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Recent advances in the study of somatic mosaicism and diseases other than cancer

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Somatic mosaicism is well appreciated as a cause of cancer and, possibly, aging. Somatic mosaicism as the cause of other diseases is becoming more appreciated. It is especially important in the causation of deforming diseases (e.g., Proteus syndrome; Sturge–Weber syndrome) which are not inherited because early developmental expression is lethal. It also known to make an important contribution to neurological, dermatological, hematological and other diseases (and probably all diseases but many in which it is harder to detect). There have been exciting recent advances in the detection of somatic mosaicism. In particular, for many diseases of somatic overgrowth in which somatic mosaicism as the sole cause was predicted, the gene somatically mutated has been found. A limited number of pathways seem involved in these disorders, some of which are also implicated in cancer.

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Introduction

For most of the history of medical genetics [5], diseases were known to be inherited because they ran in families. This is not always the case. About 30 years ago, James V. Neel, the doyen of human genetics at the University of Michigan, asked the author for an example of a genetic condition which would not be transmitted. In answer, Prader–Willi syndrome was suggested as a genetic disease (because of the uniformity of the syndrome) which is not transmitted, primarily because of delayed development and hypogonadism. We now know that it is a problem of imprinting and involves multiple genes but, while usually germ line in origin, post-meiotic events are often involved [6]. Somatic mosaicism provides a different class of non-inherited genetic disease — mutations in genes, which would be lethal if they were present in all cells of the embryo. When the somatic mosaic mutation also includes the germ line and the offspring are viable, it is usually termed 'germ line mosaicism', especially if it is not apparent in the phenotype of the individual. This is the explanation for multiple occurrences of dominant mutations in the offspring of some normal couples.

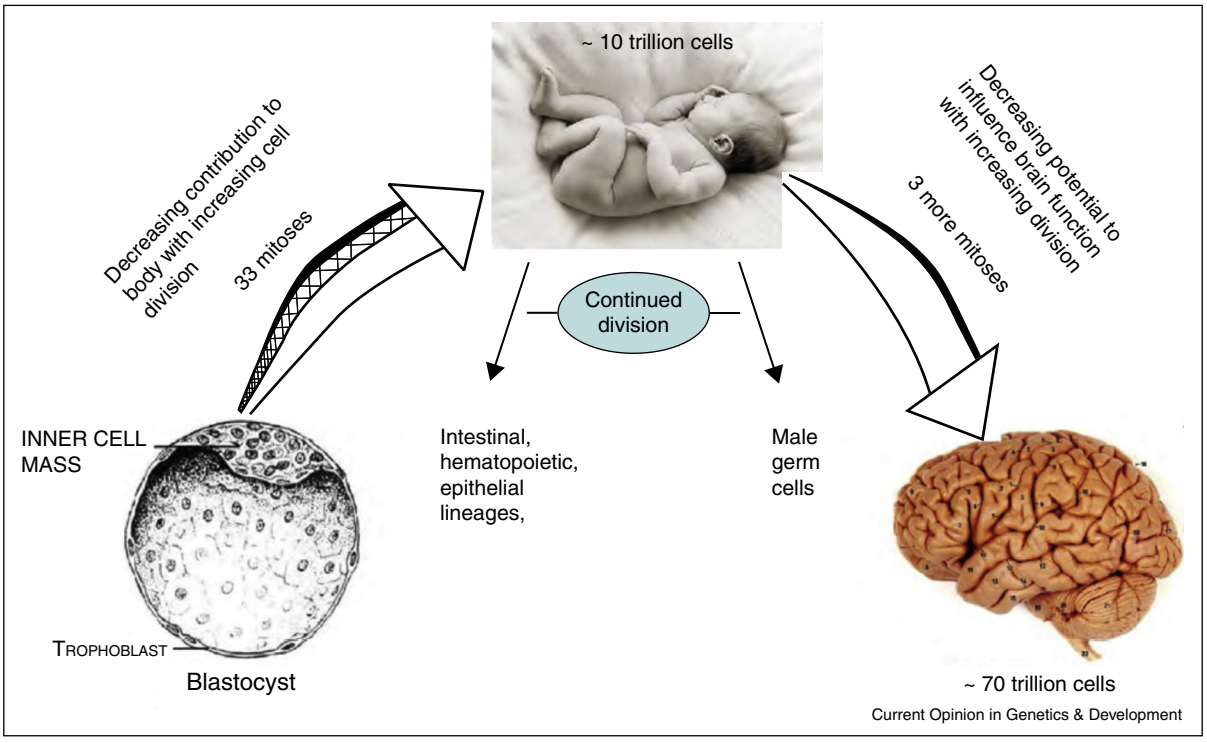
In one, among multiple recent reviews [1–4], the finding that Next Generation Sequencing (NGS) of a few individuals found homozygosity for mutations, which would be causative for serious diseases which the individuals clearly did not have, was discussed [2]. These were presumably due to somatic mutations (possibly gene conversion events or loss of heterozygosity [7•]) occurring in the initial lymphocytic DNA or in the clone(s) maintained after Epstein–Barr viral transformation. NGS has be now been performed on thousands of individuals and has revealed high numbers of potentially harmful alleles: from about 100 [8,9] to up to about 1000 [10,11] depending on the criteria for potentially damaging missense SNPs. One would like to know how many of these are due to somatic mutation. When NGS is applied to patients, somatic mosaicism is increasingly being found [12–14], as it is in cancer and aging [56].

When and where does somatic mosaicism occur?

The detection rate for somatic cell mosaicism in disease depends on the detection method used as well as the size of the clone of mutant mosaic cells. As discussed previously [2], the possibility that a somatic mutation will contribute to the developing embryo sufficiently to be detected requires it to occur within some of the earliest mitoses. As Figure 1 shows, a mutation occurring after a few mitoses of inner cell mass cells will contribute a larger clone of mutated cells than will a mutation occurring a few mitoses later. A second aspect concerning clone size is how large it needs to be to have an effect. It is generally believed that oncogenic mutations in one cell can lead to cancer. It is possible that mutations in one or a few neurons could lead to abnormal electrical activity which could progress as an epileptogenic focus.

An interesting question is whether such clones can show preferential growth (or instead, be selected against) and result in larger (or smaller) segments than would be expected solely on the number of succeeding mitoses. Such preferential growth can occur in the testes. Germ line selection for dominant mutations in the male

Figure 1



A cartoon to illustrate the possible contributions of somatic mutations at different stages of development to the soma. The increase in cell numbers from the inner cell mass, where as few as 3 cells can give rise to a normal embryo, to the soma and then to the CNS are indicated. The hatched portion of the first arrow indicates the potential relative contribution of a clone from a mutated inner cell mass cell (usually several times the minimum 3) to a final tissue while the black portion indicates the potential contribution from a cell mutated a few mitoses later (neither to scale). The second expansion for the brain is figurative in the sense that most of these divisions have occurred before birth while both further divisions and cell death go on after birth. The number of mitoses for individual organs/tissues and their number of continuing cell divisions, of course, varies greatly. The cell numbers used here are speculative since accurate cell counts of such large numbers of cells are so difficult.
From [2].

spermatogonia, resulting in high frequencies of single base pair changes for several disorders of fibroblast growth factor-RAS pathways, especially achondroplasia, is well described (reviewed in [15]). A study of 33 identical twin pairs found somatic differences for only two genes [16] and these were not mosaic suggesting very early events. The full answer to the question of possible selection for somatic clones would probably require post-mortem examination of many samples of many tissues. However, it is clear that selection for revertants can occur as has been observed in skin where they are easily visible [7•,17] and blood where cell-sorting can find them [18,19].

In addition, the possibility of detection depends on the tissue tested. White blood cells (predominantly neutrophils and lymphocytes) are the most common source of DNA studied but are mostly relevant to the immune system. For instance, they were used to detect somatic losses of T-cell receptor gamma, which were implicated in asthma [20]. The chances of finding somatic mosaicism increase if the affected tissue or a closely related tissue is studied, for example, hair bulbs (ectodermal) for central nervous system disease [21] (since it is hard to get brain biopsies). Another easily obtained source for renal disease is renal epithelial cells, which are abundant in urine. Of course, mutations continue with cell renewal in many tissues and accumulate with age [22] — see accompanying article by Jan Vijg [56].

Copy number variants and the frequency of somatic mutation

Copy number variants (CNVs), as previously discussed [2], are increasingly implicated in disease. Although they cause a relatively small proportion of autism spectrum disorders; schizophrenia; or attention deficit, hyperactivity disorder, the findings are increasingly being confirmed [23–28]. Although these studies do not look specifically for somatic mosaicism, one can infer that it must make a reasonable contribution to these disorders since a somatic mutational source of CNVs is not rare. One large study of pathogenic CNVs in children with developmental delay or otherwise unexplained congenital abnormalities found