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Human Somatic Variation: It's Not Just for Cancer Anymore

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Abstract It has long been known that cancer is caused by somatic changes. However, increasingly data are being collected that indicate that many other diseases can be caused by somatic mutation. This list is growing, as more and better data become available from high-throughput genetic analyses, to include neurological, hematological, and immune-related disorders. However, equally interesting is the observation that even in the absence of clear phenotypic effects individuals accumulate somatic variation and that this variation includes the entire spectrum of mutations observed in the germline. Of note, in some cases (e.g., mitochondrial DNA heteroplasmy) the tissue distribution of this variation may not be random. In this review we present recent work describing the effects of somatic mutations, their types, and their distribution in humans.

Keywords Somatic variation · mtDNA heteroplasmy

Introduction

Multicellular organisms develop from a single embryonic cell with a singular genetic constitution. It is generally assumed that the genetic constitution of the subsequent fully developed adult is uniform and virtually identical to the embryonic state. To a large extent, this is an assumption of convenience, not one based on known levels of somatic differences among tissues, because until recently it has been impossible to measure the number of somatic variants within an individual directly. Nonetheless, the concept of accumulating somatic changes was first proposed more than 50 years ago, and argued to be a factor in aging and even death [1]. Whether this hypothesis is accurate or not skirts the major issue with regard to somatic variation—how much somatic variation exists, and to what extent does it affect phenotypic variation in general? Until recently, the lack of feasibility of gathering appropriate data prevented us from even asking this question seriously, but next generation sequencing and other high-throughput genotyping technologies have made it practical to answer this question [2–6].

Despite the general lack of knowledge surrounding the field of somatic variation, one clear phenomenon involving somatic mutations has been well documented and accepted—cancer. Variation within and among tissues is the ultimate causative mechanism in cancer [7]. Many papers on the study of somatic mutation in cancer confirm this as a thriving and important area of research [8], but somatic variation is less commonly investigated in cancer-free subjects. Nonetheless, it is unreasonable to assume that mutations are limited to either a particular class of disease or to specific genomic regions [9]. In fact, the number of diseases that are observed as mosaics is increasingly large. It is becoming evident that other diseases, e.g., primary immune deficiencies, neurofibromatosis, secondary hypertension [10], and others, are products of somatic variation in key disease risk genes. However, to a large extent, papers on somatic mutation are more idea- than data-driven [2–5, 9, 11]. Interest is being fueled by the availability of high-density genomic data that will ultimately inform us about the load we all carry.

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In addition, recent research has documented not only single-gene somatic changes, but differences in both disease and non-disease states more generally. These changes include single nucleotide polymorphisms (SNPs), copy number variants (CNVs), and large-scale changes in chromosomal status, such as aneuploidy. Although some of these are known to have phenotypic effects, not all do, and perhaps most do not. All of this points to a large underlying load of somatic variation that needs to be better understood to grasp the role of genetics in the phenotype. The costs of such intra-organismal genetic heterogeneity, due either to somatic mutation or chimerism, have also been debated from an evolutionary perspective, but answers are not yet clear as to its role in selection [12•–18]. Because somatic variation in cancer is so well studied [19–23], in this review we focus on non-cancer-related issues of somatic variation. Although not exhaustive, we review several diseases that are of somatic origin and many types of variation that may or may not have phenotypic effects.

Diseases Other Than Cancer Caused by Somatic Mutation

Rare disorders that have a clear basis in somatic variations include those of the hematopoietic system, in which stems cells can mutate and expand to produce disease phenotypes. These include paroxysmal nocturnal hemoglobinuria 1 (PNH1) caused by *PIG-A* mutations [24, 25] and X-linked alpha-thalassemia mental retardation caused by mutations in *ATRX* [26]. PNH1 is an acquired hemolytic anemia that presents with hemoglobinuria, abdominal pain, smooth muscle dystonias, fatigue, and thrombosis. It is caused by expansion of hematopoietic stem cells with a mutation in the *PIG-A* gene—a change that is acquired somatically. X-linked alpha-thalassemia mental retardation is sometimes associated with myelodysplastic syndrome, with cases often associated with somatic mutations. Interestingly, in the case of *ATRX* mutations, somatic variants appear to confer more severe myelodysplastic syndrome disease than do germline mutations [27]. Clearly, the ability to clonally expand hematopoietic stem cells can provide a mechanism by which somatic mutation can confer disease risk.

Neurofibromatosis 1 (NF1), a disorder that maps to a segment of chromosome 17q, presents with cafe-au-lait spots, Lisch nodules in the eye, and fibromatous tumors of the skin. Several studies have shown that a large minority of NF1 cases are due to somatic mutations, often deletions or microdeletions in this chromosomal region (up to 40 % of cases) [28]. Other cases are caused by somatic mitochondrial DNA (mtDNA) mutations [29]. In either case, it is clear that somatic changes are often causative of NF1. Similarly, NF2 has been shown to often be caused by somatic mutation as well (25–30 % of cases) [30, 31].

Diseases of other tissues can be shown to be somatic in origin by careful characterization of resected tissue. Examples include diseases of the heart and kidney. For example, mutations in connexin 40, a cardiac myocyte-expressed protein encoded by *GJA5*, have been shown to affect electrical communication and associate with a large minority of atrial fibrillation cases. Most of the *GJA5* mutations found in cardiac myocytes of patients were not present in blood, indicating a somatic origin [32]. A similar situation has been found in some Alport syndrome cases. Alport syndrome is an X-linked dominant disorder characterized by kidney disease, hearing loss, and eye abnormalities. It is caused by mutations in collagen IV components, mostly *COL4A5*. Although most Alport syndrome cases are inherited through the germline, it has been reported that males with a less severe phenotype have *COL4A5* somatic mutations [33, 34]. As with many X-linked diseases that would otherwise be extremely severe in presentation or lethal in males, somatic mutations can present with milder forms of disease.

Somatic mutation has also played a role in some neurological diseases, including epilepsy, autism spectrum disorders (e.g., Rett syndrome), and intellectual disability [35], although comparisons of monozygotic twins for multiple sclerosis (MS) have been essentially negative [36]. The latter example is based on whole genomic data of discordant monozygotic twins, but the data were derived from lymphoctyes—clearly not the ideal tissue for MS. Neurological disease may be particularly sensitive to somatic mutation because even less than 10 % of cells carrying a mutation can affect phenotypes based on the distribution of these cells in the brain. For example, hemimegalencephaly (HMG), which presents with an enlargement and malformation of an entire hemisphere, is associated with somatic mutations of *AKT3* and other mutations in the PI3K-AKT3-mTOR pathway [37–39], even when as few as 8 % (and generally fewer than 35 %) of cells carry the somatic mutation. However, because of the broad distribution of the mutation-carrying cells, individuals can still present with HMG. The effects of even rare somatic mutations may be due to the unique development pattern of the brain and its complex clonal migration patterns, such that clonality is not limited to adjacent or nearby cells.

Lissencephaly, or smooth brain, can be caused by mutations in two genes: Doublecortin X (*DCX*) or Lissencaphaly 1 (*LIS1*). Mutations in *LIS1*, which maps to 17p1, are usually lethal in males, but milder forms have been associated with somatic mosaics in two patients with predominantly posterior subcortical band heterotopia [40]. In these patients, 18–24 % of blood cells and 21–34 % of hair roots were mutated. Somatic mutations of *DCX1* have

also been shown to associate with similar disease phenotypes [41]. As with the neurological diseases above, not all neuronal cells carry the mutations, but they do exist in leukocytes, suggesting early somatic mutation.

Mutations in the X-linked pyruvate dehydrogenase A1 (*PDHA1*) can present with metabolic or neurological traits. Metabolic disease usually leads to death in infancy from lactic acidosis, but the neurological form presents with symptoms including epilepsy, mental retardation, and spasticity. A continuum exits between these two presentations. A high proportion of heterozygous females present with severe disease, but a report showed that a female with mild disease had evidence of preferential X-inactivation and somatic mutation [42]. Similarly, a male with a mild form of disease had an exon skipping mutation in both skin and muscle tissue, but not lymphocytes [43]. Although limited to single clinical cases, both of these examples show that somatic mutations in a single gene can affect disease risk. And of note, both cases caused by somatic variation presented with milder forms of disease.

Lastly, autoimmune diseases can be caused by somatic mutations. A recent study of autoimmune lymphoproliferative syndrome (ALPS), a disease of benign lymphoproliferation, elevated immunoglobulins, plasma IL-10 and FAS-L, and accumulation of double-negative T cells, showed that in several cases this was due to somatic mutation [44]. Inherited heterozygosity of TNFRSF6 precedes this disease, followed by a genetic events in the second allele. In this study, seven patients fit this profile; three had somatic mutations in their second allele, and four had evidence of loss of heterozygosity. Two different types of somatic events were therefore shown to cause this disease in individuals with susceptible (heterozygote) genotypes.

The above examples of the roles that somatic mutations can play in non-cancer human disease are not exhaustive, but clearly demonstrate that even where the majority of certain disease cases are caused by germline transmission, a substantial proportion can be triggered by somatic changes. The role that somatic mutation plays in disease is also probably affected by the pattern of development of specific tissues. For example, tissues or cells that are continually derived from stem cells, e.g., hematopoietic cells, may be more likely to present with disease following somatic change. Alternatively, if cell migration is not purely based on physical proximity, such as in the brain, a relatively small number of cells with somatic mutations can cause severe phenotypes [35].

Somatic Mutation Spectrum

In the above section, we focused on somatic mutation and its association with disease, but did not explicitly discuss the types of mutations that have been observed somatically. Here we document the type of mutations, whether disease causing or not, to gain a better understanding of the distribution of mutant types and their relative frequency. We preface this by stating that comprehensive analyses are not yet available, but will be soon.

Changes in ploidy number were among the first somatic variants detected. For example, liver polyploidy and aneuploidy have been known for decades, being first noted in 1909 [45, 46]. It has been estimated that approximately 50 % of human hepatocytes are polyploid and 30–90 % are aneuploid [46]. Taken together, these data are astounding for the overall level of somatic variation observed. In the liver, based on rodent models, polyploidy has been argued to be the product of failed cytokinesis. Although it is not clear how such cells survive and thrive without pathological effects, it has been argued that this distribution has a functional role that allows the generation of genetic variation and adaptation to xenobiotic exposure [47, 48].

In addition to the liver, other tissues exhibit deviations from diploidy. For example, multiple chromosomal aneuploids that would be lethal if present in all tissues have been observed somatically. These include trisomies of 8, 12p, and 20. All of these are recognized syndromes. Trisomy 8, for example, causes severe clinical effects and often miscarriage; therefore, it usually only survives as a somatic variant. Such chromosomal abnormalities are not only observed in subjects with disease. A recent report of examining two female monozygotic twins used both a SNP array and FISH to show that nucleated blood cells were aneuploid for sex chromosomes [49]. In one twin, 7 % of cells had confirmed monosomy X. In the other twin, 1 % of cells were aberrant. These changes did not coincide with any clinical presentation, although both subjects had the sickle cell trait.

Clonal mosaicism for large-scale changes, including aneuploidy and loss of heterozygosity, has been shown to occur with increasing age [50, 51]. These studies, based on genome-wide data from blood samples, identified mosaics present in at least 5 % of cells. Many of the observed mosaic variants are those found in cancers, but were present even in subjects without clinical diagnosis at the time of their blood draws. Prior to age 50, only about 0.2–0.5 % of samples showed evidence of mosaicism, but the fraction increased rapidly after this time point to 2–3 %. Of note, having mosaicism prior to diagnosis was predictive of disease later [50]. These data emphasize the fact that we accumulate somatic mutations with age, even in the absence of concurrent disease, but that these mutations may be important in late-onset disease.

Smaller scale somatic mutations have also been detected at the genome-wide level. CNVs were detected among tissues taken at autopsy using array-comparative genomic hybridization (aCGH) [52••] and via sequencing of induced

pluripotent stem cells isolated from fibroblasts [53]. In both cases, there was compelling evidence that somatic CNV mutations existed long before the analyses, and they were in an estimated 30 % of fibroblasts [53]. These data indicate that somatic CNVs are frequent, and perhaps not random [52••]. Importantly, in these two studies there was no evidence that these variations were associated with any phenotypes.

Retrotransposons constitute a large proportion of the human genome (at least 50 %) [54], but their movements were thought to be suppressed somatically, at least following early development [55, 56]. However, recent work has shown that thousands of somatic insertions occur in the brain later than previously thought [57•]. All three major classes of retrotransposons, L1, Au and SVA, were found to be variably distributed in the brains of three individuals, providing evidence for mobilization to protein-coding regions expressed in the brain. These results indicate that retrotransposition can alter the genetic structure of the brain somatically, with implications for disease risk [58].

The least well-understood types of somatic variation at the genome-wide level are SNPs. This is mainly because data are lacking, but they will probably ultimately reveal many differences within an individual. A recent study, however, has provided suggestive results as to the level of somatic SNP variation to expect. Specifically, when monozygotic (MZ) twins discordant for multiple sclerosis were genetically and genomically characterized, twin pairs differed at up to $\sim$0.3 % of sites in the genome. Because these differences can only be attributable to somatic changes in one or the other of the MZ twins, they provide a baseline of expected changes. However, these data are only from one source, CD4+T cells, and therefore cannot provide a good representation of the overall level of somatic SNP variation within an individual. This phenomenon needs to be explored in more detail, but it would not be surprising to find more extensive differences among tissues. This claim is to some extent based on data from within tumors, suggesting large-scale sequence differences where up to $\sim$70 % of somatic mutations are not present in all samples from the same tumor [23]. Admittedly, these exome-sequence-based data may over-represent the level of sequence differences because they are from tumors, but they can serve as an upper limit. Sequence heterogeneity from somatic mutation within non-tumor tissue has been observed as well [2, 59]. More data are needed to assess the levels of SNP somatic variation, but it is clear it will be both present and non-negligible.

Mitochondrial DNA Somatic Variants

It has long been known that as people age they can accumulate mtDNA mutations that increase their levels of heteroplasmy. This has been especially well studied in muscles. In addition, some of the somatic mtDNA mutations that accumulate with age have been associated with disease. For example, T414G was reported to be present as a somatic mutation in the brain tissue of Alzheimer's patients but not controls [60]. T414G also accumulates with age in fibroblasts and skeletal muscle [61, 62].

Several other somatic heteroplasmy changes have been reported. T408A mutation has been reported as an age-related somatic mutation in muscle [63–66], as has A189G mutation [63–69]. Our recent study of mtDNA heteroplasmy variation among tissues of the same individuals has confirmed some of these patterns and extended them in an unexpected way [70••]. Using massively parallel sequences of ten common tissues taken at autopsy from two cancer-free individuals, we assessed patterns of mtDNA heteroplasmy across tissues and subjects. Of 20 observable mtDNA heteroplasmies, 10 were recurrent. That is, they were observed in both subjects in the heteroplasmic state, but importantly only in the same tissues: kidney, liver, or skeletal muscle. These heteroplasmic sites included previously identified ones, such as A189G and T408A described above, as well as ones described in another study that sequenced mtDNA from multiple autopsy tissues [71]. Importantly, the two studies showed that the tissue-specific pattern of mtDNA heteroplasmic sites was consistent, lending support to the hypothesis that certain heteroplasmies develop preferentially in very specific tissues only. Since the recurrent heteroplasmies were observable only in the highest copy number tissues and in proximity to or in DNA replication control regions, it was hypothesized that these mutations affected DNA replication [70••]. Considering their totality, the data clearly indicate that mtDNA mutations accumulate somatically in the heteroplasmic state with age, occur in a tissue-specific fashion, and may affect disease.

Distribution and Mechanisms for Somatic Mutations: Conclusions?

Mutations arise because of errors in DNA replication or chromosome segregation. This can occur at any stage of development and either during meiosis or mitosis, as we have documented in this review. For somatic mutations that affect phenotypes, it is expected that the earlier in development that a mutation occurs, the more impact it will have on embryogenesis. This may decrease its chance of survival and propagation. As a result, somatic mutations are probably more common than de novo germline mutations observable in adults, and somatic mutations in single tissues are probably more common than somatic mutations shared by multiple tissues.

Somatic mutations can be of various types, including single-nucleotide substitution, repeat instabilities, copy number variations, genomic rearrangement, and changes in chromosomal ploidy, as previously discussed. Smaller somatic mutations such as single-nucleotide substitutions may show a non-random pattern (e.g., mutational hotspots and CpG dinucleotide), but data are not yet fully available to assess this on a large scale. However, as different mutation types, especially those with phenotypic effects, may have varying impacts on cell and tissue survival, the distribution of mutation types can differ between somatic and germline mutations. As we discussed, somatic changes often confer less severe phenotypes and therefore may be more tolerated than similar germline changes. In any case, the data on these concepts to date are not definitive, but are becoming increasingly available.

Additionally, the distribution of somatic mutations may differ across cells and tissues, as we have shown for mtDNA heteroplasmy. One potential reason for this is that in any given tissue, a significant fraction of the genome might be irrelevant to its normal function, thus permitting accumulation of mutations with few consequences to the cell and its host organ. If a gene is expressed in one tissue but not in another, mutations may be selected against in the former but not in the latter. A cell-autonomous environment may also tolerate mutations more than cells in a non-autonomous environment [72]. In addition, the mutational load may differ across tissues because tissues, due to their functional differences, might tolerate mutations at different levels. This can be further compounded with age because somatic mutations may accumulate at different rates across tissues. It has been estimated that the number of somatic mutations could be thousands to tens of thousands [73].

One source of somatic de novo mutations is errors in the normal operation within a cell. For example, it has been shown that somatic mutations can arise as a result of non-allelic homologous recombination [74, 75]. They also can be caused by L1 transposition [76] or arise from recombination-restarted replication forks [77]. In addition, exogenous factors of DNA damage can influence the pattern and distribution of somatic mutations differently across tissues. For example, long-time tobacco usage may lead to mutations in the lung, but not other tissues. Excessive ultraviolet exposure could result in accumulation of mutations in sun-exposed skin but not in unexposed skin. Similarly, liver and kidney may have a constant exposure to toxic materials and thus may accumulate more mutations than other tissues.

Despite these intuitive ideas, our knowledge is severely limited regarding the accumulation of somatic variation within individuals. This is largely due to the inability to easily assay somatic variation across the genome and among tissues in a cost-effective way. This limitation is rapidly disappearing, especially with the advent of accessible next-generation sequencing (NGS) [3–5]. NGS is probably the best technology available today for detecting somatic mutations. It provides high-resolution readout of the whole genome, and with high depth it can allow estimation of the fraction of a specific mutation in a sample of cells.

Sample collection also plays a very important role in somatic mutation studies. A mutation probably will be harder to detect in a sample that contains a mixture of cell types than in a homogeneous sample. Thus, a well-designed protocol for sample collection is necessary for the success of a somatic mutation study. The protocol should include a detailed description of the location in a tissue where the DNA sample has been collected. A cost prohibitive alternative, at least for the time being, is single-cell sequencing; this will allow a full evaluation of the scope of somatic mutations within a tissue.

Conclusions

In conclusion, somatic mutation in the absence of cancer has been under-studied, but is now recognized as common, with and without discernible phenotypic effects. Future studies addressing the pattern and scope of these mutations will be critical to better evaluate the role that genetics plays in disease and individual identity.

Conflict of Interest C. Li and S. M. Williams declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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