Somatic gene mutation and human disease other than cancer

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Dedicated to the memory of James V. Neel

Abstract

While the focus of much mutation research is on germ-line mutation, somatic mutation is being found to be important in human disease. Neurofibromatosis 1 and McCune-Albright are disorders which are detected in the skin and other systems. The skin manifestations were essential for the demonstration of somatic mosaicism in neurofibromatosis 1, while analysis of blood DNA demonstrated somatic mutation in neurofibromatosis 2. Incontinentia pigmenti is also a disorder seen in skin and other tissues, but here it is the rare variant of the disorder in males, where it is usually lethal, that involves somatic mosaicism. Paroxysmal nocturnal hemoglobinuria is a disorder of the blood and cell separation of blood elements allows the demonstration of the somatic mosaicism. This review also discusses disorders in which somatic mosaicism, for mutations probably incompatible with life if the mutation had been germ-line, are likely to be involved. These include the Proteus syndrome, which involves both vascular tissues and bones, and two disorders which might be thought of as representing two subtypes of Proteus: Klippel-Trenaunay, which involves vascular tissues, and Maffucci, which involves bones. Embryonic mutations, which create mosaicism for both the soma and germ-line, are being increasingly found in a number of disorders and are discussed more briefly. Finally, reverse mutations involving the soma have been recently found in several disorders and such revertant mutations are also examined. While the review focuses on the clinical importance of somatic mutations, many of the mutations found to date are tabulated. It is too early to see if there is a different pattern of somatic mutation as compared to germ-line mutation. Although the parameters to allow careful quantitation are not yet available, it seems that the frequency of gene mutation in embryonic cells is not markedly different than that in the germ-line.

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1. Introduction

The current era of interest in mutation was largely spurred by the atomic bomb and worries about radiation exposure. Appropriately, these concerns focused on the genetic makeup of the species and on germ-line targets. However, the DNA targets of mutagenesis are present in many more copies in the soma then in the germ-line. There has been much interest in somatic mutation in the causation of cancer and it has been the subject of many reviews [1–3]. Such somatic mutation also occurs in “benign” skin conditions such as epidermal nevi [4]. However, the contribution of somatic mutation to non-malignant disease has only more recently become a subject of research, in part, due to advances in molecular genetics. While there were many interesting clinical examples of what was thought to be somatic mutation, only when particular disease genes...
were cloned and somatic mutations in them could be identified. These speculations confirmed. This review will discuss cases in which the somatic mutation causation of human disease has been confirmed and other disorders which seem to be very likely to be due to somatic mutation. The review will be limited to genic mutations. There is quite a large literature on chromosomal mosaicism, especially in the placenta and as related to prenatal diagnosis [5–7]. These, of course, are also important in cancer which, as already mentioned, will not be discussed. The review will include examples of somatic mutational events related to genetic revertants.

The logarithmic increase in cells during development means that only early mutations will be contained in progeny cells that make a significant contribution to the fetus. Given that only a few cells from the blastocyst eventually contribute to the embryo, an early mutation is likely to affect all of the organism, including its germ plasm, or none of it. Later, as that small number of cells gives rise to the embryo proper, there are soon so many cells that a somatic mutation would give rise to a very small clone in the adult organism. Thus, the window of opportunity for mutation to create a sufficiently large clone to be visible and yet be unlikely to contribute to the germ plasm is small. (Although it occurs and examples of germ-line mosaicism with or without somatic mosaicism will be discussed.) Indeed, it is more likely to be detected when there are visible manifestations on the surface of the body. Thus, somatic mutation, with its resultant mosaicism, could contribute to a variety of conditions as well as those that will be discussed. For instance, as already mentioned, the development of a cancer has a frequent contribution due to somatic mutation; some would say, “an essential and always present contribution”. It is possible that some birth defects have a contribution from somatic mutation and, indeed, some of the disorders to be discussed may be thought of as birth defects. Finally, contributions of somatic mutation to atherogenic plaques, and other common disorders, may also occur and be the subject of future research.

The frequency of somatic mutation not related to human disease has been frequently studied in vitro and in vivo. The X-linked HPRT [8,9] and autosomal APRT [10] loci have been favored targets because of the ease of selection of variants. Most of these studies have focused on T-lymphocytes while a very different spectrum of mutations was found in kidney epithelial cells [11]. A very important observation for understanding the frequency of somatic mutation causing human disease mosaicism is that embryonic stem cells (mouse) also have an apparently unique mutational spectrum [12]. The mutation frequency was lower than that found in mouse embryonic fibroblasts and non-disjunctional events (as found at high frequency in early embryos; [13]) were greatly increased. We do not yet know what cell type will best predict mutations causing human mosaicism with somatic diseases.

2. Disorders with proven somatic mutation

2.1. Neurofibromatosis 1 and 2

Neurofibromatosis 1 (NF1) is probably the single most common dominant genetic disorder. The combination of milky coffee-colored (cafe-au-lait) spots and multiple neurofibromas was first described by von Recklinghausen [14]. Probably the first general clinical delineation was made by Crowe et al. [15] in their survey of cases in the state of Michigan presented as a monograph. This study defined a clinical criteria (in Caucasians) of the presence of six cafe-au-lait spots greater than 1.5 cm in diameter as nearly always indicating neurofibromatosis. Of course, the subcutaneous tumors (neurofibromas) were also a very frequent feature. By using these two criteria, the disorder was only 85% penetrant. In more recent times, Lisch nodules of the irides have been defined as a common feature of the disorder [16]. The presence of Lisch nodules in potential carriers brings the penetrance of NF1 to more like 95% [17,18]. Plexiform neuromas, especially those present at birth, are frequently very disfiguring, and those involving the head or neck may be lethal. Neurofibromatosis 1 has so many other manifestations that, as syphilis was once described, it can be thought of as the “great imitator” [19]. An excellent historical summary of some of the various manifestations is provided by Holt [19]. While the characteristic cafe-au-lait spots, neurofibromas, and Lisch nodules are pathognomonic of the disorder, microcephaly, short stature and cognitive disorders [20,21] are also common. Neurofibromin, the gene product of the NF1 gene, is also expressed in vessels [22], and a wide variety of vascular
abnormalities, including moyamoya of the brain [23], are found.

Given a relatively common genetic disorder, with prominent superficial features, it is not surprising that cases suggestive of somatic mutation were described. A patient who had cafe-au-lait spots and Lisch nodules limited to the right half of the body was described by Zonana and Weleber [24]. Multiple cases with more limited segmental involvement have been described by Nicolls [25] and Miller and Sparks [26] while Combemale et al. [27] were able to review 88 segmental cases. The phenotype is established well enough that the Riccardi and Eichner book [28] classified it as a unique form of neurofibromatosis, neurofibromatosis type 5. With the cloning of the gene [29,30] it became possible to establish the mutational cause of segmental neurofibromatosis as being due to mutations in neurofibromin. Tinschert et al. [31] demonstrated a mutant allele in cultured fibroblasts from cafe-au-lait lesions in the affected segment which was not present in fibroblasts from normal skin or white blood cells while Colman et al. [32] found a large deletion limited to the soma but in a non-segmental patient. These mutations, and others to be discussed, are tabulated in Table 1.

It is interesting to use the frequency of segmental neurofibromatosis compared to general neurofibromatosis 1 to ascertain some ratio of the frequency of germ-line compared to somatic mutations. Ingordo et al. [33] found segmental neurofibromatosis to be about 1/10 as frequent as generalized neurofibromatosis while Wolkenstein et al. [34] found it to be about 1/30 as abundant. As already discussed, the chances of somatic mutation occurring in the right time frame to be detected is relatively small. Thus, these quite high frequencies might suggest that the rate of somatic mutation is on the same order as the rate of germ-line mutation in the neurofibromatosis 1 gene. Arguments against similar mutation rates might point to the role of the stimulatory G protein in the relevant tissues which was well reviewed by Cohen and Howell [46]. Cohen [47] has also made the point that the activating GNAS1 mutations create a situation of benign neoplasm which can readily become activated to malignancy (4% of patients). It is interesting that, because some cases of polyostotic fibrous dysplasia seem particularly limited to bone, surgical specimens from such cases have shown, as might be predicted, that the mutation is found in the bone and at low or undetectable levels in other tissues [48]. While it is sometimes hard to understand the distribution of lesions in terms of a mosaic somatic mutation, e.g. such cases with involvement apparently limited to bones without skin or endocrine organs involved,
Table 1  
Diseases with somatic mutation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Major tissue(s) involved</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Mutation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis 1</td>
<td>Skin, peripheral nervous system</td>
<td>Neurofibromin</td>
<td>17</td>
<td>One micro, one macro deletion</td>
</tr>
<tr>
<td>Neurofibromatosis 2</td>
<td>Central nervous system</td>
<td>NF2</td>
<td>22</td>
<td>Two nonsense</td>
</tr>
<tr>
<td>McCune–Albright</td>
<td>Skin, bone, endocrine system</td>
<td>GNAS1</td>
<td>20</td>
<td>Eight missense, Arg201X</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Blood</td>
<td>PKD4</td>
<td>X</td>
<td>Six frameshift</td>
</tr>
<tr>
<td>Incontinentia pigmenti (males)</td>
<td>Skin, eyes, teeth, CNS</td>
<td>NEMO</td>
<td>X</td>
<td>Three intrachromosomal rearrangement deleting exons 4–10</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteus</td>
<td>Vascular, bones</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Klippel–Trenaunay</td>
<td>Vascular</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Maffucci</td>
<td>Bones</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Germ-line and somatic mutation</td>
<td>Bone</td>
<td>COL1A1</td>
<td>17</td>
<td>Three Missense</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Muscle</td>
<td>Dystrophin</td>
<td>X</td>
<td>Proximal deletions increased in mosaic compared to germ-line mutations</td>
</tr>
<tr>
<td>Hunter syndrome</td>
<td>Connective tissue</td>
<td>IDS</td>
<td>X</td>
<td>One nonsense</td>
</tr>
<tr>
<td>Neurofibromatosis 2</td>
<td>Central nervous system</td>
<td>NF2</td>
<td>22</td>
<td>One nonsense</td>
</tr>
<tr>
<td>Congenital contractual arachnodactyly</td>
<td>Connective tissue</td>
<td>FBS2</td>
<td>5</td>
<td>One splice site</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Blood</td>
<td>HEMA</td>
<td>X</td>
<td>CpG transitions</td>
</tr>
<tr>
<td>Revertant mosaicum epidermolysis bullosa</td>
<td>Skin</td>
<td>COL17A1</td>
<td>10</td>
<td>Gene conversion</td>
</tr>
<tr>
<td>adenosine deaminase severe combined immuno-deficiency</td>
<td>Lymphocytes</td>
<td>ADA</td>
<td>20</td>
<td>True reversion</td>
</tr>
<tr>
<td>X-linked severe combined immuno-deficiency</td>
<td>Lymphocytes</td>
<td>IL2RG</td>
<td>X</td>
<td>True reversion</td>
</tr>
<tr>
<td>Wiskott–Aldrich</td>
<td>Lymphocytes</td>
<td>WAS</td>
<td>X</td>
<td>6bp insertion deleted by slippage</td>
</tr>
<tr>
<td>Fanconi A</td>
<td>Hematopoietic system, heart kidney, limbs</td>
<td>FANCA</td>
<td>16</td>
<td>Frameshift corrected by further frameshift</td>
</tr>
<tr>
<td>Fanconi C</td>
<td>Hematopoietic system, heart kidney, limbs</td>
<td>FANCC</td>
<td>9</td>
<td>One mitotic recombination</td>
</tr>
</tbody>
</table>

*See text for references.

all studies to date have found activating mutations, usually of Arg201 [49]. One can think of a mutation limited to mesodermal derivatives as causing the bone defects while the skin (ectodermal) and endocrine (mostly endodermal) were spared but the three “germ layers” do not really have such separated lineages. In conclusion, McCune–Albright syndrome, like segmental neurofibromatosis, seems well established as a disorder due to mosaic expression of a somatic mutation.
2.3. Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is an intriguing disorder in which somatic mutations interact with other factors, possibly germ-line inherited factors, to create a frequently malignant disorder. The disease is due to a deficiency of the glycosylphosphatidylinositol (GPI; note, not glucose phosphate isomerase) anchor which attaches many cell surface proteins to the plasma membrane [50,51]. The deficiency is due to mutations in a gene, \( PIG-A \) (phosphatidyl glycan class A) [52], one of four genes whose products are involved in the synthesis of GPI-anchors [53]. The mutations lead to deficiency of the surface expression of multiple GPI-anchored proteins on red cells, leukocytes and platelets emerging from a mutated stem cell clone. Decay-accelerated factor and CD59 are GPI-anchored proteins which help protect red blood cells from autolysis by complement. Some of the deficient cells may be lysed preferentially at night (reason unknown) and dark urine is noted in the morning, leading to the name for the disorder. Intravascular embolus can also occur.

Paroxysmal nocturnal hemoglobinuria is X-linked [54]. Since women are mosaics for X chromosome inactivation, mutations on the active X in females, or the only X in males, can equally cause the disease. Importantly, small numbers of cells with mutations in the \( PIG-A \) gene can be found at a frequency of 1–2 per 100,000 in normal individuals by fluorescence-activated cell sorting [55]. A major question is why these somatic mutations, which are essentially hemizygous (it would take two hits at one of the other three autosomal genes involved in GPI-anchors to cause a similar deficiency), do not cause this disorder more frequently. Luzzatto and Bessler [56] and Luzzatto et al. [57] concluded that the other acquired factor would be some type of bone marrow failure. Under these circumstances, the GPI-deficient cells might have a selective advantage if the cause of the “aplastic anemia” was due to a mechanism targeted at GPI-anchored proteins. Thus, under these circumstances, the clone can expand to significant levels and result in the paroxysmal nocturnal hemoglobinuria phenotype.

One might expect the germ-line mutation in \( Pig-a \) to be lethal in hemizygotes or homozygotes. In fact, attempts to create mouse knockouts were unsuccessful and female mice heterozygous for mutant \( Pig-a \) were not obtained. \( Pig-a \) minus ES cells could be obtained but were not competent to differentiate into mature embryoid bodies [58] although they could contribute to the hematopoietic lineage in chimeras [59]. Using the Crelox system to control the time of knockout, mosaic \( Pig-a \) minus mice were obtained [60]. These female mice had high levels of normal \( Pig-a \) activity in many tissues, while larger levels of the mutant cells were tolerated in spleen, thymus and red blood cells. Presumably, the acquired factor leading to overgrowth of these \( Pig-a \) minus cells did not occur during the short (by comparison to humans) lives of these mice.

2.4. Incontinentia pigmenti in males

Incontinentia pigmenti is a rare disorder affecting the skin, eyes, teeth, and mentation which occurs mostly in females [61]. The disorder starts as an erythematous and vesicular eruption occurring in the neonatal period. As these lesions fade, skin atrophy and marbled darker pigmentation appears. The darker pigmentation crosses the midline and does not indicate a clonal origin. Many of the patients have cone-shaped and/or missing teeth while they may also have, or others may have, ocular abnormalities including cataracts, optic nerve atrophy, retinal pigmentation, and chorioretinitis. In addition, patients may be neurologically abnormal with mental retardation, convulsions, and/or spastic paralysis.

The gene has been cloned and has been shown to code for the NF-κB essential modulator (\( NEMO \)) [62]. It has long been believed that mutations in the gene are lethal in males, and the high frequency of spontaneous miscarriage in affected females supports the notion [63]. However, with the cloning of the gene, it has been discovered that a dissimilar disorder consisting of ectodermal dysplasia and immune defects which can present with lymphedema and/or osteopetrosis is due to mutations in the same gene [64,65]. The mutations in \( NEMO \) are different and are “hypomorphs” instead of nulls.

Recently, four males with more classic findings of incontinentia pigmenti were studied [66]. All four patients were found to carry the most common mutation of \( NEMO \), an intrachromosomal rearrangement that deletes exons 4–10. On further study, one of the four patients was found to be a Klinefelter’s, i.e. 47,
XXX, while the other three were somatic mosaics [66]. Again, a skin phenotype was involved in detecting the somatic mosaicism but not as in the other cases by showing a clearly clonal origin. In other words, incontinentia pigmenti is diagnosed by characteristic swirling chocolate-shaded pigmentation but it was the cloning of the gene that allowed the demonstration of somatic mosaicism in the rare surviving males.

3. Disorders with likely somatic mutation

3.1. Proteus syndrome

Proteus syndrome was first delineated by Cohen and Hayden [67] in 1979 as a disorder characterized by overgrowth of multiple tissues. There were also connective tissue and epidermal nevi and hyperostoses. The disorder was referred to as Proteus syndrome by Weidmann et al. [68] after the Greek god Proteus who could change his shape at will to avoid capture. Happle [69], who had also suggested somatic mosaicism in other disorders (see above) pointed out that the lesions followed the lines of Blaschko, which delineate skin migration patterns, and suggested that the Proteus gene might be a dominant lethal surviving by mosaicism. An important nosological advance occurred when Tibbles and Cohen [70] presented evidence that the “elephant man”, Joseph Merrick, had Proteus syndrome, not neurofibromatosis. They pointed out that Joseph Merrick had no café-au-lait spots, no neurofibromas, and was normal at birth. Importantly, a plaster cast of Merrick’s foot showed the typical connective tissue nevi of the plantar surface characteristic of Proteus syndrome [71].

The tumors found in Proteus syndrome are most frequently subcutaneous hemangiomas, lymphangiomas, and lymphomas [72]. The hyperostoses, bony overgrowths which have not become malignant, can occur in limbs, cranial or facial bones. They are typically not present at birth and grow disproportionately to the body after birth [67,72,73]. Systematic studies of multiple patients have allowed the distinction between Proteus syndrome and a form of hemihyperplasia frequently associated with lipomatosis [74]—a disorder which could also be due to somatic mosaicism. Importantly, review of the distribution of lesions in many patients has strongly supported the notion of partial and variable involvement in the different patients, strongly supporting the notion of somatic mosaicism [71,75]. The existence of discordant monzygotic twins also supports the notion but DNA fingerprinting showing a single band difference in a pair of twins and differences in the normal and affected areas of another Proteus patient [76] may be misleading. Only when the gene involved is identified will it be possible to prove the hypothesis.

3.2. Klippel–Trenaunay and Maffucci syndromes

Two disorders, each of which can be thought of as showing a subportion of the spectrum of Proteus syndrome, are both candidates for disorders caused by somatic mutation. Klippel–Trenaunay shows the vascular lesions that can be seen in Proteus with enlargement of bone and soft tissue in those regions [77]. The vascular malformations are combined capillary lymphatic and venous with a “slow flow” pattern in contrast to the Parkes–Weber syndrome with arteriovenous shunts [78]. Limb hypertrophy is usually noted at birth, but can appear later, and continued growth is usual. Baskerville suggests that a mesodermal defect in which excess angiogenesis occurred first with subsequent effects on bony and other mesodermal growth could be the etiology [79]. Despite being quite a frequent condition, there seems to be only one well-documented case of brother–sister involvement [80], suggesting the possibility of somatic mutation. Somatic mutation leading to overexpression of vascular endothelial growth factors (VEG-F) or their receptors (VEG-F, A, B, C, or D, VEG-F receptors, angiopoietins, TIE receptors, etc.) could explain this disorder. Sturge-Weber syndrome in which hemangiomas on the face, with calcification in the brain underlying those areas and frequent mental retardation, might be thought of as a variant with potentially similar causal mechanisms.

Maffucci syndrome might be thought of as showing the other subspectrum of Proteus syndrome. It is characterized by endochondromatases and hemangiomas [81]. These cartilaginous tumors are most common in the phalanges but can occur in any cartilage and are particularly disfiguring in the face and head. The hemangiomas can also be present at birth but frequently occur much later. Since there have been no familial
cases, Hall [82] has suggested that this disorder may well be due to somatic mosaicism.

4. Germ-line and somatic mosaicism

Unlike the previously mentioned disorders which are mostly thought to be incompatible with germ-line transmission, there are a number of disorders in which somatic mosaicism, frequently with germ-line mosaicism as well, have been found. The mutational studies in these disorders are relevant to the frequency with which disease-causing somatic mutation occurs. For instance, osteogenesis imperfecta II, the lethal form, was at one time thought to be autosomal recessive because of sibship recurrences. However, as an understanding of the basis of collagen mutations became understood (missense mutations in one chain can inactivate two other chains in the triple helix), this seemed less likely and a search for somatic mosaicism with a germ-line component was performed and examples readily found [83–85]. Germ-line and somatic mosaicism has also been documented for Duchenne muscular dystrophy [86], Hunter syndrome [87], retinoblastoma [88], neurofibromatosis 2 [36], and congenital contractural arachnodactyly [89], to give examples. The hemophilias provide particularly informative examples. In hemophilia B, CpG transitions were particularly associated with mosaicism which was found abundantly [90]. A comprehensive study of 61 families with hemophilia A found somatic mutations in founders of 13% of the families [91]. These were all families with point mutations and half of the mutations were CpG transitions. All of the somatic mutations were found in carrier females, i.e. individuals expected to be symptom-free because of X-inactivation. This is in contrast to the higher ratio of de novo point mutations in males previously described [92].

5. Revertant mosaicism

Revertant mosaicism is expected to be less common than somatic mutation causing disease symptoms since so many new secondary mutations would not correct the genetic deficiency. Again, skin provides easily ascertained revertants. Jonkman et al. [93] described normal patches of skin on a woman with generalized atrophic benign epidermolysis bullosa. This disorder is due to a deficiency of collagen 17 α-1 and the authors’ demonstrated that this collagen was present only in these patches. DNA studies showed that a gene conversion event had occurred in which the maternal mutation was corrected [93]. Visible patterns of somatic reversion has also been observed in tyrosinemia I patients. These patients have a deficiency of fumaryl acetoacetate hydrolase, which can be stained histochemically and normal nodules detected in patients’ livers [94]. However, the molecular mechanism of reverse mutation was not determined although, since some of the patients were homozygous for particular mutations, gene conversion cannot be the explanation in all of the cases.

In the manner that PIG-A mutants were selected in paroxysmal nocturnal hemoglobinuria by some unexplained conditions (see above), one might expect to see reversion events more easily in situations where the revertant would be selected. Thus, mutations in the X-linked severe combined immunodeficiency causing gene, the γ receptor chain for a variety of interleukins were sought. A reversion was found in a hemizygous patient who had some normal T-cells [95]. The patient had a cys115arg mutation in his granulocytes and B-cells but not in his T-cells. Although the mother was heterozygous, in utero engraftment was ruled out by HLA typing [95]. The selective advantage of T-cells containing a normal interleukin-2 receptor gamma chain also allowed successful gene therapy for X-linked SCIDs [96]. In contrast, whereas adenosine deaminase-deficient T-lymphocytes treated with a vector to express adenosine deaminase did not seem to have a growth advantage, a patient with a true back mutation showed progressive improvement, apparently due to a growth advantage of the revertant lymphocytes in vivo [97]. Somatic reversion has also been found in another X-linked immune deficiency disorder, Wiskott–Aldrich syndrome. This disorder of eczema, thrombocytopenia and proneness to infection is due to mutations in the WAS gene. Wada et al. [98] reported a patient who had quite classic symptomatology until his early twenties, after which he had few symptoms (most patients are dead by age of 10 years). The family’s mutation was a six base pair insertion which was deleted in most of the T-lymphocytes
in the patient, presumably because of “slippage” since the six base pair insertion was a tandem repeat [98].

Fanconi anemia is an autosomal recessive disorder which is frequently associated with cardiac, renal and limb malformations, particularly of the thumb and radius, as well as pigmentary changes. Reverse mutations in several of the different complementation groups demonstrate multiple mechanisms for reverse somatic mutations. Patients with two populations of lymphocytes, one still sensitive to the DNA cross-linking agent mitomycin-C, while the other was resistant, provided the material for such studies. A frameshift mutation in Fanconi complementation group A was corrected by two additional single base pair deletions while an insertional mutation was compensated by a second insertion [99]. Although the predicted proteins had sequence differences from the wild-type protein, functional correction of the defect by the secondary deletions or insertions was shown by transfection of cells with the mutant cDNAs. In Fanconi anemia complementation group C, Lo Ten Foe et al. [100] studied other such resistant lymphocyte populations. In one case, mitotic recombination led to gene correction while in two other patients, the mechanism of correction was thought to be gene conversion. Revertant fibers expressing dystrophin have sometimes been seen in Duchenne muscular dystrophy. The mechanism is exon skipping but the molecular mechanism is not known [101,102]. Thus, it is not apparent whether or not these examples include somatic mutation.

6. Genetic counseling

The presence of undetected somatic and germ-line only mosaicism can greatly alter the predicted risks for future pregnancies. It is, of course, a greater problem the more common the disease and the more common it is present. Duchenne muscular dystrophy is both common and such germ-line mosaicism occurs relatively frequently [86,103]. The frequency of founder germ-line mosaic mutations has also been high in osteogenesis imperfecta [104] and retinoblastoma [88]. Its relevance for counseling has also been discussed for Alport syndrome [105], Gaucher disease [106] and testicular feminization [107]. However, for these quite rare diseases, there is not as much experience to allow provision of a more accurate recurrence risk.

7. Summary

Somatic mutation, both to and from the wild-type, is increasingly being found in human disease. Such mutations cause mosaicism which may or may not include the germ-line. The disease-causing somatic mutations show a full spectrum of base changes, insertions/deletions (indels) and larger changes (Table 1). Not surprisingly, the spectrum of reverse mutations is more limited. However, a more careful study of the frequency of somatic mosaicism compared to somatic and germ-line mosaicism might allow a better determination of the time during embryogenesis when the disease-causing mutations have occurred. The modern tools of molecular genetics are allowing tremendous advances in this field and cell enrichment techniques have allowed small levels of mosaicism to be studied. Future advances will probably detect somatic mosaicism in many other diseases. Greater use of stem cells, including embryonic stem cells [12], as targets for in vitro mutagenesis would be highly relevant since the mutations that can seed a large part of the soma and/or germ-line are likely to occur in cells with such self-renewal properties.

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