specific correction of the altered gene without affecting the rest of the genome.
Objectives: The aim of this study was to report the current CRISPR/Cas9 genome editing clinical trials in neurodevelopmental and mental disorders.
Methods: We conducted a search via the ClinicalTrials platform to describe clinical trials that have been conducted using the CRISPR/Cas9 genome-editing tool in neurodevelopmental disorders.
Results: Our research revealed three clinical trials that used the CRISPR/Cas9 tool for diagnostic and therapeutic purposes. The first study aimed to investigate the pathological role of KMT2D mutations in 40 Kabuki syndrome patients in order to facilitate the identification and characterization of therapeutic strategies to improve symptoms, to identify the consequences of KMT2D mutations on epigenetic marker changes and cellular structural changes and to finally attempt gene correction by CRISPR/Cas9. The therapeutic approach was an epigenome editing approach aimed at increasing the expression of the wild-type KMT2D allele to restore the functional activity of a histone H3-lysine 4 (H3K4)-methyltransferase (MLL4) in treated mesenchymal stem cells. The second clinical trial aimed to validate gene editing based on CRISPR/Cas9 technology combined with AAV delivery for the correction of the most common MECP2 mutations in Rett syndrome both in vitro and in vivo. The third GENEPI clinical trial aimed to identify acetylation profiles as epigenetic markers to assess the causality of CREBBP and EP300 variants in Rubinstein-Taybi syndrome, which is considered as a genetic model of neurodevelopmental abnormality with an epigenetic component.
Conclusions: CRISPR/Cas9 clinical trials in polygenic conditions, such as psychiatric disorders, could be envisaged at the level of the epigenetic component of these pathologies. This therapy could be applied ex vivo to perform tissue-specific gene editing.

Disclosure of Interest: None Declared

EPV0535

Female virilization related to congenital adrenal hyperplasia and psychological distress

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Introduction: In females, congenital adrenal hyperplasia (CAH), a spectrum of inherited genetic conditions related to the disruption of adrenal steroidogenesis, is among the most common conditions leading to inappropriate virilization. For adolescent and adult women, progression of hirsutism may have many psychological concerns.
Objectives: To explore the psychological distress of a young Tunisian woman who sought medical help and psychological support at a late stage, after suffering from genital ambiguity and severe virilization.
Methods: Harboring phenotypic male transformation at puberty, our patient attended genetic counselling for cytogenetics assessment. Clinical, biological, psychological and genetic explorations were thus carried out.
Results: A 17-year-old female was born from first-degree consanguineous parents, and had healthy siblings (a sister and three brothers). After a single menstrual episode at puberty, she developed amenorrhea and an unexpected progressive virilization, including hirsutism with an inappropriate beard that she had to shave every day and a male voice. Clinical examination revealed a male morphotype with an enlarged clitoris that resemble a penis, male-type pubic hair, underdeveloped of breasts, abnormal cutaneous hyperpigmentation, and a short stature. Pelvic ultrasound revealed a small uterus, but with no visualized gonads. Genetic exploration showed a female 46,XX karyotype and the absence of Y chromosome sequences. Diagnosis of a non-classic CAH was confirmed. Psychological assessment found that the psychological development of the sexual identity corresponded to the assignment of the female sex. A severe psychological suffering due to the non-acceptance of her virile appearance impaired the quality of her daily personal and social life. Stigmata of a depressive syndrome were also revealed.
Conclusions: Particular attention to the psychological assessment of patients with CAH is recommended, as changes in physical appearance have a detrimental impact on psychological and mental well-being.

Disclosure of Interest: None Declared

EPV0536

DNA methylation risk scores for depression, not today

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Introduction: After the success of polygenic risk scores (PRS) that embed a useful summary of genomic information in a comprehensive score, the wish to develop summary statistics for DNA methylation had become more pressing. Developing such a score faces challenges, as the score has to be specific and sensitive as well. Epidemiological research on DNA methylation and depression would benefit from such score.
Objectives: Here, we test a score trained on incident depression (case-control), i.e., a list of published weights for particular CpGs, for its validity in the context of depression severity as measured using MADRS in our sample with depressed patients only.
Methods: DNA methylation was assessed using the Illumina Infinium MethylationEPIC 850k BeadChip on a sample of 119 patients with a diagnosis of MDD. After data cleaning, 113 participants were included in the analysis (M_{age}= 47 years, 57.98% women, M_{MADRS}=27.7). Data processing was conducted using the RnBeads package. From the published reference for the overall sample, a list of 196 CpGs was provided, 170 of these were present in our dataset and used for the score. The list of non-smokers comprised 144 CpGs, of which 124 were available. The score per individual was built using M-values, using the formula: S(weight*DNA methylation value). The score was tested in association with depression and other typical confounders using multiple regression in

R. Confounders included ancestry, BMI, age, sex, and 6 cell types. We tested both scores in our sample: smokers and non-smokers.
Results: In contrast to our expectations, none of the regression analyses showed a significant association with depression (MADRS-score). Nonetheless, a significant association was seen with biological sex for both analysis (overall: p=0.036, non-smokers: p=0.026). A reduced model with only this predictor explained 5% and 4% of the variance of the summary score calculated (R^2), respectively (overall: p=0.013; non-smokers: p=0.019). One of the ancestry components was marginally significant too in the non-smoker summary score (p=0.065). This was not the case anymore in the reduced model.
Conclusions: Our results show that caution is still in place when using methylation risk scores as specificity and sensitivity might not yet be optimized. The score built for depression incidence does not seem fitting for depression severity at this moment. The use of DNA methylation, a marker that is generally sensitive to confounding factors, for a risk score, might pose more challenges in the context of reliable summary statistics, in particular also for cross-trait examination, which is currently a typical use of polygenic risk scores.

Disclosure of Interest: None Declared

EPV0537

Behavioral and neurocognitive phenotypes in Crigler-Najjar syndrome in Tunisia

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Introduction: Crigler-Najjar 1 (CN1) due to exon 3 mutations of the UGT1A1 gene is a not rare genetic disease in Tunisia with a founder effect. CN1 syndrome is very severe, and most of CN1 Tunisian patients die soon after birth, within a maximum of one year, due to kernicterus. Liver transplantation, which is the only available therapeutic method for CN1, remains unreachable.
Objectives: The aim of this study was to report behavioral and neurocognitive phenotypes in CN1 patients who survived to school enrollment.
Methods: We have selected all patients evaluated from 2004 to 2010, both clinically and molecularly, for a deficiency of bilirubin-UGT enzyme activity leading to a pathological elevation of unconjugated bilirubin with a suspicion of CN1 syndrome. Direct sequencing of targeted PCR amplification products was performed for molecular analysis of UGT1A1. Behavioral and mental features of patients were studied through our genetic counselling.
Results: We identified 15 patients with the homozygous c.1070 A>G Tunisian mutation. Their age at diagnosis ranged from one week to 9 months for 13 patients. Six of them died within a month of molecular investigation. Only two boys were of school age, i.e. 6 and 9 years. The first had been hospitalized at 3 months year-old for a prolonged jaundice treated with phenobarbital and phototherapy. His psychomotor and neurological development was normal, with school attendance at the age of six. The second patient presented with an unexplored jaundice at the age of 3 days, which was later complicated by seizures and treated with phenobarbital. Despite neurological and motor sequelae associated to language impairments with slurred speech, he attended school at the age of six.
Conclusions: The neurological and behavioral profile of CN1 patients depends on familial and medical management. Quick diagnosis, close follow up and early liver transplantation can improve prognosis.

Disclosure of Interest: None Declared

EPV0540

Interaction analysis of monoaminergic polymorphisms and childhood environment related to personality functioning in patients with Borderline Personality Disorder

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Introduction: Neurobiological studies have shown that genetic variations affecting the intensity of monoamine neurotransmission play an important role in aggressive behavior and borderline personality traits. Also, the effect of family environment has been repeatedly shown on aggressive behavior and interpersonal functioning. Population-based longitudinal studies pointed out interactions between the so-called monoaminergic sensitivity alleles and childhood adversities.
Objectives: Our study aimed to analyze the associations between the most studied variable number tandem repeats of monoaminergic genes and the different psychological factors in adult patient and healthy control groups, checking for the moderating effects of the parental occupation and education, childhood abuse and trauma.
Methods: The recruited 73 patients with BPD diagnosis and 98 healthy controls were assessed by the Structured Clinical Interview for DSM-5. Participants filled out online questionnaires including the Level of Personality Functioning Scale – short version (LPFS-SR) and the Buss-Perry Aggression Questionnaire (BPQ). Childhood social environment and traumatic experiences were assessed by the Barratt Simplified Measure of Social Status and the Early Trauma Inventory or the Childhood Trauma Questionnaire. Genomic DNA samples were obtained either from peripheral blood, saliva or buccal swabs using the desalting technique. Functional dopaminergic and serotonergic polymorphisms were chosen based on previous findings, implicating them as sensitivity gene variants, e.g., the variable-number tandem-repeats of the dopamine D4 receptor, serotonin transporter and the monoamine oxidase-A (MAO-A) genes. Since the MAO-A gene is located on the X chromosome, sex-stratified analyses were also carried out.
Results: Family environment indexed by the Barratt Simplified Measure Social Status had significant effect on anger, hostility and interpersonal functioning ($p < 0.01$). In the pooled sample of patients and controls, individuals carrying the high activity alleles of MAOA had elevated scores on the BPQ subscales. When analysis