Background Simple sequence repeats such as CAG trinucleotide repeats in the huntingtin gene (HTT) are regarded as a source which provides normal variation in the genetic trait they are associated with. The current study examines the influence of CAG repeat length on structural and functional modification of the normal brain.
Methods Standardised measures of behaviour, motor and executive function, as well as MRI scans were obtained from 56 children (ages 6–18 years). All of the participants came from HD families, however, were tested (for research purposes only) to have CAG repeats within the normal range. The relationship between CAG repeat length and quantitative measures of brain structure and function were determined with linear regression models.
Results Children with longer CAG repeats, yet still below disease threshold, showed 1) fewer problematic behaviours and lower incidence of behavioural/psychiatric diagnosis; 2) superior fine motor skill and 3) superior visuo-spatial skills and executive function (verbal fluency). In regard to brain morphology, increasing CAG repeats were associated with volume of the striatum and cerebellum, 2 key brain regions governing both motor and behavioural functions.
Conclusions The results suggest that increase in CAG repeat length within the normal range mediates advantageous changes of structure and function of the brain. Larger CAG repeats may sculpt a neural circuit in which the cerebellum and striatum are optimised for maximal motor, behavioural, cognitive function.

J33 THE EFFECT OF COUNTRY OF ORIGIN ON THE AGE OF ONSET – CAG REPEAT LENGTH RELATIONSHIP IN HUNTINGTON'S DISEASE IN EUROPE

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Background In Huntington's disease (HD) 50–70% of the variation in age of onset has been attributed to the disease causing CAG repeat with the rest being due to other genetic and environmental factors. Age of motor onset (AMO) of symptoms is widely used in clinical practice and in analyses of potential genetic modifiers of disease but is difficult to determine accurately. Previous reports have indicated that there are some differences in the AMO-CAG length relationship within Europe. Therefore we investigated whether such systematic differences occurred within the European HD population and where they occurred.
Methods We analysed data from 1281 subjects from Registry with AMO and CAG repeat in the range 40–50. Linear modelling and post-hoc tests examined the effect of country of residence and geographical subregion of Europe.
Results A significant influence of country on AMO-CAG relationship was found. Norway and Poland showed significantly younger ages of onset and Denmark older ages of onset with the differences increasing as CAG length increased such that at 50 CAG the difference in onset was almost 6 months. Some less significant differences between European subregions were also detected.
Conclusions All studies using AMO and potentially other clinical variables need to consider country of collection in analysis strategies. The differences observed could be due to genetic population stratification: this is likely to account for the regional differences, though the differences between countries are most likely due to systematic differences in health systems or clinical practice.

J34 NATURAL HISTORY OF HUNTINGTON'S DISEASE IN FINNISH PATIENTS

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Background Huntington's disease (HD) has been little studied in Finland. We have recently identified a nationwide cohort of 207 Finnish patients with HD.
Aim To study disease progression and survival in Finnish patients with HD.
Methods Patients treated for HD between the years 1987–2010 were identified by using the national hospital discharge registry and outpatient registry, the files of laboratories performing genetic diagnostics of HD in Finland and the files of the Family Federation of Finland. Patient records of the ascertained patients were then reviewed.
Results The mean age at diagnosis was 52.6 ± 12.1 years (range, 14–82 years). At the time of diagnosis, 23% of patients were working full-time, 72% lived independently, 65% were able to drive a car and 95% were able to walk unaided. These abilities deteriorated steadily with time and 10 years after the diagnosis all subjects were retired, unable to drive and lived independently. However, 30% were still able to walk unaided or with minimal aid. The abilities to live unaided and to drive correlated well. At the time of diagnosis, 38% of the subjects had problems in handling money and 26% had problems in dressing, but 10 years later 95% were completely unable to handle money and 48% were completely unable to dress. Mean survival was 67.4 years (95% CI; 64.4, 70.4) among men and 70.2 (67.1, 73.3) among women ($p = 0.15$ for difference, log-rank statistics). Among the 94 deceased patients the mean age of death was 59.9 years ± 12.8 years (range, 20–86 years).
Conclusions Disability begins to increase soon after the diagnosis of HD. Cognitive deterioration affects the functional status more than ambulatory deterioration during the first 10 years after the diagnosis. Mean survival is shortened compared to the general population with no difference between genders.

J35 CLINICAL FORMS OF HUNTINGTON'S DISEASE IN THE PATIENTS FROM REPUBLIC OF BASHKORTOSTAN

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Background Motor disturbances in Huntington's disease (HD) can be subdivided into hyperkinetic (choreatic) or hypokinetic-rigid form. Patients with juvenile HD (JHD) also have bradykinesia and dystonia at an early stage of the illness. In different populations the clinical characteristics of patients with HD are similar, but may be a difference in the incidence of clinical forms.
Aim Our aim was to analyse motor disturbances in patients with HD from Republic of Bashkortostan of various ethnic origins.
Materials and methods The population of Bashkortostan is 4.07 million people. The population of Bashkirs is 1.2 million (29.5%) according to the 2010 census. Two other big ethnic groups are Russians (36.0%) and Tatars (25.4%). The prevalence of HD in Bashkortostan is 3.6 per 100.000 that compared to other populations.

Results The majority of patients with HD had the hyperkinetic form of the disease. All groups (patients with HD from Bashkir, Russian, Tatar ethnic groups) showed no differences in the motor age of onset ($p > 0.02$). Cases of JHD were observed in two families: Russian and Tatar ethnicities. Cases of HD with hypokinetic-rigid form were often observed in Bashkir families with HD (motor age of onset ranged from 27 to 32 years of life, number of CAG-repeats in HTT-gene varied from 43–47).
Conclusion Analysis of the clinical features of HD and DNA-diagnostics will help to early diagnosis and effective genetic counselling in the families with HD.

J36 JUVENILE HUNTINGTON DISEASE IN VORONEZH FAMILIES

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Juvenile Huntington disease (JHD) amounts 10% of all Huntington disease (HD) cases and characterised by the manifests before 20, with a predominance akinesia and rigidity and progressive course of the disease. Although HD has an autosomal dominant pattern of inheritance, JHD in most cases is paternal inheritance with anticipation and the expansion of CAG trinucleotide repeats >60 in the IT15 gene located on chromosome 4p16.3; however, atypical cases exist, and maternal inheritance is possible. We present 6 (4 women and 2 men) JHD cases confirmed by DNA, where the number of CAG repeats varied from 60 till 66. All the patients had MRI which showed varying degrees of severity substitution hydrocephalus. Family nature of the disease was found in four cases (three maternal and one paternal inheritance). Two cases were not familial, but it is known that the mother did not have HD, and the father of one patient died at 46, and the other does not have information about his father. Four patients had akinetic-rigid form with onset between 12–19, three of them with cognitive decline. Two patients had a hyperkinetic form and cognitive decline. Diagnosis in 4 familial cases did not cause problems, although three of them had atypical maternal inheritance. Two isolated JHD cases were supposed 3 and 10 years after its onset that may indicate underestimation of JHD in practice. JHD probability should be kept in mind, even in cases with no family history, progressive akinetic-rigidy, choreic movements and cognitive decline DNA research on HD should be included.

J37 PREVALENCE OF HUNTINGTON DISEASE IN NAVARRA (SPAIN). SENSITIVITY AND POSITIVE PREDICTIVE VALUE OF DIFFERENT SOURCES OF ASECERTAIMENT

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Background Huntington disease (HD) is a rare disease that occurs worldwide but shows large geographic differences in its prevalence. Few epidemiological studies have been carried out in Spain where the prevalence of HD is uncertain.
Aims To provide accurate estimates of the overall prevalence and population at risk for HD in Navarra (Spain) and to asses the sensitivity and the positive predictive value (PPV) of multi-source ascertainment.
Methods Patients were identified through the Primary Care and Hospital (CMBD coding at hospital discharge) databases, and the Medical Genetics Department. HD cases were defined as individuals with motor or neurocognitive symptoms, confirmed by genetic analysis, or with positive family history. All individual clinical records and family trees were carefully reviewed.
Results Fifty eight HD cases in 39 families were identified, 25 of whom died before January 2014. Additionally, nine individuals were asymptomatic carriers and 245 were at 50% or 25% risk. Hospital database showed a higher PPV than Primary Care database and they were both equally sensitive. Combination of both sources detected 72% of cases with a PPV of 75%. Medical Genetics records identified 98% of HD patients. The estimated prevalence of HD was 5 per 100,000 (95% confidence interval [CI]: 4,5–5,4 per 100,000).
Conclusions HD prevalence in Navarra is lower than recently estimated in other populations of European origin and it does not show a significantly increasing trend over the time. Past low prevalence figures are likely due to incomplete ascertainment, which did not include multiple sources and genetic data.

J38 DISEASE-ASSOCIATED HTT HAPLOTYPES IN THE SOUTH AFRICAN POPULATION

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Background Huntington disease (HD) is an inherited neurodegenerative disorder resulting from an expanded CAG-tract in the huntingtin (HTT) gene. Disease prevalence varies worldwide with the highest figures reported in populations of European ancestry. Average CAG-tract size in the general population and population-specific haplotypes have been previously associated with HD prevalence in different regions. HD in South Africa (SA) occurs in all three subpopulations; similar occurrence has been reported in the Caucasian and mixed ancestry groups, with a significantly lower estimate in the black subpopulation.
Aims To assess the distribution of CAG-tract size in the South African general population and to determine what population-specific haplotypes are present in patient and control individuals.
Methods Haplotypes were constructed based on the genotypes of 96 SNPs across the HTT gene, for 72 affected and 311 unaffected chromosomes. CAG-sizing was performed for over 1000 individuals taken from the general population and representative of the three subpopulations. The polymorphic CCG repeat adjacent to the CAG-tract was also investigated in the control cohort.
Results Expanded alleles from Caucasian and mixed ancestry patients were predominantly associated with haplogroup A, signifying a similar European origin; while those from black patients were found on haplogroup B suggesting distinct origins of the mutation. In addition, average CAG-tract size in the

J35 Clinical Forms Of Huntington's Disease In The Patients From Republic Of Bashkortostan

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Notes