Attention Deficit Hyperactivity Disorder (DSM-IV Combined Subtype) Shows Familial Association with Continuous Measures of ADHD Symptom Scores in Co-Siblings

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Background:
- Twin studies have estimated the heritability of ADHD to be around 0.76, showing that genetic factors play a substantial role in the etiology of ADHD (see Figure 1).
- Two recent linkage scans using an affected sibling pair strategy show only one region of partial overlap on chromosome 5. This reflects the low power of traditional linkage analysis to detect multiple genetic variations, while each conferring relatively small risks to the complex genetic disorder.

Study Objective:
- Here we describe a quantitative trait locus (QTL) linkage scan in the IMAGE sample, an international multi-center ADHD gene project (IMAGE), which aims to take advantage of QTL methods to potentially increase power over more traditional study designs.

Results:
(1) Our review of published DZ twin correlations from twin studies shows a wide range of familial association, from -0.05 to 0.49 (see Figure 2 and 3). It appears that the variabilities are dependent on both the raters and the behavioral rating measures used. Figure 2 illustrates those using teacher-rated measures.

- The QTL strategy in IMAGE hypothesizes that the correlation (familial association) observed in DZ twins from the community twin studies is analogous to that of the siblings and probands of the IMAGE sample, which has been selected from a clinic population with the diagnosis of DSM-IV 'Combined' subtype of ADHD.
- A requirement for QTL linkage analysis using the IMAGE sample is that this assumption is valid. Although this may have been presumed in previous twin studies, this has not been hitherto explicitly demonstrated.

- We therefore (1) review and report the findings of the 'siblings familiarity' or 'DZ correlation' in previous twin studies; and (2) utilize a modified method of DeFries-Fukuler analysis to estimate the 'siblings familiarity' of the IMAGE sample.

Sample and Methods:
- The International Multi-center ADHD Gene project (IMAGE) is an international collaborative study involving: Belgium, Germany, Holland, Ireland, Israel, Spain, Switzerland, UK, USA. The probands have been recruited through the specialist ADHD clinics, with a diagnosis of DSM-IV 'Combined' subtype of ADHD.
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- All children (proband and siblings) are: between age 6 to 18, of IQ≥70 or above, of European descent, and with access to one or both biological parents for DNA collection. Exclusion criteria (apply to both probands and siblings) include autism, epilepsy, general learning difficulties, brain, medical and genetic disorders that mimic ADHD.
- Proband are diagnosed by structured parent interview (Parental Account of Childhood Symptoms, PACS), with Strengths and Difficulties Questionnaires (SDQ) and Conners' rating scale (parent and teacher).
- Dimensional scores of ADHD symptoms in the siblings are derived from Strengths and Difficulties Questionnaires (SDQ) and Conners' rating scale (patient and teacher).
- We carried PubMed search for past publications on twin studies. In addition, we estimated the correlation (r) between trait liability and the clinical disorder (r = [population mean - probe mean]/[population mean - probe mean]) – (population mean), a method modified from traditional DeFries-Fukuler twin analysis.

Discussion:
(1) There is a wide range of DZ sibling correlation: from -0.05 to 0.49. Despite this, certain patterns emerge:
(i) there is generally a narrower range of sibling correlation derived from measures rated by teachers, i.e. 0.17 to 0.42 (see Figure 2).
(ii) there is greater variability amongst parent-rated questionnaires, i.e. from -0.05 to 0.49 pair (see Figure 3).
(iii) amongst the parenteral measures, those containing DSM-IV 18-items yield higher sibling correlation, than those with fewer items, such as SDQ and Rutter A.

Near zero DZ sibling correlations are incompatible genetic etiology of a disorder. It is likely to be attributable to the either contrast effect in observer bias or sibling interactions.

Teacher measures show higher correlations and suggest that teacher measures may be more informative for QTL linkage.

(2) The 'siblings familiarity' or sibling correlations observed in the IMAGE study are comparable to published sibling correlations in DZ twin pairs (Martin et al, 2003) using the same measures: SDQ and Connors' (parent and teacher) (see Figure 4).

(i) Parent Connors' was 0.25 (or 25%), which is within the 95% CI of 0.136-0.38.6% of IMAGE data.

(ii) for Teacher Connors' was 0.38 (or 38%), which is within the 95% CI of 0.20-0.39 of the IMAGE data.

(iii) Parent SDQ was –0.44% (or 4.4%), which is within the 95% CI of -1.27-10.97% of the IMAGE data.

(iv) Teacher SDQ was 0.29 (29%) which is within the 95% CI of 23.22-45.01 of the IMAGE data.

Conclusions:
The findings demonstrate that the familial relationships between sibling ADHD symptoms scores and combined type diagnosis in probands (their siblings using group heterogeneity suggest this is predominately due to shared genes), are analogous to those of DZ twin correlations.

The IMAGE sample ascertained via probands recruited from specialist ADHD clinics can be used for QTL analysis.