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The chief focus of the conference would be on translational research in the area of genetic neuromuscular disorders. Various aspects related to this theme ranging from the molecular basis, clinical evaluation, molecular diagnosis, management, physical rehabilitation and genetic counseling to ongoing preclinical studies, clinical trials and emerging therapeutic modalities including CRISPR-Cas9 and other gene editing technologies, would be discussed by eminent national and international experts. The scientific deliberations over the course of three days of the symposium are planned to cater to the clinical and research interests of medical practitioners as well as scientists working in the area of genetic neuromuscular disorders.

The post-conference workshop on interpretation of genetic tests in the clinical setting is targeted to help clinicians from all specialties and super specialties understand the nuances of conventional as well as recently developed genetic diagnostic tests and their utility in the clinic.

For further details, please visit: siamgcon2019.iapg.in

For queries please write to: siamgcon2019@gmail.com
Health is a topic close to everyone’s heart! Health columns in newspapers and magazines and health-related programs on television are very popular. Over the decades, they have played a major role in creating awareness about common health problems and their preventive measures. The importance of a healthy, balanced diet and exercise has been perceived by all and implemented by many in their lifestyle. With the exception of self-claimed ‘knowledgeable’ laypersons who try to treat common ailments with home remedies, conventionally, the diagnosis and treatment of medical disorders has chiefly been the domain of physicians including some practitioners of various forms of traditional medicine. Now, however, over-the-counter drugs and the internet are at everyone’s service and many laypersons search for their diagnosis on the internet before coming to the physician. This may or may not be useful; but we are worried for those who use the internet as a proxy doctor and play with their lives or the lives of their loved ones. Now, they have ‘direct-to-consumer’ testing at their service. This type of testing is offered for even high-end tests like exome sequencing or whole genome sequencing.

An article in this issue discusses various issues related to whole exome or whole genome sequencing offered to consumers directly. The tests may be offered for identification of risk for multifactorial disorders, cancers and even for paternity testing or ancestry testing, though the latter do not have much market in India at present. But genetic testing to predict the future of one’s health is likely to be tempting and has a great appeal for the masses. The takers may increase as the cost is reducing rapidly. Many of the next generation sequencing (NGS) based tests, especially for multifactorial disorders like hypertension, heart disease and Alzheimer disease, are not clinically validated. The psychosocial effects of pre-symptomatic testing are also not interrogated in Indian population. The tests are also offered for carrier screening for recessive monogenic disorders or cancer susceptibility genes. The data about the disease-causing pathogenic variations in Indian population is also different from other populations in the world. Hence, testing using the powerful next generation sequencing technique, needs pretest and post-test counseling and knowledgeable physicians to order and interpret the results.

As these tests are becoming the first-tier testing for phenotypes suggestive of monogenic disorders or genomic disorders and will soon be used for pharmacogenomic testing, all physicians need to be equipped with knowledge of their appropriate applications. So also, laypersons need to be educated about the applications, limitations and other issues like secondary findings. This is because many individuals or their family members may be required to undergo such type of genomic tests. For successful use of such tests, the individual and the family need to be involved in decision-making for ordering the test and return of results. The results may have long term / lifetime implications for the individual and the family members. The time is not far where exome / genome sequencing will become the test of choice for carrier screening for reproductive decisions and newborn screening. At this juncture, when laboratories are advancing rapidly in quantum and quality of such high throughput testing, we need to educate the population about the power and limitations of these tests, whether for patient care, population-based screening or research, especially for exploring genetic etiologies of multifactorial disorders.

In this issue, the Genexpress has articles about the utility of exome sequencing in identifying treatable disorders. This is the future we are hoping for. With advances in the development of therapeutic modalities from drugs acting on pathways and receptors to gene therapy, monogenic disorders may become easily treatable in the not-so-distant future. The notion that most of the genetic disorders are untreatable may soon be forgotten and identification of monogenic disorders will become more important for the patient rather than the family. As exome and genome sequencing
are rapidly becoming common tests offered to a large chunk of population, we need to educate the population about genomic technology and prepare them to be equal partners in decision-making. As this testing has many psychosocial issues, engagement of Indian society is needed to make policies about pretest / posttest counseling, return of secondary findings, etc. Geneticists and physicians need to initiate dialogue with social groups and get them actively involved in understanding the perspective of lay persons so that the powerful technique of next generation testing is used for the benefit of the society without causing harm or undue anxiety. We need a population with more genetic literacy rather than direct-to-consumer testing.

Dr. Shubha Phadke
1st October, 2019

Confirmed speakers
- Hisham Ahamed, Kochi, India
- Valerie Cormier-Daire, Paris, France
- Katta M Girisha, Manipal, India
- Kirun Gopal, Kochi, India
- Madhuri Hegde, PerkinElmer, USA
- Maja Hempel, Hamburg, Germany
- Yskert von Kodolitsch, Hamburg, Germany
- Kerstin Kutsche, Hamburg, Germany
- Bart Loeys, Antwerp, Belgium
- Lut van Lyer, Antwerp, Belgium
- Thomas Mir, Hamburg, Germany
- Sheela Nampoothiri, Kochi, India
- William Newman, Manchester, UK
- Siddaramappa J Patil, Bangalore, India
- Pauline Schneeberger, Hamburg, Germany
- Aline Verstraeten, Antwerp, Belgium

Topics
- Marfan Syndrome: The dark side of the disease
- FBLN4 related aortopathy
- New insights on aortopathies with bicuspid aortic valve
- Non-syndromic forms of aortic aneurysms
- TGFbeta signalling and fibrillin pathways
- Loeys Dietz syndrome
- Syndromic aortopathies
- Exome and gene panels for aortopathies
- Ehlers Danlos syndrome
- Clinical validity of inherited aortopathy and related connective tissue disorders genes
- Marfan and related syndromes in Indians
- Surgical management of aortopathies
A Fetus with Trisomy 12p: Prenatal and Postnatal Presentation

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²Fetal Medicine Unit, Madhukar Rainbow Children Hospital, Delhi, India
³Department of Obstetrics & Gynaecology, Jaypee Hospital, Noida, India

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Abstract

Trisomy of the short arm of chromosome 12 is a rare chromosomal abnormality. We have compared the ultrasound features and autopsy features of a fetus with trisomy 12p with a previous reported antenatal case and Pallister Killian syndrome. Ours is the second case report on fetal features of trisomy 12p.

Introduction

Trisomy of the short arm of chromosome 12 is a rare chromosomal abnormality with an estimated incidence of 1 per 50,000 births and only over 30 cases reported worldwide (Segel et al., 2006). The first case with trisomy 12p was reported by Uchida and Lin (1973) due to a malsegregation of a balanced parental chromosome rearrangement (Uchida & Lin, 1973). Trisomy 12p syndrome is associated with moderate to severe psychomotor retardation, generalized hypotonia and facial dysmorphism characterized by a round face with prominent cheeks, prominent forehead, broad nasal bridge, short upturned nose, long philtrum, thin upper lip, broad everted lower lip, and abnormal ears (Rauch et al., 1996; Tekin et al., 2001; Tsai et al., 2005).

We report here a 23-24 weeks fetus with trisomy 12p and compare the antenatal and postnatal features with the previous reported fetus with 12p trisomy and Pallister Killian syndrome.

Case Report

A 34-year-old primigravida was referred to our fetal medicine centre in view of lower limb abnormality detected in the anomaly scan. She had no history of fever with rash, diabetes, drug intake or radiation exposure. Nuchal translucency was within normal range in the first trimester ultrasound. First trimester biochemistry showed low risk for Down syndrome (PAPPA 2.27 MoM and beta hCG 0.46 MoM). Ultrasound was done using a Voluson E10 scanner (GE Healthcare, Milwaukee, WI) equipped with a convex 4-8 MHz abdominal transducer and a 6-12 MHz endovaginal probe. Two-dimensional ultrasound showed a single live intrauterine fetus with overall fetal growth corresponding to 20 weeks gestation. However all long bones were below the 5th centile for gestation. There was lower limb length discrepancy. The left femur was below the 1st centile for gestation and showed bowing. The left lower limb showed a curved tibia and very short segment of fibula. The left foot showed valgus deformity with overcrowding of toes (Figure 1c). There was no polydactyly. Clavicle and scapula were seen. Fetal spine appeared normal. Fetal head showed brachycephaly. There was no other structural abnormality nor any other marker for chromosomal abnormalities. The couple was offered amniocentesis for microarray and advised consultation with paediatric orthopaedician. However, they opted for termination of pregnancy and consented for a complete postnatal evaluation.

On postnatal external examination, foot length was 3.5 cm corresponding to 21 weeks, crown heel length was 30 cm, consistent with 24 weeks and crown rump length was 20.3 cm, consistent with 24 weeks and HC was 20 cm, consistent with 23 weeks gestation. There was brachycephaly, short nose, depressed nasal bridge and long philtrum (Figure 1a). There was no cleft lip or cleft palate. Ears were low set. Neck was short. Anus was anteriorly placed. In left lower limb there was bowing of tibia (Fig 1b). Histopathology of internal organs like liver, spleen, kidneys and lungs was normal. Placental histopathology was normal.
Histopathology of left leg showed disorganised cartilaginous tissue.

Chromosomal microarray from fetal DNA showed a female karyotype with duplication of 18.1 MB at cytoband 12p13.33p12.1 [arr 12p13.33p12.1(803488-24653237) × 3]. This duplication has 182 genes.

Discussion

Phenotypic similarity between trisomy 12p and tetrasomy 12p has been described in the literature. We have compared ultrasound features of one antenatal case described previously and Pallister Killian syndrome fetus with our case in Table 1. However, it has to be kept in mind that mosaic tetrasomy 12p can have a similar pattern in chromosomal microarray as trisomy 12p. As conventional karyotyping was not done in this case, the possibility of mosaic tetrasomy 12p could not be entirely ruled out.

Hung et al. reported a fetus with trisomy 12p at 30 weeks in a primigravida (Hung et al., 2012). Ultrasonography features included polyhydramnios, short long bones and abnormal spine curvature. Fetal facial dysmorphism included hypertelorism, marked prenasal thickness, broad and flat nasal bridge, cleft palate, large philtrum with thickened everted upper lip, and micrognathia.

Doray et al. stated that the three most frequent ultrasound indicators were polyhydramnios (84%), congenital diaphragmatic hernia (CDH) (16%) and micromelia of predominantly rhizomelic type (10%) (Doray et al., 2002).

The fetus we described also had short long bones but there was no polyhydramnios probably because of the early gestation at detection. Left tibia was small and deformed. Histopathology of bone showed localized dysostosis. Oligonucleotide-based aCGH showed a 35.4 MB duplication of 12p [arr 12p13.33p11.1 (0–35,400,000) × 3] in the case reported by Hung et al. Our case had duplication of 18.1 MB at cytoband 12p13.33p12.1. Izumi et al. described a minimal critical region for Pallister Killian Syndrome phenotype in a case with duplication of 26 genes (Izumi et al., 2014). Three genes, ING4, CHD4, and MAGP2 represent strong candidate genes for minimal critical region of this phenotype. ING4 gene plays important role in transcriptional regulation and CHD4 gene is involved in chromatin remodelling, DNA damage response and cell cycle control.

This case highlights the importance of a well-performed antenatal ultrasound. Down syndrome may be the commonest chromosomal abnormality but a low risk on the combined first trimester screening does not exclude other abnormalities. Another point to be emphasized is that any structural abnormality warrants microarray over conventional karyotyping. A complete postnatal evaluation including infantogram and fetal autopsy is essential to confirm ultrasound findings and to establish the diagnosis, which is instrumental in assigning appropriate recurrence risk.
Table 1  Comparison of antenatal features of trisomy 12p and tetrasomy 12p.

<table>
<thead>
<tr>
<th>Antenatal ultrasonography features</th>
<th>Huang et al., 2012</th>
<th>Pallister Killian Syndrome</th>
<th>Fetus described in our study</th>
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<tbody>
<tr>
<td>Polyhydramnios</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Short long bones</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased nuchal translucency</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td></td>
<td></td>
<td>-</td>
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Table 2  Comparison of facial features of Pallister Killian syndrome and trisomy 12p.

<table>
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<tr>
<th>Features</th>
<th>Pallister Killian syndrome</th>
<th>Huang et al., 2012</th>
<th>Fetus reported in our study</th>
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<tr>
<td>Brachycephaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Round face</td>
<td>-</td>
<td></td>
<td>+, mild</td>
</tr>
<tr>
<td>Coarse facies</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Flat facial profile</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Broad nasal bridge</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anteverted nostril</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Long Philtrum</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Upper Lips</td>
<td>Thin</td>
<td>Thick</td>
<td>Thin</td>
</tr>
<tr>
<td>Short Neck</td>
<td>+</td>
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Conclusion

Our report further expands the spectrum of antenatal and postnatal phenotype of trisomy 12p.

References

Direct-to-Consumer Genetic Testing (DTC-GT)

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Abstract

Direct-to-consumer testing (DTC-GT) is a new model of genetic service delivery available to consumers without the intermediary of a health care professional. Companies marketing such a service model highlight only the benefits without stressing on the potential drawbacks of such a system. In this brief review, we describe the potential benefits and concerns of DTC-GT.

Introduction

Genetic tests identify changes in chromosomes, genes, or proteins and help to confirm or rule out a genetic disorder. They also aid in determining a person's chance of developing or passing on a genetic disorder. The most common and widely accepted model of delivery of genetic testing is in a clinical setting, under the guidance of a genetic healthcare professional, after appropriate pre-test counseling and informed consent. Appropriate post-test counseling is also provided after the return of results wherein the implications of the results are explained along with further plan of action. Increasing media coverage about genetic research and testing has made people aware and interested in learning more about their own genetic make-up. This “genetic curiosity” of healthy individuals has given rise to a new branch of genetic testing services called “direct-to-consumer genetic testing (DTC-GT)”. Though this genetic testing service model may look highly lucrative and empowering, there are many potential drawbacks. This review is aimed to give more information about delivery of these services and highlight a few caveats associated with it.

What is DTC–GT?

It is over-the-counter genetic testing available directly to consumers through private companies. It has moved genetic testing from the clinics into the comforts of the consumers’ homes. The test kits can be bought online or in a pharmacy (in the west). These tests are marketed as enabling and informative tools allowing consumers to access information on their genetics, without the involvement of a trained medical genetics professional.

Why do people opt for DTC–GT?

The demand for DTC-GT is on constant rise owing to inadvertent advertisements and publicity gimmicks evoking the curiosity of healthy, aware and ready-to-pay individuals.

1. Curiosity: Consumers claim curiosity about their past (ancestry testing), present (traits and characteristics) and future (predictive testing), as major motivators for uptake of DTC-GT (Su, 2013).

2. Recreation / infotainment: Many companies propose a relationship between an individual’s genomic makeup and lifestyle aspects like nutrition (nutrigenomics), fitness, alcohol preferences, skin care, and athletic abilities (Su, 2013). Companies also provide products and programs to modify consumers’ lifestyle according to the results. Consumers also use these tests to find the intellectual, behavioural, creative and athletic traits in their children.

3. Concerns of the ‘healthy and worried well’: DTC-GT is marketed as helpful in reproductive decision making and providing preventive or management interventions for apparently healthy individuals. People with no family history of genetic conditions and unremarkable personal health histories inadvertently worry about their potential health risks and use these tests (Schimdt et al., 2019).

4. Specific concerns about family history of genetic diseases: Individuals with a family history of genetic conditions, especially multifactorial conditions like Alzheimer disease, cancers, diabetes or
heart disease may express curiosity, worry, and/or anxiety and would like to know their risks for the same (Schimdt et al., 2019).

5. **Individuals with non-specific symptoms in search of a specific diagnosis:** Highly anxious individuals with non-specific symptoms would do genetic testing to find an answer to their symptoms.

**What are the service delivery models available?**

There are currently two service delivery models for DTC-GT:

- **Direct-to-consumer** - In this commercial model, consumers can undertake a test without any involvement of a healthcare professional. The tests are directly advertised, sold and delivered to the consumer.

- **Consumer-directed genetic testing (CD-GT)** - These tests are directly advertised to the consumers, but the tests have to be ordered by a healthcare professional and/or the results have to be returned to a healthcare professional. However, an independent third-party healthcare provider, who is not trained in medical genetics, can also act as the ordering physician and the treating doctor may not be involved directly. The consumers research the test options and request the healthcare professional for a specific test (Ramos et al., 2018).

These models are constantly being updated with newer services and genetic information being added to increase the consumers’ uptake. DTC-GT companies have started providing access to in-house or contracted genetic counsellors for post-test result interpretation, counseling and giving further plans of action. Genetic counseling is integrated in the test price in some or charged separately in some models of service delivery (Ramos et al., 2018).

**What are the potential benefits?**

Advocates of DTC-GT argue that it is an empowering tool which enhances the autonomy of consumers by giving them the right to own and use their genomic information to make health and lifestyle decisions. It allows them to be in charge of their healthcare management, without the intermediary of doctors and long waiting lists for hospital appointments (Eissenberg, 2017). It is also claimed that these tests can increase awareness about genetic disorders and disease predispositions among a larger number of individuals (Su, 2013). This in-turn could lead to advanced research in the field of personalized medicine and improved public healthcare.

**What are the concerns of DTC-GT?**

Issues in DTC-GT arise at every step of service delivery from advertising to the return of the report.

- **Marketing and advertising:** Emotional language, appealing designs, testimonials from affluent individuals and exaggerated positive claims of empowerment over one’s health are used by almost all the DTC-GT companies as their major marketing strategy. These may affect the consumers’ impression of value of the product, its actual need and usefulness for them (Niemiec et al., 2017).

- **Pre-test counseling and informed consent:** DTC-GT consumers do not know what to expect from the results due to lack of pre-test counselling. Also the consumer on purchase of the services signs a consent form, but there is no healthcare professional intermediary to discuss and highlight the utility and limitations of the tests, potential results, their implications, storage and future use of their genomic data.

- **Clinical utility, validity of the test and interpretation of results:** The scientific evidence for clinical utility of many tests offered is very limited, especially for complex traits. These tests emphasise only on the genetic cause of a condition, totally disregarding the effects of environment, medical and family history and lifestyle of the consumers. Clinical validity of the identified variants is also difficult to prove. All clinically relevant variants or even genes may not be included in analysis. Many DTC-GT companies lack involvement of clinically trained healthcare scientists or genetic professionals for variant interpretation. It is also unclear whether all DTC-GTs are performed in certified laboratories. There exists a high degree of variability in testing methods between DTC-GT companies. Some use single nucleotide polymorphisms (SNPs) for finding associations between genetic makeup and traits or disease predisposition, while some of the companies use next generation based techniques (whole exome or whole genome sequencing) to find exact variants leading to genetic predispositions. This leads to variability in interpretation and possibility of conflict in risk interpretations (Tandy-Connor et al., 2018). The information...
provided in the DTC-GT reports is often in terms of a percent increase in risk (eg, “30% more likely”) with no additional details and information about the background risk on which this risk is based. Such estimates can be misleading, especially if the background risk for a condition is low (<1%), which could lead to unnecessary panic. Age-dependent penetrance of certain conditions may also be difficult for consumers to gauge and may lead to false reassurance if negative for those conditions.

The result may not always be positive or negative. There is also a chance of receiving variants of unknown significance (VUS), whose clinical validity is extremely difficult to prove and interpret and is even more difficult for the consumer to understand and use this information without the help of a qualified genetic healthcare professional.

4. Medical actionability: Consumers are clueless about the meaning and implications of the results returned to them and they can be misled into believing that the information they receive is medically actionable. They do not realize that these are only predicted and not exact risks. No post-test counseling to explain the results further complicates this issue. This may lead to medical mismanagement wherein consumers may take a serious decision about treatment (prophylactic surgery based on BRCA variants), lifestyle choices or inappropriate dosage adjustment (following a pharmacogenomic test report).

5. Psychosocial impact: It may also cause serious psychological distress to the consumers who may not be prepared for bad news and may experience anxiety, emotional trauma, guilt, anger, denial or depression (Roberts et al., 2013). It may also cause distress to other family members who do not wish to know about their genetic risks for disease but now are incidentally found to be at-risk because their relative chose to undertake DTC-GT without proper guidance.

6. Third party interpretations, data storage and privacy: Various third party applications claim to retrieve information from the DTC-GT raw data. This can cause serious problem with variant interpretations, actionability and quality due to inexperience and reliability of the scientific evidence to prove the variant to be pathogenic (Niemiec et al., 2017).

7. Carrier testing and testing of minors: Carrier testing results have a huge impact on a couple’s reproductive choices and if not validated or interpreted appropriately, may have adverse effects on it (on their having children or abortion). Testing of asymptomatic minors for traits or even disease predispositions or carrier testing which has implications only for reproductive decisions has multiple ethical, legal and social issues is not considered ethical (Phadke & Gowda, 2013). It takes away the basic autonomy of the child to know about his/her genetic make-up. It can also lead to undue pressure on the child and psychological distress, stigmatization, discrimination (in schools, for insurance, employment) and need to undergo unnecessary medications or interventions.

8. Regulations: There are no regulations on genetic testing, especially on DTC-GT, in India. Hence the quality of reports can be highly questionable.

9. Ancestry and paternity testing: These tests can lead to unexpected results revealing false paternity or unknown sibships. This information may be distressful for some individuals and can have serious impact on the family dynamics.

Genetic counselors’ view on DTC-GT

Genetic counseling is considered the gold standard of care when conducting diagnostic genetic testing. To not offer that in the setting of DTC-GT is a deviation from that standard of care. With increase in awareness of the consumers about the need to understand the DTC-GT results, some of the companies have started offering post-test counseling (Ramos et al., 2018). However, there are limited services to make sure that the information is fully understood by the consumer. Appropriate pre- and post-test counseling is rarely offered directly by DTC-GT companies and is inconsistently accessed by consumers when available (Harris et al., 2013). In a study by Hock et al. 2011, to assess genetic counselors’ knowledge and belief about DTC-GT, about 50% of the counsellors felt DTC-GT was acceptable if genetic counseling was provided and they also agreed that they had a professional obligation to be knowledgeable about DTC-GT. The other 50% of respondents thought that genetic testing should be limited to clinical settings. This clearly indicates a disparity among the counselors and their view on their role in managing DTC-GT consumers.

Position statements from professional bodies

Several professional bodies like American College of Medical Genetics and Genomics (ACMG), National Society of Genetic Counselors (NSGC), American Society of Human Genetics (ASHG)
(Hudson et al., 2007), European Society of Human Genetics (ESHG), American College of Obstetricians and Gynaecologists (ACOG) and US Food and Drug Administration (FDA) have issued position statements on DTC-GT. Society of Indian Academy of Medical Genetics has issued a position statement on DTC-GT on August 10, 2019. They all express concerns about the limitations of tests, communication of results, impact of genetic test results, unpreparedness of consumers for results, lack of information about recommended follow-up, psychological distress and privacy of genetic data. They unanimously recommend undertaking of genetic testing under the guidance of a knowledgeable genetic healthcare professional or genetic counsellor before pursuing DTC-GT. They encourage consumers to be skeptical of these tests’ claims and realise that DTC-GT results can have important health implications for individuals and family members. They also insist that the DTC-GT company websites should clearly mention about the limitations and probabilistic nature of the tests – what they can and cannot detect, in an understandable manner. They must also address the privacy and confidentiality concerns regarding consumers' genetic data.

These statements however hold a diplomatic stance on DTC-GT. Only ACOG discourages the use of DTC-GT due to the potential harm of misinterpretation or inaccurate result.

Many professional bodies have criticized the clinical validity and utility of the health-related information provided and expressed concerns about negative downstream consequences on misinterpretation of this information by the consumers or their primary health-care providers. All the professional bodies unanimously and strongly discourage the use of DTC-GT for children due to lack of regulation on test content, accuracy and interpretation along with loss of autonomy of the child. Genetic tests if needed for a minor should be clinically indicated (for diagnosis and health-altering management) and be ordered only by a healthcare professional who will be responsible for subsequent management.

Conclusion

DTC-GT has very much arrived into the genetic testing market. Literature suggests that DTC-GT is neither as empowering as claimed nor as harmful as feared. However, before and after deciding to purchase a test, it is important for the consumers to understand the harms and benefits of the applications marketed or the actionability of results obtained. DTC-GT cannot sufficiently substitute traditional genetic testing without the expert guidance of a genetic professional.

References

1. Eissenberg JC. Direct-to-Consumer Genomics: Harmful or Empowering?: It is important to stress that genetic risk is not the same as genetic destiny. Mo Med. 2017; 114: 26-32.
Abstract

Next generation sequencing based analysis has revolutionized the field of genetic diagnostics. However, these high throughput techniques reveal thousands of variants in individuals, many of which are non-disease-causing polymorphisms. Knowledge regarding the polymorphisms in each population is essential, so that these variants can be ignored in order to identify the disease-causing variant. This article focuses on various population databases which help us to know the frequencies of these polymorphisms in different populations throughout the world.

Introduction

The genetic diversity between two unrelated human species is only 0.6% (Auten et al., 2015), which is far less diverse than the other mammalian species like apes. Studies have also reported that the genetic variation between two unrelated individuals is more diverse accounting for 87.6% of the variation, than the genetic variations between two different populations i.e., only 9.2% (Jorde 2003). The single nucleotide polymorphism (SNP) is the most abundant form of genetic variation which accounts for 90% and the other types are constituted by small insertions/deletions and large scale copy number variants (CNVs) (Collins et al., 1999; Gross et al., 2007). About 5% of the SNPs are non-synonymous with functional impact and are located in the coding regions. The SNPs from the non-coding regions also serve as important genetic markers throughout the human genome (Collins et al., 1999). The knowledge of the enormous genetic variation data has been pivotal in discovering new disease-causing genes, mapping the human genetic ancestry and evolution during the course of time. The genetic association studies of SNPs with disease phenotypic trait have been extremely successful. For instance, the association of HLA gene with several diseases such as type I diabetes, rheumatoid arthritis, coeliac disease, multiple sclerosis and ulcerative colitis, has been determined using the genome wide association strategies (Bell et al., 2002). In addition, Salla disease caused by mutation in the SLC17A5 gene in an Old order Menonite child was identified, using the SNP arrays method (Strauss et al., 2005).

Genetic databases in NGS analysis

With the emergence of massively parallel sequencing also known as Next generation sequencing technology (NGS) or deep sequencing and the increasing number of such population genetic variation databases, many more genes involved in rare diseases have been mapped (Fernandez-Marmiesse et al., 2017). The human disease association studies and clinical genetic testing are increasingly dependent on the deep sequencing-based evaluation. Population databases from across different geographical regions have become integral in the evaluation and interpretation of the genomic variants. The minor allele frequencies of variants have been shown to vary greatly in different populations. This has to be taken into consideration in the context of the disease prevalence in that particular population during variant filtering and prioritization. Some of the major population databases used in NGS-data analysis include 1000 Genomes project, Exome aggregation consortium (ExAC), Exome sequencing project (ESP), gnomAD, Complete genomics (CG69) and Great middle east (GME).

The present article describes some of these population genetic variation databases that are publicly available. The population genetic variation databases serve as sources of population allele frequency data for efficient filtering of the common variants from the rare disease-causing candidates.
and therefore useful in mapping the disease phenotype. Most of the population genetic variation databases are generated by forming consortiums with many principal investigators across multiple laboratories from various parts of the world. Some of the population databases are restricted to a particular community whereas most of the databases are the collection of exomes and genomes data with participation from every continent.

- **1000 Genomes project:** (https://www.internationalgenome.org/)
  The 1000 genomes project consortium is a widely used catalogue of genetic variation across multiple populations. The project was initiated in January 2008, and carried out in three phases. The first pilot phase involved 1092 individuals from 14 populations spread across the five major populations: Europe, East Asia, South Asia, West Africa and the Americas. The pilot phase 1 reported 38 million SNPs, 1.4 million short insertions/deletions and more than 14000 large deletions (Altshuler et al., 2010; Altshuler et al., 2012). The phase 2 of the project focused on the technical development. The latest phase 3 of the project has compiled over 88 million variants in total, out of which 84.7 million are SNPs, 3.7 million are short insertions/deletions and 60,000 structural variants, from 2504 individuals spread across 26 populations (Auton et al., 2015).

- **Exome Aggregation Consortium (ExAC):** (http://exac.broadinstitute.org/)
  The Exome Aggregation Consortium (ExAC) has the consolidated exome variants from 60,706 unrelated individuals. The ExAC is a combined effort of many principal investigators involved with various disease-specific and population genetic studies (Lek et al. 2016). The exome samples have 5 major clusters corresponding to European, African, South Asian, East Asian, and admixed American populations. The ExAC has released a total of 7,404,909 high-quality variants, including 317,381 insertions or deletions.

- **Genome Aggregation database (gnomAD):** (https://gnomad.broadinstitute.org/)
  The Genome Aggregation database (gnomAD) consists of human sequencing studies of 125,748 exomes and 15,708 genomes, generating over 270 million variants (Karczewski et al. 2019). In addition, the gnomAD project identified 443,769 high confidence predicted loss-of-function (pLoF) variants, which have been validated using animal models and engineered human cells. Besides, the gnomAD has also reported 498,257 unique structural variants (SVs) including 5,729 multi-breakpoint complex SVs and other types of SVs in the general population (Collins et al., 2019).

- **CG69:** (https://www.completegenomics.com/public-data/69-genomes/)
  The cg69 database contains the genetic data of 69 non-diseased samples along with two matched tumour and normal sample pairs, sequenced by the complete genomics (Drmanac et al., 2002). The genetic variations include SNPs, small insertions/deletions, substitutions and complex small variants, CNVs and structural variants (SVs).

- **Exome Sequencing Project (ESP):** (https://evs.gs.washington.edu/EVS/)
  The US National Institutes of Health (NIH) Heart, Lung and Blood Institute (NHBLI)-sponsored Exome Sequencing Project (ESP) has catalogued 1,146,401 autosomal single nucleotide variants (SNVs) in 15,336 protein coding genes from 6515 individuals of European Americans and African Americans. The other objectives of the ESP project were to estimate the age of mutation segregating in the contemporary human populations. The study concluded that 73.2% of SNVs are 5000 years old and are present both in the European Americans and African Americans, whereas the SNVs which are more than 50,000 years old are observed more frequently in the African American samples suggesting a genetic drift in European Americans as they move out of the Africa continent (Fu et al., 2013).

- **Great Middle East (GME):** (http://igm.ucsd.edu/gme/)
  The Great Middle East (GME) genetic variation database is a whole-exome variant database from 1111 unrelated individuals of the Great Middle East countries; Persian Gulf region, North Africa, and Central Asia. This database is essentially useful for finding recessive variants among the GME populations, as consanguinous marriage is common in those countries (Scott et al., 2016).

- **Catalogue of Somatic Mutations in Cancer (COSMIC):** (https://www.sanger.ac.uk/science/tools/cosmic)
  The Catalogue of Somatic Mutations in Cancer (COSMIC) contains 40,67,689 observed coding mutations, 9,175,462 gene expression variants, 1,271,436 CNVs and 1,87,429 structural mutations from 1,235,846 tumour samples (Forbes et al., 2017). Each mutation in the COSMIC data is tagged with SNPs status which infers if the mutation is present as polymorphism in the 1000 genomes.
database or in a panel of control samples used in the International cancer genomic consortium (ICGC) and a pathogenicity value, enabling the identification of disease driver mutations. The COSMIC data also has information about the genetic variants conferring drug resistance to various cancer drugs.

Absence of Indian population database and its consequences

The Indian population is not comprehensively represented in many population genetic variation databases. This is a limitation while analyzing NGS data in Indian patients since a large number of variants remain even after filtering for variants with minor allele frequency of 1 in 100 or 1 in 1000. This leads to increased time and effort needed to identify disease causing variants in diagnostics as well as novel disease-causing gene in research. We analysed 30 exomes sequenced using Agilent SureSelect V5 exome capture kit with an average of ~5,09,427 variants per sample. After filtering against the 1000 Genomes, ExAC, ESP, gnomAD, cg69, GME databases with MAF of 0.01, a total of 2,31,858 variants remained (about 5000 to 7000 variants in each sample). Further filtering with the in-house database consisting of exomes of ~800 Indian individuals revealed about 30% reduction in number of variants (Fig 1) (Unpublished data).

This shows that a significant proportion of the genetic variations are population specific. Thus, it is very important to have a detailed population allele frequency database for Indian population which will help in better and efficient diagnosis of genetic disorders using NGS technologies.

GenomeIndia Project

The Department of Biotechnology, Government of India is planning to launch a GenomeIndia project for sequencing of 10,000 Indian genomes with partnership of about 22 institutes. (https://www.thehindu.com/sci-tech/science/biotechnology-department-will-scan-20000-indian-genomes/article28815520.ece). The data generated in this project is likely to revolutionize the field of genetic diagnostics and research in India.

In summary, the 1000 Genomes, GME, ExAC, gnomAD, CG69, ESP, COSMIC are the population genetic variation databases that contain the genetic variations data such as SNPs, indels, SVs and CNVs, generated from thousands of exomes and genomes of normal and disease individuals across multiple populations. These databases primarily can be used for filtering the polymorphisms of allele frequency in populations, which is a fundamental process for the detection of disease-causing variant(s)/gene(s) in rare Mendelian disorders and other genetic disorders.
References


Announcement

SSIEM (Society for the Study of Inborn Errors of Metabolism)  
Course on Inherited Metabolic Disease  
First time in Asia ! A Unique Opportunity

Dates: 6-9 January, 2020 (Monday to Thursday)  
Venue: Radisson Blu, Dwarka, New Delhi, India

Organisers: SSIEM Education and Training Advisory Committee (ETAC) and Indian Society for Inborn Errors of Metabolism (ISIEM)

Local organisers: Dr Sunita Bijarnia-Mahay & Dr IC Verma

International Faculty:  
Dr Christine Vianey-Saban, Lyon, France  
Dr Johannes Haeberle, Zurich, Switzerland  
Prof Simon Heales, London, UK  
Dr Diana Balhousen, Lausanne, Switzerland

Course description: The course will provide an introduction to the common presentations, diagnosis and treatment of Inherited Metabolic Diseases (IMDs). Topics will include diagnostic strategies, the interpretation of metabolic investigations such as TMS, GCMS and aminoacid analysis, drug and dietary treatments - through lectures, workshops and case presentations.  
Target audience: Paediatricians, neonatologists, intensivists, and geneticists. It is also suitable for biochemists undertaking investigations on IEM.

Numbers are limited to 60 clinicians & biochemists from India & neighbouring countries.

Applications: October 10, 2019. Instructions are given on the SSIEM Website (http://www.ssiem.org/events).
Successful applicants will be contacted in November & asked to register.

Registration fee: 100 Euros. This includes the attendance in all scientific program, lunches & accommodation for 4 nights.
Molecular Diagnosis Aids in Specific Treatment of Rare Diseases

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Miransertib in Proteus syndrome (Keppler-Noreuil et al., 2019)

Proteus syndrome is an overgrowth disorder caused by somatic mosaicism of the variant c.49G>A (p.Glu17Lys) in AKT1 gene. Miransertib, a small molecule that inhibits AKT1 has been tried in some cancers with the same variant in somatic cells. Noreuil et al. conducted a pharmacodynamic study of Miransertib in Proteus syndrome and concluded that a dose of 5mg/m^2/day resulted in a 50% reduction in phosphorylated AKT in tissues of five out of six individuals. The authors demonstrated that 5mg/m^2/day could be used as a starting dose of Miransertib for future drug efficacy trials in patients with Proteus syndrome.

CoQ_{10} treatment in nephrotic syndrome (Starr et al., 2018)

Majority of cases of monogenic forms of nephrotic syndrome are caused due to variations in NPHS1, NPHS2 and WT1 genes. Biallelic pathogenic variants in COQ2, resulting in CoQ_{10} deficiency have been reported in at least 20 patients with phenotypes ranging from isolated nephrotic syndrome to multisystem disease. Starr et al. described three children with nephrotic syndrome and biallelic variants in COQ2. Two of these three children responded well to CoQ_{10} supplementation at a dose of 30 to 50 mg/kg/day and had complete resolution of nephrotic syndrome. The authors concluded that early molecular diagnosis helped in initiating appropriate therapy.

Deep brain stimulation in patients with dystonia (Meyer et al., 2017)

Meyer et al. described 27 individuals with early onset progressive dystonia, specific findings on Magnetic Resonance Imaging (MRI) brain and heterozygous variants in KMT2B gene. None of the patients responded to common anti-dystonic agents like levodopa. Ten patients of this cohort responded well to bilateral globus pallidus interna deep brain stimulation (GPI-DBS). Patients had reduction in torticollis and improvement in gait and motor function. Patients who were wheelchair dependent became ambulant once DBS was inserted. The authors stressed the need for genetic evaluation of patients with early onset childhood dystonia and suggested that patients with heterozygous variants in KMT2B gene should be referred for deep brain stimulation.

References
Direct-to-consumer Genetic Testing: Position Statement of the Society for Indian Academy of Medical Genetics (SIAMG)

Correspondence to: info@iamg.in

Background

With rapid technological advances, genomic testing has become widely available and affordable to the public. ‘Direct-to-consumer genetic testing (DTC-GT)’ refers to genomic/genetic testing offered to consumers by commercial service providers without the supervision and guidance of a health care professional, predominantly for the purpose of finding their ethnic origins, paternity, genomic variants that might affect disease pre-disposition, life style, or disease status, and management. Due to wider access to online advertisements and publicity gimmicks evoking the curiosity of consumers, there has been a rise in the demand and uptake of DTC-GT in India. The Society for Indian Academy of Medical Genetics (SIAMG) believes that DTC-GT without involving a health care professional causes more harm than good and the society strongly discourages the use of DTC-GT in any circumstance.

Present status

No strict regulations for DTC-GT services exist in India. Currently, worldwide more than 300 commercial organisations offer DTC-GT and information is easily available over the internet (organisations’ websites or e-commerce websites) with unmoderated access, with or without the intermediation of a healthcare professional. These commercial organizations often make exaggerated claims and promises on benefits of these services by providing scientifically unproven information.

Society for Indian Academy of Medical Genetics position on direct-to-consumer genetic testing has discussed this issue among its executive committee members and has resolved that:

The SIAMG does not endorse DCT-GT and strongly dissuades the use of over-the-counter DTC-GT for healthcare purposes (for the diagnosis, predisposition testing, carrier testing and management) or in any other form of service delivery (paternity testing, ethnic origin, predisposition to life style disorders, pharmacogenomics etc.) without a healthcare professional and/ or pre and post-test genetic counseling. SIAMG condemns the use of DTC-GT for testing of minors for carrier or disease predisposition testing.

Explanations

1. Genetic tests and interpretation of their results are complex and are associated with ethical, social and legal issues. Any form of genetic testing should be undertaken for an appropriate medical indication under a certified genetic healthcare professional after appropriate pre-test counselling and informed consent. Post-test counseling should be provided while providing the results back.

2. The clinical utility and validity of DTC-GT are questionable as they emphasize only on the genetic variants, totally disregarding the clinical signs/ symptoms, medical and family history, effects of environment, and lifestyle of the consumers. In India, there are no quality assurance guidelines for most of the genetic assays and pathogenicity prediction of the detected genetic variants and hence clinical implications of DTC-GT are extremely doubtful.

3. There is a huge scope for misinterpretation of the genetic results as neither the commercial organizations nor consumers understand the complexity of genomic assays in the absence of health care professionals. They may fail to realize that the genetic test performed may not be able to provide an etiological diagnosis for condition in question. Moreover, this might lead to a sense of false assurance, if genetic test has not detected any clinically relevant variant. DTC-GT may also generate undue anxiety if result is positive, as there is no healthcare professional to explain the implication of the results.

4. The consumers may not completely under-
stand the utility, implications and actionability of the detected genetic variants and thus may receive inappropriate medical advice which may cause immense psychological distress and discrimination. Such unsupervised and unwarranted testing can cause a huge burden on the healthcare system and genetic counsellors, who will be requested to interpret the complex genetic results.

5. Concerns over consumer data storage, privacy and sharing also exist.

6. Predictive testing in minors raises many ethical, legal and social concerns.

References


Drafted by Dr Dhanya Lakshmi N¹ and Urja Asher² on behalf of Society of Indian Academy of Medical Genetics (SIAMG)

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The executive committee of SIAMG approved this statement on 10 August 2019
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This fetus was referred for autopsy evaluation in view of antenatal ultrasound findings of bilateral short humeri. This was the second pregnancy of a third degree consanguineous couple. The fetus in the first pregnancy of the couple was also similarly affected. Identify the condition.

Please send your responses to editor@iamg.in
Or go to http://iamg.in/genetic_clinics/photoquiz_answers.php to submit your answer.

Answer to PhotoQuiz 45
The radiographs show cortical hyperostosis of the tibia with irregularity of the bony cortex. These findings are typical of Caffey disease (OMIM # 114000). Caffey disease is caused by heterozygous mutation in the alpha-1 collagen type I gene (COL1A1) on chromosome 17q21.

Correct Responses Were Given By:
1. Dr M L Kulkarni, Davangere
2. Dr J P Soni, Jodhpur
3. Dr Chakshu Chaudhry, Chandigarh
4. Dr Meenakshi Lallar, Panchkula
5. Dr Ravneet, New Delhi
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11. Dr Anirbaan Palit, Midnapore
12. Dr Vibha Jain, New Delhi
13. Dr. Ashka Prajapati, Ahmedabad
14. Dr Nishant Rathod, Mumbai
Are you suspecting a Lysosomal Storage Disorder (LSD) in your patient?

GAUCHER DISEASE
- Enlarged liver and spleen
- Delayed or stunted growth in children
- Easy bruising and bleeding
- Anemia and Thrombocytopenia
- Unexplained Bone pains
- Unexplained Avascular necrosis of Head of femur

POMPE DISEASE
- “Floppy” appearance in infants or young children
- Unexplained Cardiomyopathy
- Progressive respiratory muscle weakness or insufficiency
- Progressive Limb-girdle muscle weakness (in late-onset cases)

MPS I DISEASE
- Coarse facial features
- Early onset joint stiffness/ claw-hand deformities/ contractures
- Corneal clouding (leading to light sensitivity or impaired vision)
- Recurrent respiratory infections (including sinuses & ears)
- History of recurrent hernia repair in young age

FABRY DISEASE
- Severe burning pain in hands & feet
- Intolerance to heat & cold
- Inability (or decreased ability) to sweat
- Red, purple spots on skin (angiokeratomas)
- Evidence of early renal involvement (nephropathy)
- History of stroke in young age

NIEMANN PICK - B DISEASE
- Enlarged liver & spleen
- Bleeding manifestations
- Skeletal abnormalities & Growth delays

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