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INDIVIDUAL CAPACITY FOR MAINTENANCE OF GENOMIC INTEGRITY - A NOVEL TOOL IN THE ASSESSMENT OF THE RISK FOR COMMON ADULT-ONSET HUMAN DISEASES AND CONDITIONS AND THEIR LATE COMPLICATIONS

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Abstract: Not until long ago, common diseases and disease-associated conditions with onset in adult life (obesity; insulin resistance; diabetes type 2; atherosclerosis; vascular disease; degenerative joint disease; neurological diseases; some types of cancer, and others) were considered to be a cumulative product of multiple lifestyle choices, despite the ample evidence that late-onset diseases tend to run in families. It is known now that genetic predisposition plays a significant role in the risk for development of adult-onset disease, albeit some environmental factors (e.g. diet and exercise, exposure to tobacco smoke, UV irradiation, and others) may increase or decrease the risks conferred by the genetic background. This study analyses the major effects of the carriership of common genetic polymorphisms in genes coding for proteins functioning in damage-associated signalling detection and maintenance of genomic integrity (TP53 P72R, XPC ins83); specific DNA repair pathways such as NER (XPC ins83, ERCC1 C8092A; XPD Lys751Gln), BER (XRCC1 Arg399Gln), strand break repair (XPCC1 Arg399Gln; XRCC3 Thr241Met) and disordered DNA methylation (MTHFR C677T) in clinically healthy individuals and in patients affected with specific diseases with late onset. Preliminary studies of the normal variance of these polymorphisms may be useful in establishment of a basis for more accurate risk assessment and individualization of therapies for common late-onset diseases and conditions.

1. Introduction

The typical timeline of the life cycle of higher mammals, including humans, consists of a thriving childhood, followed by active adulthood and middle age, then slowly progressing to a more or less lengthy period of decline of physical

and, sometimes, mental capacities, terminating in 'death of old age'. There are variations of this 'default' route from birth to death, depending on many factors, endogenous as well as environmental. In most cases, one's health in their advanced age and the causes of disease and, eventually, death are predetermined by specificities of one's health profile in earlier life cycle phases (Giaimo & d'Adda di Fagagna, 2012; Khalil et al., 2012). However, young age is usually not laden with disease and the first symptoms that something is not right are rarely shown before the age of 35-40. It is not uncommon to reach adulthood feeling and acting completely healthy only to discover, in one's 40-ties, some or all the hallmarks of metabolic syndrome (fasting hyperglycemia, arterial hypertension, microalbuminuria, central obesity) or diabetes type 2; atherosclerotic plaque clogging the major coronary vessels; degenerative diseases of the connective tissue such as lung fibrosis; various precancerous conditions, such as Barrett's oesophagus secondary to gastroesophageal reflux disease, high-grade cervical intraepithelial neoplasia (CIN), or overt cancer - and these are just a few that are most commonly seen in people of middle and advanced age. Certainly, at least some of these diseases and conditions may be products of lifestyle and environment. For example, cervical neoplasia is very rarely unconnected to previous infection with certain types of human papillomavirus.

It has been known for a very long time that many diseases and conditions occur more commonly in some families than in others. This pertains specifically to monogenic disease - that is, in cases when defined genetic factor/s have been identified that are associated with very high (close to 100 %) risk for development of severe disease. However, diseases and conditions with multifactorial genesis - that is, those that require specific genetic background but the risk for their development is influenced by environmental factors to a significant degree - tend also to run in families. Unlike monogenic disease that often has its onset at early age and may be severe enough to decrease the chances for transmission to the next generation, multifactorial disease usually manifests at later age, when the reproductive plans have already been completed and the culprit genes passed on.

The genetic component of the risk for development of disease plays a peculiar role in diseases and conditions with age of onset around middle age. On the one hand, the genetic factor/s predisposing to disease usually have relatively mild effects on functioning of cells, tissues and organs (or else the resultant phenotype is likely to be severe since early age). On the other hand, these effects act on a fundamental molecular level and are, therefore, likely to involve more than one aspect of the functioning of cells, tissues and organs and to affect many different cell types. Being of hereditary nature, these factors have existed in the carrier cells and, respectively, the carrier organism, since the cell or the organism began to exist. Thus, it is not difficult to comprehend why late-onset disease usually has profound effects on multiple organs and systems; a potential for a legion of complications.

In some (but not all) cases the development of late-onset diseases and conditions may be prevented by extensive lifestyle modification (e.g. balanced diet and regular exercise preventing the development of obesity and insulin resistance). As a matter of fact, lifestyle-based intervention is rarely very efficient. This may be because the culprit factors have had plenty of time to act (since conception) whereas the unspecific measures that potentially may reduce the risk are usually started much later (if at all) and specific intervention begins around the time of onset, at the time when the disease has already developed, and the opportunities for pre-emptive action are already limited. The degree of reduction of the risks for development of multifactorial disease may be very different between different individuals, depending on many factors of endogenous and exogenous origin.

The genetic component of multifactorial disease may not only play a role in the establishment of the risk for development of disease, but may also pre-determine the risk for various complications that may occur throughout the disease. It is known that even the most common complications occur only in some patients with the same disease and that even though some patients develop a certain type of complications more commonly than others, it is difficult to predict who exactly of the at-risk group would develop it. For example, patients with diabetes type 2 often develop neuropathy, retinopathy and microvascular complications. However, these do not develop in all diabetic patients and not even in all of those with poorly controlled hyperglycemia. The case is similar with diseases that are strongly dependent on factors of environmental origin, e.g. carcinogenesis associated with tobacco smoking. Smoking increases the risk for many cancers (specifically, small-cell lung cancer) but cancer does not develop in all smokers, and even when it develops, it does not happen in patients of the same age and not even after the same number of pack-years of smoking.

The main reason why multifactorial diseases and conditions usually become manifest only after four of five decades of life is that there are highly efficient natural mechanisms that promptly correct the errors in the functioning of the cell and/or compensate for aberrant cellular processes. This ensures rapid growth and development in childhood and successful reproduction and child-rearing in adult life. Only when these mechanisms fail - repeatedly - the associated condition or disease may begin to show.

Mechanisms for maintenance of genomic integrity are a major mechanism set in place by Nature to reverse or correct errors that may affect the blueprint of the cell's genetic information. The mechanisms for maintenance of the integrity of the genome comprise the machinery for identification and repair of DNA damage, the mechanisms for assessment of the scale of damage; damage-associated signalling and the closely associated mechanisms of induction of programmed cell death in the presence of DNA damage. Inherited deficiencies in the capacity for identification or repair of DNA damage or in the signalling associated with the presence of DNA damage usually manifest as severe disease with early onset,

sometimes diagnosable at birth - xeroderma pigmentosum, Cockayne syndrome, ataxia-telangiectasia, and others. It was not until about a decade ago when it was definitively shown that some of the common late-onset diseases were, actually, products of disordered DNA repair. The first clinically significant associations were of decreased levels of expression of HMGA1 (a master chromatin structure regulator and repressor of virtually all types of DNA repair) being found in some patients with severe diabetes type 2 with early onset (in adolescence) (Foti et al., 2005). Similarly, rare polymorphic variants of the human gene NEIL1 (coding for one of the endonuclease/lyases of the base excision repair, recognising and excising oxidised bases from DNA such as thymine glycol, 5-hydroxycytosine and 5-hydroxyuracil) were identified in some patients with diabetes type 2 (Roy et al., 2007). Since increased levels of oxidative stress have long been identified as a hallmark of insulin-resistant diabetes, these findings are hardly surprising (Baynes, 1991). The same deviations from what is considered 'normal' or 'average', however, were found, albeit with lower prevalence, in the general population, which means that their carriership would not always produce a phenotype of clinically significant hyperglycemia, but, rather, in selected groups only.

In young and clinically healthy individuals, the mechanisms of maintenance of integrity of the genome are very sensitive and efficient (almost 100 %-proof). Indeed, they may sometimes fail. Broadly speaking, this may occur when one or more of the following criteria are fulfilled:

1) When the damage done exceeds the capacity for its detection and/or repair.

2) When the efficiency of the detection and/or repair mechanisms is lower than what is considered average for individuals of the same species and, roughly, the same age.

As a rule, either of these two conditions or both must act for long enough time to significantly increase the risk for development of disease.

3) When the organism ages, as the natural capacity for maintenance of genomic integrity typically declines as age advances. The latter actually occurs mainly because of accumulation of errors (resulting from the separate or combined action of the first two conditions) throughout many decades.

The prevalence of late-onset diseases and conditions with multifactorial origin typically increases with advancing age. They are quite common in individuals over 65 years of age (fulfilling the third criterion), to the point that it is very rare to find an individual over the age of 65 that would not have at least a couple of age-related diseases, although their clinical presentation may be essentially mild. Multifactorial diseases and conditions may occur in younger individuals as well - especially individuals who fulfil the requirements of the first and/or the second criterion but the prevalence rates are usually lower. If we take insulin resistant diabetes as example, again, according to data from the US Centers for Disease Control and Prevention (http://www.cdc.gov/diabetes/consumer/research.htm, retrieved 15 Oct 2014), only about 1 % of people aged 20 years or less are diagnosed

with diabetes type 2 (although a larger proportion of them may have clinically significant fasting hyperglycemia). The prevalence rises to over 10 % in the age group of >40 years of age, to become >25 % among individuals aged 65 or more. Hyperglycemia increases greatly the production of reactive oxygen species and, respectively, of oxidative stress in virtually all tissues, causing increased rates of occurrence of damage in DNA. On its own, this factor may, with time, produce the tissue and organ damage seen in individuals with untreated diabetes. Usually, development of overt diabetes type 2 is preceded by a prolonged (in a matter of years) pre-symptomatic phase of decreased glucose tolerance and, respectively, increased levels of oxidative DNA damage. If the presence of hyperglycemia is coupled, by chance, with lower-than-average capacity for identification and repair of DNA damage, the risk for development of diabetes type 2 naturally increases, and the age of onset may shift towards younger age. For example, carriership of the 40Thr allele of the Ala40Thr polymorphism in the gene coding for extracellular superoxide dismutase SOD3 (one of the enzymes that catalyses the detoxification of reactive oxygen species) is associated with lower sensitivity to insulin and earlier age at diagnosis than in carriers of the 40Ala allele (Tamai et al., 2006).

Environmental factors increasing the risk for development of disease may act in a similar manner. For example, smoking increases the overall risk for development of lung cancer. The risk is, however, increased in individuals carrying specific components in their genetic background that decrease the capacity for detection and repair of DNA damage (including damage inflicted by genotoxic products in tobacco smoke). It could also be expected that the onset of carcinogenesis may be earlier in these individuals than in individuals with near-normal capacity for DNA damage.

When the disease has already developed, individual capacity for maintenance of genomic integrity may affect its course and the risk for complications. This may or may not be related to the risk for development of disease. For example, carriership of the variant allele of the Ala16Val polymorphism in the gene coding for the mitochondrial superoxide dismutase SOD2 is associated with increased risk for development of microvascular complications, nephropathy and retinopathy in patients with diabetes type2, although no association of the carriership of the 16Val allele with the risk for diabetes has been elicited yet (Möllsten et al., 2009; Tian et al., 2011).

Cancer is common in the age group of > 60 years of age, and the risk for development of virtually any type of cancer increases as age advances (except in the age group of the ‘oldest old’ (> 95 years of age), where the prevalence of cancer may be actually lower than in younger individuals) (Harding et al., 2012). In cancer, the individual capacity for maintenance of genomic integrity plays a specific and complex role, and the assessment of the associated risks may be not straightforward. It is related, on the one hand, to the mechanism of

carcinogenesis as a process driven by accumulation of 'errors' in DNA and, on the other hand, on the therapeutic principle of most of the currently existing anticancer agents (causing enough damage to the DNA of cancer cells so that they potentially would cease their division - albeit temporarily - or die). Carriership of genetic factors that decrease the capacity for detection and repair of damage may increase the risk for cancer and/or shift age of onset to younger age. At the same time, cancer cells that have lower potential for repair of damage and/or increased propensity for apoptosis are more likely to be killed or slowed down by anticancer therapies (for details, see below). Thus, the risk for development of cancer may be greater in individuals with lower-than-average capacity for repair of DNA damage, but the outcomes after anticancer therapy (in terms of efficiency in inducing growth arrest of the tumour) may be significantly better. At the same time, in the latter case, it could also be expected that genotoxic therapies would result in higher general toxicity, as the healthy cells would also repair damage at lower-than-nominal rate.

As degenerative disease is also associated with accumulation of errors in DNA, the risk for many types of degenerative disease increases with advancing age. For example, the risk for senile (developing after the age of 60) cataract may be increased in individuals carrying genotypes conferring lower capacity for repair of DNA (see below for details). This is believed to occur because of accumulation of errors in DNA, causing accelerated ageing of the crystallin proteins of the eye lens. The risk for development of pulmonary fibrosis (idiopathic or secondary to treatment with certain agents) may also be greater in individuals with lower-than-average capacity for detection and repair of errors in DNA and/or lower capacity for tissue renewal (Kinnula & Crapo, 2003; Tsakiri et al., 2007).

Outcomes after interventions seemingly unrelated to capacity for maintenance of genomic integrity, such as success rate after tissue and organ transplantations may also be dependent on carriership of specific allelic variants of genes coding for proteins acting in damage-associated signalling, such as poly-ADP-ribose polymerase 1 (PARP1) and replication factor 1 (RFC1), a component of the BRCA1-associated genome surveillance complex (BASC) (Thyagarajan et al., 2010; Arora et al., 2010).

The knowledge about the basic mode of action of genetic and environmental factors may facilitate the understanding of the processes that manage the balance of possibilities determining the risk for development of certain diseases and conditions with late onset and the risk for potential complications. The amount of information about the impact of individual capacity for maintenance of genomic integrity in health and disease is still far from critical. Nevertheless, considering the rapid development of the field, there is hope that in the not-so-distant future, some of these parameters may be manipulated in order to prevent, delay or permanently arrest the development of human disease.

At present, several dozens of genetic polymorphisms that are associated with the risk for common diseases and conditions, and their late complications have already been identified. In this study, we would only review these that are very common, and for which the associations with risk for multifactorial late-onset disease were confirmed in multiple studies.

2. Polymorphisms in genes coding for products functioning in the maintenance of genomic integrity and DNA damage identification and repair

2.1. P72R (rs1042522) polymorphism in the TP53 gene

Several 'neutral' (that is, their carriership has not been associated with risk for inherited disease) polymorphisms have been identified in the TP53 gene, but only a couple of these have been studied well enough. The P72R polymorphism is a C-to-G transversion in exon 4 of the TP53 gene, resulting in a proline-to-arginine substitution at amino acid residue 72 of the p53 protein (Ara et al., 1990). p53 is the major molecular player responsible for the decision, whether a damaged cell should initiate checks of genomic integrity and attempts to repair the damage, or that it should be sacrificed by programmed cell death. Carriership of the one or the other allele of the P72R polymorphism may reflect significantly on the properties of the protein without affecting its DNA-binding capacity (Thomas et al., 1999). Specifically, the G (arginine) allele of the P72R polymorphism was found to be more effective in induction of apoptosis in the presence of DNA damage than the C (proline) allele. The C (Pro) allele is more effective than the G allele in the transactivation of the expression of genes coding for products functioning in induction of cell cycle arrest and attempt at DNA repair (Thomas et al., 1999).

The P72R polymorphism is very common in virtually all populations, although its distribution exhibits a distinctive South-to-North cline, with the Pro allele being more common (60-70 %) in areas close to the Earth's equator and the Arg allele being more prevalent in the North (where it constitutes 70-80 % of all alleles) (Sergentanis & Economopoulos, 2010).

Carriership of the one or the other allele of the P72R polymorphism may be associated with advantages as well as disadvantages, depending on the age of the individual, its health status and when affected by disease, by the disease type.

Individuals with Pro/Pro homozygous genotype may live several years longer than individuals carrying at least one Arg allele. The effect becomes significant in the age group over 85 (Donehower et al., 2005; Ørsted et al., 2007). The Pro/Pro homozygotes, however, have >2-fold increased risk for cancer compared to Arg allele carriers (Donehower et al., 2005). The latter may mean that the increased life expectancy in this group is secondary to improved survival after diagnosis of cancer. Cells carrying the Pro allele are more prone to 'error accumulation' than the cells carrying Arg alleles. Therefore, the Arg allele carrier cells may be routed to apoptosis in the presence of even minor damage, rather than attempt to repair it, whereas the Pro allele carrier cells may try repairing the damage first, which is associated with increased risk for introduction of errors in DNA.

Carriership of the P72R polymorphism may modify phenotypes that are defined exclusively by other genetic factors. In individuals with hereditary nonpolypous colorectal cancer (due to carriership of mutations in either MSH2, MLH1 or MSH6 genes) that are concomitant carriers of at least one Arg allele, the first tumours may appear years later than in carriers of two Pro alleles (Krüger et al., 2005). However, carriership of the Arg allele of the Pro72Arg polymorphism is not always a good prognostic factor in cancer. In HPV-associated cancers (carcinoma of the uterine cervix, squamous cell carcinoma of the head and neck) and in some types of non-small cell lung cancer and breast cancer, there is distinct prevalence of Arg alleles (Zehbe et al., 2001; Nelson et al., 2005; Smith et al., 2011; Mitra et al., 2007). It has been shown that tumours from patients with heterozygous Pro/Arg genotype in their normal somatic cells may physically delete the TP53 loci containing the Pro allele and retain the Arg alleles (Burroni et al., 2013). The latter are likely to be converted to cancer-specific p53 isoforms later, with presence of cancer-specific p53 being always a poor prognostic factor.

Effects of carriership of the two variants of the TP53 Pro72Arg on susceptibility to cancer may be dependent on age. It has been shown that the proline variant of TP53 may be associated with increased risk for lung carcinoma developing in age >60 whereas the arginine variant was more common in patients with the same type of cancer who were below 60 years of age (Cherdyntseva et al., 2010).

Carriership of the TP53 P72R polymorphism may be associated with other diseases and conditions with late onset. Carriership of at least one Arg allele may be associated with increased risk for diabetes type 2 (Burgdorf et al., 2011). It may also modify the disease phenotype. The insulin resistance coefficient (HOMA-IR) in Pro/Pro homozygotes with diabetes type 2 is generally lower than in patients with Arg-allele containing genotypes (Bonfigli et al., 2013). These effects may be related to the increased propensity for apoptosis on the beta-cells of the pancreas carrying the Arg allele under conditions of increased oxidative stress due to prolonged hyperglycemia.

2.2. ins83 polymorphism in the XPC gene

XPC is one of a pair of proteins that function together as a dimer (XPC-hHR23B) in the recognition of DNA damage occurring in untranscribed genomic regions. The need for a designated mechanism functioning specifically in untranscribed DNA arises from several specificities of DNA damage detection and repair in eukaryotic cells. Most cells tend to prioritise DNA repair in different parts of the genome, with transcribed DNA being repaired at higher rates than untranscribed DNA (Mellon et al., 1986). Untranscribed DNA makes up for the larger portion of genomic DNA at any given moment. The presence of an RNA polymerase II stalled at a lesion site is a sufficient signal for summoning the cell machinery for repair in a transcribed gene (Ljungman & Lane, 2004), whereas damage in untranscribed portions of the genome must 'wait' until the machinery for repair gets to it in its own time. Thus, the risk for occurrence of errors in untranscribed DNA is always

higher than in transcribed DNA. After many years and, potentially, many cells' divisions, accumulation of such errors may trigger neoplastic growth. Thus, it is not unexpected that carriership of polymorphisms in the XPC gene is associated primarily with increased risk for cancer. The polymorphism in intron 9 of the XPC gene known as XPCins83 was discovered first and is, respectively, best studied. The XPCins83 polymorphism is actually a bipartite alteration in DNA, made of an insertion of 83 bp coupled with a deletion of 5 bp, both occurring in the same intron of the gene (Khan et al., 2000).

The insertion allele of the XPCins83 polymorphism confers slightly lower capacity for detection and repair of DNA damage than the average for the age-matched healthy population. Carriership of the insertion allele has been associated with increased risk (1.5 0-2-fold) for cervical cancer, lung cancer, melanoma, and other types of cancer (Blankenburg et al., 2005; Lee et al., 2005; Kietthubthew et al., 2006). These risks are modifiable by other factors, including environmental factors (e.g. smoking) (Lee et al., 2005; Qiu et al., 2008).

2.3. Lys751Gln (rs13181) polymorphism in the XPD gene

The XPD gene codes for one of the two ATP-dependent helicases that unwind the double helix of DNA in the vicinity of damage sites in order to facilitate the access to the cell machinery for repair by excision. XPD Lys751Gln is an A-to-C transversion in exon 23 of the XPD gene resulting in lysine-to-glutamine substitution in position 751 in the protein (Sturgis et al., 2002). Carriership is associated with increased risk for several types of cancer - carcinoma of the colon and rectum, of the female breast, of the lung and the prostate gland (Sturgis et al., 2002; López-Cima et al., 2007; Mandal et al., 2010). These risks are modifiable by environmental factors. For example, the risk for lung cancer in carriers of XPD gene polymorphism is specifically significant in smokers and individuals who are habitually exposed to fuel fumes and hot oil fumes (e.g. during cooking) (Sturgis et al., 2002; Yin et al., 2009).

Carriership of the XPD Lys751Gln polymorphism is one of the several polymorphisms in genes coding for proteins of DNA damage identification and repair that confer increased risk for common late-onset diseases other than cancer, such as senile cataract (Unal et al., 2007; Padma et al., 2011).

2.4. A8092C (rs3212986) polymorphism in the ERCC1 gene

The ERCC1 gene codes for one of the subunits of the enzymatic complex ERCC1-XPF that makes the 5'-incision in damaged DNA in nucleotide excision repair. The A8092C substitution occurs in the 3'-untranslated region of the gene. The C allele is associated with lower stability of the transcript and, respectively, with lower levels of ERCC1 mRNA and protein (Woelfelschneider et al., 2008). Low or undetectable levels of ERCC1 expression in some tumours are usually associated with decreased risk for development of resistance with adduct-forming agents (e.g. platinum derivatives) and improved overall survival (Olaussen et al., 2006; Bauman et al., 2013). Respectively, increased levels of ERCC1 expression

may be associated with increased rates of repair of iatrogenically induced adducts in DNA and decreased sensitivity of the tumour to genotoxic treatments.

The A allele of the ERCC1 A8092C polymorphism (associated with normal transcript stability) was found to be associated with shortened survival in patients with non-small cell lung cancer and colorectal cancer treated with platinum-based chemotherapy, compared to homozygous carriers of the C allele (Park et al., 2003; Zhou et al., 2004). The effect was apparently dose-dependent (differential in carriers of one or two copies of the variant allele) (Takenaka et al., 2010).

For ERCC1 A8092C, radically different effects of the same polymorphism may be reported in different populations. For example, the above mentioned A allele of the A8092C polymorphism was reported by some authors as being associated with increases in the survival rates in patients with non-small cell lung cancer treated with platinum agents (Kalikaki et al., 2009). However, even when the effects were reported as opposite in different reports, they seemed to be consistent within studied populations. Therefore, it is likely that the reported differences reflected intra-population variance.

Carriership of the A8092C polymorphism of ERCC1 gene may be associated with increased risk for adult glioma and head and neck cancers (Chen et al., 2000; Sturgis et al., 2002; Yin et al., 2009).

Carriers of the variant alleles of ERCC1 A8092C, as well as the already mentioned XPD Lys751Gly may be increased risk for high-grade mucocutaneous and haematological toxicity in the course of anticancer therapies because of the decreased capacity of the healthy cells in the body to repair the damage inflicted by genotoxic agents (Chang-Claude et al., 2005; Sakano et al., 2010).

2.5. Arg399Gln (rs25487) polymorphism in the XRCC1 gene

XRCC1 functions as a stabilising factor of ligase III, which is the major ligase of base excision repair and repair of single-strand breaks in DNA. One of the most common polymorphisms in XRCC1 is the A-to-G transition in exon 10 of the XRCC1 gene, resulting in arginine-to-glutamine substitution in position 399 in the XRCC1 protein.

Carriership of the variant allele of the XRCC1 Arg399Gln polymorphism is associated with increased risk for colorectal carcinoma and lung cancer (Skjelbred et al., 2006; Hou et al., 2003; López-Cima et al., 2007), as well as late-onset diseases other than cancer. This polymorphism is one of the few that may deploy their effects more potently when carried in heterozygous state rather than in homozygous state. Heterozygous carriership of the XRCC1 Arg399Gln polymorphism is a genetic factor associated with increased risk for senile cataract (Padma et al., 2011). Arg399Gln polymorphism is also associated with susceptibility to endometriosis (Hsieh et al., 2012).

Polymorphisms in genes coding for different proteins functioning in DNA damage repair/maintenance of genomic integrity may have effects on other gene loci, also related to maintenance of genome integrity. For example, carriership of

the variant allele of the XRCC1 Arg399Gln polymorphism and polymorphisms at the XPD locus may be associated with increased rates of mutagenesis at the TP53 locus and emergence of cancer-related p53 isoforms (Gao et al., 2003; Hou et al., 2003). These risks are, once again, modifiable by environmental factors. For example, in patients with non-small cell lung cancer that have never smoked, the risk for mutagenesis at the TP53 locus conferred by carriership of polymorphisms in the XPD gene is negligibly low (Gao et al., 2006).

2.6.Thr241Met (rs861539) polymorphism in the XRCC3 gene

XRCC3 gene codes for a protein that is part of the complex XRCC2/XRCC3/RAD51 ensuring the uneventful migration of the cruciform structure and the successful resolution of the recombinant molecules in double-strand break repair by homologous recombination.

The C-to-T transition in exon 7 of the XRCC3 gene results in a substitution of threonine to methionine in position 241 in the XRCC3 protein (Thr241Met). Carriership of the variant allele may be associated with increased risk for head and neck tumours and cancer of the mammary (Santos et al., 2010; Wang et al., 2013).

Carriers of the XRCC3 Thr241Met polymorphism and the already mentioned XRCC1 Arg399Gln may be more likely to develop subcutaneous fibrosis and telangiectasias after transcutaneous radiotherapy (Andreassen et al., 2003).

Carriership of some of the polymorphisms in genes coding for proteins of DNA repair and maintenance of genome integrity may decrease overall genomic stability.

The XRCC3 Thr241Met polymorphism as well as XPD Lys751Gln and XRCC1 Arg399Gln polymorphisms results in increased levels of DNA breakage and increased rates of occurrence of chromosomal aberrations in cultured human lymphocytes (Vodicka et al., 2004).

2.7. C677T (rs1801133) polymorphism in the MTHFR gene

5,10- methylene tetrahydrofolate reductase (MTHFR) is a key enzyme of the folate metabolism, functioning in the biosynthesis of amino acids (specifically, methionine) and nucleotide precursors (thymidine monophosphate). The transition of C-to-T in the exon 4 of the MTHFR gene results in lower enzymatic activity of the protein (Frosst et al., 1995). The T allele is very common worldwide, with the prevalence of homozygotes by the T allele up to 30 % in selected populations (Wilcken et al., 2003). Because of the latter, MTFHR C677T is nowadays classified as a polymorphism rather than a mutation.

MTHFR C677T is best known as a marker for cardiovascular risk. Homozygous carriership of the T variant allele is associated with increased risk for venous thromboembolism and vascular disease (Frosst et al., 1995; Schneider et al., 1998; Den Heijer, 2005).

Carriership of the MTHFR 677T allele is associated with a several-fold increase of the risk for colorectal carcinoma and carcinoma of the upper gastrointestinal tract (Sarbia et al., 2005; Izmirli et al., 2013). This risk pertains

mainly to homozygotes by the T allele. At the same time, cancer cells with TT homozygous genotype may be more sensitive to some 'classic' anticancer agents who work by interference with nucleotide synthesis (antimetabolites) - methotrexate, 5-fluorouracil, pemetrexed, etc. (Sohn et al., 2004; Toffoli & De Mattia, 2008).

Carriership of the C677T substitution may be associated with disordered genomic methylation and misincorporation of uracil into DNA (Sohn et al., 2009). The effect of the carriership of the polymorphism, however, only becomes significant in conditions of folate deficiency.

As the TT genotype has very high prevalence, it is commonly seen in compound genotypes with other polymorphisms in the genes coding for proteins of DNA repair and maintenance of genomic integrity.

Each and every one of the different genetic factors that makes up the individual capacity for maintenance of genomic integrity has but a subtle effect. Nevertheless, most of these polymorphisms are very common and may group and regroup in many different combinations. The resultant phenotypes may be very dissimilar in different patients, as the effects conferred by different polymorphisms are modulated by other genetic factors and factors of the environment. Some of these polymorphisms may act synergistically. For example, carriership of polymorphisms that confer 'lower-than-average' capacity for detection and repair of DNA damage coupled with carriership of the pro-apoptotic allele of the TP53 gene may cause accelerated tissue ageing under conditions of increased genotoxic stress (Chelenkova et al., 2014).

3. Potential applications of the knowledge about the individual capacity for maintenance of genomic integrity - from the lab benchtop to the patient's bedside

Objective data about individual capacity for maintenance of genomic integrity may, potentially, become useful in the assessment of individual risks for development of various common diseases with late onset. It may facilitate prognostication about the course of the disease and its complications, so that pre-emptive action could be taken. Nevertheless, at present, our knowledge in the field of individual capacity for maintenance of genomic integrity is still largely based of phenomenology, and its potential for practical applications is still limited.

It is not uncommon for the specialists in the field to hear the question "Suppose we know how our own individual capacity for repair is shaped up. What can we do to improve our health?" At this moment in time, it may be challenging to answer this question with any degree of reliability. On the one hand, considering the major risk factors from the genetic background and the environment, there are several things that may be beneficial in the long run - e.g. wearing UV protection when going out in the sun; quitting (or never starting) smoking and taking measures to minimise the risk for infection with human papillomavirus. These

recommendations, however, are very unspecific, as they may do well to almost everyone, regardless of their skin colour, sex or age by decreasing the overall risk, but may have no measurable effect in a potential decrease of individual risk.

We are still far away from being able to create a reliable individualised risk assessment for common diseases or a list of recommendations that may reduce the risk for their development, delay the age of onset or ameliorate their course when they finally became manifest. This is still a matter of the future, but the bases have already been laid. Future studies of the role of DNA polymorphisms in the maintenance of genomic integrity in health and disease may benefit from approaches based on integration of knowledge...

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