Climbing the Branches of a Family Tree: Diagnosis of Fragile X Syndrome

Visootsak J, Hipp H, et al


Objective: To determine the average number of family members diagnosed with a Fragile X Mental Retardation-1 (FMR1) mutation after a proband receives the initial diagnosis of fragile X syndrome (FXS).

Study design: We reviewed pedigrees of families who had been evaluated at the Fragile X Syndrome Center at Emory University in Atlanta, Georgia. Through these pedigrees, we determined the number of additional family members diagnosed as FMR1 premutation carriers or with full mutation FXS after the initial diagnosis in each proband.

Results: The fragile X pedigree review identified 176 probands, including 108 males (61%) and 68 females (39%). A total of 785 family members were diagnosed with expanded fragile X alleles, including 278 males (35%) and 507 females (65%). These family members included 227 individuals with full mutation FXS (219 males and 8 females) and 558 premutation carriers (59 males and 499 females). After the initial diagnosis of a proband with FXS, on average at least 5 additional family members were diagnosed with an FMR1 mutation.

Conclusion: Our findings confirm that obtaining a detailed family history after diagnosis of a proband with FXS is likely to identify multiple family members with FMR1 mutations. It is important that the pediatrician or other health care provider making a diagnosis of FXS recognize the value of a detailed family history for timely diagnosis and treatment of additional individuals who may be FMR1 premutation carriers or have full mutation FXS.
Objective: The authors evaluated a sequential treatment strategy of fluoxetine and relapse prevention cognitive-behavioral therapy (CBT) to determine effects on remission and relapse in youths with major depression disorder.

Method: Youths 8 – 17 years of age with major depression were treated openly with fluoxetine for 6 weeks. Those with an adequate response (defined as a reduction of 50% or more on the Children’s Depression Rating Scale – Revised [CDRS-R]) were randomly assigned to receive continued medication management alone or continued medication management plus CBT for an additional 6 months. The CBT was modified to address residual symptoms and was supplemented by well-being therapy.

Primary outcome measures were time to remission (with remission defined as a CDRS-R score of 28 or less) and rate of relapse (with relapse defined as either a CDRS-R score of 40 or more with a history of 2 weeks of symptom worsening or clinical deterioration).

Results: Of the 200 participants enrolled in acute phase treatment, 144 were assigned to continuation treatment with medication management alone (n= 69) or medication management plus CBT (n=75). During the 30-week continuation treatment period, time to remission did not differ significantly between treatment groups (hazard ratio = 1.26, 95% CI = 0.87, 1.82).

However, the medication management plus CBT had a significantly lower risk of relapse than the medication management only group (hazard ratio = 0.31, 95% CI = 0.13, 0.75). The estimated probability of relapse by week 30 was lower with medication management plus CBT than with medication management only (9% compared to 26.5%).

Conclusion: Continuation-phase relapse-prevention CBT was effective in reducing the risk of relapse but not in accelerating time to remission in children and adolescents with major depressive disorder.
We demonstrate CRISPR-Cas9-mediated correction of a \textit{Fah} mutation in hepatocytes in a mouse model of the human disease hereditary tyrosinemia. Delivery of components of the CRISPR-Cas9 system by hydrodynamic injection resulted in initial expression of the wild-type \textit{Fah} protein in \( \sim 1/250 \) liver cells. Expansion of \textit{Fah}-positive hepatocytes rescued the body weight loss phenotype. Our study indicates that CRISPR-Cas9-mediated genome editing is possible in adult animals and has potential for correction of human genetic diseases.
The Effects of Poverty on Childhood Brain Development
The Mediating Effect of Caregiving and Stressful Life Events

Luby J, Belden AD, et al.


**Objective:** To investigate whether the income-to-needs ratio experienced in early childhood impacts brain development at school age and to explore the mediators of this effect.

**Design, Setting, and Participants:** This study was conducted at an academic research unit at the Washington University School of Medicine in St Louis. Data from a prospective longitudinal study of emotion development in preschool children who participated in neuroimaging at school age were used to investigate the effects of poverty on brain development. Children were assessed annually for 3 to 6 years prior to the time of a magnetic resonance imaging scan, during which they were evaluated on psychosocial, behavioral, and other developmental dimensions. Preschoolers included in the study were 3 to 6 years of age and were recruited from primary care and day care sites in the St Louis metropolitan area; they were annually assessed behaviorally for 5 to 10 years. Healthy preschoolers and those with clinical symptoms of depression participated in neuroimaging at school age/early adolescence.

**Exposure:** Household poverty as measured by the income-to-needs ratio.

**Main Outcomes and Measures:** Brain volumes of children’s white matter and cortical gray matter, as well as hippocampus and amygdala volumes, obtained using magnetic resonance imaging. Mediators of interest were caregiver support/hostility measured observationally during the preschool period and stressful life events measured prospectively.

**Results:** Poverty was associated with smaller white and cortical gray matter and hippocampal and amygdala volumes. The effects of poverty on hippocampal volume were mediated by caregiving support/hostility on the left and right, as well as stressful life events on the left.

**Conclusions and Relevance:** The finding that exposure to poverty in early childhood materially impacts brain development at school age further underscores the importance of attention to the well-established deleterious effects of poverty on child development. Findings that these effects on the hippocampus are mediated by caregiving and stressful life events suggest that attempts to enhance early caregiving should be a focused public health target for prevention and early intervention. Findings substantiate the behavioral literature on the negative effects of poverty on child development and provide new data confirming that effects extend to brain development. Mechanisms for these effects on the hippocampus are suggested to inform intervention.

See Also: Next Page for Accompanying Article
Early Life Stress and Trauma and Enhanced Limbic Activation to Emotionally Valenced Faces in Depressed and Healthy Children

Hideo Suzuki, PhD, Joan L. Luby, MD, et al

Objective: Previous studies have examined the relationships between structural brain characteristics and early life stress in adults. However, there is limited evidence for functional brain variation associated with early life stress in children. We hypothesized that early life stress and trauma would by associated with increased functional brain activation response to negative emotional faces in children with and without a history of depression.

Method: Psychiatric diagnosis and life events in children (starting at age 3-5 years) were assessed in a longitudinal study. A follow-up magnetic resonance imaging (MRI) study acquired data (N=115 at ages 7-12, 51% girls) on functional brain response to fearful, sad and happy faces relative to neutral faces. We used a region-of-interest mask within cortico-limbic areas and conducted regression analyses and repeated-measures analysis of covariance.

Results: Greater activation responses to fearful, sad, and happy in the amygdala and its neighboring regions were found in children with greater life stress. Moreover, an association between life stress and left hippocampal and globus pallidus activity depended on children’s diagnostic status. Finally, all children with greater life trauma showed greater bilateral amygdala and cingulate activity specific to sad faces but not other emotional faces, although right amygdala activity was moderated by psychiatric status.

Conclusions: These findings suggest that limbic hyperactivity may be a biomarker of early life stress and trauma in children and may have implications in the risk trajectory for depression and other stress-related disorders. However, this pattern varied based on emotion type and history of psychopathology.
Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study.

Grønborg TK, Schendel DE, Parner ET.

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IMPORTANCE: To date, this is the first population-based study to examine the recurrence risk for autism spectrum disorders (ASDs), including time trends, and the first study to consider the ASDs recurrence risk for full- and half-siblings.

OBJECTIVES: To estimate the relative recurrence risk for ASDs in a Danish population, including recurrence in full- and half-siblings, and to examine time trends in ASDs relative to the recurrence risk.

DESIGN, SETTING, AND PARTICIPANTS: Population-based cohort study in Denmark. All children (about 1.5 million) born in Denmark between January 1, 1980, and December 31, 2004, were identified and followed up to December 31, 2010. We identified a maternal sibling subcohort derived from mothers with at least 2 children and a paternal sibling subcohort derived from fathers with at least 2 children.

EXPOSURES: Children having an older sibling with ASDs are compared with children not having an older sibling with ASDs.

MAIN OUTCOMES AND MEASURES: The adjusted hazard ratio for ASDs among children having an older sibling with ASDs compared with children not having an older sibling with ASDs.

RESULTS: The overall relative recurrence risk for ASDs was 6.9 (95% CI, 6.1-7.8), and it did not change significantly over time; similar risks were observed in maternal and paternal full-siblings. The relative recurrence risks were 2.4 (95% CI, 1.4-4.1) for maternal half-siblings and 1.5 (95% CI, 0.7-3.4) for paternal half-siblings.

CONCLUSIONS AND RELEVANCE: Our population-based recurrence risk estimate is lower than the recently reported estimates from clinical samples. Our results demonstrate no time trend in the ASDs recurrence risk as seen in the ASDs prevalence. The difference in the recurrence risk between full- and half-siblings supports the role of genetics in ASDs, while the significant recurrence risk in maternal half-siblings may support the role of factors associated with pregnancy and the maternal intrauterine environment in ASDs.
Cognitive function and other risk factors for mild traumatic brain injury in young men: nationwide cohort study.

Nordström A, Edin BB, Lindström S, Nordström P.

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OBJECTIVE: To investigate cognitive function and other risk factors for mild traumatic brain injury in young men.

DESIGN: Nationwide prospective cohort study.

SETTING: Sweden.


MAIN OUTCOME MEASURE: mild traumatic brain injuries in relation to cognitive function and other potential risk factors assessed at conscription and follow-up.

RESULTS: Men with one mild traumatic brain injury within two years before (n=1988) or after cognitive testing (n=2214) had about 5.5% lower overall cognitive function scores than did men with no mild traumatic brain injury during follow up (P<0.001 for both). Moreover, men with at least two mild traumatic brain injuries after cognitive testing (n=795) had 15% lower overall cognitive function scores compared with those with no such injury (P<0.001). Independent strong risk factors (P<1×10(-10)) for at least one mild traumatic brain injury after cognitive testing (n=12 494 events) included low overall cognitive function, a previous mild traumatic brain injury, hospital admission for intoxications, and low education and socioeconomic status. In a sub-cohort of twin pairs in which one twin had a mild traumatic brain injury before cognitive testing (n=63), both twins had lower logical performance and technical performance compared with men in the total cohort with no mild traumatic brain injury (P<0.05 for all).

CONCLUSION: Low cognitive function, intoxications, and factors related to low socioeconomic status were strong independent risk factors for mild traumatic brain injuries in men. The low cognitive function in twin pairs discordant for mild traumatic brain injury suggests a genetic component to the low cognitive function associated with such injuries. The study included only men, so inferences to women should be made with caution.
Cystatin C as a marker of early renal insufficiency in children with congenital neuropathic bladder.

Fox JA, Dudley AG, Bates C, Cannon GM Jr.

PURPOSE: Due to decreased muscle mass in children with congenital neuropathic bladder there may be significant inaccuracy when using the creatinine based estimated glomerular filtration rate. Cystatin C is highly sensitive and specific for measuring changes in the glomerular filtration rate in children and in patients with muscle wasting conditions. We hypothesized that a cystatin C calculated glomerular filtration rate would be more sensitive than the standard creatinine based modified Schwartz equation to detect renal insufficiency in children with congenital neuropathic bladder.

MATERIALS AND METHODS: We prospectively identified children with congenital neuropathic bladder at a multidisciplinary spina bifida clinic who underwent serum creatinine and serum cystatin C testing. Clinical history and anthropomorphic variables at the time of laboratory testing were catalogued. The creatinine based glomerular filtration rate was estimated using the modified (bedside) Schwartz formula and the cystatin C based rate was calculated using the Zappitelli cystatin C formula.

RESULTS: Dual estimated glomerular filtration rate calculation was done in 69 children at a total of 74 patient encounters. Absolute creatinine was within age range normal limits in each patient, including 1 with chronic kidney disease stage 3A. The median creatinine based estimated glomerular filtration rate was 123 ml per minute/1.73 m(2) (range 58 to 229). The median cystatin C based estimated rate was 103 ml per minute/1.73 m(2) (range 47 to 144) for an absolute median rate reduction of 15.4%. Using cystatin C estimates chronic kidney disease stage was upgraded from stage 1 to 2 in 13 patients (18.8%).

CONCLUSIONS: In children with neuropathic bladder the cystatin C estimated glomerular filtration rate is a better screening test for early renal insufficiency that is not detected by creatinine based rate calculations. To our knowledge it remains to be determined whether the cystatin C estimated glomerular filtration rate can ultimately improve the clinical outcome in this population.

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Oropharyngeal dysphagia and gross motor skills in children with cerebral palsy.

Benfer KA, Weir KA, Bell KL, Ware RS, Davies PS, Boyd RN.


**OBJECTIVES:** To determine the prevalence of oropharyngeal dysphagia (OPD) and its subtypes (oral phase, pharyngeal phase, saliva control), and their relationship to gross motor functional skills in preschool children with cerebral palsy (CP). It was hypothesized that OPD would be present across all gross motor severity levels, and children with more severe gross motor function would have increased prevalence and severity of OPD.

**METHODS:** Children with a confirmed diagnosis of CP, 18 to 36 months corrected age, born in Queensland between 2006 and 2009, participated. Children with neurodegenerative conditions were excluded. This was a cross-sectional population-based study. Children were assessed by using 2 direct OPD measures (Schedule for Oral Motor Assessment; Dysphagia Disorders Survey), and observations of signs suggestive of pharyngeal phase impairment and impaired saliva control. Gross motor skills were described by using the Gross Motor Function Measure, Gross Motor Function Classification System (GMFCS), Manual Ability Classification System, and motor type/distribution.

**RESULTS:** OPD was prevalent in 85% of children with CP, and there was a stepwise relationship between OPD and GMFCS level. There was a significant increase in odds of having OPD, or a subtype, for children who were nonambulant (GMFCS V) compared with those who were ambulant (GMFCS I) (odds ratio = 17.9, P = .036).

**CONCLUSIONS:** OPD was present across all levels of gross motor severity using direct assessments. This highlights the need for proactive screening of all young children with CP, even those with mild impairments, to improve growth and nutritional outcomes and respiratory health.

**KEYWORDS:** cerebral palsy; deglutition disorders; dysphagia; feeding; prevalence
**Infant temperament and childhood psychiatric disorder: longitudinal study**

K. Sayal, J. Heron, et al.

*Child: care, health and development, 40, 2, 292–297. 2013*

**Background:** Temperamental characteristics emerge early in life and can shape children’s development, adjustment and behaviour. We aimed to investigate the association between early infant temperament and later childhood psychiatric disorder in a community sample.

**Methods:** This prospective, population-based study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). In a sample of 7318 children, we investigated whether temperamental characteristics assessed at the ages of 6 months and 24 months are associated with an independent diagnosis of psychiatric disorder ascertained at age 7 years.

**Results:** After adjusting for confounders, temperamental characteristics assessed at 6 and 24 months of age were associated with psychiatric disorder at age 7 years. In particular, intensity of emotional reaction at age 6 months was associated with later disorder (adjusted odds ratio = 1.56; 95% confidence interval 1.19, 2.04; \( P=0.002 \)). These associations were stronger in girls and in those children with high levels of intensity at both 6 and 24 months of age.

**Conclusions:** Temperamental characteristics involving high levels of emotional intensity within the first year of life are longitudinally associated with psychiatric disorder in mid-childhood, suggesting that the roots of psychiatric disorder may, in some cases, lie very early in life.
**I-CAN: The Classification and Prediction of Support Needs.**

Samuel R, Arnold C, Riches VC, Stancliffe RJ.

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**Background:** Since 1992, the diagnosis and classification of intellectual disability has been dependent upon three constructs: intelligence, adaptive behaviour and support needs (Luckasson et al. 1992. Mental Retardation: Definition, Classification and Systems of Support. American Association on Intellectual and Developmental Disability, Washington, DC). While the methods and instruments to measure intelligence and adaptive behaviour are well established and generally accepted, the measurement and classification of support needs is still in its infancy. This article explores the measurement and classification of support needs.

**Method:** A study in presented comparing scores of the ICF (WHO, 2001) based I-CAN v4.2 support needs assessment and planning tool with expert clinical judgment using a proposed classification of support needs. A logical classification of support needs. A logical classification algorithm was developed and validated on separate sample.

**Results:** Good internal consistency (range 0.73-0.91, N = 186) and criterion validity (κ = 0.94, n = 49) were found.

**Conclusions:** Further advances in our understanding and measurement of support needs could change the way we assess, describe and classify disability.