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NEWS AND COMMENTARY

The Genome

The genome: you gain some, you lose some

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Turner *et al*[1] have estimated germline rates of *de novo* meiotic deletions and duplications by non-allelic homologous recombination (NAHR) between highly similar duplicated sequences. By using real-time PCR they assayed NAHR on sperm of five donors. They could show these NAHR hot spots to be specific to meiosis, and deletions to occur at a higher rate than their reciprocal duplications. Their results indicate that some rearrangements, in particular the deletion of 17p and the duplication of 7q, are being underascertained clinically, possibly due to a lack of characteristic symptoms.

A key proposition of Darwinian theory is that animal species need to be able to modify their properties by mutating their DNA to adapt to environmental change and to evolve. Thus a certain rate of spontaneous mutation is not only a reflection of the fallibility of the DNA replicating machinery, but also a prerequisite for survival of the species, and the origination of new life forms. Since the vast majority of arising mutations are either neutral or detrimental, and only a minute proportion is beneficial, this adaptability to the environment comes at a very high price in terms of disease.

Recent results of large-scale analysis of the human genome indicate remarkable plasticity of the sequence which generates prolific polymorphism from the level of single nucleotides up to the microscopically visible chromosome. Of course, much of this has been known for a very long time, with chromosomal variants detected in the early days of microscopic karyotyping, single nucleotide polymorphisms (SNP's) identified in the first genes that were sequenced,[2] and also as restriction fragment length polymorphisms (RFLP) with the earliest single copy probes.[3] Deletions and extra copies of sequences have already been detected at that time, both as neutral variants and as disease causing mutations, for example in the alpha globin gene cluster.[4] Since these early reports, 'genomic disorders' have been delineated as a new category of genetic disease caused by unequal exchange between highly homologous sequences leading to deficiency or excess of dosage sensitive genes.[5]

One of the early examples of variable gene copy number, the cluster of amylase genes,[6] was recently found to be loyal to Darwinian logic. Populations with high-starch diets have, on average more AMY1 copies than those with traditionally low-starch diets.[7]

Now that two human genomes have been entirely sequenced, high density SNP arrays are widely used, and high throughput sequencing is gathering momentum, we can see that indeed the variations of the sequence as well as the copy number are as numerous as predicted or even more so, and spread throughout the genome.[8–10]

The results obtained by Turner *et al*[1] clearly confirm the suspicion that our germ cells always contain a subset of unbalanced products from meiosis. Those deletions and duplications that cause such major defects to be embryonically lethal, may cause early spontaneous abortion, or even inability to fertilize. In man, such defects have yet to be identified. Those that can cause congenital malformations and/or mental retardation are increasingly recognized by clinicians and by high resolution molecular karyotyping. Those deletions and duplications that have little or no effect on the phenotype will largely pass unnoticed.

In many cases the haploinsufficiency or increased dosage of the genes involved have highly variable clinical effects. The variable phenotype often complicates the distinction between pathogenic rearrangements and neutral variants. A complete characterization of the effects of copy number variants is not only necessary for diagnosis and genetic counseling, it will also improve our understanding of the diseases involved.

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References

1 Turner DJ, Miretti M, Rajan D *et al*: Germline rates of *de novo* meiotic deletions and duplications causing several genomic disorders. *Nat Genet* 2008; **40**: 90–95.
2 Jeffreys AT: DNA sequence variants in the Gγ, β and δ genes in man. *Cell* 1979; **18**: 1–10.
3 Kan YW, Dozy AM: Polymorphism of DNA sequence adjacent to the β-globin structural gene: relationship to the sickle mutation. *Proc Natl Acad Sci USA* 1978; **75**: 5631–5635.
4 Higgs DR, Old JM, Pressley L, Clegg JB, Weatherall DJ: A novel alpha globin arrangement in man. *Nature* 1980; **284**: 632–635.
5 Lupski JR: Genomic disorders: structural features of the genome can lead to DNA rearrangements and human disease traits. *Trends in Genet* 1998; **14**: 417–420.
6 Groot PC, Mager WH, Henriquez NV *et al*: Evolution of the human α-amylase multigene family through unequal, homologous, and inter- and intrachromosomal crossovers. *Genomics* 1990; **8**: 97–105.
7 Perry GH, Dominy NJ, Claw KG *et al*: Diet and the evolution of human amylase gene copy number variation. *Nat Genet* 2007; **39**: 1256–1260.
8 Iafrate AJ, Feuk L, Rivera MN *et al*: Detection of large-scale variation in the human genome. *Nat Genet* 2004; **36**: 949–951.
9 Sebat J, Lakshmi B, Troge J *et al*: Large scale copy number polymorphism in the human genome. *Science* 2004; **305**: 525–528.
10 Redon R, Ishikawa S, Fitch KR *et al*: Global variation in copy number in the human genome. *Nature* 2006; **444**: 444–454.