part of their life but what you touched on is something more comprehensive and holistic that they are real people. These are the stories of real people who are operating in the real world. They have the same kind of issues and challenges to deal with but at the same time it is so heartening to see that they also have people like you who are supporting them and who are creating that safety net and being able to sort of helping them not just survive but thrive.** So thank you so much for this conversation.

D- Thank you so much for having me here and I would just end with one word that when you go out and second also sometimes just in your mind have this thing that If you see somebody be compassionate. Somewhere they do not actually need sympathy. so the reason you said that why we cannot is because we do not think about the other human being and thank you so much for having me.