

Vol 20 | January 2022

GeKNOWme

Internal Quarterly Newsletter

Cover Story

17q12 Deletion Syndrome: A case study complicated by MODY, Diabetes and Autism

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Book Review

The Code Breaker

WORDS FROM THE FRONTLINE



Vachana Jayaram, Associate Director, Human Resources

Dear MedGenome Family,

Wishing everyone a very happy, and most importantly a Healthy New Year 2022!

If the past 2 years has taught us anything, is to focus on our well-being & that of our loved ones. Not limited to physical well-being, but also emotional and social well-being. Here's to that!

So, my journey with MedGenome started about a year and a half ago, right at the onset of COVID, while the entire world was still grappling to understand what a pandemic was and the consequences thereon. However, better late than never, the whole world rose to the occasion and identified numerous ways of managing the crisis, be it at home or work or in society.

The only way I would like to remember these times is as to how grateful I am to this entire experience. I agree there has been a lot of pain, loss of jobs/lives, a huge disruption to the "normalcy" we were comfortable with, however, it did allow us to 'stop' & 'think.' Gave us a whole distinct perspective of life, our priorities, and a reason to focus on 'things' that matter!

As we are in the business of essential services, other than the fact that I am associated with an organization that's providing the need-of-the-hour services, I am also grateful for the fact that I got an opportunity to come to the office regularly, be it to engage with my manager, team, stakeholders or because I got away from the "new routine" that most of the world was struggling to cope with.

My 16 years of work experience has been with the IT sector, and one of the main reasons I made the shift to the healthcare sector is because of the people who were involved in interviewing me. I am thankful to Surajit, Ram & Sam who provided me with this opportunity to work with such an amazing company – MedGenome! One of India's leading Genomics companies and a trailblazer in this space. Finding these details while you are researching about the company is a proved fact, however, experiencing it on the job is more gratifying and fulfilling.

Working with each of the intellectual group of stakeholders/colleagues has been an amazing experience, with everyone being extremely welcoming, especially my team. I admire the simple culture, which emulates from the Leadership team and transcends through others as well – highly passionate, hands-on, and available always!

During these 2 years, amongst the several initiatives that the Organization implemented, I am proud of how efficiently and swiftly we managed the COVID-19 situation, with little or no impact on the ongoing business. It is applaud-worthy how an entire organization came together and stood by the vision of the organization of "**Clinical Genomics for India | Indian Genomics Platform for the World.**"

Some of the key changes implemented, keeping the safety & well-being of our employees as a top priority, were providing cabs for regular office comers, increasing our group medical insurance coverage, flawless execution of the CARE program which took care of more than 180 employees, and their families – above & beyond the medical insurances, provided accommodation to either those who were impacted by the virus or the ones who were sharing space with them, several vaccination drives, the introduction of the first-ever recognition program – Elite club – to felicitate our frontline heroes and employees who went beyond their call of duty, hiring & combination onboarding of close to 200 new joiners in the FY, engaging with the employees via one on ones, team meetings, leadership offsite and above all, it wasn't just about work – with celebrations of festivals and other events that showed overwhelming participation and appreciation!

I would like to extend my sincere gratitude to my entire team – HR & Admin, without whom none of these initiatives would successfully be implemented and activities be well executed. Thanking all the senior stakeholders, management is a given.

MedGenome continues to provide a great learning platform for everyone. If you are willing to invest the time to learn and grow, opportunities are ample. With additions of new partnering labs and expansion of our presence across pan India, location is not a limitation either.

Wanted to end this note on something I read recently – Ten years from now, you'll put on a jacket and find a mask in the pocket. "Oh man! What a weird year it was!." You'll chuckle to yourself.

Always remember - This too shall pass.

Let us just stay strong, focus on the positives, and grab the opportunities along the way that benefit self, family, and society at large. Let us be kind and do our bit to support the less fortunate, as best as we can.

Looking forward to being with you all, as part of many more successful milestones that MedGenome is set to be on.



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Activities to engage with clinicians, researchers and thought leaders

From our US Office

MedGenome engagements, participation in events, symposiums, etc.



Gender through a feminist lens



77 From our Colleagues

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Most Talked About

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EDGENOME NEWS

October to December 2021

MEDGENOME NEWS

Industry Outlook TOP

BIOTECH STARTUPS - 2021

ACTIA • CLARIA • PRIMA • MICRA • Business • Research • Awards • Genetic Counselling • Health Care

HEALTHCARERADIUS RED People v Features v Diagnostic & Radiology Products & So

MedGeno me and Emmes launch genomics strategic partnership focused on advancing rare disease research

Rare diseases affect a small percentage of the population but are often chronically disabling and life-limiting with few treatment options.

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eddenome, a leading genomics research and diagnostics company announced a urtnership with Emmes, a global, full-service Clinical Research Organisation dedicates supporting the advancement of public health and biopharmaceutical innovation, med at accelerating breakthrough treatments, powered by human genomics, for rare supporting the second second

am Ramprasad, CEO, MedGenome Labs said, *Few people realize that India a b: Vedam Ramprasad, CEO, MedGenome Labs said, "Few people realize that India and point Asia have the work's larges population of people affected by rare and inherited lisease. Oven the high unnet need of these patients and families, we are dedicated to spanning support and apportunities of the rare disease community in South Adia to ontribute to and benefit from, the substantial treatment advances being made in rare liseases globally. Rare disease clinical trials face substantial resourtment and guidatory challenges globally. Our rare disease alliance with Emmet is positioned to tate these es and is a natural exte on of MedG ment to support rare disease patients and clinicians in South Asia."

MedGenome Labs Ventures into Direct-to-Consumer (D2C) Business, Offers Easy-To-Do Genetic screening in

In a shady published in the Journal of Generics, the estimated prevalence of EAd in the graphitum which entropolates to a bodien of about 21 million effection indebudant, and in the last the same, the involves of about 21 publics entropolation and about 24 bits of the entry Age of reviet is a new monitorial to be about 25 to tablets in the and the entry Age of reviet is a new monitorial to be about 25 to both the income, by Weller Rampessel, GEO, Meedlemann, stati "Heart dimension can new Amount" on the Areal about the about 25 to the same Amount" on the Areal about the same monitorial to be about 25 to the same Amount of the Areal about the same new Amount 25 to the Area.

India

Global Pharma Times

Healthworld.com

News
 Interviews Ellogs Feature
 Medical Speciations
 Data & Analytics
 HealthTV

MedGenome to expand portfolio through Trident Diagnostics acquisition

MedGenome Labs has acquired Trident Diagnostics & Healthcare Pvt Ltd, a diagnostics and radiology healthcare Centre based in Bengaluru. settiwood + novemen 24 2021 12:27 GT

(f) (n) (0) (B)



(A) (A+) (A-)

Earlier this year, MedGenome Labs also ventured into direct-to-consumer (DTC) category under the brand name Genessense, offering specialized, evidence-based genetic screening tests that provide insights into a person's health much before the onset of symptoms. This acquisition will help expand the access to these tests to consumers in Tier II and III markets.

Speaking on the acquisition, Dr. Ramprasad, CEO, Diagnostics, dedGenome Labs, said, "At a time when coronavirus has turned the vorld's attention towards genome sequencing and its role in timely revention of infectious diseases, we are taking another step orward to convey the importance of genomics and personalized medicine in healthcare to larger population.

MEDGENOME LABS **PIONEERS IN IMPROVING HEALTHCARE THROUGH** PRECISION MEDICINE

<text><text><text><text>



For video, please click https://www.facebook.com/middayindia/videos/267841948461498/

For press articles, please click https://diagnostics.medgenome.com/press/

MedGenome Connect

Clara Reproductive Genetics

The last quarter has been a very busy one for Claria. We concluded our FOGSI webinar series with 7 webinars in December. The second webinar for Sonogenetic series with Dr. Ladbans Kaur was also concluded. The team continues to conduct regional CMEs and participate in multiple conferences like – USCON, Society of Fetal medicine-Gujarat Chapter etc.







Dr. Ramesh Dargad

Dr. Vaibhav Dedhia

er Pagad

Dr. Zakia Kha

Dr. Girish Sabnis

Dr. V. T. Shah



It was an action packed quarter for the Actia portfolio. There were multiple online & offline initiatives / activities that were planned and executed in the months from October to December 2021. Few notable events were the one on the NGS testing in the current era of diagnostic where prolific speakers like Dr. Sumita Danda & Dr. Sheela Namboothiri shared their thoughts with a highly capitative audience. Another activity was done in collaboration with Cardiology Society of India (Mumbai Chapter) about the importance of genetic in Cardiology. This was a well-received session where over 250 eminent cardiologists participated and agreed about the active role genetics plays in certain diseases with respect to cardiology.

MedGenome Connect

Prima Cancer Genetics

Prima

29% to 45%

Lung Cancer awareness month

The last quarter was a very busy one for Prima, the team engaged clinicians in multiple physical as well as digital activities. We did webinars with KOLs like Dr. Aju Mathew and Dr. Indranil Ghosh as well as participated in major conferences like PHOCON, ABSICON, etc. October also happens to be breast cancer awareness month for which a digital campaign on social media was conducted along with KOL engagement activity with our key doctors-Dr. Pramod Kumar Jhulka & Dr. Amit Rauthan. We also launched our HRDTrack test.

Prima



lia are reported in the advanced stages¹

Early detection is the key Take BRCA1 and BRCA2



The last quarter has been a very busy one for Micra. We are introducing a couple of new tests to our infectious disease portfolio. An article was also published in CNBC on the surge of dengue and chikungunya cases, the author for the same was Dr. Gunisha Pasricha- Principal scientist



(https://www.cnbctv18.com/views/surge-in-dengue-double-trouble-during-c ovid-19-pandemic-11615302.htm). Many new variants of SARS-COV-2 have been detected recently and we will be resuming our COVID RT-PCR campaigns.



Prostate Cancers Date and Time: 22nd October 2021. 8 pm onwards

Dengue is a viral disease that is transmitted by the bite of a female mosquito named Aedes Aegypti, which is already infected by the virus. Aedes aegypti is a daytime feeder and the peak biting periods are early in the morning and in the evening before dusk.

What's new



Profile Of Pathogenic Mutations And Evaluation Of Germline Genetic Testing Criteria In Consecutive Breast Cancer Patients Treated At A North Indian Tertiary Care Center - Annals of Oncology

To read, click-(https://www.annalsofoncology.org/article/S0923-7534(21)01047-4/fulltext

MedGenome and Emmes launch genomics strategic partnership

With a high burden of rare diseases in India and South Asia, MedGenome has entered into partnership with Emmes, a global, full-service Clinical Research Organization (CRO) to support the advancement in biopharmaceutical innovation through human genomics, for rare disease patients, with initial emphasis on hemophilia, Duchenne muscular dystrophy & muscular atrophies and retinitis pigmentosa.



Trident Diagnostics Healthcare Pvt. Ltd. has joined MedGenome Labs.

Trident provides diagnostics and radiology services of over 500 tests to Government projects, ESIC, General Hospitals and other individual practitioners.



HRDTrack Test Launched

Proud moment

MedGenome has been awarded the 20 wonderful workplaces to shape your career by The CEO Story.





Launched MedGenome Intranet

Hello MedGenome Family!

We launched our first intranet site - a common platform where you will find all internal information and communication.

As a start, we have launched the version which has a few basic features such as announcements, news, HR initiatives, quick links to Eazework, event photos & videos, GeknowMe - newsletters, and much more!

We aim to upgrade it with some more useful and informative features for all of you to benefit from.

How to access?

Intranet has been set as a default brower. You can also access it by clicking <u>https://intranet.medgenome.com</u>. and use your medgenome email id to login. In case of any difficulty, please reach out to the IT department.

What you need?

Office network- LAN or VPN. For those outside office network, we will shortly share the access process.

Of course, your feedback is important to us!

It will be great to get your suggestions that will help us to make the platform more interactive and engaging. Visit the platform, spend time on the available features and do drop us your suggestions at <u>edify@medgenome.com</u>.

We encourage everyone to leverage this platform to the fullest.

From Our US Office

We continue to add information, rich articles to our blog. Some of the recent ones are:

- 1. Next Generation Sequencing: A Historical point of view and its Emergence
- 2. Impact and applications of NGS: Opening the doors into the world of "omics"
- 3. High-throughput antibody discovery using single-cell B-cell receptor sequencing (scBCR-seq)

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Research Services Blog

RESOURCES

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Please visit our blog at https://research.medgenome.com/blog/ to see the archives. You can share your viewpoints and articles at mgus-blog@medgenome.com

Also, MedGenome US conducts regular internal trainings for Commercial and NGS lab members on assays offered. One of them on 'RNA Sequencing' is available in the link below.

https://www.youtube.com/watch?v=Qm1KD6UuMwM

The recordings are archived in LIMS for all the team members to review at any time.

We leave with some Halloween Celebration Pictures from our US Office!



Sneak Peek into the World of Science

17q12 Deletion Syndrome:

A case study complicated by MODY, Diabetes and Autism



Dhriti Chendil Nathan

Genetic counsellor and clinical report coordinator

Introduction

Diagnosis of kidney dysplasia is based on ultrasonography, which shows an echo-bright kidney either with or without cysts and poor corticomedullary differentiation (Vester et al., 2010). In a significant number of cases, the underlying root cause of kidney dysplasia has been traced to gene mutations in Hepatocyte nuclear factor-1-beta (HNF1β) gene along 17q12 (Okorn et al., 2019). Hence, when an ultrasound scan on George Jones (name changed) confirmed the existence of renal cysts, he and his family (names changed) (figure 1) were referred to clinical genetics.



Figure 1. Pedigree of George Jones' (names changed) family (Image made using pedigree progeny genetics).

Diagnostic tests and results

Ultrasound results

Study conducted by Vasileiou et al. (2019) established that approximately 92.7% of patients with microdeletion of 17q12 are afflicted with kidney abnormalities postnatally. Hence, renal ultrasonography was conducted on selected relatives of the proband (Table 1) under the possibility that renal abnormalities are indicative of 17q12 deletion.

Family member(s)	Ultrasound scan(s)
Carly Jones	Presence of renal cysts detected
Diane Smith	Absence of renal abnormalities
Nigel Smith	Absence of renal abnormalities
Bernie Smith	Absence of renal abnormalities
Table 1. Results of ultrasonog	raphy

SNP array result

SNP array concluded a heterozygous deletion on 17q12 of approximately 1.4Mb, spanning the genes ZHNIT3 to HNF1 β (Figure 2 and Table 2) in the proband.



Figure 2. Depiction of the SNP array result and the genes impacted. (a) LogR chart showing a heterozygous deletion of 17q12. (b) Genes involved in the deletion of 17q12 based on *Ensembl*. (Images taken from Palumbo et al., 2014, and Cunningham et al., 2019)

Table 2. SNP array result

Family member(s)	Molecular ISCN	Interpretation			
George Jones	arr17q12 (36479944-37777999)×1	Heterozygous deletion at 17q12			

MLPA results

MLPA analysis was performed on selected members of the family. Results are summarised in Table 3 from which it can be derived that either Paul Smith or Mandy Smith likely has a de novo mutation causing germline mosaicism for 17q12 deletion (reviewed by Mitchel et al., 2016). This was inherited by Terry Smith, Carly Jones and passed onto the proband.

Table 3. MLPA results							
Family member(s)	Molecular ISCN	Interpretation					
Paul Smith	rsa17q12(P241)X2	17q12 heterozygous deletion is not present.					
Mandy Smith	rsa17q12(P241)X2	17q12 heterozygous deletion is not present.					
Carly Jones	rsa17q12(P241)X1	Heterozygous whole gene deletion of $HNF1\beta$ is detected.					
Diane Smith	rsa17q12(P241)X2	17q12 heterozygous deletion is not present.					
Terry Smith	rsa17q12(P241)X1	Heterozygous whole gene deletion of $HNF1\beta$ is detected.					
Kevin Smith	rsa17q12(P241)X2	17q12 heterozygous deletion is not present.					
Kate Jones	rsa17q12(P241)X2	17q12 heterozygous deletion is not present.					
Ann Jones	rsa17q12(P241)X1	Heterozygous whole gene deletion of $HNF1\beta$ is detected.					

Autism Spectrum Disorder

Introduction

Autism spectrum disorder (ASD) is a heterogenous neurodevelopmental disorder, which affects approximately 1-2% of the general population, with male-to-female ratio of 5:1 (Wiśniowiecka-Kowalnik and Nowakowska, 2019). Causes of autism includes environmental factors (e.g. maternal lifestyle), genetics (e.g. Fragile X Syndrome), epigenetics (e.g. erroneous DNA methylation), and/or errors in metabolism like abnormal calcium homeostasis (Fakhoury, 2015; Kim, 2015). Either of these causes ultimately lead to changes in brain development, influencing neurological processes which manifest as autism (reviewed by Fakhoury, 2015).



Clinical features

There are three common cardinal clinical features of ASD: qualitative social impairments, deficits in verbal and nonverbal communication, and repetitive behaviour (Kim, 2015). However, it is important to consider that epigenetics, stochastic fluctuations, and/or environmental factors on the genetic variants is known to cause the ASD phenotype, resulting in complete concordance (Huguet et al., 2013). Hence, ASD is considered to have a complex heterogeneity. ASD's inheritance patterns are classified as monogenic, oligogenic, polygenic and multifactorial (figure 4; Griesi-Oliveira and Sertié, 2017).

Single high-risk variants are usually highly-penetrant, de novo, and often associated with monogenic disorders. ASDs associated with these disorders account for only 5-10% of cases (Benger et al., 2018; Ayhan and Konopka, 2018; Woodbury-Smith and Scherer, 2018). Genome-wide association studies (GWAS) have been carried out on large cohorts to discover and validate the causative genes for ASD and the associated syndromes.

Genetics of ASD

CNVs which account for about 10% of ASD are either sporadic or non-recurrent (Griesi-Oliveira and Sertié, 2017; Benger et al., 2018). The most common CNVs detected in ASD patients are listed in Table 6.

Locus	Clinical features associated with CNV
1q21.1 deletion	Mild to moderate intellectual disability (ID), schizophrenia, mild dysmorphic facial features, congenital heart abnormality, microcephaly, cataracts
16p11.2 deletion	Mild to severe ID, epilepsy, multiple congenital anomalies, variable dysmorphic features, macrocephaly, obesity
11.23 duplication	ID, schizophrenia, abnormal brain MRI, variable dysmorphic features
17q12 deletion	Mild to moderate ID, schizophrenia, epilepsy, MODY, dysmorphic facial features
15q11q13 duplication	Mild to severe ID, epilepsy, ataxia, behavioral problems, hypotonia
22q11.2 duplication	ID, schizophrenia, speech impairment, learning difficulties, heart defect, dysmorphic features, microcephaly

Type 2 Diabetes Mellitus

Introduction

Diabetes mellitus is a group of heterogeneous disruptions characterised by impaired glucose tolerance due to insulin deficiency and/or insulin insensitivity. It can be classified into different groups depending on its aetiology and clinical features, including types 1 and 2 diabetes. Within T2DM's multifactorial nature, certain lifestyles, genotypes, and populations have a higher predisposition for developing T2DM within their lifetime.

Among widespread comprehensive analysis, T2DM is most highly associated with obesity (a body-mass index; BMI of 30 and above). Individuals who consume a diet high in glucose, calorie intake and are obese may initially begin to exhibit increased, but not total, insulin resistance (Zheng et al., 2017). The link between T2DM and obesity remains more complex.



Maturity-Onset Diabetes of the Young (MODY)

Introduction

Maturity-onset diabetes of the young (MODY) is an autosomal dominant disease that affects approximately 2-5/100,000 children and 1/10,000 adults (Kim, 2015). At the onset, MODY cannot easily be differentiated from type 1 and type 2 diabetes mellitus (T1/2DM) based only on clinical characteristics. In the UK, approximately 80% of individuals with MODY are estimated to be initially misdiagnosed with Type 2 Diabetes; current calculations indicate that there is a 15-year delay from the diagnosis of diabetes, to a genetic diagnosis of MODY (Kim, 2015; Urakami, 2019). Clinical manifestations of youth-onset type 2 diabetes may be similar to those of MODY; however, patients with T2DM usually are obese, whereas those with MODY are not.

17q12 recurrent deletion syndrome

Clinical Features and Inheritance

Features of 17q12 recurrent deletion syndrome (Table 12) include structural or functional renal disease, MODY5, and a spectrum of neurodevelopmental or psychiatric diseases, including autism spectrum disorder, schizophrenia, and developmental delay among others. These findings occur at variable combinations, the most frequent being kidney anomalies (80-85%), followed by neurodevelopmental manifestations (50%) and MODY5 (40%) (reviewed by Mitchel et al., 2016). Females may also develop Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome which has an incidence of 1 in 4,500 (Ledig and Wieacker, 2018). In addition, dysmorphic features in 17q12 recurrent deletion syndrome have been reported in a study by Laffargue et al., 2015. The observed features included highly arched eyebrows and epicanthal folds, but only three features (high forehead, deep set eyes and chubby cheeks) were found to be statistically significant.



Frequency	Features
Most Common (>50%)	 Renal structural or functional defects Neurodevelopmental/neuropsychiatric disorders Mild dysmorphic features
Common (25%-50%)	 Maturity-onset diabetes of the young type 5 Genital abnormalities Liver abnormalities Eye abnormalities Nonspecific Structural brain findings
Common (25%-50%)	 Other endocrine Cardiac Musculoskeletal Gastrointestinal Seizures Macrocephaly Congenital diaphragmatic hernia Hypotonia Sensorineural hearing loss Hypoplastic, thick nails / onychodystrophy Prenatal oligohydramnios

* Data combined from 27 studies of 152 patients with the syndrome.

17q12 recurrent deletion syndrome follows an autosomal dominant inheritance pattern. The majority of deletions occur de novo and only 30% of deletions are inherited with a possibility of gonadal mosaicism. The syndrome exhibits high penetrance. However, clinical features may vary greatly between family members who share the same deletion (reviewed by Mitchel et al., 2016). This may be due to the effects of genetic or environmental modifiers (reviewed by Clissold et al., 2015).

Diagnosis and Genes

1.4 Mb heterozygous deletion at 17g12 using CMA (which has a 100% sensitivity) or targeted deletion analysis diagnose 17q12 recurrent deletion syndrome. This deletion encompasses 15 genes (Figure 5) the most clinically significant being HNF1ß and LHX1 (reviewed by Mitchel et al., 2016). The renal and extra-renal manifestations of 17q12 deletion syndrome are a result of HNF1 β mutations as previously discussed. The syndrome has been found to be associated with neurological manifestations. Laffarque et al., (2015) proposed three hypotheses. The first, attributes neurodevelopmental disease be direct result of HNF1_β to а haploinsufficiency. Also, the interaction of HNF1 β with Hox-A1, a transcription factor, may impact neurocognition because HOXA1 infers autism susceptibility. Thirdly, the deletion of other genes like LHX1 may also cause neurological symptoms as it is expressed in the brain during development.

Name	Description			Morbid	Morbid		DDG2P		%HI		pLI	
						т	0	-	0		0	ł
AATF	apoptosis antagonizing transcription factor	-		-		-			1.45		0.00	
ACACA	acetyl-CoA carboxylase alpha	-		-		4			2.39		1.00	1
C17orf78	chromosome 17 open reading frame 78					2			76.26		0.00	7
DDX52	DExD-box helicase 52	-		÷.		÷			18 33		0.00	
DHRS11	dehydrogenase/reductase 11	-				-			34.53		0.03	
DUSP14	dual specificity phosphatase 14	-		-		4			15.35		0 77	
GGNBP2	gametogenetin binding protein 2	-				•			10.96		1.00	•
HNF1B	HNF1 homeobox B	-				Y			0.75		1.00	
LHX1	LIM homeobox 1	-		-					3.72		0.29	
MRM1	mitochondrial rRNA methyltransferase 1	-		÷		-			70.75		0.00	
MYO19	myosin XIX	-		÷		-			44.05		0.00	
PIGW	phosphatidylinositol glycan anchor biosynthesis class W	-		*					42.97		0,00	
SYNRG	synergin gamma	-		4		2			26,85		0.97	
TADA2A	transcriptional adaptor 2A	-				4			5.60		0.00	
ZNHIT3	zinc finger HIT-type containing 3	-		1					45.72		0.00	

Figure 5: DECIPHER database results of genes deleted in 17q12 recurrent deletion syndrome. There are 15 protein coding genes in this region. HNF1 β , the gene implicated in 17q12 recurrent deletion syndrome, is an OMIM, Morbid and DDG2P gene. It is a haploinsufficient gene and is extremely intolerant to loss-of-function mutations. Morbid genes are those known to be associated with a disease phenotype, DDG2P refers to Developmental Disorders Genotype-Phenotype Database, pLI refers to the probability that a gene is intolerant to loss-of-function mutations, %HI predicts haploinsufficiency (Firth et al., 2009)

Interestingly though, the study found that the cohort of children with 17q12 microdeletion who were diagnosed secondary to renal manifestations, displayed milder neuropsychological features. In addition, LHX1 pathogenic variants have been detected in patients with Müllerian duct aplasia/MRKH syndrome (Ledig and Wieacker, 2018).

Conclusion

This case proved to be complex due to the presence of two multifactorial diseases, ASD and T2DM, along with the presence of renal cysts in the proband George. Many genes, along with several environmental factors, have been shown to be involved in the onset of T2DM and ASD as previously discussed. A deletion of 17q12, which includes HNF1B, was also found in several family members. This deletion has been associated with autism and diabetes; however, it was concluded that there was no causative relationship between these diseases and the deletion in this case. The 17q12 deletion shows variable expressivity, explaining the phenotypic differences between family members such as renal cysts in George, Anne and Carly, and MODY5 in Terry. The case was further complicated due to the unknown origin of the familial mutation and it was deduced that germline mosaicism is the most probable explanation for this discrepancy.



Featured article

Gender through a **feminist lens**



Chhavi Dawar, Bioinformatics Scientist I, R&D

Dear Reader,

I wanted to write something of social significance, which influences our day-to-day choices and behaviours. The first thing that comes to my mind is gender. Through this article I wish to discuss what gender is, how we perceive it and how does it impact us personally and professionally.

What is a gender? What comes to our mind when we read or someone says gender? For most of us it's "male"/ "female" or "woman" / "man". For some of us it's just something that has got too much attention in the previous decade, and others wonder why all the façade about gender and for some others it's like any other political propaganda, they don't have to worry about it as it doesn't concern them.



Well whichever category you belong to, I have a news, I want you to know that gender affects you, your behaviour and those around you and their behaviours so deeply that it constitutes a larger percentage of what you perceive as yourself and how you express yourself.

Gender not until very long ago was believed and taught in sociology as a "social construct". What roles and responsibilities were given to you as a consequence of the biological sex assigned at birth was your gender. So basically, any society depending from which part of the globe you are reading this, has different roles, behaviours, expressions and identities associated with being a male or a female. And this became a person's gender. For example, I was assigned a sex of male based on different biological and physiological characteristics, such as reproductive organs, chromosomes, hormones, etc. But my characteristics as a man are defined by the culture I come from and I am expected to adhere to them. As a man I am expected to be strong, dress a certain way, earn a living, support my family, etc. So what being a man or woman is varies from society to society and can be changed.



Just to understand how deep the roots of gender are in our society, let's do a small but honest thought experiment; just close your eyes and visualize. What image comes to your mind when you think of the word Doctor? And now what image comes to our mind when you think of the word Nurse? Just give yourself a moment and think about these two professions and do you think they have been gendered?

Well, for most of us we see a man with a white coat and a stethoscope around his neck as a doctor; don't we? And for a nurse, it's without any doubt a caring, slightly older woman wearing a certain uniform. Now what are these images? These images are the social construct given to us from a very young age; remember those textbooks with happy family images, Dad going to work with a briefcase in hand, mom cooking a meal with a beautiful smile and kids running to school. These are images that have been around us from the very beginning and so they create these powerful narratives around what a gender is and what the roles around a certain gender are supposed to be. So we are in a way conditioned to perceive gender and its associated expressions in a certain way. But I hope, that in this little experiment, I have been able to give you a sense of what gender means in our society and how it influences some very basic ways in which we perceive people, things, language, cultures and professions around us. In addition, I also want to inoculate a thought in your mind that may be these perceptions are a bit biased and these rigid gender norms might be difficult for everyone to follow.

GENDER ROLES

litter

Sex which is given at birth and depending on if you were a baby boy (blue box) or a baby girl (pink box) certain things around you are conditioned and you grow up to be a certain way. That's gender. Until last decade gender was binary; man and woman and its expression was also acceptable in binary; masculine and feminine. But now feminists and gender experts are talking about gender as a spectrum.



Like gender, the definition of feminism has evolved overtime too. From a social movement of equal rights for women (in an era when women were not even allowed to vote) to now a social movement for equality irrespective of gender, caste, religion, race, sex, sexuality, nationality, political ideology and life forms, Feminism has evolved as an ideology and anyone who believes in it and works towards achieving it in any small or big way is a feminist. If you are someone who believes that irrespective of if you are born a human or any other species on this planet, you have the right to live well then you are a feminist because you believe in equality irrespective of the species and life form.

Now some people believe that since the word "feminism" has "femin" in it, it is only people with feminine attributes who can be feminist. Well that's not true. This confusion arose because the term originally coined by a utopian socialist Charles Fourier from the French word "feminisme" simply meant "being feminine," or "being a woman,". But it was in the 1st wave of feminism in the 19th and early 20th century when the word was actually used and became a synonym for women's rights and throughout the western world, it was used by social activists fighting for equal legal and political rights of women. But today anyone who believes in equality is a feminist. Feminism is now an intersectional approach to issues of equality and equity.





Now, I am sure, some of us might just enjoy the blue and pink boxes we were raised in, maybe we have made those boxes our world and being in them make us who we are, well that's just amazing. No one is asking you to tear down your pink or blue boxes; rather, we simply need to recognize that there are many more boxes than just these two. There might be someone who wants a new box for every day or every mood or someone who likes some walls of their box pink some blue or just any other color and that's ok too. As complex as it may sound, it is a very simple concept, "Acceptance without judgment". While a person's biological sex is assigned at birth, what they identify with and the way they express themselves is a choice they must be able to make for themselves.

Now how does this idea of accepting infinite gender identities help us as an organization or as any unit that is striving to work towards excellence?

Well by now, I hope we understand that how we perceive gender reflects in our behaviour and perceptions. Now imagine an organization that has people like you and me, who understand gender and don't look at it (or for that matter any diversity) from a biased eye. What then happens is that we create these inclusive spaces where no matter what identities you walk in with you have the space, liberty and the right to express yourself and be yourself without the fear to be judged. Who wouldn't want to be in such a space or organization that values you for who you truly are? A space that allows the perception and ideas of all those in the space to be expressed equally ultimately becomes a unit of people that is motivated to actually functioning at its full capacity. In the end, let me leave some pointers for us as an organization and individual to create such inclusive spaces.

- 1. Don't assume anyone's gender identity
- 2. Use gender neutral pronouns like "they/them" rather than "he/her" to address someone whose gender is not known to you
- 3. Don't engage and call out jokes that demean a certain gender or gender identity in your work and friend circle
- 4. Change the words you use; our language is deeply gendered and so we need to be very cautious of the words we use
- 5. Hire, encourage and embrace diversity
- 6. Use skills to asses an individual and pay based on skills
- 7. Ensure training and conversations on unconscious bias
- 8. Have regular trainings on POSH and ensure legal compliance

*The opinions expressed in this article are solely those of the author.





Book Review

Book The Code Breaker



Book review by

Ravi Gupta, PhD, Chief Scientist

This book talks about CRISPR technology that can easily program RNA molecules to target specific genes and change them. For humanity, this was a momentous step into a new age. The book covers nobel laureate Jennifer Doudna and her path that led to the discovery of CRISPR. This book also covers several scientists connected to the pioneering work in the area of CRISPR and its application in human cells. This book is divided into nine parts. I will cover four parts in this review.

The first part of the book covers the initial life of Doudna. She was grown up in Hilo, an old town in a volcano-studded region of the Big Island of Hawaii. This part covers the journey of Doudna from high school to Berkeley. When she was in the sixth grade when her father bought a copy of James Watson's The Double Helix. She read about Rosalind Franklin in the book and for the first time she realized that Women could be scientists. Rosalind Franklin was a structural biologist and crystallographer whose data was used without her permission in the discovery of DNA structure. It was so unfortunate that Rosalind Franklin missed the Nobel prize. Basics of genes and discovery of DNA structure is also covered in this part.



The second part of the book talks about CRISPR. I find this section very interesting. More than anything in the book I like the story of Francisco Mojica and his discovery of virus defense. He was the first researcher to figure out the function of the clustered repeated sequences. He and his thesis advisor termed it as tandem repeats and they initially thought that it could be related to cell replication. After completing two quick post-doc he returned to Spain and launched a research group to study the mysterious repeated sequences. It was difficult for him to get funding for his work and was suggested by many to stop working on it. The basic premise of Mojica was that the bacteria and archaea have a small genome, and they cannot afford to waste a lot of it on sequences that have no important function. So, he kept trying to understand what these clustered repeats were. He came up with a new name CRISPR clustered repeated interspaced short palindromic repeats. His wife said that this sounds like a good name for a dog. He also found that the repeated sequences were flanked by one of these genes, which encoded directions for making an enzyme. He named these "CRISPR-associated" or Cas enzymes.



To improve yogurt and cheese two young food scientists on different continents (Rodolphe Barrangou in North Carolina and Phillippe Horvath in France) were working on CRISPR. They worked for the Danish food company Danisco that makes starter cultures that are used to control fermentation of dairy products. The viruses that attacked the bacteria was one of the biggest threats to the food industry so that company invested a lot of money to study it. While studying the bacteria that has been recently attacked by viruses they found spacer sequences from them, perhaps suggesting that the bacteria has developed a system to defend from future attacks. This was another eureka moment. They did further experiment and showed that when you add sequences of virus in the CRISPR locus of bacteria they develop an immunity against the virus. When they went ahead and knocked out the CRISPR-associated (Cas) enzyme from bacteria it lost the resistance against the virus. They published their finding in the March 2007 edition of Science. Their finding was an experimental proof that Moijca proposed in his study. But still they did not know how things worked inside the cell.

Initially it was thought that the CRISPR system attacked through the RNA interference mechanism but instead CRISPR system attacked the DNA of the invading virus. This was shown by Luciano Marraffini and his advisor Erik Sontheimer of the Northwestern University at Chicago. Doudna never heard of CRISPR until she met Jillian Banfield at the Free Speech Movement Café in 2006 who was finding CRISPR clusters in the bacteria that she was studying. Doudna soon decided that the goal of her lab would be to dissect the CRISPR system into its chemical components. Until Doudna jumped into studying CRISPR components in test tubes it was under the preview of microbiologists. In 2009 her lab published a work on Cas1. They found that Cas1 has a distinct fold that helped the bacteria to cut DNA from the invading viruses and insert it back to the bacteria. This was the first explanation of one of the CRISPR mechanism from a structural point of view.

In spite of being in the forefront of CRISPR she ran into a midlife crisis. She was eager to do more applied and translational science. She wanted to convert the basic discoveries into therapies. She joined Genentech in late 2008. As soon as Doudna started working at Genentech in 2009 she started having a feeling that she is not at the right place. Her constant bad feeling was leading to mental breakdown. In two months, she returned to Berkley and left Genentech after she became aware of her passions and weaknesses. She liked being a researcher in the lab and not good at managing corporate environment where the competition was for promotion and power. Soon after returning to Berkley, she realized that she needed a good team instead of she doing all the bench work. This was the same feeling that Steve Jobs had. He said it is important to create a team that can continuously churn out great products than just few great products. Similarly, Doudna realized that she has to spend more time cultivating her lab rather than her bacterial cultures. It was a transition from player to coach.

In 2011, Doudna met a French scientist Emmanuelle Charpentier at a conference in Puerto Rico. They both got excited to work on Cas9. They began with a series of Skype calls to plan out a strategy for figuring out how the CRISPR-Cas9 works. Doudna was initially unsuccessful in making CRISPR-Cas9 chop up the DNA of a virus by adding two components – Cas9 enzyme and crRNA. In 2011, Charpentier published that tracrRNA was required to produce crRNA guide. When Doudna and team put tracrRNA into the test tube along with Cas9 and crRNA it worked. This was a major breakthrough. Once CRISPR-Cas9 components were cracked Doudna realized that we can program it to cut DNA of our interest. On June 8, 2012 Doudna hit the send button to submit an article on CRISPR-Cas9 system to Science. This was for the first time someone has isolated the different components of CRISPR-Cas9 and discovered the biochemical working. The paper also contained an important invention– a single guided RNA. The paper was accepted in Science on June 20, 2012.

Part three of the book talks about gene editing in human cells. It covers George Church, Feng Zhang, Luciano Marraffini and Doudna racing to publish the CRISPR-Cas9 application in human cell editing, forming companies and epic patent battles.

Just like we race to publish articles before being beaten by someone else working in the same field, Doudna also faced the same challenges to publish their work on the use of CRISPR-Cas9 in humans. At one point she thought whether it is worth publishing it after she came to know from George Church that his paper was accepted in Science solving the same problem. Church was supportive and behaved as a great colleague when he recommended that she should publish whatever experimental data that her team has generated so far. Church's suggestion was that her study would add as additional evidence to the field. One of statement that I really liked when Doudna said to Martin (her team member) that if even though it is not a quite the story that we wish to tell but we must publish the best story that we have because if we don't do it now then we will never publish it and it will be a sheer waste of our effort.



Church and Zhang published a few weeks before Doudna. But what was interesting is that there were other groups – a South Korean researcher, Jin-Soo Kim working in human cells and other one by Keith Joung from Harvard in zebrafish embryos. So even though Doudna was beaten to publish first but this discovery was inevitable after their group had shown that it could work in a test tube.

"There are some great discoveries and inventions such as Einstein's theories of relativity and the creation of the transistor at Bell labs are singular advances but there are many other great discoveries and inventions such as invention of the microchip and the application of CRISPR to editing human cells were accomplished by many groups around the same time"

This part covers a controversial article written by Eric Lander related to Heroes of CRISPR published by Cell in January 2016. The main theme of the article was correct that Scientific breakthroughs are rarely Eureka moments, but an ensemble act played out over a decade or more. The main problem with the article was that it clearly downplayed the role of Doudna and wrote lavishly about Zhang's contribution to the field. Some of the critics said that Lander twisted the history with specific goals – a Nobel prize for Zhang and Broad institute, an insanely lucrative patent.

Part three of the book also covers forming companies using CRISPR-based gene editing as a medical technology. Multiple scientists including Doudna, Charpentier, Church, Zhang tried to start a company because CRISPR-based gene editing was a powerful tool. Doudna tried but she was not getting a good feeling from Zhang because he was being cagey about his filed patent. They did not pool the CRISPR-Cas9 intellectual property that would lead to epic patent battles. Doudna, Church and Zhang formed Editas Medicine, but Doudna quitted only after a few months. She was not happy especially with Zhang because she was getting a feeling that he was doing something behind her back. Within a month after resigning from Editas Doudna joined a spinoff called Intellia from Caribou Biosciences that her student Rachel Haurwitz had founded. At the end the CRISPR-Cas9 pioneers ended up in three different companies: CRISPR Therapeutics founded by Charpentier and Novak; Editas Medicine included Church and Zhang; and Intellia Therapeutics founded by Doudna, Marraffini and others.

The bitter CRISPR patent battle is another topic that is covered in this section. When Doudna and Charpentier discovered CRISPR-Cas9 they were not sure about it's application. Doudna knew little about patents. Although Doudna and team applied for the patent before Zhang, but it was Zhang's patent that was reviewed first because he used the Accelerated Examination Request option by paying a small additional fee. Initially the patent office did not approve Zhang's application and asked for more information. Zhang made wrong allegations in his application that outraged Doudna. Zhang said that Doudna plagiarized Church's data. While Zhang was waiting for a ruling from the patent office, he and Broad dropped the name of his collaborator Luciano Marrafini from the patent. Marrafini gave the suggestion to Zhang to work on Cas9. This is a tale of greed and a sad example of distorting effects that patent law can have on scientific collaboration. Instead of fighting out the patent the author suggested that they could have perhaps followed the example of Jack Kilby of Texas Instruments and Robert Noyce of Intel who agreed to share the patent rights for the microchip by cross licensing the intellectual property to each other and splitting the royalty.

Part four of the book talks about CRISPR based therapies and it's benefit to the patient. The first therapy based on CRISPR-Cas9 was given to a thirty-four-year-old African American woman from a small town in central Mississippi, USA. This was to cure her sickle-cell disease. After nine months of treatment the patient was found to be fully healthy and did not need blood transfusion which was frequently needed before. Most of the initial attention of CRISPR-Cas9 was given to cure inheritable diseases but now there are many being used to fight Cancer. Affordability of CRISPR-Cas9 based treatment is a big challenge. Treatment of a patient can cost up to 1 million or more. This will bankrupt the healthcare system and hence there is a need to find affordable treatment solutions.

An interesting topic covered in this part of the book is about Anti-CRISPR. The prospect that CRISPR technology if it falls into the hand of terrorists or hacker can lead to a disaster. For example, when Doudna attended a conference in 2014 a researcher showed how a virus could be used to carry CRISPR component into mice and edit a gene that led to development of lung cancer. This fear resulted in Doudna joining the effort led by the U.S. Defense Department to protect from misuse of CRISPR.

Art meets Science

Man is unique not because he does science, and he is unique not because he does art, but because science and art equally are expressions of his marvelous plasticity of mind. — Jacob Bronowski



•

By: Tabassum, Customer Support









Our employee's little Picasso :)



Ananthajith M S (12 years) DNA of Santhosh Kumar, Administration





By Gurusharan J, (11 years) DNA of Pavithra N, Sales support







By Sumit Kharbanda, Bioinformatics Analyst, Ops Dept.



Employee Connect

Our New-Joiners



















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Shashikala

Balaji

Atul

Vipin

Saxon

Narashimhulu

Vijaykumar



Ranjith





Poorna



Suneetha



Chunduru Phaneendra



Rajeswari



Senthamil

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Vishwa



Madhurya







Murali

Virender







Mini

















Arya Prasad

Edwin

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Shivkanya

Shrishali

Salonee



















Sreenidhi



Sandeep

Akash

Simran

Aditi

Suresh

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Durga

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Partha J P





Mohana Sndaram





Romiya debabrata Mishra

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Manasa

Prama

Tamanna









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Silpa Sivan



Amitabha Mondal Arpudha Mary

Sanoop

Sushil

Sachin

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Satish Ponraj

-

Employee Connect



1) A person with a genotype AA is _____

- a) homozygous dominant
- c) heterozygous

b) homozygous recessived) haploid

- 2) If two heterozygous individuals mated and their first three children should a dominant trait, which of the following would be true?
 - a) their next child would have the dominant traitb) their next child would have the recessive traitc) there is a 25% chance their next child would show the recessive traitd) they cannot have a child with the recessive trait
- 3) If a R1R1 individual which was red was mated with a R2R2 individual that was white and they produced a pink flower, what could you say about the relationship between the R1 and R2 alleles?

a) R1 is dominant over R2	b) R1 and R2 are codominant
c) R1 is incompletely dominant over R2	d) these alleles are sex-linked

- 4) If a red flower is crossed with a white flower to produce an offspring with red and white petals, what is the relationship between the alleles for flower color?
 - a) R1 is dominant over R2 b) R1 and R2 are codominant
 - c) R2 is dominant over R1 d) R1 is incompletely dominant over R2
- 5) A parent that has two alleles for huntingtons disease mates with a normal person. What is the chance that their offspring will have the disease?
 - a) 0% b) 25% c) 50% d) 100%
- 6) A husband and wife are both are carriers for phenylketonuria. What are the chances they will conceive an offspring with that disease?
 - a) 0% b) 25% c) 50% d) 75%
- 7) Concerning blood type, an AO mates with a BO. What are the possible blood types of the offspring?a) A b) B c) O d) all of these

Previous puzzle Winner



Ashok Kumar Business Development Manager-Oncology Kindly mail your answers by 28th February 2021 to editor@medgenome.com. The first two people to answer the quiz correct will be featured in the next edition of our newsletter.



A thoughtfully curated gift box were presented to all employees consisting of customised goodies and health gift voucher. The gift has been very well received by everyone. Sharing a few kind words from our colleagues!



I received the Gift box and this is awesome. Feeling grateful for being a part of Medgenome Family. Thank you for making the effort to send us such a wonderful gift. I have to say that every detail in the box was fantastic, and each thing inside was one-of-a-kind. The phrase "specially curated gift box" is really appropriate. It's now my turn to call my friends who work at different organizations and tell them about the gift I received from my office and make them envy :)

Dear mam,

It gives me immense pleasure to receive such kind gesture from the team who have curated this token of love. Some gifts are priceless and this is one of them.

Thanking you and all the team members!

Rise and shine

Dear HR & Admin Team,

Many many thanks for such beautiful initiatives which was abstained till now from our culture.

Great thinking and meticulously designed gift has been dispatched particularly picking daily usage item be it Food or Coffee Mugs.

Thanks for making sales team feel privileged. I have distributed the boxes to my team today.

P.S:- Gratitude cannot be shown by words unless it is within.

___ Dear Ma'am

I have received the gift box and it is awesome. Thank you so much for the gesture.

It is indeed an honour to be part of the MedGenome family.

Dear Ma'am,

Received my gift box today, it's not just box, it is "#boxoffullofsurprises".

First of all Thank You so much!! for considering me as MedGenome family. It is indeed honour to be part of MedGenome.

I would like to thank everyone who all are involved in selecting these amazing gifts items, must be very thoughtful process of selection. Definitely going to helps us in respective aspects.

Really would like to appreciate everyone who has put in their thoughts, ideas while selecting each gift item, to make this "#amazingbox!!

Surely will be sharing this awesome gift on my social media very soon.

Thank you!!

Photo Feature

Christmas celebration at office means a lot of decoration, fun activities, gifts exchange and of course, food! Various fun filled activities were organised such as secret santa, desk decoration competition, online games, etc.





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