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Initial study of candidate genes on chromosome two for relative hand skill

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Abstract. Relative hand skill (HSR) is a trait of potential use as a physical characteristic in forensic analysis. The HSR gene has not been discovered but is mapped to chromosome 2p12-q11. Using high density SNP mapping we aim to refine the linkage signal and detect the gene. © 2005 Published by Elsevier B.V.

Keywords: Hand skill; Forensic analysis; SNPs; Genetic mapping

1. Introduction

Relative hand skill or handedness (HSR, OMIM: 139900) is a physical characteristic trait that divides people into two groups: comprising 89–91% of individuals with a preference to use the right hand for complex manipulative tasks (for example handwriting) and 9–11% with a left hand preference. Until recently this trait was thought to have a significant environmental component and low heritability [1]; due principally to the repeated observation of discordance for hand skill in half of left-handed monozygotic twin groups studied, together with, often, inadequate measurement of subjects in hand skill studies. However, following the development of the random recessive, non-determinate theory for the genetic control of hand skill and other laterality traits, a robust and predictive model now exists that is consistent with the simple, Mendelian inheritance of a single locus. This model implies a recessive allele frequency of ~0.48 based on an observed total of 18% discordant individuals amongst all monozygotic twin groups tested

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to date [2]. So, despite being a complex trait, hand skill could have a simple system of control and be amenable to genetic analysis.

Evidence for such a system comes from the discovery of the node in vertebrate embryos [3]: a cup shaped midline cavity containing a small group of mono-ciliated cells that atypically rotate anticlockwise. In mice with inverted viscera (an inverted laterality trait also found at low frequency in humans) the node cilia are immotile and it is thought this upsets the embryonic signalling required to establish normal visceral laterality. If a similar system controls neuronal laterality in human embryos then motor protein variants creating dysfunctional cilia would be strong candidates for the cause of hand skill laterality. Other inversions of ectodermal tissue lateralization are strongly associated with hand skill, including hair whorl direction and hemispheric dominance, suggesting a common randomized process in individuals homozygous for the variant allele.

Finally, a strong, unequivocal linkage signal has been reported for a single candidate region for HSR in a 3.5 Mb peri-centromeric segment of chromosome 2 at 2p12-q11 [4]. We aim to use single nucleotide polymorphism (SNP) mapping to refine this linkage signal and find the HSR gene. The genotyping efforts required to scan such a large chromosome segment are considerable. The workload may be reduced by selecting gene candidates for study on the basis of probable function, SNP allele frequencies, haplotype block distribution and gene orthology. It is appropriate to begin with SNP markers found within the strongest part of the signal, concentrating our efforts initially on loci at allele frequencies of 0.4–0.5 and sited in or near motor protein genes.

2. Materials and methods

Subjects were measured for hand skill using the PegQ test [4] with 48 individuals taken at the extremes of range to create the case (left-handed) and control (right-handed) groups. Additionally, 24 families with left-handed offspring have been sampled to date. Genes were scrutinized within a 3.5Mb section of chromosome 2 with the strongest linkage signal (defined by the short tandem repeat loci: D2S2333 and D2S2216), this was

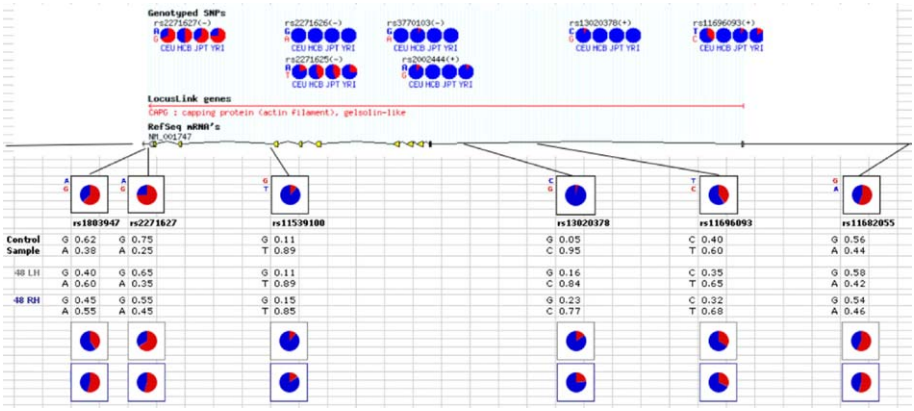

Fig. 1. SNP allele frequency distributions for six markers for the CAPG gene. Distributions charted at the top half are from Hapmap, and those charted below are from this study, from top to bottom: a control sample, the left hand group and the right hand group of subjects.

extended to ~1 Mb up and downstream. SNP candidates were chosen using dbSNP and Hapmap databases, with emphasis on markers that created non-synonymous substitutions or were representative of the haplotype block in a particular span. SNP typing was performed using the Sequenom MassArray™ system.

3. Results and discussion

Two genes were found in the segment of chromosome 2 described above that have functions related to cilia structure and motility: CAPG, encoding a gelsolin-like actin capping protein and LOC200383, encoding a protein similar to Dynein heavy chain at 16F. CAPG lies close to the middle of the linkage peak and is a member of the gelsolin/villin family of actin-regulatory proteins reversibly blocking the barbed ends of F-actin filaments. LOC200383 lies just upstream of the main linkage peak region and the protein coded has not been fully described to date. The SNP results obtained so far from CAPG are outlined in Fig. 1. Although typing of all coding SNPs is not complete, no SNP markers so far examined show any differences between case and control groups. Allele frequencies obtained match those recorded in the Hapmap database when listed.

The use of HSR as part of a physical characteristic trait set in forensic analysis will depend to a large extent on the heritability and penetrance of the gene, once characterized. In the case of HSR the heritability is likely to be 100% given the most probable genetic model but the penetrance will be only 50% for the left hand defining allele, since the occurrence of the phenotype will be randomized in individuals homozygous for this allele. This means a test for hand skill can simply predict that a person is right handed and only for ~80–82% of all right handed individuals.

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