Paucimorphic Alleles versus Polymorphic Alleles and Rare Mutations in Disease Causation: Theory, Observation and Detection

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Abstract:

Definitions of polymorphism in a gene include occurrence of a rarer allele of at least 1% frequency; or occurrence of the commonest allele at less than 95% frequency. Many alleles of single nucleotide polymorphisms (SNPs) in genes occur at much higher frequency (up to 50%). Many common diseases have a substantial genetic component. The prevailing hypothesis for the molecular basis of common diseases is that it involves the combinatoric action of common polymorphic alleles of minor effect (common disease / common variant, CD / CV hypothesis). The ready development of genome-wide databases of high frequency SNPs is enabling the testing of this hypothesis. A contrasting approach has been the study of very highly selected cases and families by linkage and mutation detection techniques to identify rare mutations of large effect on a gene, often private to a single family (rare disease / rare variant, RD / RV hypothesis. These approaches have formed the mainstay of disease gene discovery, the latter having been feasible for a decade, the former just now becoming feasible. However, an intermediate possibility exists. Sequence changes at an intermediate frequency (herewith, “paucimorphisms”, arbitrarily $0.0005<q<0.05$) may exist and may have a moderate effect. A number of different loci may predispose to the same disease, although only one paucimorphic allele of one particular gene will be found in any one individual. Exploring the “paucimorphisms hypothesis” will require mutation detection applied both at the level of large numbers of relatively unselected cases and at the population level. In this review we consider

the foundations of this hypothesis, relevant available technologies and possible future approaches to systematically explore this hypothesis.

Keywords: paucimorphic aleles; polymorphic alleles; rarer allele; single nucleotide polymorphisms

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