Abstracts

3rd International Workshop on Klinefelter Syndrome, Trisomy X and XYY

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Oral presentations

O1

The genetic architecture of sex chromosome aneuploidies – new developments.

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This lecture aim to present recent advances in the genetics behind sex chromosome aneuploidies (SCAs), such as Klinefelter and Turner syndrome. SCAs give rise to a broad range of phenotypic traits and diseases. However, genotype-phenotype relations in SCAs are largely unexplained. Emerging literature on the impact of altered sex chromosome dosage on the genome elucidate a ripple effect on both the methylome and transcriptome. In addition, there is a growing evidence indicating that the classic X chromosome dosage compensation theory should be revised, and that the pool of X chromosomal candidate genes, which may play an important role in the phenotype of sex chromosome aneuploidies, should be expanded. Furthermore, data indicate that Y chromosomal genes may have a regulatory function on X chromosomal genes thereby adding a dimension more to the complex nature of the genetics behind SCAs. In addition, both shared and non-shared gene regulatory mechanism between SCAs as well as tissue-specific regulatory mechanisms may exist. Notably, unpublished data support the pseudoautosomal gene *SLC25A6* being involved in the cardiac phenotypes in SCAs. Overall, the genetic architecture of sex chromosome aneuploidies is much more complex than hereto thought with multiple molecular mechanism playing in concert. We advocate for collaborative genomic research project of SCAs to elucidate the nature of the genetic labyrinth of SCAs.

O2

Sex Chromosome Dosage Effects: From the Genome to the Brain

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Sex chromosome dosage (SCDs) effects are potentially relevant for diverse aspects of human health and disease. First, direct SCD effects are a candidate biological contributor to normative phenotypic differences between XX females and XY males. Second, SCD abnormalities cause clinically impactful sex chromosome aneuploidy syndromes (SCAs) in humans - thereby offering concrete evidence for direct SCD effects on non-gonadal tissues, and further motivating research to understand these effects. I will present recent studies of SCD effects on human genome structure and function within participant cohort spanning diverse karyotypes: X, XX, XXX, XXXX, XY, XXY, XYY, XXYY, and XXXXY. High-throughput cellular imaging studies reveal stereotyped X-chromosome dosage effects on X-chromosome territory position – which include an unexpected influence of inactivated X-chromosome count on the size of the active X. Transcriptomic studies of lymphoblastoid, fibroblast and iPSC-induced neuronal cell lines define a core cross-tissue program of X- and Y-chromosome gene dosage sensitivity to SCD variation which includes: (i) near-linear changes of Y-linked and pseudoautosomal gene expression with varying SCD, (ii) sub-linear increases in X-linked genes escaping X-inactivation with mounting X-chromosome count, and (iii) a subset of inactivated X-linked genes that show a paradoxical decrease in their expression with mounting X-chromosome count. We also observe profound SCD effects on autosomal gene expression, which are more tissue-specific in nature. These genomic insights are accompanied by parallel clinical studies which map SCD effects on brain structure and function – with the long-term bridging levels of biological analysis to promote our understanding of SCD effects for the benefit of both basic and clinical science.
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O3

Sex chromosome aneuploidies give rise to pervasive changes in the circular RNA profile: A circular transcriptome-wide study of Turner and Klinefelter syndrome across different tissues

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Aim: The landscape of circular RNAs (circRNAs), an important class of non-coding RNAs that regulate gene expression, has never been described in human disorders of sex chromosome aneuploidies. We profiled circRNAs in Turner syndrome females (45,X;TS) and Klinefelter syndrome males (47,XXY; KS) to investigate how circRNAs respond to a missing or an extra X chromosome.

Methods: Samples of blood, muscle and fat were collected from individuals with TS (n = 33) and KS (n = 22) and from male (n = 16) and female (n = 44) controls. CircRNAs were identified using a combination of circRNA identification pipelines (CIRI2, CIRCexplorer2 and circRNA_finder).

Results: Differential expression of circRNAs was observed throughout the genome in TS and KS, in all tissues. The host-genes from which several of these circRNAs were derived, were associated with known phenotypic traits. Furthermore, several differentially expressed circRNAs had the potential to capture micro RNAs that targeted protein-coding genes with altered expression in TS and KS.

Conclusion: Sex chromosome aneuploidies introduce pervasive changes in the circRNA transcriptome, demonstrating that the genomic changes in these syndromes are more complex than hitherto thought. CircRNAs may help explain some of the genomic and phenotypic traits observed in these syndromes.

O4

The proper interplay between the expression of Spo11 splice isoforms and the structure of the pseudoautosomal region leads XY recombination

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Aim: Identification of the molecular mechanisms beyond XY recombination and synapsis in mammals.

Background: In humans, a lack of recombination between XY chromosomes is the leading cause of chromosomes mis-segregation. Meiotic recombination is initiated by the formation of double strand breaks (DSBs) by Spo11, which have to main splicing isoforms: Spo11a and Spo11b

Methods: Using knock-in mice models expressing either Spo11b or Spo11a we investigated SPO11 splice isoforms function in XY recombination

Results: We demonstrate that in mice expressing only the Spo11b isoform XY synapsis fails due to the lack of DSBs formation in the pseudo autosomal region (PAR), the short region of homology between sex chromosomes. Moreover, we provide experimental evidence that high-order chromatin organization of the PAR play a key function in shaping XY recombination proficiency. Namely, PAR chromatin loops in mice with XY recombination failure are longer than in males with normal XY synapsis. In addition, by characterizing the phenotype of male mice expressing either Spo11aorSpo11bandSpo11awe demonstrate that concomitant expression of these isoforms boost DSBs formation between XY chromosomes.

Conclusion: alterations of the conformation of the PAR and/or expression of SPO11 splice isoforms leads to XY recombination defects, increasing the risk of generating sperms aneuploid for the sex chromosomes

O5

The impact of X-polysomy during early embryogenesis in Klinefelter Syndrome and High-grade X chromosome aneuploidy

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Aim: Klinefelter Syndrome and High-grade X chromosome aneuploidy (HGA) patients display a broad spectrum of clinical features, including infertility, intellectual disability, and metabolic disorders, among others. However, only a few gene-to-phenotype correlation studies have been reported, and the molecular mechanisms leading to the progressively worsening traits in patients with supernumerary Xs remain an open quest. We investigated the impact of X-polysomy during early embryogenesis in KS and HGAs through an induced pluripotent stem cells (iPSCs) disease-modeling approach.

Method: We generated a paradigmatic cohort of iPSCs from KS, HGAs, and healthy donors' fibroblasts from two demographic groups. We then differentiated these iPSCs towards disease-relevant cell types, such as definitive endoderm (DE) and neural progenitor cell (NPCs), precursors of pancreatic cells and neurons, respectively. Combining transcriptomic and allele-specific expression (ASE) analyses, we then investigated the transcriptional profiles of X overdosage in iPSCs, DE, and NPCs with 49,XXXXY, 48,XXXY, and 47,XXY karyotypes.

Results: We compared KS- and HGA-iPSCs transcriptomes derived from European and Saudi cohorts and demonstrated that escape genes within the pseudoautosomal region 1 (PAR1) and a few non-PAR escapes, including the histone modifier KDM6A, are the most susceptible to dosage-dependent transcriptional dysregulation regardless of the geographical area.

Conclusions: The expression sensitivity of the histone demethylase KDM6A to X-overdosage is conserved among KS- and HGA-iPSCs and differentiated derivatives. This is particularly relevant in the nervous system where KDM6A plays a major role during development. Therefore, the possibility to fine-tune KDM6A enzymatic activity through pharmacological inhibition has a high potential for translational applications.

O6

Testis function, hypogonadism and bone metabolism

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Low bone mass (osteoporosis) is present in up to 40-50% of subjects with Klinefelter syndrome (KS) and has usually been attributed to low testosterone levels, similarly to other forms of hypogonadism, as it is well known that testosterone has an anabolic role on bone metabolism both directly through the androgen receptor (AR) and indirectly by aromatization to oestrogens promoting periosteal bone formation during puberty and reducing bone resorption during adult life. However, reduced bone mass might be present also in KS men with normal testosterone levels and testosterone replacement therapy does not always restore bone density in KS patients. Possible other determinants for osteoporosis in KS might be related to low insulin-like factor 3 (INSL3, that exerts anabolic effects on osteoblasts and osteocytes), 25-hydroxyvitamin D, and oestrogen levels, unfavourable fat/muscle ratio, CAG length and inactivation pattern of the AR, and high FSH, with different levels of evidence. Other than reduced bone mineral density (BMD), alterations in bone microstructure have been described in KS. However, the determinants of skeletal fragility and fracture rates (that represent the clinical manifestation of osteoporosis) in KS are less known. Indeed, KS may be associated with risk of vertebral fractures in close relationship with delay in disease diagnosis but independently of BMD values and serum testosterone levels or testosterone therapy. Therefore, it is essential to assess bone density and bone fracture risk in patients with KS from a young age, and consider vitamin D supplementation (and testosterone replacement therapy when needed) as early as possible.

O7

Klinefelter in transition: auxological, endocrine and metabolic changes during puberty

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Klinefelter syndrome was originally described in 1942 based on phenotypic characteristics in adult men by Harry F Klinefelter and his colleagues. Only decades later was the presence of an additional X chromosome suggested as causative.
Only approximately 40% of patients are identified leaving 60 % undiagnosed. Clearly, phenotypic, biochemical and metabolic characteristics are based on identified patients, and imposing a risk of bias. The marked changes that can be observed in adults diagnosed with a 47XXY karyotype develop over time, and may be subtle in childhood and adolescence. Thus, we do not know the natural course of hormone levels and changes in body proportions and composition in subjects with a 47XXY karyotype. In our cross sectional and semi-longitudinal cohort of boys, adolescents and adults with Klinefelter syndrome we have assessed growth, body composition by DXA and reproductive hormone levels including inhibin B, AMH and INSL3. In addition, we will try to characterize individual hormone profiles by PCA to identify and distinguish prepubertal 47XXY boys from healthy prepubertal boys.

O8

Aging in Klinefelter patients: knowledge gaps and methodological considerations to fill them

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Research on Klinefelter syndrome focusses on young people, children, adolescents and young adults. Little is known about aging with Klinefelter syndrome. In my talk I would like to review current knowledge on aging and identify issues that need further attention for patient, caregivers, clinicians and researchers. The introduction of electronic health records and other databases offers new ways to study the life course of specific patient groups. This might be relevant for studies in the field of Klinefelter syndrome. In my talk I will discuss these opportunities and the methodological and ethical concerns of this approach.

O9

Focal spermatogenesis in men with Klinefelter syndrome requires loss of XIST expression and of the additional X-chromosome in Sertoli cells

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Aim: We previously described differences in sex chromatin patterns of Sertoli cells in adults with 47,XXY Klinefelter syndrome (KS) depending on whether the Sertoli cells resided in either Sertoli-cell-only (SCO) tubules with morphological differentiated (type A) or undifferentiated (type B) Sertoli cells (Skakkebaek Nature 1969; Frøland and Skakkebaek JCEM 1971).
In this study, we aimed to investigate the expression of XIST, a non-coding RNA involved in X-inactivation, and X-chromosomal content in type A and B Sertoli cells as well as in Sertoli cells that support focal spermatogenesis.

Methods: Using ultra-sensitive RNA in situ hybridization (ISH) on testicular biopsies from 11 men with KS, we showed that the undifferentiated type B Sertoli cells highly express XIST, while the differentiated type A have lost XIST expression. In addition, Sertoli cells in tubules with spermatogenesis also lack XIST expression. To investigate if Sertoli cells negative for XIST expression have lost the additional X-chromosome or only X-inactivation, we performed DNA ISH targeting the X-chromosome.

Results: We confirmed that the differentiated type A Sertoli cells and the Sertoli cells in tubules with spermatogenesis only contained one X-chromosome. Using testis specimen from second trimester fetuses and prepubertal boys with KS, we observed XIST expression in Sertoli cells until puberty, with a gradual loss of XIST in some Sertoli cells.

Conclusions: We hypothesize that an additional X-chromosome in Sertoli cells arrests them in an undifferentiated prepubertal-like stage incapable of supporting spermatogenesis. However, if Sertoli cells lose the additional X-chromosome and germ cells remain in these tubules, then focal spermatogenesis can occur.

O10

Randomized-controlled trial of testosterone in 70 infants with 47,XXY

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Aim: Mini-puberty testosterone concentrations are modestly lower in boys with XXY, and observational studies report beneficial effects of testosterone treatment in infancy. The objective of this double-blind, randomized controlled trial was to assess the effect of infant testosterone on short-term physical and neurodevelopmental outcomes in infants with XXY.

Methods: Seventy-one term infants with prenatally-identified non-mosaic 47,XXY were enrolled between 1-3 months of age and randomized 1:1 to receive testosterone cypionate 25 mg intramuscular injections every 4 weeks for 3 doses or saline placebo. Outcomes were measured at baseline and 4 weeks (± 10 days) after the third injection.

Results: Demographic variables including average age upon enrollment (66±16 days), race/ethnicity (60% non-Hispanic White), socioeconomic status (53±11 Hollingshead score), parental age (35±5 yrs), gestational age (39.3±1.2 wks), and birthweight (3.3±0.4 kg) were similar between groups. The testosterone-treated group had a greater increase in body length z-score (0.7 ± 0.7 vs 0.2 ± 0.7, $p<0.001$), greater increase in stretched penile length z-score (1.1 ± 0.5 vs 0.1 ± 0.5, $p<0.001$), and less of an increase in percent fat mass z-score (-0.1 ± 1 vs 0.5 ± 1, $p=0.03$) secondary to a greater increase in lean mass (1.5 ± 0.4 kg vs 1.2 ± 0.4, $p=0.001$). There were no differences for any standardized neurodevelopmental outcomes ($p>0.15$ for all). The treatment group experienced more penile erections (66%) and pubic hair (17%), but no other side effects were reported.

Conclusion: Testosterone treatment in infants with XXY has physical effects but does not yield short-term benefits on neurodevelopment.

O11

Sex Chromosome Aneuploidies and Fertility: 47 XXY, 47XYY, 47XXX, and 45X/47XXX

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Alan D. Rogol, MD, Ph.D is professor emeritus of Pediatrics and Pharmacology at the University of Virginia where he has taught and evaluated patients for the past 48 years. He has been Chief of the Division of Pediatric Endocrinology and Diabetes and continues to teach and mentor the junior faculty and pediatric endocrine fellows. His academic path has included an undergraduate degree in chemistry from MIT and professional degrees in medicine and pharmacology from Duke University. Pediatric training occurred at Johns Hopkins with additional postgraduate research training at the NIH. Most of his subsequent research involved growth and puberty, both physiological and pathological, especially those related to growth hormone and the sex steroids with special emphasis on treatment of adolescent males including those with the Klinefelter syndrome with testosterone. The goal of this presentation is to review the hypothalamic-pituitary-gonadal axis in the various trisomy conditions, 47,XXX, 47,XXY, 47,XYY and 45,X/47,XXX and present data relevant to natural and assisted reproductive therapy with some recent data for the in vitro maturation of spermatogonial stem cells.

O12

Neurocognitive and behavioral development in young children (1-7 years) with Sex Chromosome Trisomy: the TRIXY Early Childhood Study

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In this presentation I will provide an overview of studies from our TRIXY lab at Leiden University. Our research is focused on neurocognitive functioning in relation to risk for psychopathology and psychosocial problems in individuals with sex chromosome trisomy (47,XXX, 47,XXY, 47,XYY). In a recent longitudinal study including 110 children with SCT and 102 typically developing children, aged 1 to 7 years, we studied vulnerabilities in early neurocognitive and behavioral development. Clinical assessments and structured behavior observations showed an increased risk for social, emotional and behavioral problems. Using neuropsychological tests, eyetracking, and psychophysiological measures (heart rate, skin conductance), we have gained insight in the underlying mechanisms driving this increased risk. Based on this, three key neurocognitive domains of vulnerability were identified in young children with SCT: social cognition, language and executive functioning (i.e. cognitive control functions involved in the regulation of thought, emotion and behavior). I will present data illustrating 1) to what degree neurocognitive development may be compromised in SCT, 2) how a developmental perspective is key to understanding 'at risk' pathways, 3) how this may help explain risk for social, emotional and behavioral problems, and 4) to what extent these aspects of neurodevelopment may be impacted by environmental factors such as cognitive-behavioral intervention.

O13

The eXtraordinarY Babies Study: A Prospective Natural History Study of Health and Neurodevelopment in Children with a Prenatal Diagnosis of Sex Chromosome Trisomy

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Sex chromosome trisomies (SCT), including XXY/Klinefelter syndrome, are historically underascertained and research remains tainted with ascertainment bias. Prenatal diagnoses of SCT have drastically increased as noninvasive prenatal screening practices evaluating fetal DNA in maternal blood have been adopted in the US, providing opportunity for much-needed prospective research on a newborn infant cohort ascertained prior to development of clinical symptoms. The eXtraordinarY Babies Study is an NIH-funded prospective study of health and neurodevelopment in infants and young children with a prenatal diagnosis of SCT. The study aims to describe the natural history, identify predictors of developmental and health outcomes, and evaluate developmental screening measures for use in this high-risk population. Participants are enrolled between 2 to 12 months of age, and followed at regular intervals with a protocol that includes developmental assessments, health history and examination, hormonal profiles, body composition, and parental questionnaires of temperament and quality of life. Biological samples are banked for future study and collaborative research. This presentation will describe preliminary results from 240 participants, including over 160 with XXY/Klinefelter syndrome. Results will include medical features, hormone profiles, and developmental trajectories from birth to 36 months of age. Successes, challenges, and future directions will be discussed.

O14

System-Based Diagnoses in Youth with XXY, XYY, and XXX: A PEDSnet Study

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Aim: Knowledge on health risks among youth with sex chromosome trisomies (SCTs) are primarily from small convenience samples or extrapolated from adult studies. A collaboration of six large pediatric academic centers in the US (PEDSnet) offers a unique opportunity to examine clinical outcomes for a large cohort of youth with SCTs compared to a general clinical population.

Methods: Electronic medical records for all individuals with a diagnosis of Klinefelter syndrome (XXY, n=1,198), XYY (n=253), and XXX (n=262) were obtained from PEDSnet and each matched to four controls on site, sex, age at last visit, duration in PEDSnet, race, ethnicity, and payor type. Log-binomial regression models with generalized estimating equations were used to calculate the relative risk (RR) and 95% confidence intervals (CI) between cases and controls for any diagnoses within one of 15 different system-based SNOMED categories, with an alpha of 0.003 (Bonferroni correction).

Results: All three SCT conditions had higher risks of diagnoses within the Endocrine (RR [95%CI] for XXY 5.4 [4.7-6.2], XYY 2.0 [1.3-3.1], XXX 2.1 [1.3-3.2]), Cardiovascular (XXY 1.2 [1.1-1.4], XYY 1.6 [1.2-2.1], XXX 1.6 [1.2-2.1]), Mental Health (XXY 2.1 [2.0-2.3], XYY 3.2 [2.7-3.7], XXX 3.8 [3.2-4.5]) and Nervous (XXY 1.5 [1.3-1.6], XYY 2.1 [1.7-2.5], XXX 1.8 [1.4-2.4]) system categories. Males with XXY also had a higher risk of Genitourinary diagnoses (2.6 [2.3-2.8]).

Conclusions: SCT in childhood is associated with an increased risk of comorbid diagnoses in some but not all body systems. Specific diagnoses within these systems and prescription medications will also be presented.

O15

Oral narrative skills in preschool children with sex chromosome trisomies

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Aim: The neuropsychological profile of children with sex chromosome trisomies [SCTs] is frequently characterised by delays and impairments in language development, though their cognitive level is generally in the normal range. No studies so far have specifically examined their narrative competence. The present study aimed to analyse the oral narrative competence of preschool children with SCTs due to the implication of this skill on the following learning abilities.

Method: Participants were 34 preschool children with SCTs, ranging from 48 to 64 months, one-to-one matched by age and sex to 34 typically developing [TD] children. A storytelling task (the Narrative Competence Task) was used to assess the macrostructural and microstructural features of the narratives produced by children.

Results: Children with SCTs showed significantly lower scores than TD peers in all the narrative indices considered, except for mental state lexicon and story length. Fifteen per cent of children with SCTs scored lower than the 10th percentile in all the oral narrative measures considered.

Conclusion: The problems found in narrative competence confirmed the existence of delays and impairments in the language development of children with SCTs. The identification of a risk factor in oral narrative competence could lead to early intervention to support these children's following learning skills and academic achievements.

O16

Neuropsychiatric difficulties in Klinefelter Syndrome and supporting tool checklist

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Aims: Klinefelter syndrome (KS) is associated with various neuropsychiatric difficulties related to behaviour, communication, and social interaction. This study aimed (1) to explore the experiences of individuals with KS and their families with respect to these comorbidities and (2) to develop a checklist that can be used as a supporting tool for conversations about these problems between families and clinicians.

Methods: After reviewing the literature about neuropsychiatric difficulties in KS, qualitative in-depth interviews were conducted with a group of 9 adults with KS and 11 parents of individuals with KS. In parallel, we used the a checklist that was developed and validated to capture Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND Checklist) to guide the development of a preliminary checklist for KS ('Klinefelter Syndrome Associated Neuropsychiatric Disorders Checklist' or 'KAND Checklist').

Results: The reported difficulties were structured across six levels, including a behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial level, in line with the TAND Checklist, and were complemented with a number of additional KS-specific findings. In addition, a pilot version of the KAND Checklist was developed.

Conclusions: Clinicians and other healthcare providers should be aware of the KS-associated needs and vulnerabilities that can more easily be captured when using a structured checklist. Building further on the results of this study, the preliminary KAND Checklist will be validated in a larger study population.

O17

Morbidity of 47,XXY and 47,XYY syndromes - similarities and differences

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Klinefelter syndrome (KS; 47,XXY) and 47,XYY are sex chromosome aneuploidies with a prevalence of 150 and 100 per 100,000 newborn boys, respectively. The gain of a supernumerary sex chromosome affects the majority of patients with KS and 47,XYY at multiple organ levels and consequently both morbidity and mortality is raised. KS and 47,XYY continue to pose significant diagnostic challenges, as many patients are still misdiagnosed, or remain undiagnosed. In fact, as few as 25% of KS patients and 10% of 47,XYY are accurately diagnosed, and most of these diagnoses are not made until adulthood. Shared characteristics of the two syndromes include cognitive impairment and a generally raised level of morbidity, related to psychiatric, neurologic, respiratory, urogenital, endocrine, circulatory, gastrointestinal, and musculoskeletal system disorders. Each syndrome is also characterized by specific and differing stigmata. KS is associated with hypergonadotropic hypogonadism in most patients. However, hypogonadism also seems to be more frequent among 47,XYY syndrome patients, although not as frequent as among KS.
Both syndromes are also associated with more general health markers, in addition to higher morbidity and mortality rates, also lower socio-economic status (which likely affects both morbidity and mortality). Males with KS benefit from medical treatment with testosterone replacement therapy (TRT) and it also now seems clear that neurocognitive treatment may improve outcome. It is presently more unclear which treatment males with 47,XYY syndrome may benefit from, although it is likely that neurocognitive treatment will be beneficial for this group of males. Many kids with KS and 47,XYY will in addition also benefit from support during schooling and also neurocognitive therapy during early adulthood. Here, I will make a comparative analysis of the two syndromes in relation to morbidity and mortality and focus on similarities and differences.

O18

Non-Invasive Prenatal Testing (NIPT) Results for Participants of the eXtraordinarY Babies Study: Screening, Counseling, Diagnosis, and Discordance

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Aim: The impact of noninvasive prenatal testing (NIPT) on prenatal ascertainment of sex chromosome aneuploidies (SCA) is understudied, particularly when diagnostic testing (DT) is deferred postnatally. This study evaluates timing of DT following positive NIPT, potential factors influencing decisions and results discordant with NIPT.

Methods: Participants from the eXtraordinarY Babies Study with NIPT were included for this analysis. Data abstracted included demographics, family and birth history, and a questionnaire regarding counseling experiences. Pearson’s chi-square and T-tests analyzed differences between groups.

Results: 152 participants were included (104 XXY, 27 XXX, 15 XYY, and 6 XXYY). Eighty-seven (57%) delayed DT postnatally. We found no difference between timing of DT and demographics, NIPT indications, maternal health, family history, ultrasound findings, SCA, or PPV. Participants earning <$100k were less likely to pursue prenatal DT (p=.010-.017). 102 (67%) parents completed a counseling experience questionnaire. Top indications for NIPT were maternal age (60%) and elective/gender discovery (42%). Participants informed about SCA prior to NIPT were more likely to pursue postnatal DT (p<0.01). We found no difference in timing of DT based on quantity of information provided or if providers were “well-informed” (WI). The majority believed provider(s) were not WI and those WI offered significantly more information (p<.001). Eleven (7%) DT results were discordant with NIPT. Of these, 2 mosaic with typical cells and 9 with different SCA diagnoses, including 6 with 48,XXYY.

Conclusions: The majority of NIPT results positive for SCA defer DT postnatally, however, discordant results may impact genetic counseling.

O19

The onset and progression of testicular dysfunction in Klinefelter Syndrome

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Aim: KS is the most common chromosomal disorder in men, and the most common cause of hypergonadotropic hypogonadism. The onset of puberty is accompanied by a progressive degeneration of the testicular environment; however, the beginning of testicular damage is controversial. We aimed to describe the onset and progression of testicular dysfunction in KS through the integration of clinical, hormonal and ultrasound data.

Materials and methods: This is a prospective cohort study of consecutive KS patients aged from 7 months to 25 years followed from 2012 to 2021. We included 114 subjects with classic karyotype (47,XXY) who underwent a total of 332 clinical and US evaluations. We also included a cohort of 41 adult KS patients testosterone naïve. Pubertal stage evaluation according to Tanner, hormone blood tests and testicular US were performed at each evaluation.

Results: Sertoli and germ cell impairment is not hormonally detected before Tanner stage 4, but there is a significant reduction in the testosterone/LH ratio at stage 5, when Leydig cell deterioration begins. Testicular echotexture worsens during the transition age, reflecting this dysfunction. Both FSH and LH have a primary role in these changes and chronic LH stimulation aggravates testicular structural alterations, namely the onset of Leydig cell micronodules.

Conclusions: The findings from this large prospective study of a sizable patient population indicate a need to revisit guidelines regarding the need for testicular US in infancy and childhood, as well as in puberty and adolescents, for the optimal care of KS patients.

O20

Psychological Effects of Testosterone in Tanner 2-3 Males with XXY: Results of a randomized, placebo-controlled trial

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Aim: Clinical questions frequently arise related to the effects on testosterone replacement on internalizing and externalizing behaviors, mood, cognitive skills, executive functioning (EF) and self-esteem in XXY. This study aimed to investigate these questions using a double-blind, placebo controlled study design.

Methods: Forty-nine Tanner 2/3 males with XXY were randomized to receive testosterone 1% (T) or placebo gel (P) daily for 12 months; 44 completed the study (n=26 testosterone; n=18 placebo). Direct performance-based assessments, questionnaires (parent and self report), and clinician impression measured domains of cognitive skills, EF, behaviors, and self-esteem at baseline and 12 months. Factor analysis allowed creation of composite scores for each domain. Independent-samples t-tests compared baseline scores in each domain between treatment groups and one-sample t-tests compared the total cohort to standardized norms. Repeated measures ANOVAs assessed testosterone treatment effect. Effect sizes on difference scores were calculated.

Results: The study cohort showed variability and differences in all domains compared to norms, consistent with prior literature. Treatment groups were well-matched on age (p=0.99), full scale IQ (T 86.7sd16.4 vs P 82.8sd13.7; p=0.44), maternal education (p=0.89), and race (p=0.67). Testosterone neither significantly worsened nor improved cognitive skills (verbal IQ, nonverbal IQ) or EF, but small effect sizes were noted in EF subdomains for inhibition (Cohen's d = 0.3/0.2), planning/switching (Cohen's d = 0.3) and attention (Cohen's d = 0.3). Results of behavioral domains and self-esteem will be presented.

Conclusions: Testosterone therapy for 12 months in early puberty does not lead to improvement in verbal or nonverbal cognitive scores. Effect sizes of some EF subdomains support mild improvement. Results of randomized, placebo-controlled trials are needed to guide evidence-based treatment guidelines.

O21

Klinefelter Syndrome- a novel view into testicular function

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Background and Aims

Animal models are essential for clarifying underlying pathologies. Male mice obtained during breeding of the B6EI.Lt-Y* strain resemble many general molecular and cellular mechanisms of the human 47, XXY Klinefelter syndrome (KS). Numerous findings from the mouse models by us and others are obviously consistent with results from patients like cognition impairment, bone metabolism, infertility, and testicular degeneration as well as hypergonadotropic hypogonadism, whereas others are not, like the cardiac phenotype and other morbidities. The 41, XX^{Y}* model also elucidates several unsolved questions concerning the hallmarks of KS such as the endocrine phenotype of hypergonadotropic hypogonadism.

Results

We previously studied the well-known Leydig cell (LC) hyperplasia in KS-patients and could surprisingly identify normal to hyperactive LC function and the presence of apparently normal intratesticular testosterone values, a finding which in terms of testosterone production was also confirmed in human KS patients. To decipher the underlying mechanisms of this phenomenon we are now addressing testicular vascularization and hormone-receptor interaction of LC cells. We will present recent findings of these experiments during the workshop.

Conclusions

Taken together, the 41, XX^{Y} mouse model for KS is a highly suitable tool to study the genetic condition in its complexity *in vivo* and provides novel insights into testicular function of KS patients.

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Poster presentations

P1

Gender identity in Klinefelter Syndrome

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Aim: The prevalence of Klinefelter Syndrome (KS) in the transgender population is reported being as high as 1.36%, and as many as 2.3% of KS patients report not identifying with the gender binary. However, the exact prevalence of gender dysphoria within the KS population has not been determined. To support a qualitative review of the issues regarding gender identity in KS, a 23-item questionnaire on gender identity was developed and distributed amongst a sample of KS patients.

Methods: Participants were recruited via emails to the Klinefelter Syndrome Association membership base and advertisements in a private Facebook group of LGBTQ+ KS individuals. A total of 114 responses were received from an outreach of 289 individuals, achieving a response rate of 39%. Questions covered three overarching themes: current gender identity, physical gender presentation, and alignment with the gender binary.

Results: The mean average age of participants was 55. Nine percent of participants identified as transgender, and 22% reported a gender identity other than strictly man or woman. Fifty-five percent of participants felt that some of their physical features did not align with their gender identity. Fourty-three percent of participants had considered changing their physical features to align with their gender.

Conclusions: There is an unmet need to determine the incidence of gender dysphoria in KS and to establish clear standards of care for gender support. This is especially relevant as there is a growing recognition of gender dysphoria - and the inequalities in access to its management - within the KS population.

P2

Hormone stimulation treatment for infertility in Klinefelter Syndrome - patient information

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Introduction: Adult patients with Klinefelter Syndrome (KS) can experience difficulties in their fertility as a result of Non-Obstructive Azoospermia (NOA). Guy's and St Thomas' NHS Foundation Trust started a specialist KS clinic in 2019 which has a MDT including a Urologist, Endocrinologist, Assisted Reproduction Specialist, Urology specialist, pharmacist and A Psychosexual Specialist Consultant. We have developed hormone stimulation (HS) protocol for NOA with KS.

Objective: To check the effect of distributing patient information leaflets to all KS patients attending our clinic in increasing their awareness about their condition and management pathway (hormone stimulation (HS) – semen analysis (SA) – Microscopic Testicular Sperm Extraction (Micro-TESE))

Methods: Prospective data collection over a 6 months period of all elective cases (July-December 2020) including all KS patients attending KS MDT Clinic.
Data collected on HS leaflet:
- Whether the HS leaflet:
o Helpful
o Easy to understand & read
o Detailed
o Clear and answered questions on the subject
- Any previous knowledge
- If there were any words or concepts difficult to be understood
- Comments/ suggestions to improve the leaflet

Results:
10 cases in total:
- 90% do not find any part difficult to understand
- 80% do not have any knowledge about the treatment before
- 70% reported that the leaflets easy to understand
- 10% reported needing for more details

Conclusion: Overall, increase patient satisfaction, awareness of their condition and HS management and subsequent compliance with the treatment option proposed

P3

Psychosexual issue affecting men with Klinefelter Syndrome seeking fertility management

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Introduction and Objective: Klinefelter Syndrome (KS) is the commonest hypo-androgenic chromosomal anomaly affecting fertility (1:600 men). However, beyond fertility issues there is little known of the psychological effect of KS on these newly diagnosed men.

Methods: Prospectively compiled data from 18 recently diagnosed KS patients with subfertility attending a multidisciplinary KS clinic were analyzed. A baseline patient-centered psychosexual function questionnaire (NSOG) was used to identify issues with body image, sexual function and wellbeing whilst erectile dysfunction (ED) issues were specifically sought using the validated IIEF-5 questionnaire.

Results: 89% (17/18) of KS men rated their sex life as highly important but less than 44% rated the quality of intercourse and a similar proportion were anxious about having sexual intercourse. This was in keeping with a mean IIEF-5 score of 16 (range 24- 12) in this group indicating mild to moderate ED. 56% felt that their body could adequately work sexually but 17% felt their mood negatively affected influencing sexual performance, with only 38% satisfied in their sex life. 50% of men also reported perceived delayed ejaculation. Whilst the majority reported noticed libido issues, 5% of men reported hyperactive sexual desire which impacted on social functioning.

Conclusions: Psychosexual difficulties are common in KS patients undergoing fertility treatments and yet this aspect of their management is often neglected. Psychosexual treatment should be discussed with all KS patients as all patients reported wanting to receive help and advice on improving their sexual lives.

P4

Risk of thromboembolism, and testosterone therapy in KS patients

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Aim: The aim of this study was to determine the awareness of KS patients regarding their increased risk of thromboembolism, and the potential increased risk that comes with their testosterone therapy.

Methods: Members of the Klinefelter association (KSA), and patients at the national Klinefelter clinic at Guys’ and St Thomas’ hospital trust were invited to complete an online questionnaire. The questionnaire collected data regarding thromboembolism incidence, details of testosterone treatment and knowledge of increased thromboembolic risk.

Results: Of the 281 respondents, 188 (67%) said they had no awareness of the increased risk of thromboembolism that has been associated with KS or testosterone therapy, where 10% (27 patients) were aware of the risk associated with both. 5% (14) of respondents were aware of the risk of VTE associated with the condition only. 7 respondents (2%) were aware of only the potential VTE risk that testosterone therapy carries.

Conclusions: The data from this study shows a clear lack of awareness amongst patients with KS. The consequence of this could be potentially life threatening, if not educated regarding lifestyle choices and other medications that could increase this risk further. Further studies are needed to establish the physiology underlying this risk, which remains currently unknown. Moreover, further investigation is needed to understand the relationship between testosterone therapy and thromboembolic disease. Nevertheless, this study has identified the need for educational materials for patients with KS to prevent or reduce their chance of a VTE, and to increase their awareness of other factors that could potentiate their risk of thromboembolism.

P5

Unique plasma metabolite signature for adolescents with Klinefelter syndrome reveals altered fatty acid metabolism

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Aim: Conditions related to cardiometabolic disease, including metabolic syndrome and type 2 diabetes, are common among men with Klinefelter syndrome (KS). The molecular mechanisms underlying this aberrant metabolism in KS are largely unknown, although there is an assumption that chronic testosterone deficiency plays a role.

Methods: This cross-sectional study compared fasting plasma metabolites in pubertal adolescent males with KS (n=31) to 32 controls of similar age (14 ± 2 yrs), pubertal stage, and body mass index z-score (0.1 ± 1.2); and then between testosterone treated (n=16) and untreated (n=15) males with KS.

Results: The plasma metabolome in males with KS was distinctly different from controls, with 22% of measured metabolites having a differential abundance and seven metabolites nearly completely separating KS from controls (AUC>0.9, $p<0.0001$). Multiple saturated free fatty acids were higher in KS while mono- and polyunsaturated fatty acids were lower, and the top significantly enriched pathway was mitochondrial ß-oxidation of long-chain saturated fatty acids (enrichment ratio 16, $p<0.0001$). In contrast, there were no observed differences in metabolite concentrations between testosterone- treated and untreated individuals with KS.

Conclusions: The plasma metabolome profile in adolescent males with KS is distinctly different from males without KS independent of age, obesity, pubertal development, or testosterone treatment status, and is suggestive of differences in mitochondrial ß-oxidation.

P6

Health risks among youth with SCT in a large cohort

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Aims: Knowledge on health risks among youth with sex chromosome trisomies (SCTs) are primarily from small convenience samples or extrapolated from adult studies. A collaboration of six large pediatric academic centers in the US (PEDSnet) offers a unique opportunity to examine clinical outcomes for a large cohort of youth with SCTs compared to a general clinical population.

Methods: Electronic medical records for all individuals with a diagnosis of Klinefelter syndrome (XXY, n=1,198), XYY (n=253), and XXX (n=262) were obtained from PEDSnet and each matched to four controls on site, sex, age at last visit, duration in PEDSnet, race, ethnicity, and payor type. Log-binomial regression models with generalized estimating equations were used to calculate the relative risk (RR) and 95% confidence intervals (CI) between cases and controls for any diagnoses within one of 15 different system-based SNOMED categories, with an alpha of 0.003 (Bonferroni correction).

Results: All three SCT conditions had higher risks of diagnoses within the Endocrine (RR [95%CI] for XXY 5.4 [4.7-6.2], XYY 2.0 [1.3-3.1], XXX 2.1 [1.3-3.2]), Cardiovascular (XXY 1.2 [1.1-1.4], XYY 1.6 [1.2-2.1], XXX 1.6 [1.2-2.1]), Mental Health (XXY 2.1 [2.0-2.3], XYY 3.2 [2.7-3.7], XXX 3.8 [3.2-4.5]) and Nervous (XXY 1.5 [1.3-1.6], XYY 2.1 [1.7-2.5], XXX 1.8 [1.4-2.4]) system categories. Males with XXY also had a higher risk of Genitourinary diagnoses (2.6 [2.3-2.8]).

Conclusions: In conclusion, SCT in childhood is associated with an increased risk of comorbid diagnoses in some but not all body systems. Specific diagnoses within these systems and prescription medications will also be presented.

P7

Evidence of Leydig Cell Dysfunction in Infants with 47,XXY During the Mini-Puberty of Infancy

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Aim: While previous studies have suggested lower serum testosterone in infants with 47,XXY during the mini-puberty period of infancy, these studies were small and used variable methods. The aim of this study was to assess endogenous serum hormone concentrations in a large group of infants with XXY using gold-standard assays.

Methods: Prenatally identified males (n=72) with non-mosaic 47,XXY and no exogenous hormone exposure had a fasting morning venous blood draw at ~2 months of age (mean 72± 16 days). Serum was stored at -80°C until batch analysis for total testosterone (TT) by mass spectrometry and luteinizing hormone (LH), follicle stimulating hormone (FSH), and inhibin B (INHB) by immunoassays. Values were compared to a normative sample of males at 2 months of age.

Results: Most infants with 47,XXY had hormone concentrations within the normal ranges, however lower median TT (6.0 vs 6.9 nmol/L, p=0.0003) and higher LH (3.7 vs 2.1 iU/L, p<0.0001) compared to controls. There was minimal difference in FSH (2.1 vs 1.9 iU/L, p=0.02 and higher INHB in the XXY group (248 vs 218 ng/ml, p=0.0002).

Conclusions: There is evidence of impaired Leydig cell function in infants with 47,XXY, however Sertoli cell function appears normal. Results for additional subjects in the eXtraordinarY Babies Study, including longitudinal measurements, will be presented.

P8

Testosterone treatment during the mini-puberty period of infancy affects the hypothalamic-pituitary-gonadal axis

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Aim: To assess the effect of testosterone injections on the hypothalamic-pituitary-gonadal (HPG) axis in infant boys with 47,XXY.

Methods: Infants with prenatally identified 47,XXY were enrolled between 30-90 days of age and randomized to receive testosterone (25mg) or placebo intramuscular injections every 4 weeks for 3 doses in a double-blind fashion. Total testosterone (TT) by mass spectrometry, luteinizing hormone (LH), follicle stimulating hormone (FSH), and inhibin B (INHB) were measured at baseline and ~4 weeks following the third injection. Hormone values after intervention were compared between groups; alpha was set at 0.05.

Results: Baseline values for measured parameters were all within the normal ranges for age. After intervention at a mean age of 150±18 days of age, boys who received testosterone (n=37) compared to those receiving placebo (n=32) had a higher median TT (2.8 vs 1.8 nmol/L, p=0.01) with lower LH (0.22 vs 2.0 IU/L, p<0.001), FSH (0.45 vs 1.5 IU/L, p<0.001), and INHB (158 vs 241 ng/ml, p<0.001). The TT to LH ratio was ten times higher in the group receiving testosterone (10.8 vs 0.9, p<0.001).

Conclusions: Treatment with testosterone during the mini-puberty period of infancy in boys with XXY suppresses the HPG axis. Additional longitudinal data to evaluate recovery of the HPG axis will be presented.

P9

Males with a 47,XXY and 47,XYY genotype who are not clinically identified still have significant medical comorbidities

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Aim: To compare medical comorbidities in males with a 47,XXY or 47,XYY genotype who have not been clinically ascertained to matched controls.

Methods: The Veteran's Administration's Million Veterans Program (VAMVP) combines genetic data with a comprehensive, nation-wide electronic health record (EHR) for individuals who have served in the US military. The EHR for all males identified by genetic analysis to have 47,XXY or 47,XYY were queried for a diagnosis of these conditions. Each male with XXY or XYY without a clinical diagnosis was matched with 5 controls on age, sex, and race. Comparison of medical diagnoses between XXY/XYY and their matched controls was conducted using the PHEWAS R package with odds ratio (OR) and Benjamini-Hochberg adjusted p-values presented.

Results: Seventy-four percent (636/862) of males with XXY did not have a clinical diagnosis by a mean age of 65 years, and only 1/757 males with XYY had a clinical diagnosis (>99% undiagnosed). Compared to matched controls, undiagnosed males with either XXY or XYY had a much higher odds of numerous conditions, including venous thrombosis (XXY OR 5.7, p=3.2e-32; XYY OR 5.5 p=2.2e-34), type 2 diabetes (XXY OR 2.1, p=9.5e-12, XYY OR 2.1, p=7.8e-18), and glaucoma (XXY OR 2.4, p=4.8e-17; XYY OR 4.1, p=2.0e-24).

Conclusions: Medical comorbidities commonly attributed to sex chromosome aneuploidies are still present in men with 47,XXY and 47,XYY genotypes who have not been clinically ascertained. The VAMVP cohort is a unique resource for studying morbidity in both aging and undiagnosed individuals with these conditions.

P10

Eosinophilic esophagitis in individuals with sex chromosome aneuploidies: Clinical presentations and management implications

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Aim: Our interdisciplinary clinic observed patients with sex chromosome aneuploidies (SCA) report increased rates of eosinophilic esophagitis (EoE). This study aims to investigate the prevalence and presenting features of EoE in patients with SCA as this association is not currently reported in the literature.

Methods: Retrospective review of 667 patients with SCAs seen between 2005-2018 at the eXtraordinarY Kids Clinic. Medical records reviewed included endoscopy biopsy results. EoE was confirmed with ≥ 15 eosinophils (eos) per high power field (HPF) by esophageal biopsy. Clinical data including symptoms related to GI dysfunction and allergic diseases were recorded. All participants provided informed consent as approved by the local IRB.

Results: Forty-six patients with SCA were suspected to have EoE based on history of gastrointestinal symptoms. Endoscopic pathology reports were reviewed for all 46 patients. Twenty-nine patients had biopsy-confirmed EoE, including XXY (13/29), XXYY (7/29), XXXY (4/29), XYY (3/29), XXX (2/29), with the risk significantly greater than expected in all karyotypes ($p < .006$). All 29 patients reported at least one atopic disease. Twenty-three patients reported food allergies (mean 5 foods, range 1–12). The most common signs included dysphagia and reflux (all ages), feeding problems (children <10 years) and food impaction (children >10 years) These results demonstrate EoE in 4.5% of our patients with SCA and conservatively represent an odds ratio of 32 (95% CI 6-185) compared to general population prevalence rates.

Conclusions: Our results support routine screening for EoE in patients with SCA and atopic conditions or feeding difficulties.

P11

Testicular architecture of patients with SCO caused by 46,XX testicular DSD, Klinefelter syndrome and *AZF* deletions

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Aim: We examined the testicular composition and differentiation and the somatic Sertoli (SCs) and Leydig cells (LCs) of men with 46,XY, 47,XXY, 46,$XY^{azf-/-}$ and 46,XX testicular DSD to evaluate the impact of sex chromosomes on overall testicular composition.

Material and methods: Testicular biopsies of 17 men assigned to four study groups were analyzed: 46,XY men with normal spermatogenesis (*n=4)*; 47,XXY (*n=4)*; 46,$XY^{azf-/-}$ (*n=5)*; 46, XX testicular DSD (*n=4)*. Testicular architecture was analyzed employing the point counting method. SCs and LCs were quantified and immunohistochemically analyzed for markers of differentiation and maturation of Sertoli cells (SOX9, DMRT1) and of Leydig cells (INSL3).

Results: While tissue composition was similar in euploid men (46,XY) and those with 46,$XY^{azf-/-}$, the proportion of the SCO tubules was decreased ($p \leq 0.01$) and interstitial tissue increased in testes of males with a karyotype 47,XXY ($p \leq 0.05$) and 46,XX testicular DSD ($p \leq 0.01$). In addition, 47,XXY ($p \leq 0.05$) and 46,XX^{sry} men ($p \leq 0.05$) had higher proportions of SOX9-negative SCs in their seminiferous tubules. Proportions of DMRT1 negative SCs in men with 46,XX^{sry} men were not different from healthy controls. LC hyperplasia and different INSL3 expression patterns were observed in 46,$XY^{azf-/-}$, 47,XXY and 46,XX^{sry} men.

Conclusions: Testicular cell composition is severely disturbed in 47,XXY and 46,XX testicular DSD men, but not in males with 46,$XY^{azf-/-}$. Supernumerary X chromosome effects, causing alterations in SC and LC morphology and in marker expression seem more detrimental for development of normal cellular maturity and function

P12

Resting-state functional connectivity in adult women with 47,XXX: a 7 Tesla MRI study

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Aim: Triple X syndrome is a sex chromosomal aneuploidy (SCA) characterized by the presence of a supernumerary X chromosome, resulting in a karyotype of 47,XXX in affected females and has been associated with a variable cognitive, behavioural and psychiatric phenotype. At present, it remains unclear whether resting-state functional connectivity (rsFC) is affected in females with a supernumerary X chromosome. We examined rsFC in adult women with 47,XXX using ultra-high field 7T resting-state functional magnetic resonance data. Given previous evidence of impaired social functioning and cognition, and executive functioning in 47,XXX we examined the relationship of these functions with rsFC.

Methods: Nineteen adult women with 47,XXX and 21 age-matched healthy control women were included. Functional connectivity was assessed using 7 Tesla resting-state functional magnetic resonance imaging. Rs-fMRI data were analyzed and compared between groups using independent component analysis and dual regression. Additionally, we examined potential relationships between cognitive outcome measures and social functioning scores and mean functional connectivity values in 47,XXX using correlation analyses.

Results: Adults with 47,XXX showed significantly increased functional connectivity of the fronto-parietal resting-state network with the right postcentral gyrus. rsFC variability was not associated with cognitive outcome measures and social functioning deficits in adult women with 47,XXX.

Conclusions: Results suggest an effect of a supernumerary X chromosome in adult women on fronto-parietal rsFC organization. These findings provide additional insight into the role of the X chromosome on functional connectivity of the brain at rest. Further research is needed to understand the clinical implication of altered rsFC in 47,XXX.

P13

Identifying KS-specific fibrotic genes by analyzing transcriptome of (non-)fibrotic testicular tissue

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Introduction and aim: Klinefelter syndrome (KS; 47,XXY) affects 1-2 in 1000 males. Most KS men suffer from azoospermia due to the loss of spermatogonial stem cells and testicular fibrosis. However, mechanisms responsible for these processes remain unknown. Previous research revealed a pertinent role for genes related to the extracellular matrix (ECM). This current study aimed to identify ECM proteins involved in the testicular fibrotic process.

Methods: Testicular tissue from patients with (KS and testis atrophy) and without (Sertoli cell-only syndrome and fertile controls) testicular fibrosis (n=5, each) were decellularized in 1% sodium dodecyl sulfate (SDS). Protein extraction was performed by incubating the samples on a shaker for two days at 37°C in 10% SDS and 1% β-mercaptoethanol in 50 mM Tris. Sample fragmentation was carried out using the Pixul sonicator. Mass spectrometry was then used to compare protein intensities and reveal differentially expressed proteins (FDR < 0.05 and |log2FC| = 2).

Results: In total, 221 protein groups were identified while 52 protein groups were reliably quantified. A total of four proteins were found significantly downregulated in the fibrotic group compared to the non-fibrotic group: EGFL2, WNT2B, FBLN2 and FBLN5. No significant upregulated proteins were found between the two groups.

Conclusion: A total of four differentially expressed proteins were found between fibrotic and non-fibrotic testis tissue (e.g. EGFL2, WNT2B, FBLN2 and FBLN5). FBLN2 is known to be required for basement membrane integrity. Downregulation of this protein may be the initiator of the destruction of the seminiferous tubules in KS patients.

P14

Description of Klinefelter sample

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Our Klinefelter clinic accepts national referrals and offers multidisciplinary expertise. 32 participants were identified for the cohort of this study.

Participants were selected from our database of National KFS referrals, seen in clinic between 2015 to 2021. Those undergoing MT were identified. Mean age was 34.75yrs. Mean pre-operative testosterone level was 11.4. 7 patients had SSR success (22%). 94% (n=30) proceeded with AC; 5 underwent ICSI and 3 became pregnant, with 2 LBs (6%). Mean age of successful SSR was 29.8yrs and unsuccessful was 36.1yrs (p = 0.014).

Female partners were all <35yrs; maternal ages at LB were 29 and 30yrs. 24 (75%) underwent HS prior to MT. 71% (n=17) received clomiphene for >6 months. Mean pre-stimulation testosterone was 6.0 (1.7-11); post-stimulation 10.4 (3.1–20.7). 5 had successful SSR (21%); 3 have undergone ICSI, with 2 pregnancies and 1 LB. 17 (71%) responded to HS; 5 (29%) had successful SSR, with 1 LB. 7 (41%) did not respond and none had successful SSR. Fisher's test comparing HS and SSR was not statistically significant (P-value 0.137).

In those that did not receive HS (n=7, 22%), mean testosterone pre-MT was 15.9 (range: 10.4-19.1). One (14%) had successful SSR but no pregnancy, despite ISCI.
All had testicular biopsy, with no neoplasia found; Leydig Cell tumour: n=2; tubular sclerosis: n=1; mean Johnson score 1.84 (R:1.6, L:1.53). 2/32 had mosaic KFS; 1 had successful SSR.

Implications of the findings: KFS patients should be counselled regarding their fertility options and managed with a multi-specialty approach.

P15

The dose-effect of supernumerary X chromosomes on clinical, metabolic and cardiac outcomes of male subjects

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Aim: High grade aneuploidies of sexual chromosomes with a male phenotype (HGAs) are exceedingly rare conditions. For long HGAs were considered as complex variants of Klinefelter syndrome (KS), until recent evidences prompted to reconsider the two as distinct conditions. Through this paper, we aimed to investigate the impact of the number of supernumerary X chromosomes on clinical, hormonal, metabolic and echocardiographic features of male subjects with HGAs.

Methods: We compared 46 HGAs and 15 KS subjects according to the number of supernumerary X chromosomes: 25 subjects with two supernumerary X (47,XXY and 48,XXYY), 5 with three supernumerary X (48,XXXY and 49,XXXYY) and 8 with four supernumerary X (49, XXXXY). Clinical, hormonal, metabolic and echocardiographic parameters were analysed.

Results: The increase in the number of extra-Xs was associated with a progressive decrease of ultrasonographic bitesticular volume ($p < 0.001$); total testosterone ($p = 0.01$); DHEAS ($p < 0.001$); ∆4-androstenedione ($p = 0.001$); fT4 ($p = 0.01$); right and left ventricular tele-diastolic diameters ($p = 0.016$ and $p = 0.001$, respectively). Conversely, a progressive linear increase in ACTH levels was found ($p = 0.02$). oGTT 2-hour insulin levels and in HOMA-index were also higher in patients with ≥ 2 supernumerary X chromosomes, with a threshold effect (respectively $p = 0.047$ and $p = 0.01$). Cardiac ejection fraction was also found associated with the karyotype , but without an apparent dose-dependent trend ($p < 0.001$).

Conclusions: The increase in supernumerary X chromosomes is associated with a “dose-dependent” progressive impairment in steroidogenic function, insulin resistance and worse cardiac performance.

P16

Altered thyroid feedback loop in Klinefelter syndrome: a longitudinal study from infancy, through transition-age to adulthood

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Context. Thyroid dysfunction has been claimed contributing to the clinic of patients with Klinefelter syndrome (KS); however, studies are scarce.

Objective. We aimed at describing thyroid function and ultrasonographic (US) appearance in patients with 47,XXY (KS) throughout the life span.

Design and Setting. Retrospective longitudinal study carried out between 2007 and 2019 in an academic referral center.

Patients. 254 patients with KS were classified according to their pubertal and gonadal status (prepubertal/pubertal/adult, eugonadal/hypogonadal or under testosterone therapy), followed-up for a median [IQR] of 6 years [4.4-8.3] and compared with randomly selected groups of 254 age-matched 46, XY subjects with normal thyroid function (euthyroid cohort) and 61 subjects with chronic lymphocytic thyroiditis (CLT cohort).

Main Outcomes. Serum TSH, fT3, fT4, anti-thyroglobulin and -thyroperoxidase antibodies, thyroid US volume (TV) and quantitative measures of thyroid echostructure.

Results. As expected, thyroid autoimmunity was significantly more prevalent among 47,XXY subjects at all ages; however no differences in thyroid function and structure were present when comparing 47,XXY Ab negative vs. Ab positive. The 47,XXY cohort, as a whole, exhibited reduced TV, lower echogenicity, and increased inhomogeneity compared with the euthyroid cohort, and not differently from the CLT cohort. Compared to controls, free thyroid hormone levels were lower in prepubertal, pubertal, and adult subjects with KS ($p = < 0.001$ for all) while TSH values were lower only in adults with KS ($p = 0.017$). Total testosterone (T) and calculated free T were the only factors associated with thyroid function tests and thyroid US appearance.

Conclusions. KS is characterized by highly prevalent morpho-functional abnormalities of the thyroid gland that are often combined with a dysregulation of the central feedback mediated by T, presenting early in children and persisting in adult life.

P17

Increased complement activation in men with Klinefelter syndrome

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Aim: 47,XXY Klinefelter syndrome presents with an overall increased morbidity risk including for autoimmune diseases. Dysregulation of the complement system has been involved in the pathogenesis of several autoimmune diseases. We investigated complement activation in men with Klinefelter syndrome compared with healthy controls.

Methods: Plasma samples from men with Klinefelter syndrome (n=48) and age matched controls (n=44) were assessed to evaluate complement activation through the classical-, the lectin-, and the alternative pathway by ELISA.

Results: Complement activation through the lectin pathway was increased in men with Klinefelter syndrome compared with controls ($p<0.0001$). Complement activation through the classical- or the alternative pathway was not different comparing men with Klinefelter syndrome and controls. No difference in complement activation through the lectin pathway was seen comparing testosterone treated and untreated men with Klinefelter syndrome.

Conclusion: Increased complement activation through the lectin pathway could potentially modulate the risk of autoimmune disease in men with Klinefelter syndrome.

P18

Supervised machine learning based prediction models for identification of Klinefelter Syndrome

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Aim: Due to the highly variable clinical phenotype, Klinefelter Syndrome is underdiagnosed. We aimed to assess supervised machine learning based prediction models for identification of Klinefelter Syndrome among azoospermic patients, providing comparison to expert clinical evaluation.

Method: Retrospective patient data (karyotype, age, height, weight, testis volume, follicle-stimulating hormone, luteinizing hormone, testosterone, estradiol, prolactin, semen pH and semen volume) collected between January 2005 and June 2019 were retrieved from a patient data bank of a University Centre. Models were trained, validated and benchmarked based on different supervised machine learning algorithms. Models were then tested on an independent, prospectively acquired set of patient data (between July 2019 and July 2020). Benchmarking against physicians was performed in addition.

Results: Based on average performance, support vector machines and CatBoost were particularly well-suited models, with 100% sensitivity and >93% specificity on the test dataset. Compared to a group of 18 expert clinicians, the machine learning models had significantly better median sensitivity (100% vs. 87.5%, p = 0.0455) and fared comparably with regards to specificity (90% vs. 89.9%, p = 0.4795), thereby possibly improving diagnosis rate. A Klinefelter Syndrome Score Calculator based on the prediction models is available on http://klinefelter-score-calculator.uni-muenster.de.

Conclusions: Differentiating Klinefelter Syndrome patients from azoospermic patients with normal karyotype (46,XY) is a problem that can be solved with supervised machine learning techniques, improving patient care. Machine learning could improve the diagnostic rate of Klinefelter Syndrome among azoospermic patients, even more for less-experienced physicians.

P19

Adopting machine learning techniques to describe the phenotype of Klinefelter Syndrome using multiple categories of clinical measurements

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Aim: Investigate a large number of clinical measurements from Klinefelter Syndrome (KS) males and describe how the different clinical measurements combine to constitute the Klinefelter syndrome phenotype.

Method: Seventy-three KS males were included and clinical measurements were obtained within the following categories: body composition (anthropometry, bone densitometry), clinical biochemistry, serum lipid profile, sex hormones, neurocognitive profile and neuroanatomical signature. The control group consisted of seventy-three age-matched healthy males. Using principal component analysis (PCA) and multi factor analysis (MFA), we reduced the dimensionality of the collected dataset in order to elucidate patterns between the different clinical categories, and the specific clinical measurements belonging to each category, to evaluate their differential impact on the KS phenotype.

Results: We found three patterns that were significantly associated with KS males compared to healthy males. Pattern 1 was mainly described by differences in body composition and the serum lipid profile, while pattern 2 arose from differences in neurocognition and neuroanatomy. Pattern 3 was associated with differences in sex hormone levels. Based on these patterns, we used regression, symbolic and partial least squares, to explain how KS hallmark traits could be explained based on a subset of clinical measurement from each category (e.g. height and IQ).

Conclusion: We identified KS specific patterns of clinical measurements and used these patterns to predict KS phenotypical traits.

P20

Temperament of very young children with SCT

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Aim: Temperament of very young children with sex chromosome trisomy (SCT) has yet to be described in the literature. Temperament consists of a child’s activity level, rhythmicity, approach or withdrawal tendencies, adaptability, threshold of responsiveness, intensity, mood, distractibility, and persistence. This project aimed to evaluate temperament profiles in infants with prenatally identified SCTs using standardized measures.

Methods: The eXtraordinarY Babies study is a longitudinal natural history study examining developmental, medical, and psychosocial factors in children with prenatally identified SCT (XXY, XYY, or XXX). The Carey Temperament Scale (CTS) was completed by parents at the 12-month-visit. Descriptive statistics were used to describe the sample, one-sample t-tests compared the SCT sample to the norming sample, and a one-way ANOVA was used to compare SCT groups.

Results: Results suggest that there are statistically significant differences in many domains when compared to the norming sample showing low activity level (p<.001), high rhythmicity (p<.001), low intensity of reaction (p<.001), low persistence (p<.001), and high threshold of responsiveness (p=.006). 82% of parents rated their child’s overall manageability as very easy.

Conclusion: Results indicate that 12-month old infants with SCTs have temperamental differences from the general population, confirming parent-report of child behavior and previous studies which suggest similar temperamental differences in older children with SCTs. The temperament profile reflects which characteristics make these children easier to manage in the first year of life and defines a new constellation of behavioral patterns that comprise what is commonly referred to as an easy baby in SCTs.

P21

A review of the relationship between Klinefelter Syndrome and Gender Dysphoria

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Aim: The diagnosis of gender dysphoria (GD) is particularly delicate due to the pathologisation of gender variance and its continuing stigmatisation. Several studies have shown that the prevalence of GD is higher in individuals affected by Klinefelter Syndrome (KS). This review considers the potential relationship between KS and GD and the tools that can aid a clinical diagnosis of GD.

Methods: A systematic review of the literature was carried out in order to survey the existing tools for assessment of GD. Limitations of current tools to assess GD as well as factors to consider in designing such tools are discussed.

Results: An assessment tool solely for GD does not exist. Many of the tools found assess features of GD alongside other factors such as gender identity, making it harder to distinguish GD from gender questioning. The most salient limitation found is tools being outdated, this is regarding cultural and social views and the DSM-5 definition of GD. Furthermore, there is a great paucity of research, further limited by sample size.

Conclusions: Whilst tools to identify GD cannot be used as a stand-alone diagnostic tool, their wider use in practice could allow for earlier referral and identification for further investigation. For this to be done effectively, up to date, specific and accurate tools for GD in KS individuals are required. Clinicians should be aware of the referral pathways available for these individuals such as to Gender Identity Clinics. This should further cumulate to a change in treatment options such as offering both testosterone and oestrogen.

P22

Educational Supports for Children With Sex Chromosome Aneuploidies in the U.S.

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Aim: Children with sex chromosome aneuploidies (SCAs) are at increased risk for neurocognitive and behavioral disorders that may interfere with school success, including early developmental delays, learning disabilities, executive function problems, and social communication deficits. This study aimed to update and extend our understanding of educational supports and outcomes for students from the United States with these increasingly common genetic diagnoses.

Methods: Parents of children with SCAs, 5-21 years, living in the U.S. (N=248), consented to participate in an electronic survey study. Descriptive statistics quantified rates of school support plans, academic accommodations, educational therapies, and school completion. Logistic regression was used to calculate group differences.

Results: Parents reported high rates of delayed kindergarten (20%), grade retention (17%), and individualized educational programs (71%). A majority of respondents with children over age 18 (N=41) reported their child successfully completed high school, and nearly half pursued post-secondary education opportunities. Many continued to receive supports in college. A significant majority of parents described their child's teachers as having little to no knowledge of SCAs.

Conclusions: Providers should be aware of the frequent need for accommodations and individualized support plans in children with SCAs so they can educate families and advocate for early and comprehensive evaluations and intervention plans. Findings justify a need to train teachers and policy makers in the unique educational needs of students with SCAs. We recommend increased collaboration between schools and medical teams and acknowledgement of the significant role the genetic condition plays in the educational experiences of students with SCAs.

P23

Emotional reactivity and expressivity in young children with sex chromosome trisomies: evidence from psychophysiological and observational data

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Aim: Although sex chromosomal trisomies (SCT) in children are highly prevalent and associated with an increased risk for neurodevelopmental difficulties including socio-emotional problems, little is known about underlying mechanisms that could drive this risk. Studying emotional reactivity and expressivity of young children with SCT in early childhood could identify deviations in early emotional development and potentially serve as risk markers to guide clinical care in developing interventions.

Methods: Participants in the current study were 90 SCT children and 97 population-based controls, aged 1 to 7 years, who experienced a stress-inducing event in which physiological (heart rate) and observational data (expression of negative emotions) were collected.

Results: Results showed early disturbances in the emotion system of young children with SCT, in terms of blunted but prolonged emotional reactivity and a reduced emotional expressivity in response to stress. Further, the concordance between emotional reactivity (arousal response) and expressivity was significantly lower in SCT, compared to controls.

Conclusions: Given the significant impact of emotions on adaptive day-to-day functioning, deviations in processing emotions could be an important underlying mechanism in explaining the heterogeneity and variability in developmental outcomes often described in individuals with SCT.

P24

The early impact of Sex Chromosome Trisomy (47XXX, 47XXY, 47XYY) on social cognition: evidence from eyetracking

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Aim: About 1:650-1000 children are born with an extra X or Y chromosome (XXX; XXY; XYY), which results in a Sex Chromosome Trisomy (SCT). This study aims to cross-sectionally investigate the impact of SCT on early social cognitive skills. Basic orienting towards social cues, joint attention and Theory of Mind in young children with SCT were evaluated.

Methods: 105 children with SCT (range 1-7 years old) were included in this study, as well as 96 age-matched non-clinical controls. Eyetracking paradigms were used to investigate eye gaze patterns indicative of joint attention skills and orienting to social interactions. ToM abilities were measured using the subtest Theory of Mind of the NEPSY-II neuropsychological test battery. Recruitment and assessment took place in the Netherlands and in the United States.

Results: Eyetracking results revealed difficulties in children with SCT in social orienting. These difficulties were more pronounced in children aged three years and older, and in boys with 47,XYY. Difficulties in joint attention were found over all age groups and karyotypes. Children with SCT showed impairments in ToM (26.3% in the (well) below expected level), increasing with age. These impairments did not differ between karyotypes.

Conclusions: An impact of SCT on social cognitive abilities was found already at an early age, indicating the need for early monitoring and support of early social cognition. Future research should explore the longitudinal trajectories of social development, in order to evaluate predictive relationships between social cognition and outcome later in life, in terms of social functioning and the risk for psychopathology.

P25

The eXtraordinarY Babies Study: Early Social Communication Skills in Infants with Sex Chromosome Trisomy (SCT)

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Aim: The eXtraordinarY Babies Study is a natural history study of health and neurodevelopment in infants with a prenatal diagnosis of SCT. Given increased risk for social difficulties and autism in SCT, this study explores trajectories of early social communication to identify early predictors of outcomes.

Methods: We describe social communication profiles in a subset of 56 participants (XXY=43, XYY=4, XXX=9) from the eXtraordinarY Babies Study who completed the Autism Diagnostic Observation Schedule- 2nd edition (ADOS-2), Toddler Module as part of the 12-month visit. The ADOS-2 provides ratings of 0 (typical development), 1 (mild atypicality), and 2 (atypical) for communication, social interaction, and other behavioral items. An algorithm classifies scores into three categories: Little-No Concern, Mild-Moderate Concern, Moderate-Severe Concern. Analyses were limited to assessments completed prior to COVID19 mask/shield requirements.

Results: High rates of delayed or atypical development of early social communication skills were found, with >75% showing scores of 1 or 2 in frequency of babbling, spontaneous vocalizations, gesture use, and pointing and 58% showing unusual eye contact and vocalizations. Few restricted and repetitive behaviors (RRBs) were displayed. Results of total scores: Little-no concern: 50%, Mild-Moderate concern: 35.7%, and Moderate-severe concern: 14.3%. No children were assigned a clinical diagnosis of ASD.

Conclusions: Even at an early age, toddlers with SCT are at increased risk for social communication delays. While no participants were diagnosed with ASD at 12 months of age, “red flags” known for later diagnosis of ASD were seen in a subset of toddlers with SCT. Prospective follow-up will allow determination of trajectory of these deficits and those that may predict higher risk for more significant clinical symptoms.

P26

Social communication in children with sex chromosome trisomy (XXY, XXX, XYY): How children attend and respond to short communicative interactions

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Aim: Children with sex chromosome trisomy (SCT) have an increased risk of experiencing difficulties with neurocognitive functions, including language. More knowledge on the broader communicative abilities of these children is needed, for example how children perceive and respond to communicative interactions beyond language interactions.

Methods: This study examined social orientation with eye tracking and physiological arousal responses during different types of communicative interactions in children with SCT and controls aged 1-7 years. In addition, associations between social orientation and language outcomes, concurrently and one year later, were evaluated.

Results: Results showed that, compared to controls, children with SCT attended less to the face and in particular the eyes of an on-screen communicative partner, but they attended similarly to objects and the mouth. In 1-year-old children, strong correlations were found between social orientation to the eyes and mouth and concurrent and future language outcomes. In addition, whereas children in the control group showed sensitivity in physiological arousal levels depending on direct versus averted gaze, this sensitivity was not found in the SCT group. Findings were irrespective of SCT karyotype or time of diagnosis.

Conclusions: Taken together, results of this study hint at a reduced ability in young children with SCT to understand and/or respond to social demands in the environment, suggesting there might be broader social communication difficulties in children with SCT that extend past well-recognized risk for early (structural) language delays. These early communication impairments may underlie components of the social behavioral difficulties that have been described in the SCT population, and are a promising target for early intervention studies.

P27

The eXtraordinarY Babies Study: Early Adaptive Skills Profile of Infants and Toddlers with Prenatally Identified Sex Chromosome Trisomies

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Aim: Children with sex chromosome trisomies (SCT) are at risk for cognitive, language, and motor deficits. However, few studies have investigated early development of children with SCTs. The eXtraordinarY Babies Study characterizes adaptive and cognitive skills in infants and toddlers with SCT.

Method: 211 children with SCT were assessed at 6-, 12-, and 24-months of age. The Bayley Scales of Infant Development-Third Edition and the Vineland Scales of Adaptive Behavior-Third Edition were administered at each visit. One sample t-tests were conducted to compare Vineland-3 scores to normative expectation. Repeated measures ANOVAs were conducted to examine differences between Vineland-3 scores at each timepoint. Secondary analyses were conducted with a subset of the sample (n= 60) seen at all three time points to examine differences in Vineland-3 scores over time and the relationship between adaptive and cognitive skills.

Results: There were no differences between SCT subgroups (XXY, XYY, XXX). All Vineland-3 subdomains fell below expectation at all timepoints except Personal at 12 months and Play at 24 months. At 6 and 24 months, the Communication domain was significantly lower than other domains; this pattern was not seen at 12 months. Secondary analyses found that Communication, Socialization, and Motor skills remain stable over time. At all timepoints, cognitive skills were higher than adaptive skills.

Conclusions: Infants and toddlers with SCT show deficits in adaptive skills which remain stable from 6 to 24 months of age, with the greatest deficit in communication. Cognitive skills are higher than adaptive skills at all age points. This information can be used to identify early risk factors and targets for early intervention.

P28

Psychiatric symptoms in women with triple X-syndrome (TXS)

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Aim: Research on psychiatric symptoms in women with triple X-syndrome (TXS) is scarce, particular in adults, although previous case series mentioned an increased vulnerability to psychiatric disorders. Our aim is to fill this gap.

Method: We will present results of a cross-sectional study in 34 TXS women and 31 controls. The MINI International Neuropsychiatric Schedule and the Adult Behaviour Checklist (ABCL) were used to assess psychiatric symptoms. We compared psychiatric symptoms of the TXS group to the control group and we compared women with TXS with autism-related social problems with women with TXS without autism-related social problems.

Results: Preliminary results showed that women with TXS appeared to be more vulnerable to psychotic, depressive and anxiety symptoms. Moreover, women with TXS more often showed suicidal thoughts and behavior. In addition, women with TXS and autism-related social problems had more psychiatric symptoms than women with TXS without autism-related social problems. During the conference, the final results can be presented.

Conclusion: adults with TXS show an increased vulnerability to psychiatric symptoms, maybe especially if they have autism-related social problems.

P29

An International Survey of Academic and Character Strengths in Youth with Sex Chromosome Aneuploidies

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Aim: Children with sex chromosome aneuploidies (SCAs) are often characterized in the literature by limitations and pathologies related to the genetic diagnosis. This study aimed to broaden the SCA phenotypes by describing parent reported character and academic strengths.

Method: An international sample of parents of children with SCAs ages 3-21 (N=377) responded to an electronic survey asking them to describe their child's strengths in academic settings. Data were analyzed using a mixed-methods content analysis approach. Responses were coded for strengths-based content using a positive psychology framework. Codes were collapsed and combined into categories and developed into broad, descriptive themes. Code frequencies and proportions were calculated and graphed for the trisomy conditions and Pearson's chi-square analyses were used to determine statistically significant group differences.

Results: Qualitative findings included two overarching themes comprised of six subthemes: 'Social Strengths' were extraordinary kindness and an eagerness to please. 'Assets for Learning' were creativity, love of learning, hardworking students, and strengths in STEM (science, technology, engineering, and mathematics). Quantitative results showed a pattern of overlapping strengths among trisomy conditions (perseverance, love of learning), with some significant differences between children with supernumerary X chromosomes (strengths in kindness) and those with an additional Y chromosome (strengths in curiosity, humor, and teamwork).

Conclusions: This study suggests educators and clinicians should be aware of strengths profiles associated with SCA phenotypes. By recognizing and promoting assets, we may be able to protect against risk for educational failure and psychological problems and ultimately enhance quality of life for individuals with SCAs.

P30

Parenting young daughters with prenatally identified trisomy X

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Aim: There is a paucity of research on the experiences of parents of children with trisomy X syndrome (47,XXX). Increased prenatal diagnoses associated with advances in noninvasive prenatal screening require a more in-depth understanding of how trisomy X impacts family systems. This qualitative investigation aimed to describe the phenomenon of parenting young daughters with prenatally identified trisomy X.

Methods: Ten semi-structured qualitative interviews were conducted via teleconferencing with parents (n=11) of children with trisomy X ages 6-29 months. A descriptive phenomenological approach was used to code transcripts for significant statements and reduce data into themes describing the essence of participants' lived experiences.

Results: Five themes were comprised of 13 subthemes: 'Diagnostic Experience' highlighted poor delivery and ambivalence toward prenatal identification. 'Emotional Journey' described stress at the time of diagnosis, positive attitudes toward daughters at present, and emotional differences between partners. 'Addressing Risks' characterized a life stage of seeking proactive medical care and early intervention. 'Uncertainty' involved parents wondering about their child's prognosis and how to parent as well as whether to disclose the diagnosis. 'Coping Strategies' included doing research, reframing, and reaching out for support.

Conclusions: Genetic counseling implications include careful consideration of word choice, timing, and location for the diagnosis, and providing expectant parents with current research specific to trisomy X. Providers should be prepared to support families in their decisions about disclosure and provide connections to other parents, given the phenotypic uncertainty and emotional journey associated with trisomy X. Future research should expand this work to other sex chromosome aneuploidy conditions.

P31

Early preventive intervention for young children with Sex Chromosome Trisomies (XXX, XXY, XYY): Supporting social cognitive development using a neurocognitive training program targeting facial emotion understanding

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Aim: Sex Chromosome Trisomies (SCT; XXX, XXY, XYY) are genetic conditions that are associated with increased risk for neurodevelopmental problems and psychopathology. There is a great need for early preventive intervention programs to optimize outcome, especially considering the increase in prenatal diagnoses due to recent advances in noninvasive prenatal screening. This study is the first to evaluate efficacy of a neurocognitive training in children with SCT. As social behavioral problems have been identified as among the key areas of vulnerability, it was targeted at improving a core aspect of social cognition, the understanding of social cues from facial expressions.

Methods: Participants were 24 children with SCT and 18 typically developing children, aged 4-8 years old. Children with SCT were assigned to a training (*n* = 13) or waiting list (no-training) group (*n* = 11). Children in the training group completed a neurocognitive training program (The Transporters), aimed to increase understanding of facial emotions. Participants were tested before and after the training on facial emotion recognition and Theory of Mind abilities (NEPSY-II), and on social orienting (eyetracking paradigm). The SCT no-training group and typically developing control group were also assessed twice with the same time interval without any training. Feasibility of the training was evaluated with the Social Validity Questionnaire filled out by the parents and by children's ratings on a Visual Analogue Scale.

Results: The SCT training group improved significantly more than the SCT no-training and TD no-training group on facial emotion recognition (large effect size; η_p^2 =.28), performing comparable to typical controls after completing the training program. There were no training effects on ToM abilities and social orienting. Both children and parents expressed satisfaction with the feasibility of the training.

Conclusions: The significant improvement in facial emotion recognition, with large effect sizes, suggests that there are opportunities for positively supporting the development of social cognition in children with an extra X- or Y-chromosome, already at a very young age. This evidence based support is of great importance given the need for preventive and early training programs in children with SCT, aimed to minimize neurodevelopmental impact.

P32

Social Management Training for men with Klinefelter Syndrome

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Aim: One in 500-600 males have an extra X chromosome (Klinefelter Syndrome, 47,XXY), which is associated with difficulties in social interaction and adaptation. So far there have been no studies evaluating psychosocial therapeutic interventions in individuals with KS. To meet this therapeutic need a Social Management Training tailored to specific vulnerabilities in KS was developed. The SMT aimed to increase the ability of individuals to regulate emotions and behavior in ways that are socially adaptive.

Method: Sixteen men with KS participated in SMT. This novel group treatment program consists of 10 sessions and includes psychoeducation, cognitive-behavioral skills training, home-assignments and relaxation exercises. There were pre- and posttest evaluation of social behavior by means of informant and self-report and cognitive assessments of executive function including sustained attention, inhibition, cognitive flexibility and working memory.

Results: Informant reports showed a significant decrease in attention problems (effect size 0.93), aggression (effect size 0.95), rule breaking behavior (effect size 0.87) and internalizing problems (effect size 0.76). Self-reports showed a significant decrease in anxiety and depression (effect size 0.87), and a trend for reduced social distress (effect size 0.50). Self-report evaluation of autism-like behaviors showed increasing awareness of social adaptive shortcomings (effect sizes 0.63, 0.73, 0.65). Significant pre- to posttest improvements were found in inhibitory control and metacognition skills (effects sizes of 1.3 and 0.5 respectively).

Conclusions: These findings suggest that SMT tailored to the behavioral and cognitive profile of males with KS, may be a promising treatment approach for improving awareness, self-control and social adaptation.

P33

Neuropsychiatric assessment of a post zygotic mosaicism – 45x0/47xyy: a case report

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Aim: Mosaicism describes an individual that has two or more lines differing in genotype, born from a single fertilized egg. The mutational events occur after the zygote formation, during the mitotic cell divisions. Classifications can differ from: size of variation or location, affected tissues and postzygotic mutational mechanism. Our aim is to describe the case report of a somatic mosaicism, probably resulting as a nondisjunction of chromosomes in early mitosis (from an embryo XYY). Analysis of the fetal karyotype, diagnosed with trans abdominal amniocentesis at the 18th week of pregnancy, showed a mosaic with two cell lines: 45% 47XYY; 55% X0. Typical for mosaicism is to change during time and in different tissues, so at the time of the pre-natal diagnosis was not possible to anticipate the sex development. Our patient is 39 months old, phenotypically male, and presents facial features as wide forehead, hypertelorism, long palpebral fissures, large ears.

Methods: we have done a neuropsychological assessment with: Griffiths III developmental scale; ABAS II for the adaptive behavior; ADOS-2 for the autism symptoms; Peabody test for evaluating the language.

Results: Griffiths III showed an equivalent age of 24 months; a global adaptive behavior lower than the estimate for his age; ADOS-2: SA 12, RRB: 4; CSS: 7/10; Peabody test showed a score lower than expected for his age.

Conclusions: The neuropsychological profile is characterized by a Global Developmental Delay with lower adaptive behavior and Autism Spectrum Disorder with a receptive language disorder.

Video pitches

V1

Social experience of girls and women with Triple X

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My Triple X daughter was born during my PhD. Following antenatal diagnosis I wanted to conduct this sociological research; however we became full-time expert service-users of medical appointments instead. Ten years later, my academic focus is on the social experience of girls and women with Triple X. Triple X is largely unheard of in society, both in global medical science where there is perhaps a 'laboratory' level of niche knowledge, and in welfare and educational institutions, which have virtually no knowledge of it at all.

This oral presentation focuses on the unpublished reflections of participant parents I met discussing the overall life quality and educational experiences that their daughters with Triple X had throughout their childhood and into young adulthood. Women with Triple X, and their parents represent real people with fallible lives, trying their best to get through them. This article focusses on the reflections of UK parents on the educational experiences that their daughters with Triple X had throughout school and colleges. Layers of daughters' individual characteristics, education bodies' knowledge and preparedness to adapt, and parent/daughter co-created interventions in daughters' education are assessed to consider these young women's own consolidating autonomy and social citizenship. Families with privileged social status have an obvious material advantage in attempting to mitigate educational inadequacy, where cultural capital enhances nurture and network. However the complexity of daughters' adversity diverges; parents vary in their success in collaboratively intervening to secure their daughters' life paths, and daughters vary in establishing their own growing social positions.

V2

Peergroups on Facebook: an Xtra valuable option for information and interaction in Trisomy X

Jessica Langenhoff

Aim: As an adult I was diagnosed with mosaic triple X syndrome. Shortly after, I became a member of several Facebook groups which aim at people with my diagnosis and their families. The aim of my presentation is informing professionals about the importance of peer groups on Facebook.

Method: An oral presentation of the importance of peer groups on Facebook.

Results: Topics we discuss, comprise almost the whole lifespan. From non-invasive prenatal testing until adulthood and all stages in between. Only advanced age is not yet a topic.

Group members state
- They feel at home in the group
- Not being alone anymore with questions or issues
- They value the sharing of information, experiences and opinions
- Expecting parents often have more trust in the future of their child. That is important because they often found or were given confusing or outdated information. Sometimes they consider termination of the pregnancy.
- Adults with the diagnosis mentioned the group learned them to accept themselves better and understand themselves better

These groups need active moderators and clear group rules to be a safe place for the members. Then, the groups can be a great place for information, exchange of experiences and reassurance.

Conclusion: Peer groups on Facebook are a valued addition to information on websites and information given by professionals.