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Abstract Submission Form

**When Unique Locus-Specific Disease Genotypes are not Associated with Identical Phenotypes
– Is it time to Consider a New Genetic Hypothesis?**

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Before the establishment of LSDBs it was assumed that a unique genotype always led to a highly specific phenotype. Mutations in the androgen receptor (AR) gene produce a distinct disease phenotype known as androgen insensitivity syndrome (AIS). The androgen receptor gene database (ARDB) has now revealed discrepancies in genotype-phenotype correlations that have often been explained, by invoking factors such as, epigenetics, variable expressivity, altered penetrance, developmental variation, etc. In almost all such cases the explanation for dissociation between genotype and phenotype has been speculative. Further, the degree of human genome variation discovered has made simple genotype-phenotype correlations much more difficult to prove conclusively. In particular, high somatic mutation rates have resulted in different tissues within an individual having in effect different genomes. In the case of the AR gene as many as 10 variant forms have been identified in a few thousand prostate cells. We believe that the presence of such a high degree of genetic heterogeneity may help to explain some cases of genotype-phenotype disassociation. Our hypothesis proposes that selection as opposed to mutation is the critical biological process involved. In this hypothesis, multiple variant genomes, identified in specific tissues are a distinct minority when compared to the majority genome that is present in most tissues and blood. Such minority genomes may however replace the majority genome in specific tissues due to strong selection pressures, as a result for example, of altered environmental conditions or epigenetic factors. In the case of the AR, unique AR mutant genotypes have produced different disease phenotypes that in some cases exhibit somatic mosaicism. Our hypothesis would in particular help explain the high degree of phenotypic variation found associated with many genetic diseases and disorders.

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