The cell ancestral line - personalizing the sub-telomere profile through generations as a translatable cancer hypothesis

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Abstract

Cellular diversity and heterogeneity are the highlights of evolution through pedigrees, and bridging insight could translate these definitions to the applicable elements. Amongst these, subtelomeres, as the gift provided by nature; they are the sensitive and reliable destination for "personalizing" (customizing) parts of the genomic make-up. The personalized subtelomeric profile may be considered as a translatable cancer hypothesis.

Introduction

Since the discovery of the cell, many valuable facts and insights have been provided in different living populations (including man), making the cell the centre of life. But, the pedigree would promote the fate of traits through inheritance. Findings in pre-cytogenetic-, classic-, and modern-eras could unmask the facts by cytogenetic and/or molecular techniques, and the rapid progression in technology has uncovered much in recent years. But, there are many unknown characteristics of cells that need to be discovered.

Theodor Boveri in 1914 referred to "an inhibitory mechanism in every normal cell" that influences cell division, the inhibitor probably residing in the chromosomes as the original base (1). The clonal aspects of chromosomal aberrations in cancer were subsequently published (2,3). The effect of chromosomal alterations on tumour formation and progression were elucidated by Yusida (4). It took another 40 years for the key facts about clonal diversity occurred through tumour progression emerged (5). In the interium, karyotypic evolution in a tumor was described (5,6). Collectively, this golden period of about 60 years has unmasked many basic facts about chromosomes.

The fundamental genetic makeup of specific cells is relatively same, and they have normal traits in common, but the neoplastic cells reflects diversity in the "required-acquired nature" of some genes, which could be *de novo* or inherited from their ancestral lines (7).In addition, the known traits at the genomics level could be easily detected through the pedigrees; amongst these the subtelomeres seem to be the traceable cellular target.

The initial roles and location of telomeres, as capping of the chromosomal termini, was discovered by Muller (8, 9). Forty years later, the restricting and regulating capacities of telomeres on chromosomal

ends and cell replication was stated **(**10), and importantly, the heterogenic nature of telomere length (TL) in human chromosomes was also reported (11). Beyond this region, human subtelomeres (ST), as the neighbouring region of telomeres, are characterized with mosaic duplicon patchworks (12-14). This alteration seems have originated from terminal chromosome translocations (15), and is influenced by sister chromatid exchanges (16).

Subtelomeres interact with telomeres, other molecular and cellular targets. Subtelomeric sequences locate at proximal sites of the telomeric complex repeats. In addition, the complex nature of telomeres is involved in forming the characteristics of the subtelomeric evolution; so diversity of genes located in this region would be clarified (17-19).

There are further facts about subtelomeres, summarized as follows:

1. As far as a developmental event is concerned, there are subterminal sequences at the ends of different chromosomes with diverse hybridization model at somatic levels as in germ-line territory.

2. Human germline subterminal DNA seems to be epigenetically hypomethylated (20).
3. The human subtelomeric district harbors the mosaic duplicons patchworks (21-23).
4. This change is as the result of the terminal chromosome translocations (15).

5. Telomere and the sequences at the subterminal region are predisposed to the sister chromatid exchanges DNA breakage and repair system (16).

6. All these facts could lead to the genomic evolution.

Interestingly, telomere and subterminal sequences are both predisposed to sister chromatid exchanges **(**16). The essence of health relies on the ratio of mitotic cells/apoptotic cells, which defines the status of life, with or without health (24). Furthermore, we have described the novel evolutionary models given by the Periodic Charts in p- and q-individual chromosomes of auxiliary lymph node and buccal cells (25). Cellular structure and function reflect some part of the body machinery, and a reasonable normal health status requires the harmonic behaviour of group of cells (tissues) to provide the crucial and specific fundamental requirements for the body.

However, these findings could define the subtelomeres as an evolutionary genomic territory. As a supportive and complementary insight, pedigree-based research could lead to identification of an ancestral line for a specific cell. By considering the evolution and cellular heterogeneity of the subtelomeric profile, our aim here has been to initiate the human genomic cell pedigree and compare neoplastic cells within a cancer-prone pedigree.

By relying on cellular discipline, alteration in subtelomeric behaviour could influence the machinery of aging and cancer. However, as a hypothetical statement, the degree of behaviour and the nature of evolution also depend on the initial and diverse role of different cellular clones.

The data and discussion

To clarify the flow of data through pedigree, ST- signal copy number (SCN) of chromosome 1 was assayed in lymphocytes as an accessible biologic material within three generations Figure 1). The number of cells in the population analyzed ranged between 534 and 1075.

It is essential to narrow and specify the analysis to the cellular level and evaluate individual chromosomes for subtelomeric region. This would clarify the cellular heterogeneity. Let us take a couple including a man affected with Hodgkin disease at the age of 69 (generation II/1) and woman with breast cancer at 38 (generation II/2), as shown in Figure 1. Within this pedigree, a daughter is affected with breast cancer at the age of 33 (generation III/1) and her sister is apparently healthy (at 26). There is a great concern regarding the fate of the healthy sister and her offspring of being prone to cancer in future.

The mean subtelomeric signal status is diverse in the p- and q- arms of chromosome 1 for 1-3 signal copy number (SCN) and lacking any signal ($p < 0.01$). There are gold standard tools in cancer diagnosis, but these have come rather late. Therefore, an early strategy is essential to trace the cell(s) in which the events are accessible, sensitive, reliable and traceable. Amongst those subtelomere (ST) signals, profiling could provide an array signature at genomics level as early as possible with a translational impact. Such informative array could be screened through pedigree and puzzle the status of signal copy number (SCN), together with the signal intensity, as quantitative and qualitative values in cancer, as also apparently in normal individuals (Figure 1). With such a ST signature, collectively the cellular pedigree could be applied as a personalized strategy for both cancer patients and their healthy relatives for early management.

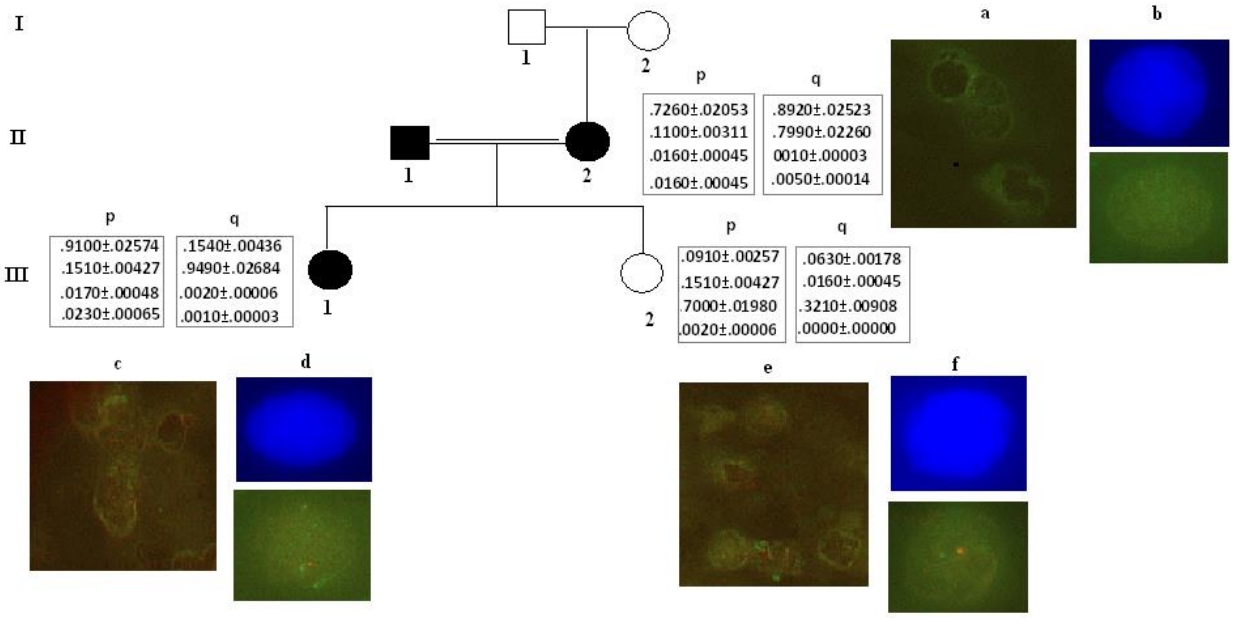

Figure 1. Pedigree of a cancer-prone family based on genomic subtelomeric signal copy number

The parents (generation II/1 and 2) are 3rd degree relatives, as 2nd maternal cousins.
SCN: Signal Copy Number
II/1: is affected with Hodgkin's lymphoma at age of 50.
II/2: is affected with breast cancer at age of 38.
III/1: is affected with breast cancer at age of 32.
III/2: is unaffected so far (26 years old).
Left boxes indicate mean subteleomeric SCN for the p-arm of chromosome 1.
Right boxes indicate mean subteleomeric SCN for the q-arm of chromosome 1.

The subtelomeric SCN include: row 1 - lacking SCN; row 2 - 1 SCN; row 3 - 2 SCN (as normal); and row 4 - reflects 3 SCN.
Boxes are accompanied by merged image of subtelomeric signal statue:
Green signals are of the p-arm, conjugated with FITC. x400 magnification.
Red signals are of the q-arm, conjugated with Pe-cy5. x400 magnification.
II/2: a) Cells at x4000 conjugated with FITC and Pe-cy5; b) An example cell at x1000 magnification (a-top: with dapi; a-down: same cell conjugated with FITC and Pe-cy5).

III/1: c) Cells at x4000 magnification indicative of diversity in SCN of 2 chromosomal arms; d) One example cell at x1000 magnification indicating the presence of 2 normal signals for p- and q- arms (d-top: with dapi; d-down: conjugated with FITC and Pe-cy5);
III/2: e) Cells at x4000 magnification indicative of the diversity in SCN of 2 chromosomal arms;
f) One example cell with x1000 magnification indicative of the presence of 2 normal signals for p- and q- arms (f-top: with dapi; f-down: conjugated with FITC and Pe-cy5.
These images have been adapted from the Mehdipour archive (26).

By comparing p- and q- arms between different individuals, the specific informative data is remarkable, and is indicative of cellular heterogeneity. The parental line affects the ancestral cells (Figure 1); individual II/ 2 has a dominant p-arm ST-SCN with very low signal intensity. The inheritance of basic ST territory from individuals II/1 and II/2 with aberrant genomic makeup may be inherited by the next generation. Besides, ST with close cooperation with telomeres could also affect aging. In this case, the nature of the ST signature could reflect diverse behaviour at different ages. At the initial point, and by considering these facts, the genomic cells of individual III/2 need to be screened.

According to the mean distribution of ST-SCN, diversity is remarkable among the p- and q- arms of chromosome 1 in individuals II/2, III/1, and II/2, through 2 generations of this pedigree (Figure 1). The cells of II/2 reflect very weak or lack of p- and q-arm signals, respectively. Cells of III/1 harbor dominant SCN for the q-arm and different categories of SCN for the p-arm. The cells of III/2 reflect more harmonic SCN of both chromosomal arms, but the minor clone with lack of SCN can still be seen and considered as a warning message. Interestingly, the q-arm is more prominent in generation 3 than p-arm, which is just a matter of cell-based personalized ST characteristics in this specific pedigree, and is required to be defined in different pedigrees.

The mean SCN confirms the diverse ST behavior between p- and q-arm. The mean for lack of SCN, presence of one- and three- SCN in the lymphocytes of III/2 is a wake-up call for early managing. Collectively, the target individuals through 2 generations have a ST- profile in common, which is mainly an affected p-arm, but with diverse degrees of SCN and signal intensity.

In fact, the parents of individual II/2 are unaffected, but the parents of II/1 and II/2 are both affected with cancer, which gives a more complicated genetic makeup through inheritance. Furthermore, the age of these individual, the impact of environmental factors and style of life between the 3 generations are noticeable elements. A personalized evolutionary hypothesis on subtelomeric signal profile - at both the genomic and somatic levels of a patient affected with breast cancer – has already been published by our group (19). Evolution and diversity in p- and q- arms of chromosomes is reflective of novel findings in 2 domains in a personalized manner. We argue here that ST array profiles are characterized as a personalized pattern in breast neoplasm, which could be translated to the clinic as a potential predictive factor (26). Moreover, interactions between the ST profile and other cellular/molecular targets, specifically with telomere length, are also remarkable. These facts lead to personalized subtelomeric-based insight through cellular pedigree.

In conclusion, multidisciplinary insight is essential in world of cancer, and bridging cellular aspects to their potential clinic applications can (at least partially) solve some the current problems. Such an approach would be led to an early personalized approach.

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