In this special issue of Genetic Clinics, we are publishing the 30 best abstracts selected from the ones that were submitted for the Fourth National Conference of SIAMG (SIAMCON 2017), held in Thiruvananthapuram, Kerala, on 8th and 9th December, 2017. These abstracts were selected based on the scores given by the experts who judged these papers during the conference. These thirty abstracts are published here in no particular order.

ABSTRACT 01

Our Experience in Microarray Based Evaluation of Developmental Disabilities and Congenital Anomalies

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Chromosomal microarray analysis (CMA) is now widely used diagnostically for the molecular karyotyping of patients with intellectual disability, congenital anomalies and autistic spectrum disorder and has more recently been applied for the detection of genomic imbalances in prenatal genetic diagnosis. The diagnostic yield has increased significantly with the help of this high resolution genomic technique. Here we present our experience of CMA for pre and postnatal diagnosis. CMA has been done in 569 samples in the last 5 years (2012 to 2017). This included patients with idiopathic intellectual disability, malformations and developmental delay (n=382) and autism (n=18). Nineteen of these patients with developmental disabilities were from consanguineous families analysed for loss of heterozygosity (LOH) regions. CMA was done in 10 cases with microscopic chromosomal anomalies for deciphering the imbalances. CMA was done in 140 prenatal samples for indications including increased risk of trisomy 21, USG detected abnormalities, history of previous child with intellectual disability or developmental delay or other associated abnormalities. Among 569 patient samples, 61 (10.7%) had pathogenic variants, likely pathogenic variants (1.9%), and variants of unknown significance (VUS - 3.9%). In this patient group, microarray was performed for 140 prenatal samples. The abnormalities identified were complex chromosomal rearrangement and 2p16.3 microdeletion in one patient each, while 16p11.2 microduplication was identified in two cases. CMA in patients with chromosomal abnormalities detected by traditional karyotyping showed interesting results and are of great use in counseling for prenatally detected marker chromosome or apparently balanced translocations. The CMA done in patients from consanguineous families gave clues to the candidate gene in 10 cases in addition to identifying copy number variations. The results of our data regarding diagnostic yield of CMA are consistent with the published literature.

ABSTRACT 02

Clinical and Molecular profile of Cerebellar ataxias: A Journey from Simple PCR to Next Generation Sequencing Based Diagnostics

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Background: Cerebellar ataxias are etiologically heterogenous, the commonest causes being spinocerebellar ataxias and Friedreich ataxia. However, the diagnosis is elusive in many cases, as the clinical/neuroimaging profile often does not indicate a specific diagnosis. We present a prospective study on the clinical and molecular spectrum of cerebellar ataxias conducted between June 2016-October 2017 at a tertiary care centre.

Materials & Methods: All patients presenting with cerebellar ataxia at the out-patient department were enrolled in the study, after obtaining informed consent. Evaluation included a detailed history, three

generation pedigree, neurological examination and neuroimaging. Targeted testing was done in patients who had clinical features consistent with specific spinocerebellar ataxia or Friedreich ataxia. Clinical, neuroradiological profile & pedigrees of undiagnosed patients were reviewed for any diagnostic clues. Patients with autosomal dominant pattern of inheritance or SCA features were serially tested for SCA 6, 7, 12, 17 and 36. Those with possible autosomal recessive pattern or syndromic/complex presentations were evaluated using phenotype guided tests and shortlisted for NGS-based Multi gene panel testing/Whole exome sequencing.

Results: 72 patients were enrolled out of which, 15 tested positive for SCA (SCA-1 = 6, SCA-2 = 4, SCA-3 = 5) & 14 tested positive for Friedreich ataxia (total 39%). Among the 43 undiagnosed patients, 8 had a positive family history and the remaining 35 were simplex cases. Of these, 27 patients were tested for SCA 6,7,12,17 & 36, using short PCR, all showing no repeat expansions. Phenotype directed targeted testing and Multi gene panel testing provided a diagnosis in 4 patients, which included one case each of SCA 34, Charlevoix Saguenay ataxia, Ataxia Oculomotor Apraxia Type 1 & Dystroglycanopathy. WES revealed a putative pathogenic variant in *PCDH12* gene in two sibs with a complex phenotype of cerebellar ataxia, dystonia and exudative retinopathy.

Conclusions: SCA 1,2,3 and FA comprised a significant proportion of cerebellar ataxias in our cohort, while SCA 6,7,12,17,36 were absent. NGS based testing was of utility in establishing the diagnosis of rarer ataxias in few cases, and revealed a putative novel gene for ataxia-dystonia phenotype in one sib-pair.

ABSTRACT 03

Exome first: An Efficient Approach to Diagnosing Inherited White Matter Disorders

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Inherited white matter disorders are clinically and genetically heterogeneous disorders, predominantly affecting the white matter of the central nervous system with or without involvement of the peripheral nervous system. These disorders can be subdivided into leukodystrophies and genetic leukoencephalopathies. Leukodystrophies involve primary defect in myelination whereas genetic leukoencephalopathies are caused by neuronal, vascular or systemic defects with secondary involvement of myelin. At present, variations in approximately 150 genes are known to cause inherited white matter disorders. Owing to heterogeneity of these conditions, whole exome sequencing (WES) was employed as a first line testing to determine definitive molecular diagnosis of affected individuals with inherited white matter disorders.

We recruited 21 individuals from 19 families with neuroimaging findings suggestive of bilateral and confluent white matter changes in the brain. WES was performed for index patients of 18 families and trio was performed for one family. Of these, six families were diagnosed with inborn errors of metabolism [Maple syrup urine disease type 1A (MIM #248600) (n=2), ACER3 related progressive leukodystrophy (n=1) mitochondrial neuro-gastrointestinal encephalopathy (MIM #603041) (n=1), 3-methylglucatonic aciduria type I (MIM #250950) (n=1), Perrault syndrome type 3 (MIM #614129)(n=1)], three families with congenital muscular dystrophies [Muscular dystrophy, congenital merosin-deficient (MIM #607855) (n=2), Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 4 (MIM #253800) (n=1)], one family each with megalencephalic leukoencephalopathy with subcortical cysts (MIM #604004) and Mental retardation, autosomal dominant 18 (MIM #615074). A total of 10 pathogenic variants were identified in this study, of which 7 variants are novel. Overall, definite diagnosis was established for 11 families (57.8%). Other investigations, such as tandem mass spectrometry, enzyme assays and other biochemical tests were performed to validate the exome results.

This is an ongoing study which would help in further delineation of phenotypes and molecular mechanisms of inherited white matter abnormalities prevalent in India. The study would help in definitive genetic counseling and prenatal diagnosis as a direct benefit for families with inherited white matter disorders.

ABSTRACT 04

Epigenetic Abnormalities of 11p15 region in BWS and RSS - A Report of Eight Cases from a Tertiary Care Centre

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The 11p15 chromosomal region contains a cluster of imprinted genes which play an imperative role in regulating growth. The expression of the genes within this cluster is regulated by two imprinting control regions - ICR1 and ICR2. Growth is generally enhanced by paternally expressed genes whereas growth appears to be suppressed by maternally expressed genes. Dysregulation of 11p15 genomic imprinting results in two opposite growth disorders- Beckwith-Wiedemann Syndrome (BWS) and Silver -Russell Syndrome (SRS). Macrosomia at birth is a major feature in BWS while SRS is characterized by both prenatal and postnatal growth retardation.

Here we report eight cases with dysregulated 11p15 genomic imprinting. We retrospectively reviewed the clinical features of five cases of Beckwith-Wiedemann Syndrome and three cases of Silver- Russell Syndrome enrolled in the genetic clinic from January 2014 to September 2017. All the cases were tested using Methylation Specific Multiplex ligation dependent probe amplification (MS-MLPA) for BWS/SRS to detect abnormal methylation status of IC1 (H19DR) region and IC2 (KvDMR) regions.

Result: The age at presentation ranged from 4 months and 5 years. 3/5 (60%) of the BWS cases were female while 1/3 (33%) of the SRS cases were female. In patients with BWS, two patients were detected to have hypermethylation of IC1 region while 3 patients had hypomethylation of IC2 region. Hypomethylation of IC1 was observed in all the three patients with SRS.

Conclusion: This study was done to analyse the genotype and phenotype correlation between the various imprinting abnormalities associated with the two clinically opposite congenital imprinting disorders- BWS and SRS. Accurate diagnosis helped in appropriate counselling and further management of these patients.

ABSTRACT 05

Spectrum of Genetic Etiology of Short Stature - A Retrospective Study of 455 Cases

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Background: Short stature is a frequent presentation in the pediatric clinics. Patients with a genetic etiology may have associated dysmorphism, intellectual disability, hepatosplenomegaly, eye manifestations and skeletal anomalies.

Objectives: To review the genetic etiology of short stature in children visiting the genetic clinic.

Methodology: The patient list of 10,550 patients attending the genetic clinic from January 2016 through October 2017 was scanned. Patients with height less than 3rd centile were recruited in the study. Clinical data and investigations including genetic tests were tabulated and analysed. Patients with proportionate and disproportionate short stature were categorized and assessed for etiology.

Results: A total of 455 patients had short stature of which 81% (n=369) were proportionate and 18.9% (n=86) were disproportionate. Of the latter, 44.1% (n=38) were diagnosed to have lysosomal storage

disorder by enzyme analysis, 45.3% (n=39) had skeletal dysplasia or resistant rickets and 9 patients could not be classified. In the proportionate short stature group, 83.7% (n=309) constituted recognizable syndromes of which 69.5% (n=215) were Downs syndrome. Excluding Down syndrome, a chromosomal etiology was confirmed in 28.7% (n=27) by karyotype and or fluorescent in situ hybridization technology. Single gene disorders were diagnosed in 30.8% (n=29) using molecular tests and in 38 patients genetic tests were not performed. Nine cases (2.9%), were due to miscellaneous causes including constitutional delay, familial short stature and endocrine causes. Suspected skeletal dysplasia constituted 3.8% (n=12) while 12.6% (n=39) were unrecognizable syndromes. Genetic testing (karyotype/microarray/exome sequencing, whichever appropriate) was done in 21 of the unrecognizable syndrome and an etiology was identified in 47.6% (n=10).

Conclusion: An algorithmic approach involving family history, systematic phenotyping followed by laboratory and radiological investigations allows confirmation of clinical diagnosis by appropriate genetic test. In unrecognized cases, newer advanced tests help to achieve a definitive diagnosis in 47.6%.

ABSTRACT 06

A Decade's Experience of Molecular Characterization of Skeletal Dysplasias in a Tertiary Centre from India

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Skeletal dysplasias are a heterogenous group of disorders characterized by abnormal growth and development of bones and cartilage. The overall birth incidence of these skeletal dysplasias is estimated to be 1 in 5000 live births. Genetic disorders of skeleton have been classified into 436 disorders under 42 nosology groups in the 'Nosology and Classification of Genetic Skeletal disorders: 2015 revision'.

The current study was a retrospective analysis of 598 patients who presented with clinical suspicion of skeletal dysplasias, at our Medical Genetics Department over a period of ten years. This study was supported by various national and international funding agencies. All the patients were provided molecular genetic testing for all the known skeletal disorders by targeted mutation analysis and many rare, novel skeletal dysplasias through exome sequencing and further categorized according to the nosology groups.

In our patient cohort, we found that the autosomal recessive entities were more common (85%) followed by autosomal dominant conditions (17%). The total consanguinity rate in our patients was 37%. Interestingly, we also found that 37% of the non-consanguineous families presented with autosomal recessive entities.

In the current study, the most common diagnostic nosology group was found to be dysostoses multiplex group constituting about 45% of the total patient cohort followed by genetic inflammatory/rheumatoid-like osteoarthropathies group. Noteworthy is that, most of these patients were diagnosed in collaboration with different national and international medical genetic centres. This had led to the delineation of new clinical phenotypes, new genotypes, discovery of four new genes thus contributing to the scientific knowledge in the skeletal dysplasia research.

ABSTRACT 07

Prenatal Diagnosis of Beta Thalassemia: A Six Year Review from a Joint Fetal Medicine-Genetics Clinic

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Beta-thalassemia is the commonest serious autosomal recessive haemoglobinopathy worldwide. In India, carrier status ranges from 1 to 17% (mean 3.9%). Five common mutations in the *HBB* gene accounts for 90% of all Indian cases, the commonest of which is the IVS1-5G>C mutation.

Invasive prenatal diagnosis by chorionic villus testing (CVS) or amniocentesis is offered to couples for diagnosing beta thalassemia in pregnancy. In our centre, the majority of couples referred (98%) had a previous child or family member with beta thalassemia and suggestive haemoglobin electrophoresis results. The index patient is tested by full sequencing of the beta globin gene *HBB*. 58% of our cohort had the common IVS1-5 G>C mutation in one or both alleles. Both parents are then tested for mutations identified in the index case. Counselling before prenatal testing is done by a clinical geneticist. Trans-abdominal CVS is performed from 11 weeks onwards after informed consent by a qualified fetal medicine specialist. CVS DNA sample is tested for the familial mutations only with exclusion of maternal cell contamination by standard methodology. Results are available within three weeks and informed to the couple by the clinical geneticist.

The total number of CVS procedures for beta thalassemia performed (2011-2017) were 84, including two sets of di-chorionic twins. Results were obtained in 82 with 2 sample failures (both contaminated samples). 26 (30%) were unaffected, 34 (40.5%) were carriers and 22 (26%) were affected. Both sample failures had subsequent amniocentesis with results indicating an unaffected fetus. In all affected pregnancies the couple chose to discontinue. With unaffected / carrier results, a consultation was arranged with the hematopoietic stem cell transplantation (HSCT) transplantation team to discuss cord blood storage at delivery and its usage in future transplantation in the affected sibling. Our study highlights the optimal management of a common genetic disorder.

ABSTRACT 08

A Clinical and Genetic study of a Cohort of 52 families with Developmental Abnormalities of Corpus Callosum

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The development of corpus callosum is a complex process likely involving interplay of various genes and regulatory developmental mechanisms. It is the most common brain malformation and is genetically heterogeneous. We carried out an observational study in patients with agenesis or dysgenesis of corpus callosum.

We recruited 57 probands from 52 families. Subjects were classified based on clinical phenotype and structural abnormality of the corpus callosum. Parental consanguinity was noted in 55% (28/52) of families. 42% (24/57) of the cases with corpus callosum abnormalities were associated with a genetic syndrome. Non-syndromic form of corpus callosum abnormalities were seen in 58% (32/57) of the subjects, out of which majority were associated with other brain malformations (90%, 29/32). The associated malformations noted in complex non-syndromic type were abnormalities of white matter (52%), posterior fossa anomalies (15%) and neuronal migration defects (23%).

Chromosomal microarray was performed in 16 patients with a 35% yield. Exome sequencing analysis in 31 families led to a definitive molecular diagnosis in (73%, n=42). The phenotypic spectrum consisted of rare autosomal recessive neurodevelopmental disorders, neurometabolic disorders and leukoencephalopathies. We also identified two novel candidate genes, *ISCA1* in multiple mitochondrial dysfunctions syndrome 5 and *AIMP2* a severe neurodegenerative disorder.

The study demonstrates wide phenotypic and genetic heterogeneity observed in patients with abnormalities of corpus callosum. Several known and novel phenotypes with developmental abnormalities

of corpus callosum were characterized. The corpus callosum abnormalities were more often observed in association with complex brain malformation, white matter abnormalities and as a part of various genetic syndromes, than as an isolated malformation. This study is the largest cohort of patients with abnormalities of corpus callosum from Asia.

ABSTRACT 09

High Prevalence of Profound Biotinidase Deficiency and Experience of Newborn Screening Program in Uttar Pradesh, India

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Biotinidase deficiency is a rare autosomal recessive inherited metabolic disorder with an estimated incidence of 1 in 61,000 for profound and partial deficiency. This disorder causes severe neurological and cutaneous symptoms which can be easily prevented and treated with biotin supplementation. To prevent the severe clinical sequelae due to biotinidase deficiency, it was included in our newborn screening program in December 2015. Total 28,067 newborns were screened from December 2015 to October 2017, out of which 173 were found to be screen positive. From these screen positives, venous samples were collected from 113 neonates for confirmatory enzyme testing. One neonate (1%) with profound deficiency (<10% enzyme activity) and 22 neonates (19%) with partial biotinidase deficiency (10-30% enzyme activity) were identified. Because we noticed a higher prevalence of partial deficient cases in our population as compared to the literature, we further analyzed the samples for mutation detection. The case with profound deficiency had a homozygous mutation (c.98_104delinsTCC) which is known to cause severe phenotype. Out of the 22 partially deficient cases, 15 were tested for mutation: 12 cases had both their alleles mutated while 3 cases had heterozygous mutations. The variation c.1330G>C, which is reported to be mild was present in 11 of the 12 cases (biallelic mutations), supporting the enzyme level more than 10%. In addition, mutation analysis was also performed in a few cases (7) with normal enzyme activity but less than 50%. Out of the 7 cases tested, 3 had both their alleles mutated, 2 were heterozygous and 2 of them did not carry any mutation. The newborn with profound biotinidase deficiency and those with partial biotinidase deficiency are on biotin therapy and none has any manifestations on regular follow up. A larger population data from other regions of India is required to determine whether such high prevalence is reported in other parts of the country.

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ABSTRACT 10

Incidental Findings in Next Generation Sequencing

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Next generation sequencing (NGS) is increasingly used to identify genetic alterations associated with defined phenotypes or for discovery of variants for improved patient care. One consequence is the increased identification of variants that are incidental (or secondary) to the diagnostic indication for which the sequencing test was done. In this study we evaluated clinical exome sequencing data of 51 patients to look for mutations in genes that are not apparently relevant to a diagnostic indication of patient. Pathogenic or likely pathogenic variants reported in ClinVar database in these patients were filtered to look for incidental findings.

Twenty-six (51%) patients were found to be carrier for mutations in genes for autosomal recessive conditions. Eighteen (35.3%) patients, were carrier for pathogenic mutation in one gene while eight (15.7%) patients were heterozygous for mutation in more than one gene. Interestingly 11 (21.5%) patients were carrier for mutation in *HBB* gene. Three (0.6%) patients were found have compound heterozygous mutation in *HBB* gene. One female carried heterozygous mutation in *ABCD1* gene on X chromosome responsible for adrenoleukodystrophy. Three patients were found to harbor mutations in genes responsible for autosomal dominant conditions. Details for all the mutations will be discussed.

NGS is a powerful tool for genetic analysis which also results in the detection of secondary, possibly pathogenic variants. The large amount of data generated by these methods has to be thoroughly evaluated for significance. As secondary findings are often of clinical significance for the patient and their family, detailed reevaluation and counseling for them will be required.

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ABSTRACT 11

Clinical Spectrum of Disorders of Segmental Overgrowth at a Tertiary Care Centre

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Segmental overgrowth syndromes affect a particular segment of body which may include tissues like fat, muscles, bone, blood vessels, skin and nerves. It encompasses various clinically diverse conditions such as CLOVES (Congenital lipomatous overgrowth, vascular malformations and epidermal naevi, scoliosis and skeletal deformities), Proteus syndrome, Cowden syndrome, HHML (Hemihyperplasia-multiple lipomatosis syndrome) Fibroadipose hyperplasia, Macrodactyly, Macrodystrophica lipomatosa, Infiltrating facial lipomatosis, Complex epidermal naevus syndrome, Hemimegalencephaly, Klippel-Trenauney Syndrome (KTS), Isolated lymphatic and vascular malformations etc. Somatic activating mutations in the phosphatidylinositol-3-kinase (PI3K)/Protein Kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway have been reported in several of these segmental overgrowth conditions. Due to clinical diversity and overlapping features of these conditions, accurate diagnosis is difficult. In this report, we retrospectively collected the clinical data from patients with segmental overgrowth syndrome reporting in our genetic clinic from January 2012 to September 2017.

Here we report twenty five patients of clinically diagnosed segmental overgrowth over a period of five years (January 2012 September 2017) from a tertiary care centre. Molecular analysis could not be performed in all.

Result: The age at presentation ranged from one month to eighteen years. Based upon the clinical criteria, about 44% (11/25) was classified as presumptive AKT related, 48% (12/26) as presumptive PIK3A related, 0.04% (1/25) presumptive PTEN related, and 0.04% (1/25) TSC1/2 related.

Conclusion: This retrospective clinical review enabled us to recognize the clinical spectrum at our centre in order to plan a systematic molecular evaluation and further management of segmental overgrowth syndromes.

ABSTRACT 12

Etiological and Clinical Profile of Children with Disorders of Sexual Development in a Tertiary Care Hospital

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Background & objectives: Disorders of Sex Development (DSD) with or without atypical genitalia require medical attention to reach a definite diagnosis. The definitive etiological diagnosis in DSD is important for

the management of the affected child and genetic counseling for the family. The objective of our study is to find out the clinical and etiological profile of children with disorders of sex development.

Methods: Data was collected using a proforma from all patients with DSD attending SAT Hospital, Trivandrum – the Genetic, Endocrine and Paediatric OPD. The definite diagnosis was established by clinical and appropriate laboratory investigations- imaging ultrasound abdomen, MRI (if required), basal and stimulated hormone levels, serum electrolytes, karyotyping and molecular testing as required.

Result and discussion: Out of 26 cases included in this study,13 were 46, XX DSD and 13 were 46,XY DSD. In the 46,XX DSD group, the etiology was congenital adrenal hyperplasia in all cases where 69% was salt wasting type and 31% simple virilizing type. Of the 46,XY DSD, the main etiology was 5 –alpha reductase deficiency which constituted 38% of 46,XY DSD. The most common presenting complaint was atypical genitalia in 96% of the cases. Most of the DSD's presented in the newborn period. Among CAH, 38 % presented with complaints other than atypical genitalia. 19% of the total cases needed gender reassignment.

Conclusion: Clinical, chromosomal and hormonal assessment may help in making a etiological diagnosis. This stresses the importance of early identification including newborn screening. Management of DSD is a multidisciplinary approach. Genetic testing and prenatal diagnosis can be offered to the affected families especially in cases of congenital adrenal hyperplasia.

ABSTRACT 13

Molecular and Histopathological Characterization of Patients Presenting with the DMD Phenotype in a Tertiary Care Centre in Southern India

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Introduction: Duchenne muscular dystrophy (DMD) is the commonest genetically inherited primary muscle disease affecting boys in their first decade and causes severe progressive muscular weakness. Other rare muscular dystrophies can also present with the DMD phenotype.

Aim and Objectives: To identify the proportion of DMD cases that can be diagnosed with the Multiplex Ligation-dependent Probe Amplification (MLPA) technique and to study the histopathological and molecular findings in patients with the MLPA-negative DMD phenotype.

Material and Methods: This was a prospective and retrospective observational study involving 275 patients conducted from 1st January 2014 to 31st August 2016. *DMD* gene MLPA was used for detecting deletions and duplications. In MLPA-negative patients, muscle biopsy with immuno-histochemistry (IHC) and Next generation sequencing were done for further characterization, wherever possible.

Results: MLPA detected pathogenic mutations in 72.36% of cases (64.72% deletions and 7.63% duplications). Exons 45-55 were most commonly involved in deletions (67.97%) while exons 1-10 were the commonest in duplications (61.90%). Muscle biopsy and IHC were done in 21 MLPA-negative patients, 12 of which were confirmed to be dystrophinopathies. In the remaining 9 patients, dystrophin staining was positive along sarcolemma and further IHC with sarcoglycans (alpha, beta, gamma, delta) was performed in 4 of these. Three were found to be beta sarcoglycanopathies and 1 could not be characterized. NGS-based multigene panel sequencing for muscular dystrophy-associated genes, helped in identification of mutations in 5 MLPA-negative patients – 4 cases with DMD and 1with sarcoglycanopathy.

Conclusion: MLPA has high sensitivity and specificity and is recommended as the first line investigation for patients with DMD. Muscle biopsy with immunohistochemistry helps to confirm the diagnosis of muscular dystrophy in MLPA-negative patients but would not be conclusive for the exact disease-causing gene mutation. Next generation sequencing technology is a useful non-invasive method for identifying point mutations/small indels in the *DMD* gene and for detection of other muscular dystrophies mimicking DMD.

ABSTRACT 14

Clinical and Genetic Evaluation of Six Families with Rare Hereditary Spastic Paraplegias identified by Whole Exome Sequencing

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Hereditary spastic paraplegias are a group of genetically heterogeneous neurological disorders characterized by progressive weakness and spasticity of lower limbs. The complex genetic basis of HSP involving more than 70 genetic subtypes are inherited in all patterns of Mendelian inheritance (autosomal dominant, autosomal recessive, X-linked) and mitochondrial inheritance. We ascertained six families with 11 individuals presenting with features suggestive of HSP. Whole exome sequencing in solo or sibship followed by Sanger validation and segregation analysis was carried out in these families.

We observed developmental delay, progressive hypertonia, spasticity with poor speech development and abnormality of corpus callosum in three families with spastic paraplegia type 47 (#614066, *AP4B1*). A common pathogenic variant in *AP4B1*, c.304C>T, p.(Arg102Ter) was observed in two families with SPG 47. They shared a common region of homozygosity of 0.2 Mb around the variant suggesting a possibility of founder effect. Another male child with pathogenic variation in *AP4B1* showed periventricular white matter abnormality in addition to other clinical features. Two siblings with a complex phenotype which included developmental delay, progressive lower limb spasticity and thin corpus callosum were diagnosed to have mutation in *SPG11* causing spastic paraplegia type 11 (#604360) in addition to two more Mendelian disorders in them. Two male siblings with intellectual disability, difficulty in swallowing, speech delay, mild facial dysmorphism, progressive spasticity, contractures were diagnosed to have X-linked spastic paraplegia 2 (#312920, *PLP1*).

This cohort shows the phenotypic and genetic heterogeneity observed in patients with hereditary spastic paraplegias. WES also led to the identification of candidate pathogenic variants in *KIF26A* in siblings with hereditary progressive spastic paraplegia as a cause of human disease for the first time.

ABSTRACT 15

Exome Sequencing Identifies Novel Mutations in Five Human Fetuses with Meckel Syndrome and Expands the Genotypic and Phenotypic Spectrum

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Meckel syndrome (MKS) is a perinatal lethal autosomal recessive condition caused by defective primary cilium formation leading to classical features such as polydactyly, multiple cysts in kidneys and brains malformations. We performed exome sequencing in five unrelated fetuses with a clinical diagnosis of MKS on fetal autopsy. Exome sequencing revealed novel mutations in *TNXDC15* [c.844C>T (p.R282X)], *B9D2* [c.15C>A (p.H5Q)], *CC2D2A* [c.4088G>T (p.G1363V), c.4555T>G (p.W1519G)], *CEP290* [c.2456A>T (p.Q819L), c.4805C>T (p.T1602M)] and *TMEM67* [c.2114G>C (p.G705A)]. Here we present the second mutation report for *TXNDC15* and *B9D2* and novel mutations in *CC2D2A*, *CEP290* and *TMEM67*. The present study signifies the power of exome sequencing in establishing a definite diagnosis in a clinically and genetically heterogeneous condition such as MKS. This study further expands the phenotypic variability and genotypic spectrum of Meckel syndrome.

ABSTRACT 16

Morphological and Etiological Spectrum of Joint Deformities: A Fetal Autopsy Study

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A total of 150 autopsies were performed during the period of 3 years from January 2013 to December 2016 in a tertiary center in Southern India. Joint deformities were noted in 59 (39%) fetuses. Lower limb varus deformities were the most common, seen in 33 cases. Arthrogryposis multiplex congenita was seen in 12 cases, predominant upper limb deformities in 6, and distal joint deformities in 8 cases. Major malformations co-existed in 17 cases and included the central nervous system, cardiovascular, genitourinary system and gastrointestinal system. Fetal hydrops or nuchal edema was seen in 9 cases. A definitive genetic diagnosis was possible in 12 cases (20%) by molecular/cytogenetic/biochemical testing or histopathology, including four cases of aneuploidies, 5 of metabolic disorders (Gaucher disease-3, Sly disease-2), 2 with dystroglycanopathy and one fetus with blended phenotype of Beals and Marfan syndrome. Additionally, spectrum of autopsy findings and/or family history indicated a genetic diagnosis in 18 cases, these comprising a fetus with oto-palatodigital syndrome, 2 with skeletal dysplasia, 3 with possible multiple pterygium syndrome, and 12 with unclassified multiple malformation/dysmorphic syndrome. In 7 cases joint deformities occurred as part of a developmental field defect, 11 as a deformative sequelae with intrauterine fetal demise, 9 remained unclassified, and 2 were miscellaneous. Overall, in at least 30 out of 59 cases (51%), a genetic etiology could be confirmed/strongly suspected.

To conclude, joint deformities were a common abnormality found in fetuses undergoing autopsy and were found to be etiologically associated with a broad spectrum of genetic disorders as well as other fetal pathological states including deformative sequelae.

ABSTRACT 17

Whole Exome Sequencing and Homozygosity Mapping Reveals a Synonymous Splice-site Variation in *ARMC9* as a Cause of Joubert Syndrome 30

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Intellectual disability (ID) is prevalent with 1-3% frequency in population, resulting from heterogeneous causes like genetic (monogenic/chromosomal) or environmental/nutritional. Around 230 genes are known to be involved in causation of syndromic ID. Joubert Syndrome (JS), characterized by ID, ptosis, polydactyly, appearance of "molar tooth sign" in hindbrain MRI, and retinal dystrophy, has been reported to result from pathogenic variants in about 35 genes. Homozygosity mapping and whole exome sequencing in a consanguineous family with three affected children with syndromic ID, revealed c.879G>A in *ARMC9* as a cause for JS30 in the family. ARMC9 is a conserved ARM (Armadillo repeat motif) domain containing protein with lesser known functional involvement with ciliary machinery. Homozygous c.879G>A in *ARMC9*, is a synonymous variant, absent in 1000G, EVS, cg69, ExAC and our in-house database of 100 exomes, and was predicted to be deleterious by various splice site mutation prediction software. Sanger validation in family confirmed autosomal recessive pattern of inheritance. Functional validation using pCAS2 minigene system and RT-PCR revealed, c.879G>A leads to abolition of splice site and causes skipping of exon 9 of *ARMC9*, which may lead to in-frame deletion of 33 amino acids in ARM domain of ARMC9. In-silico structural analysis indicates that ARM domain acts as platform for protein-protein interactions, thus deletion of part

of ARM domain may lead to distortion of the domain resulting in abolition of interactions. Our finding of pathogenic variant in *ARMC9* leading to JS30 not only expands the genetic heterogeneity of JS and extends the list of genes related to ciliopathies but also facilitates better counselling of affected families.

ABSTRACT 18

Cornelia de Lange Syndrome: Detection of Low Level Mosaicism in a Previously Mutation Negative Case

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Cornelia de Lange syndrome (CdLS) is a rare and clinically variable disorder that affects multiple organs. It is characterized by intellectual disability (mild to severe), distinctive facial features, prenatal and postnatal growth retardation, and hirsutism. It is inherited in autosomal dominant and X-linked dominant fashion. To date, mutations in five genes [*NIPBL* (MIM #122470), *SMC1A* (MIM #300590), *SMC3* (MIM #610759), *RAD21* (MIM #614701) and *HDAC8* (MIM #300882)] are known to cause CdLS.

We ascertained a seven years old male child born to non-consanguineous parents. He presented with facial dysmorphism and mild intellectual disability [IQ 63]. On examination, head circumference was 46 cm (-6 to -7 SD), height was 113 cm (-2 to -3 SD) and weight was 20 kgs (-1 to -2 SD). He had facial dysmorphism characteristic of CdLS, small hands and feet. Rest of the systemic examination was unremarkable. Next-generation sequencing based gene panel test was employed from peripheral blood DNA to determine the underlying mutation which did not reveal any pathogenic variation in the known genes. Whole exome sequencing (WES) from saliva sample was performed which also failed to detect a pathogenic mutation. This was followed by WES from skin fibroblasts of the proband and parents, which identified a heterozygous variant c.231-1G>T with 17% frequency in *NIBPL* gene. Retrospectively, 12% frequency of the said variant was found in WES data of saliva sample. This helped to confirm the diagnosis of Cornelia de Lange syndrome 1 (MIM #122470) at molecular level.

Mosaic mutations in NIPBL have been reported from saliva/tissue testing in additional 23% of mutation-negative CdLS cases. The pathogenic variant in the low-level mosaic state (12%) was not called in the bioinformatic algorithm which had 20% frequency threshold for variant calling for exome data analysis. The above case demonstrates that in disorders with mosaicism as possible genetic mechanism, the bioinformatic pipelines should be adjusted to detect variants with low frequency for disease conditions. Also, manually checking concerned genes on integrated genomic viewer could prove to be helpful in avoiding false negatives.

ABSTRACT 19

Visionary Father with Visually Impaired Sons: Family with Congenital Blindness Due to *FOXE3* Mutation

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Father of four sons, made his initial visit 16 years ago in genetics OPD of our hospital. He brought his four sons with history of visual impairment noticed since birth. All the sons have normal intellect, hearing and there is no dysmorphism. Eye evaluation revealed anterior chamber dysgenesis of both eyes. The available genetic testing at that time did not add any further information and diagnostic dilemma continued. Father took pride in the rarity of the condition and plight of geneticists. He paid regular visits to the genetics OPD. His visit fructified after 15 years when next generation sequencing revealed a homozygous missense variation in exon 1 of the *FOXE3* gene (chr1:47882707C>A; c.720C>A) in all affected sons. Parents are heterozygous for the same mutation. The mutation detected is a known pathogenic mutation and matches with the disease phenotype. Presently, sons are 35, 32, 30 and 28 years old,

educated, socially and emotionally well adjusted. Despite all efforts, father has not come to terms with the fact that diagnostic odyssey has been resolved. With this familial case report, we want to highlight the importance of next generation sequencing in diagnosing rare disorders and commitment of father and family. The psychological issues of the family with rare genetic disorder and their pursuit for search of etiology without any hope for treatment will be discussed.

ABSTRACT 20

Association of Sleep Apnoea with Development and Behaviour Related Abnormalities in Down Syndrome

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Introduction: Down syndrome(DS) is the most common chromosomal anomaly worldwide and these patients are at high risk of developing sleep disordered breathing (SDB) as compared to general population. Although association between SDB and developmental delay and behavioural abnormalities are proven among typically developing children, such studies are less among children with DS. Given the multitudes of established comorbidities associated with DS, SDB is often a neglected entity, management of which may have significant impact in the cognitive, developmental and behavioural domains of these children. So it is essential to assess the magnitude of the impact SDB has on development and behaviour of children with DS.

Objective: To assess the relationship between severity of obstructive sleep apnea diagnosed by overnight polysomnography (PSG) and development as assessed by Developmental Profile 3 (DP 3) and behavioural abnormalities as assessed by Child behaviour Checklist (CBCL).

Materials and methods: In a cross sectional prospective study conducted at a tertiary centre in north India 53 children with DS were assessed for SDB by overnight PSG. Behavior was assessed for all children using CBCL and development using DP 3. Association between various domains of behaviour and development with Apnea Hypopnea Index (AHI) were assessed separately.

Observation and results: Out of 53 subjects 51 (96%) were found to have OSA. In both the 3-5 year and 6-12 year age groups, the Spearman correlation co-efficient, *Rho* was found to be statistically significant (0.773 and 0.825 respectively) when evaluating the correlation between the overall CBCL scores with the AHI values. The correlation between the developmental quotient scores and AHI was also found to be statistically significant with a *Rho* value of -0.624.

Conclusion: Statistically significant positive correlation was found between OSA severity and behavioural abnormalities especially attention deficit and hyperactivity. Statistically significant negative correlation between OSA severity and IQ was also found.

ABSTRACT 21

Classification and Phenotypic Spectrum of Atypical Orofacial Clefts from a Single Centre

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Orofacial clefts, among the commonest birth defects can extend atypically onto craniofacium.

Objectives: To analyse the phenotypic spectrum of atypical orofacial clefts and relate clinical diagnosis with other topographic and morphogenetic classifications.

Methods: A cross-sectional descriptive study of 500 children aged ≤18 years with orofacial clefts over three years. Pattern of malformation and clinical diagnosis were established in children with atypical clefts. Evaluation focused on type of cleft, laterality, dysmorphology examination and associated anomalies.

Topographic and morphogenetic classifications were tabulated against clinical diagnosis. Statistical analyses were descriptive.

Results: Atypical clefts constituted 4.2% of all clefts and 18.1% of associated. Clefts were bilateral in eleven (52.4%). Oculo-auriculo-vertebral spectrum constituted the largest group with nine children. Others included Treacher Collins syndrome phenotype, amniotic band sequence, frontonasal dysplasia sequence, holoprosencephaly sequence and heminasal aplasia. Majority were male (16, 76.2%). Risk factors included advanced paternal age, young maternal age and first birth order. Neuroimaging abnormalities included semilobar holoprosencephaly, interrupted ventricular system with schizencephaly and acranialis. Majority were lateral clefts (9, 42.9%) corresponding to Tessier 7. Others included oblique (6, 28.6%) and median (6, 28.6%). Morphogenetically, malar and mandibular hypoplasia were significant in nine each.

Conclusion: Atypical orofacial clefts though rare, constitute an important group of conditions with phenotypic heterogeneity. Topographic or morphogenetic classifications based on different principles would aid in the clinical diagnosis and guide in further work up.

ABSTRACT 22

Prevalence of Intellectual Disability in Vellore District

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Background: The National scenario of community-approaches in the area of health care for physically and mentally challenged is of great concern. Tamil Nadu, like other states, is faced with major challenges in providing comprehensive and up-to-date health services to these children and their families. In our state, intellectual disability is caused by consanguinity and chromosomal abnormalities along with other causes like infection and prematurity. With many high-risk newborns surviving, disablement is coming to the fore and becoming a major health problem.

Objectives of the Study: To find out the prevalence of intellectual disability in special children in Vellore district.

Methodology: Vellore district has a total of 22 community development blocks. A cross-sectional survey was conducted in all the blocks. 2901 disabled children were analyzed between the age group of 5-14yrs. Patients details were documented in the case record for further cytogenetic testing.

Results: During the survey it was observed that out of 2901 children, 2618 (90.2%) were intellectually disabled, 46 (1.58%) had autism and 237 (8.16%) had Cerebral palsy with cognitive impairment.

Conclusion: Genetics is becoming an essential part of most medical specialties. Increased awareness about the role of genetics in diseases and great advances made in medical genetics in recent years has a considerable impact on the practice of Clinical Genetics. Generally, prevention of genetic and congenital disorders can be addressed at three levels: i. Primary prevention: premarital screening and counseling and preconception counseling; ii. Secondary prevention: prenatal counseling, screening, and testing with the option of termination of affected fetus or prenatal and neonatal management; and iii. Tertiary prevention: newborn screening with proper management (can be considered as secondary or tertiary prevention). Care of the affected, prevention of complications and rehabilitation of the handicapped can be done at the primary health care or at tertiary care centers. Genetic counseling and prenatal diagnosis related to mental handicap raises sensitive ethical issues, especially for the milder forms of cognitive dysfunction or for carrier females who manifest subtle cognitive deficits. Assessing cognitive function is complex. Academic performance and social behaviour can be subject to profound social and environmental factors in the family and in schools. Early detection of disablement with early intervention paves the way for a more inclusive life in the community. Greater care should be exercised in the diagnostic and genetic counseling applications in this fascinating research domain.

The valuable experiences and information that are gained and gathered will be used to execute the research in a successful way to help the needy. The report will be made available to the Health care officials to improve facilities for the benefit of the children and their families.

ABSTRACT 23

Non Immune Hydrops Fetalis: A 10 Year Review from a Tertiary Care Center

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Introduction: Non-immune hydrops fetalis (NIHF) constitutes 90% of all hydrops fetalis cases. Identification of etiology in NIHF is important for genetic counseling of affected families.

Aims and Objectives: To evaluate the clinical profile and etiology in patients presenting with NIHF and to determine the diagnostic yield of the tests done in the investigative protocol.

Material and methods: From September 2007 through October 2017, medical records of patients who presented with non-immune hydrops were tabulated. These were analysed and detailed clinical profiling was done.

Results: Total cases of NIHF were 194.The mean gestational age at diagnosis was 18.5 weeks (range 11-36 weeks). Consanguinity was present in 6.1% and 9.7% had a recurrence of hydrops. An etiopathogenic diagnosis was confirmed in 64.4% cases and included chromosomal anomalies in 19.5%, syndromic etiology in 7.7%, cardiovascular defects in 13.4% and congenital infections 6%. Lysosomal storage disorders were present in 4.1% cases. Malformations of the thorax including skeletal dysplasias were present in 4.1% cases. Arthrgryposis was present in 4.1% cases and 3.6% cases were attributed to maternal causes. In 69 cases (35.5%) an etiology was not defined.

The diagnostic yield of cytogenetic tests was 27%, fetal echocardiography 20.6%, whole exome was 33.3%, Antibody testing for infections was 13.8%, AF PCR for infections 40.2%, lysosomal storage enzymes estimation was 13.2%.

Conclusion: A definitive diagnosis was established in 63% cases with chromosomal and cardiovascular causes being the major contributing factors. Based on the study results a cost effective stepwise testing can be offered in cases where an extensive battery of tests is not feasible, especially in the Indian scenario.

ABSTRACT 24

Cytogenetic Evaluation of Children with Developmental Delay

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Introduction: Developmental delay (DD) / mental retardation (MR) appears in children with global prevalence of 2.3%. 2.5 to 3.4% of children in Kerala have some form of developmental problems. In many cases, DD/ MR indicates some underlying genetic disorder as one among the many other causes for it. The distortion in the amount or arrangement of genetic information in the cells results in problems in growth, development and proper functioning of the body. These genetic disorders put lot of pressure on social and educational skill of the affected children. In such cases, genetic counseling is often recommended and supportive counseling for the parents is usually helpful.

Aim: The study intends to carry out cytogenetic evaluation in children with MR and to determine the prevalence of chromosomal abnormalities in such cases.

Method: The study was conducted at Child Development Centre, Govt. Medical College, Thiruvananthapuram, India during the time period of December 2013 to August 2017. Cytogenetic analysis was performed on 614 children with MR, of which 185 cases were with Down Phenotype. The remaining cases were classified in to three categories (i) DD/MR with Multiple Malformation (MM), (ii) DD/MR with Dysmorphism and (iii) isolated DD/MR. Chromosomal study was performed for all classes using GTG banding Technique. Parental Karyotyping was also done in cases with chromosomal structural anomalies.

Results: Chromosomal analysis of these 614 children resulted in 229 (37%) abnormal karyotypes. Out of the 185 Down syndrome cases, non- disjunction was identified in 87%, Robertsonian translocation 11% and mosaicism in 2% of cases. In the remaining 428 cases, abnormality was detected in 44 cases (10.3%) (Numeric-17, Structural-27) with a high prevalence in DD/MR/MM group 23%, [20 / 87 cases (Numeric-6, Structural-14)] compared to DD/MR/Dysmorphism, 8.6%, [16 / 186 cases (Numeric-7, Structural-9)] and 5% in isolated DD/MR group, [8 / 155 cases (Numeric-4, Structural-4)]. Further, parental karyotyping was carried out on 22 cases with structural abnormalities, in 12 out of 22 cases carrier status was identified in one of the parents (54.5%).

Conclusion: The cytogenetic studies help to identify the chromosomal abnormalities in 10.3% of children with DD/MR group excluding Down syndrome, with a high prevalence in children with MR/MM group compared to other groups. All cases with Down phenotypes were abnormal. Hence it is highly desirable to carry out genetic analysis as first line of diagnostic test in mentally retarded children in order to provide timely genetic counseling and prevent the risk of recurrence in the family.

ABSTRACT 25

Spectrum of Rare Beta Globin Gene Mutations in Indian Population

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Introduction: Beta-thalassemias are a group of hereditary blood disorders, characterized by anomalies in synthesis of β-globin chains of hemoglobin resulting in variable phenotypes, ranging from severe transfusion-dependent anemia to clinically asymptomatic individuals. These anomalies cause point mutations, large deletions and frameshift mutations which can be identified by Reverse- Dot Blot Hybridization, Amplification-refractory mutation system (ARMS-PCR), DNA sequencing etc. In India, overall prevalence of Beta thalassemia carriers varies from 1.5% to 17% in different states. There is considerable molecular heterogeneity within 64 mutations identified, of which 5 common mutations account for 80-90% of mutant alleles. Rare beta-thalassemia mutations are found in approximately 7% of carriers.

Methods: Our study was performed at state of the art genetic laboratory-Lilac Insights, Navi Mumbai. Current study included four hundred and ninety (n=490) beta thalassemia patients, identified on basis of hematological parameters. They were screened for Beta (HBB) globin gene mutations using a combination of multiplex ARMS and Sequencing-based PCR. Emphasis was on maternal contamination check for purpose of prenatal diagnosis.

Results: Molecular investigations on all study patients resulted in identification of 28 different beta globin gene mutations, responsible for disease. These mutations have different frequencies in different provinces of India, with various ethnicities. Out of 14 rare mutations frequently reported among Indian population, our study identified 3 mutations (c.374 C-A, c.316-238C>T and c.332 TC) that are extremely rare. These mutations were identified in individuals from West Bengal and Maharashtra province. Our study identified rare mutations that will help in prenatal diagnosis and subsequently assist in prevention and management of beta thalassemia in high-risk families.

Conclusion: Findings from our study propose an ethnicity-based HBB mutation detection panel. This distinctive panel may evade need for extensive mutation screening of monogenic disorders. Diagnosis of monogenic disorders holds great potential for alleviating human suffering in India.

ABSTRACT 26

BACs-on-Beads Technology: A Reliable Test for Genetic Evaluation of Products of Conception

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Objective: Majority of the first-trimester abortions are cytogenetically abnormal and these abnormalities are identified by GTG Karyotype currently considered as gold standard for chromosomal analysis. However, products of conception (POC) specimens are highly contaminated and are prone to high failure rate of cell culture. Karyolite BoBs assay is a bead-based, low density array technology, designed to detect aneuploidies, gains and losses in all chromosomes. It requires minimal DNA, has rapid turn around time and is cost effective when compared with microarray. However, the limitations include inability to detect ploidy changes and balanced translocations. In the current study various chromosomal abnormalities were reported from POC specimens.

Methods: Our study was performed at state-of-the-art Genetic Laboratory-Lilac Insights. We tested 975 POC specimens over a period of 18 months using Karyolite BACs on Beads technology. In few cases FISH was also performed to rule out ploidy.

Results: Abnormalities were identified in 20% of POC specimens studied. Observed abnormalities were as - Trisomies (60.63%), Monosomy X (23.93%), Ploidy changes (9.04%), arm specific gains and losses (2.65%), double aneusomy (1.06%), autosomal monosomies (1.59%) and mosaic (1.06%). Most common Trisomy was of chr21, chr16, chr18, chr 13 and chr22. Others trisomies included chromosomes 2,7,8,9,11,14,17 and 20. One case of triploidy showed XXY pattern in sex chromosomes with a tetrasomy of chr21. Another case of BOH showed loss of p arm and gain of q arm in chr8. Subsequent microarray analysis confirmed hemizygous deletion of 42.23Mb at p arm and duplication of 99.2Mb at q arm of Chr8. Parental karyotyping was recommended to rule out possible translocation.

Conclusion: Molecular karyotyping by BoBs assay is a beneficial first-tier test that gives prognostic information regarding subsequent pregnancy outcomes. It enables further analysis by genetic counseling to determine recurrence risk in subsequent pregnancies. It also saves patient from more extensive investigations and treatments of dubious values.

ABSTRACT 27

Cytogenetic Abnormalities, *FMR1* Expansion and *BMP15* & *NOBOX* Sequence Variants in Premature Ovarian Failure

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Background: Premature ovarian failure(POF) is an etiologically heterogenous condition, with genetic contribution believed to be causative in 20-25% cases. Majority of cases remain unexplained, and various genes are reported to contribute to syndromic as well as non-syndromic forms of POF. This is a prospective study involving genetic characterization of POF conducted between May 2015 and June 2017 at a Medical Genetics centre.

Materials & Methods: All patients presenting with premature ovarian failure (POF), defined by amenorrhea and FSH levels >40 IU/L were recruited, after obtaining informed consent. Evaluation included a detailed history taking and clinical examination, with search for specific dysmorphological features and syndromic characteristics. Karyotype was performed in all the patients to screen for chromosomal

abnormalities. Patients with normal karyotype were tested for *FMR1* pre-mutation by TP-PCR followed by Sanger sequencing of *BMP15* and *NOBOX* genes.

Results: 48 patients were enrolled in the study, out of which 32 had primary and 16 had secondary amenorrhea. Dysmorphic features were noted in 10 patients on clinical examination. A positive family history was ascertained in 7 cases. 45 patients could be successfully karyotyped, out of which 13 had various abnormalities involving the X chromosome. Among the remaining 32 patients who had normal karyotype, 7 were lost to follow up and 25 underwent molecular testing. One intellectually normal patient with secondary amenorrhea was found to be a *FMR1* full mutation carrier, whereas no pre-mutation was detected in any other tested individuals. The study detected polymorphic sequence variants in *BMP15* & *NOBOX*, but no pathogenic variants in these genes were found.

Conclusions: Karyotypic abnormalities contributed to 28.9% of POF cases in our cohort. No significant contribution of *FMR1* premutation, *BMP15* or *NOBOX* mutations were detected, barring one case of full *FMR1* mutation, indicating that the prevalence of these mutations may be low among POF patients in our population.

ABSTRACT 28

Identification of Different Cytogenetic Patterns in Patients with Acute Myeloid Leukemia (AML): A Study from South India

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Acute Myeloid Leukemia (AML) is biologically complex and clinically heterogeneous disease characterized by clonal expansion of myeloid progenitors (blasts) in the bone marrow/peripheral blood through the acquisition of chromosomal rearrangements and multiple gene mutations. The cytogenetic study confirms a wide variety of common, rare and novel chromosomal aberrations in patients with haematological disorders providing valuable diagnostics, prognostic stratification and appropriate treatment protocols. Clinical guidelines for AML recognize three groups of cytogenetic risk which include favorable, intermediate and unfavorable risk group. Although, AML therapy is not targeted, the intensity of therapy is driven by the prognostic risk group. The present study was carried out to identify the incidence of different cytogenetic abnormalities in patients with AML. Bone marrow (BM) or peripheral blood (PB) samples (2ml) were collected from patients with informed consent. This study population included cytopathologically confirmed 153 AML patients, of which 78 were males and 74 females (ratio 1.05:1) with median age 48 years ranging from 16 to 78 years during the period of 2016 -2017. Karyotype were analyzed (International System for Human Cytogenetic Nomenclature-ISCN,2013) and Interphase *Fluorescent in Situ Hybridization* (FISH) were carried out using AML-ETO, PML-RARA (DCDF probe) and inv16 (break apart probe) [ASI-Band View software (Applied Biosystems)]. Complex/rare chromosomal aberrations can be detected in a substantial proportion of AML, which are mainly associated with unfavorable prognosis. Conventional cytogenetic analysis cannot accurately define the specific alterations in Complex/rare chromosomal aberrations. To address this question, the conventional cytogenetic findings were confirmed by using Metaphase FISH and Spectral Karyotyping (SKY) analysis in selected cases. In this series of 153 patients, apart from normal and recurrent chromosomal aberrations, 11 patients with numerical abnormalities (+4, +8, +16, +21, hyperdiploids and polyploids), 2 patients with structural abnormalities (4q- and 20q-) and 4 patients with Complex/rare abnormalities were identified. Among the Complex/rare abnormalities, a variant of t(8;21) involving chromosomes 8, 13 and 21 was identified as novel abnormality in AML-M2 case according to the Mitelman database. Another significant finding of this study is that most of the numerical and additional abnormalities were identified in AML-M2 sub group.

ABSTRACT 29

Turner syndrome: A Retrospective Analysis in a Tertiary Care Hospital

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Objective: To assess the mode ascertainment, age of presentation, clinical phenotype and karyotype abnormalities in patients with Turner syndrome attending the genetic clinic in a tertiary hospital in Kerala.

Methods: Retrospective study of patients with Turner syndrome followed in Genetic clinic attached to Department of Pediatrics, SAT hospital, Government Medical college, Trivandrum since 2009. All patients with cytogenetic diagnosis of Turner syndrome were included in the study. The major parameters assessed were the age of presentation/diagnosis, the mode of ascertainment, clinical features and various karyotype abnormalities. The information was entered in a proforma and later in a master chart. Results were analyzed by simple statistical techniques recording number and percentage of cases.

Results: The total cytogenetically diagnosed Turner syndrome in this period was 54 cases. Of these 31 cases were identified and diagnosed after 12 years with history of amenorrhea (57%). The patients diagnosed in the Pediatric age group were 21 cases with typical phenotype and short stature (39%). In 2 cases the presentation was in antenatal period with non-immune fetal hydrops. The average adult height in those cases presented after 15 years was 138 cm. The physical stigmata of Turner phenotype was present in 14 cases and all theses patient had karyotype as 45,X. One patient had ambiguous genitalia where the karyotype is 45,X/46,XY. The various karyotype abnormalities are aneuploidy (45,X) in 28 (52%) cases, mosaic pattern 18 (33%) cases and structural chromosome abnormalities in 8 cases (15%).

Conclusion: The age at diagnosis of most of our patient is adolescents or adults. Awareness among pediatricians for evaluation of short stature to identify Turner syndrome should be stressed for early diagnosis.

ABSTRACT 30

The Phenotypic and Genotypic Spectrum of 51 patients with Noonan syndrome from a Tertiary care centre in Kerala

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We present a series of 51 patients with mutation-proven Noonan syndrome (NS) who were referred to our genetic clinic between 2005-2017, for evaluation of craniofacial dysmorphism and short stature. All patients with the classical phenotype were offered genetic testing. *PTPN11* being the commonest gene associated with NS was tested first followed by other causative genes. There were 25 females and 26 males with age group ranging from day 1 to 42 years which included three parents of children with proven NS. They had clinical features of NS and tested positive for the same mutation as found in their children. The youngest individual who was a one day old baby who was antenatally detected to have hydrops and expired on day 2 of life. 88.2 % (45/51) of our patients had mutation in *PTPN11*, 5.8% (3/51) in *RIT1* and 1.9% (1/51) each in the *RAF1*, *SHOC2* and *LZTR1* genes. Echocardiogram was done in all our patients except the 3 parents. Heart disease was present in 83.3%, and the commonest heart disease was pulmonary stenosis which was present in 45.8% (22/48) either isolated or in combination with other cardiac abnormalities, followed by ASD (37.5%;18/48) and hypertrophic cardiomyopathy (20.8%;10/48). 8/48 (16.6%) had normal echocardiogram. Two children had acute lymphoblastic leukemia (B ALL and Pre B ALL) with mutation in *RIT1* and *PTPN11* respectively. Only one among the 51 patients had lymphedema involving bilateral lower limbs and the scrotum and he had a mutation in *RIT1*. This is the largest case series from a tertiary care centre in Kerala.