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Non-coding RNAs and disease: the classical ncRNAs make a comeback

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Abstract

Many human diseases have been attributed to mutation in the protein coding regions of the human genome. The protein coding portion of the human genome, however, is very small compared to the non-coding portion of the genome. As such, there are a disproportionate number of diseases attributed to the coding compared to the non-coding portion of the genome. It is now clear that the non-coding portion of the genome produces many functional non-coding RNAs and these RNAs are slowly being linked to human diseases. Here we discuss examples where mutation in classical non-coding RNAs have been attributed to human disease and identify the future potential for the non-coding portion of the genome in disease biology.

Keywords

ncRNA; snRNA; tRNA; snoRNA; TERC; RNase MRP

Introduction

Eukaryotic genomes are pervasively transcribed producing a plethora of RNA species. These RNAs are essential for many of the important functions in the cell, from the making of proteins to the copying of DNA during cell replication. It is, therefore, not surprising that mutations in RNA can lead to disease. While much recent attention has been given to the role of newly identified long non-coding RNAs (lncRNAs) and micro RNAs (miRNAs) in human disease, mutations associated with the more classically defined ncRNAs have also been increasingly recognised as causing disease. These classical ncRNAs are the transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), telomerase RNA, small nucleolar RNAs (snoRNAs) and the RNA component of RNase mitochondrial RNA processing (MRP) endoribonuclease that have been known to researchers for many years. In the past, it was believed that mutations in any one of these essential, classical, ncRNAs would more than likely be lethal. Over time it has become apparent that mutations in classical ncRNAs, that partially alter their function, can result in diseases with very specific phenotypes.

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Advances in sequencing technologies have made it easier to identify mutations associated with human diseases. But techniques like exome sequencing, which have been extensively exploited to identify disease mutations associated with the protein coding regions of the genome, are not useful for detecting mutations in ncRNA genes. It is usually when exome sequencing has failed to provide any strong candidate disease associated mutations that researchers then turn to other genetic techniques like linkage analysis to narrow down a genomic region to sequence, or resort to whole genome sequencing. Therefore, mutations associated with the classical ncRNAs have been traditionally slower to identify. The first disease linked classical ncRNA mutations were found in a mitochondrial tRNA (mt-tRNA) gene associated with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) [1] and the nuclear gene for the RNase MRP RNA associated with CHH (cartilage-hair hypoplasia) [2]. While more difficult to identify, mutations in classical ncRNAs are now emerging as an increasingly significant class of ncRNA associated with human diseases. In this review we will consolidate what is currently known about disease associated mutations in the classical ncRNAs.

tRNAs

The tRNAs are present in all living organisms and in human cells they constitute about 10% of total RNA [3]. The tRNAs are crucial components of the protein translation machinery, serving as adaptor molecules between the mRNA and the growing chain of amino acids. In the human nuclear genome, at least 597 tRNA genes decoding the standard 20 amino acids have been identified [4], whilst mitochondrial DNA encodes 22 unique, single copy tRNAs [5]. Human genetic disorders associated with tRNAs result from either mutations within the tRNA or alteration of the tRNA processing endonucleases, tRNA modifying enzymes and aminoacyl-tRNA synthetases [5]. This section only focuses on the direct link between mutation in tRNA and disease.

For all human disorders associated with mutations in tRNAs, mutations only occur in mt-tRNA [6], as the 22 mt-tRNAs are single copy and are unlikely to be compensated for by other tRNAs. There are over 250 mt-tRNA mutations reported to date and catalogued in the MITOMAP database (http://www.mitomap.org/MITOMAP; [7]). Most of mt-tRNA mutations appear to influence high energy requiring tissues such as those found in the muscular and nervous systems. Mutations in mt-tRNAs can either be polymorphic or pathogenic and can be located in both the loops and stems of mt-tRNA [8]. Polymorphic neutral mutations are found in all mt-tRNAs, however they usually have no, or little, effect on function or structure of mt-tRNA [9]. Pathogenic mutations have been associated with a wide range of diseases in humans, including myopathy, cardiomyopathy, diabetes, deafness, encephalopathy, epilepsy or other neurological disorders [8,10]. Point mutations in mt-tRNA affect their three-dimensional structure, stability, folding, aminoacylation and can also influence mitochondrial protein synthesis itself [11]. The effects of mutations can lead to cellular respiration defects or decrease in activity of the respiratory chain complexes. The most deleterious effects on the function of mt-tRNAs have point mutations in the anticodon bases. However, only a handful of known mutations occur in such critical positions as they are likely to be lethal [10]. One example of such an anticodon mutation was described in a patient suffering from mitochondrial myopathy, where a nucleotide within the mt-

$tRNA^{Pro(UGG)}$ anticodon was substituted to UGA which encodes serine [12]. The mutation was only detectable in patient's muscles and caused severe impairment of mitochondrial protein synthesis and oxidative phosphorylation.

Point mutations that lie outside the mt-tRNA anticodon not only can affect the whole mt-tRNA molecule but can alter the structure of the anticodon and thus change the decoding efficiency of mt-tRNA. Two well-known examples are maternally inherited MELAS and myoclonic epilepsy with ragged red fibers (MERRF). These diseases are usually caused by altered modification of uridine in the wobble position in anticodons of $mt\text{-}tRNA^{Leu(UAA)}$ and $mt\text{-}tRNA^{Lys(UUU)}$, respectively [13,14]. Patients with MELAS lack 5-taurinomethyluridine (τm^5U) on $mt\text{-}tRNA^{Leu(UAA)}$, resulting in a UUG-codon–specific translational defect, leading to a translational depression of ND6, a component of the respiratory chain complex I and reduction in complex I activity. MERRF patients lack 5-taurinomethyl-2-thiouridine (τm^5s^2U) on $mt\text{-}tRNA^{Lys(UUU)}$ which causes translational defects for both cognate codons (AAA and AAG). Such patients show a general defect in mitochondrial translation.

The correlation between mutation in mt-tRNA and disease phenotype is complex. The same mutations can lead to different disease phenotypes, and similar phenotypes can be associated with different mt-tRNA mutations. For example, the MELAS phenotype has been associated with at least ten point mutations within the $mt\text{-}tRNA^{Leu(UAA)}$ but also with several mutations in other types of mt-tRNA (http://www.mitomap.org/MITOMAP). Moreover, the same mutational genotype can produce disease in one family member but other family members with the mutation can have no clinical symptoms. This phenomenon is dependent on the level of heteroplasmy (the coexistence of mutated and non-mutated mt-tRNA) within the cell, organ or an organism. If all mt-tRNA are mutated (homoplasmy), the mutation effect is enhanced. Since mt-tRNA mutations manifest themselves with phenotypic variation between patients, and their expression and abundance varies between tissues, there is a need for better diagnostic tools to understand the genotype-phenotype relationship. Sequencing and quantification of mt-tRNA present in the affected tissues combined with measurement and analysis of respiratory chain enzymes could lead to better diagnosis of mt-tRNA associated diseases.

RNase MRP RNA

The RNase MRP is an RNP that contains an RNA component (*RMRP* in humans) that is required for RNase MRP function [15]. The functions of RNase MRP are varied and include processing of RNA primers required for mitochondrial DNA replication, pre-rRNA processing and cleavage of mRNA to induce its degradation [16]. Mutations in human *RMRP* have been associated with CHH [2]. CHH is characterised by short-limbed dwarfism, sparse fine hair, immunological defects, gastrointestinal malabsorption, anaemia and predisposition to cancer. The *RMRP* mutations found in CHH are insertions, duplications, deletions and single point mutations found within the *RMRP* sequence and within the promoter of this Pol III transcribed ncRNA [17]. Mutations in *RMRP* have been related to cellular defects in rRNA processing and mRNA cleavage, with these defects relating

specifically to the disease phenotypes of bone dysplasia and immune deficiency respectively [17].

Interestingly, *RMRP* has recently been found to be associated with two other distinct RNP complexes that may explain some of the other disease phenotypes. *RMRP* has been found associated with the helicase DDX5, a new regulatory partner of the sterol-responsive nuclear hormone receptor RORγt that controls transcription for the differentiation of T helper 17 lymphocytes [18]. DDX5 interacts with *RMRP* and together the DDX5-*RMRP* complex induces the assembly of RORγt complexes on specific genes required for the T helper 17 lymphocyte effector program. Significantly, introduction of an *RMRP* CHH mutation into mice resulted in reduced expression of RORγt-dependent genes. Therefore, the defective T-cell-dependent immunity seen in CHH may be linked to compromised activity of *RMRP* at RORγt-dependent genes.

RMRP has also been found associated with the telomerase reverse transcriptase TERT [19]. TAP-tagged TERT is able to pull down *RMRP* indicating that TERT-RMRP form a novel complex distinct from the TERT-TERC telomerase RNP. Together, the TERT-RMRP complex has RNA dependent RNA polymerase activity that produces double stranded RNA that are precursors for production of *RMRP*-specific siRNAs. Mutations in RMRP associated with CHH may, therefore, have two effects, first *RMRP* mutations may disrupt the function of the TERT-RMRP complex and second RMRP mutations may change the specificity of any siRNAs derived from *RMRP* [20].

snRNAs

Splicing of pre-messenger RNAs (pre-mRNAs) is an essential process that is mediated by a ribonucleoprotein complex called the spliceosome. The spliceosome consists of five snRNAs that are associated with proteins forming small nuclear ribonucleoprotein particles (snRNPs) [21]. During splicing, introns are removed and exons are joined together to form a mature mRNA that will later be translated into proteins by the ribosome. In mammals, there are two types of spliceosomes, the major and minor, and they differ in their composition. The major spliceosome consists of U1, U2, U4, U5 and U6 snRNPs, and the minor spliceosome consists of U11, U12, U4atac, U5 and U6atac snRNPs [22]. Only the U5 snRNP is shared by both spliceosomes [22]. The major spliceosome is responsible for removing >99% of human introns, whereas the minor spliceosome is responsible for removing approximately 700-800 introns. Mutations in the RNAs and/or proteins of the spliceosome disturb the normal level of splicing and in some cases, lead to diseases [23–25]. Examples, where mutations in the snRNAs cause diseases are discussed below.

Mutations in the single copy U4atac snRNA have been linked to patients with brain and bone malformations and unexplained postnatal death called microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1), also known as Taybi-Linder syndrome [26]. To date, nine mutations associated with MOPD1 have been described, six of the MOPD1 mutations are located in the 5’ stem loop of the U4atac snRNA, a binding site for the spliceosomal protein 15.5K [27]. The 15.5K protein creates a platform for binding of another protein, PRPF31, that in turn interacts with PPIH/PRPF3/PRPF4 to form the U4atac/U6atac.U5 tri-

snRNP complex [27]. Mutations in the U4atac snRNA decrease the formation of the U4atac/U6atac.U5 tri-snRNP complex leading to a small splicing defect and retention of introns that are usually removed by the minor spliceosome [26,27]. Although the splicing defect is small, MOPD1 is very severe resulting in death in the first 3 years of life [26]. The other disease mutations are located in different regions of the U4atac snRNA, one adjacent to the Sm protein binding site, one in the 3' stem-loop and one in the 3' end of stem I extending this helix by one base pair [27].

Mutation in U4atac causes another congenital disorder named Roifman syndrome. Roifman syndrome differs from MOPD1 and consists of growth retardation, the inability to produce certain antibodies, retinal dystrophy, spondyloepiphyseal dysplasis, cognitive delay and facial dysmorphism [28]. Six individuals from four unrelated families with Roifman syndrome were found to be compound heterozygous, with one U4atac variant overlapping an MOPD 1 mutation in the 5' stem loop, whilst other variants occurred in the stem II or the Sm protein-binding site of the U4atac snRNA [28]. Mutation in the stem II may affect binding of the PPIH/PRPF3/PRPF4 protein complex [27] and mutation in the Sm protein binding site may interfere with snRNP assembly and snRNP import into the nucleus [28].

Mutation in the U2 snRNA gene leads to disruption of alternative splicing and neurodegeneration [29]. Mutation in one of the mouse multicopy U2 snRNA genes, Rnu2-8, causes ataxia and neurodegeneration through dysregulation of pre-mRNA splicing [29]. This U2 mutation is a five nucleotide deletion in U2 located in the U2/U6 Helix Ia linker which is found between U2 and U6 Helix I and the branch site U2 duplex [29]. This five nucleotide deletion removes two nucleotides of the branch site recognition sequence, an important sequence required for spliceosome assembly and the first catalytic step of splicing.

Since intron retention by the minor spliceosome in mammalian cells is higher compared to the major spliceosome [30] any disruption that causes minor splicing to be even less efficient may have a more dramatic effect compared to a similar situation with the major spliceosome. Replacing a minor intron by a major one with identical context gives up to eight fold increase in protein yield demonstrating that the minor spliceosome is not only slower but splices minor introns less efficiently [31,32].

The minor spliceosome has been less studied compared to the major spliceosome, but now it is known that mutations in the minor spliceosome can have drastic consequences that, in some cases, are incompatible with life. Mutations leading to severe diseases in other snRNAs are yet to be discovered and may be complicated by many of the snRNAs existing as multiple functional copies.

snoRNAs

Based on their structure, small nucleolar RNAs (snoRNA) fall into two classes; box C/D snoRNAs and box H/ACA snoRNA. Box C/D snoRNAs and box H/ACA snoRNAs guide 2'-O-methylation and pseudouridylation of their nucleotide targets, respectively. SnoRNAs are mainly responsible for post-transcriptional modification of rRNAs [33]. Prader-Willi syndrome (PWS) is probably the best understood example of a disease involving snoRNA

mutation. PWS is the result of the complete loss of the paternally inherited region 15q11–q13 of chromosome 15 [34]. This region contains 47 and 28 tandem repeats of the box C/D RNAs called *SNORD115* and *SNORD116,* respectively [35]. Unlike the majority of snoRNAs, *SNORD115* and *SNORD116* are not involved in modification of rRNAs or snRNAs [36]. Using a genome wide array, *SNORD116* has been shown to regulate the transcription of roughly 200 genes [37]. *SNORD115* has complementarity with the serotonin receptor 5-HT_{2C}R transcript and is involved in alternative splicing of the 5-HT_{2C}R pre-mRNA [36]. Using mouse models, deletion of the *SNORD115* repeats has a significant impact on the ability of *SNORD116* to control gene expression suggesting, that PWS therapies should target both snoRNAs [37].

There are known mutations in genes coding for proteins associated with snoRNAs that lead to disease. One example is the *DKC1* gene encoding for dyskerin that is associated with X-linked dyskeratosis congenita (DC) [38]. Analysis of the expression levels of 27 H/ACA snoRNAs in X-linked DC patients revealed significant variation between these snoRNAs [39]. It is possible that differential expression of H/ACA snoRNAs in X-linked DC is responsible for the wide variety of symptoms observed between sufferers. It would be useful to expand on this work in the future, to see if certain snoRNA expression patterns correlate with specific symptoms. However, these studies demonstrate the possible involvement of snoRNAs in human diseases.

Analysis of the human genome has shown that roughly 40% of snoRNAs contain at least one single nucleotide polymorphism (SNP) with 298 SNPs found to be located across 151 snoRNAs [40]. By using the SNPfold algorithm, it was shown that the SNPs in six of these snoRNAs could have a significant effect on RNA secondary structure [40]. This study indicates the potential for snoRNA mutations to cause disease, especially if a snoRNA is involved in the regulation of a critical cellular pathway.

A study of prostate cancer cell lines showed a two base-pair deletion in the box C/D snoRNA *U50* [41]. The same two base-pair deletion in *U50* was found in a similar study using breast cancer cell lines [42]. Based on these results, it is suggested that snoRNA *U50* is linked to the development of cancer. While only a few snoRNAs have been associated with human disease to date, as disease gene identification moves away from the exome, we are likely to see more examples of snoRNA mutations being implicated in human disease in the future.

Telomerase RNA

The RNP complex telomerase, a specialized DNA polymerase that maintains chromosome ends, is composed at its core of the telomerase reverse transcriptase (TERT) and the telomerase RNA component ncRNA (TERC or hTR) that acts as a template for telomere repeat addition to chromosome ends [43]. Mutations in the single copy ncRNA TERC have been associated with DC, idiopathic pulmonary fibrosis, aplastic anaemia, myelodysplastic syndrome and liver disease [44]. TERC contains three major functional and structural domains which include 1) a TERT binding core domain that forms a pseudoknot and a loop that contains the telomere template sequence, 2) the CR4/CR5 domain which also interacts

with TERT and 3) a CR7 domain (or scaRNA domain) that contains the H/ACA motif and binds the H/ACA RNP proteins that includes dyskerin [45]. Disease associated mutations occur throughout TERC and comprise either single nucleotide changes or small to large deletions. These TERC mutations compromise telomerase function causing shortening of telomeres which triggers a DNA damage response leading to apoptosis or cellular senescence [46–48]. Three mechanisms have been proposed to explain the varied phenotypes associated with TERC mutation [44]. First, in proliferating tissues stem cells lose their potential to provide new cells, second, in tissues with slower turnover additional mutations to those in TERC are required to induce disease associated tissue changes, and third, cell senescence causes changes in cellular function (ie – gene expression) without tissue disruption.

Conclusions

In this minireview, the known human diseases associated with the classical ncRNAs have been described (Figure 1). As the non-coding genome is significantly larger than the protein coding portion of the genome, there is great potential for the identification of further diseases associated with the classical ncRNAs and other ncRNAs. The development of sequencing techniques targeted to ncRNAs, akin to exome sequencing, would be useful in probing the non-coding portion of the genome when exome sequencing has failed to identify any meaningful disease mutations. In addition, while disease associated mutations in classical ncRNAs have been identified, in many cases the molecular mechanisms of how these disease mutations result in a tissue and/or developmentally specific disease phenotype are still lacking. Uncovering the molecular mechanisms behind how classical ncRNA mutations cause diseases will be key to developing treatments but will also surely provide new information on the functions of these essential ncRNAs.

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Abbreviations

lncRNA	long non-coding RNA
tRNA	transfer RNA
snoRNA	small nucleolar RNA
snRNA	small nuclear RNA
MRP	mitochondrial RNA processing
mt-tRNA	mitochondrial tRNA
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MERRF	myoclonic epilepsy with ragged red fibers

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pre-mRNA	pre-messenger RNA
snRNP	small nuclear ribonucleoprotein particle
MOPD1	microcephalic osteodysplastic primordial dwarfism type 1
PWS	Prader-Willi syndrome
DC	dyskeratosis congenital
SNP	single nucleotide polymorphism
TERT	telomerase reverse transcriptase
TERC	telomerase RNA component
CHH	cartilage-hair hypoplasia

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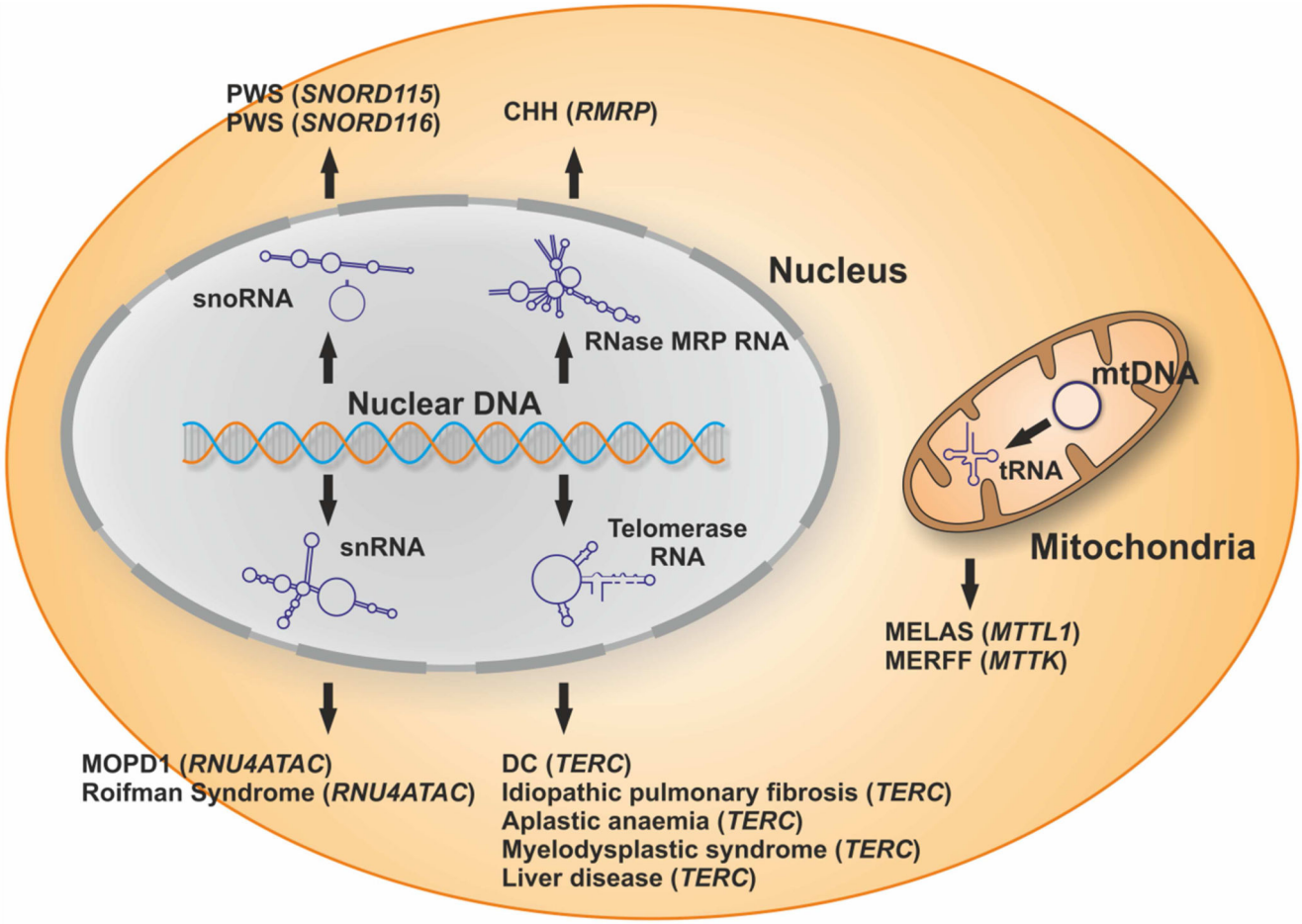

Figure 1. Human diseases associated with classical ncRNAs

Mutations in both the nuclear DNA and mitochondrial DNA (mtDNA) that encode classical ncRNAs have been found to cause a number of human diseases. The diseases are listed along with the genes (in brackets) where mutations are found and have been described in this review. RNA secondary structures presented are not completely accurate representations of the specific ncRNAs.