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Chromosomal aberrations in prostate cancer

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1. ABSTRACT

Prostate cancer incidence is steadily increasing in Western industrialized countries where it has become the most common male malignancy and second most common cause of cancer death among men. Despite efforts to understand the mechanisms of prostate cancer development and progression, the reasons for the disease remain unclear. Although recurrent DNA copy number aberrations in prostate cancer have been well documented in the past 15 years, most of the target genes for these aberrations remain to be identified. The most common DNA copy number aberrations are losses in chromosomes 5q, 6q, 8p, 10q, 13q, 16q, 17p, and 18q, and gains in 7p/q, 8q, 9p, and Xq. In addition, a chromosomal rearrangement in 21q has been observed in over 50% of prostate cancers. The target genes for two common chromosomal aberrations have been identified: the androgen receptor (*AR*) gene at Xq12, and *TMPRSS2* and *ERG* at 21q. Putative target genes for other copy number aberrations include: *NKX3-1* (8p loss), *PTEN* and *MXI1* (10q loss), *FOXO1A* (13q loss), *CDH1* and *ATBF1* (16q loss), *MCM7* and *EZH2* (7q gain), *TCEB1*, *EIF3S3* and *MYC* (8q gain). The identification of target genes for the chromosomal aberrations will provide new prognostic markers and therapeutic targets for future drug development.

2. INTRODUCTION

Prostate cancer is the most common male malignancy in the Western industrialized countries, including Finland, and its age-adjusted incidence is still increasing (1). The steady increase cannot be accounted for by improved diagnostics alone, and the reasons for it remain, for the most part, unknown. Prostate cancer afflicts predominantly old men. The mean age at diagnosis is around 70 years and the late onset of the disease, often combined with a slow rate of progression, results in most patients dying of other causes before the cancer progresses to a fatal stage. Nevertheless, about 20% of prostate cancer patients die of their cancer, regardless of treatment (1).

Already in the beginning of the 20th century Theodor Boveri suspected that aberrant mitoses, which lead to aneuploidy, may be a cause of cancer (2). Since then it has been shown that chromosomal instability is a common phenomenon in cancer (3). Because prostate cancer is an inherently heterogeneous disease, a single genetic aberration responsible for most of the cases has not been found.

2. DNA COPY NUMBER ABERRATIONS

Most of our knowledge of DNA copy number aberrations in prostate cancer has been obtained by loss of

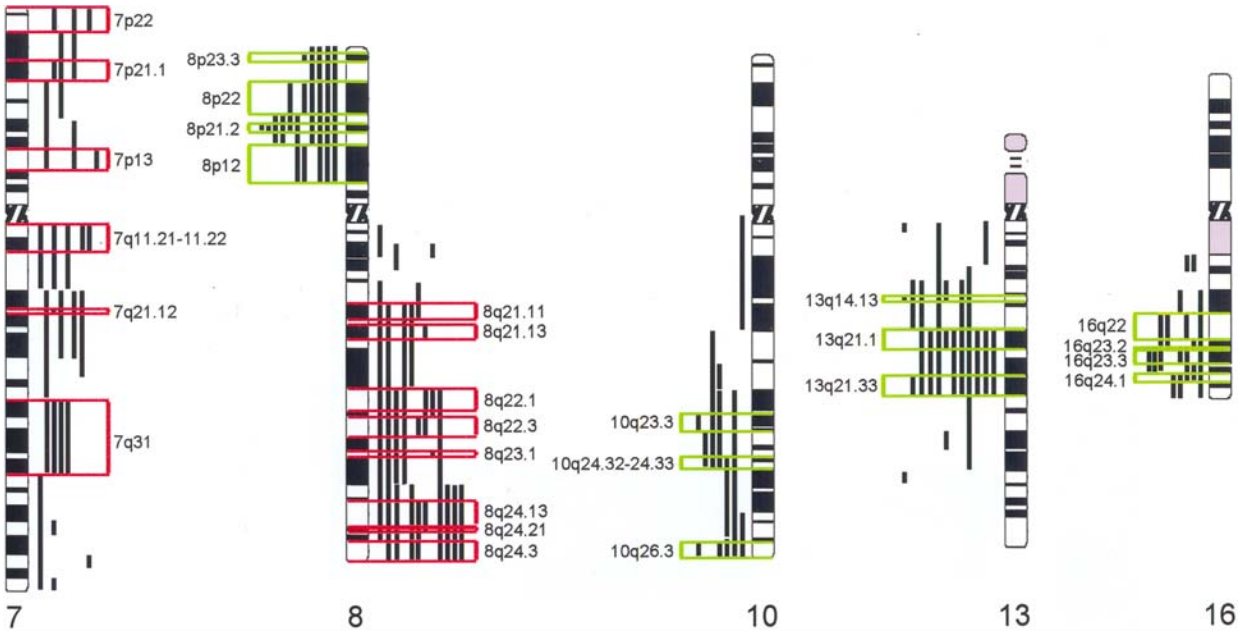

Figure 1. The minimal common regions of DNA copy number aberrations from selected chromosomes according to references 23-27, 34, 37-38, 43-44, 86, 98, and 147-148. The bars on the left of the ideograms represent minimal regions of loss identified by the individual studies and the bars on the right represent minimal regions of gains. The red and green bars represent minimal common regions of the minimal regions of loss and gain, respectively.

heterozygosity analysis (LOH), comparative genomic hybridization (CGH), and microarray based CGH (aCGH). Classical cytogenetic analyses of prostate tumors are difficult due to problems in obtaining good-quality metaphases for karyotypic analysis. Despite this, classical cytogenetics has been able to identify, for example, frequent losses in 8p and 10q (4).

LOH, a polymorphism-based method that requires normal and tumor DNA from the same patient, has been widely used to detect losses of polymorphic DNA sequences. LOH data cannot always be interpreted as physical copy number losses, since the remaining allele may be duplicated after the loss of the first allele (5, 6, 7). Nonetheless, LOH analyses have been helpful in determining regions of allelic loss in prostate cancer**.**

Before the invention of CGH, first described in 1992 by Kallioniemi *et al*., (8) knowledge of the genomic composition of solid tumors was scarce. CGH eliminated the need for metaphases of tumor cells and allowed the identification of copy number alterations from a relatively small amount of tumor DNA. Unfortunately, CGH has a limited resolution of about 5–10Mb (8, 9). aCGH was first introduced by Solinas-Toldo *et al*., (10) and since then, the variety of platforms has been widened to include BAC/PAC/cosmid arrays, cDNA microarrays, oligo arrays, and SNP arrays (10, 11, 12, 13, 14, 15, 16, 17). The resolution of aCGH depends on the genomic distribution, size, and number of the features on the array. Sub-megabase resolution has been reached with a tiling resolution DNA microarray constructed of over 30,000 overlapping BAC clones (18), and even higher resolution may be possible within a few years with oligo arrays.

Other genomewide tools to analyze chromosomal alterations are multiplex fluorescence *in situ* hybridization (M-FISH) and spectral karyotyping (SKY), which enable the simultaneous identification of copy number changes and translocations between chromosomes (19, 20, 21). These methods are also reliant on metaphases, and cannot therefore be readily used to study clinical prostate cancers. However, M-FISH and SKY are useful in studying cell lines. SKY analysis has revealed, for example, recurrent breakpoints in chromosome arms 5q11, 8p11, and 10q22 in prostate cancer cell lines (22).

3.1. Common aberrations

Chromosomal copy number aberrations in prostate cancer have been identified by numerous CGH studies since the mid-1990s, and corroborated by aCGH studies in the past 5 years. The most common chromosomal alterations found by CGH and aCGH in early stage clinical prostate cancer are losses in 5q, 6q, 8p, 13q, 16q, 17p, and 18q, and gains of 7p/q and 8q. These are found in 10–50% of untreated primary prostate cancers and to some extent in pre-malignant lesions, such as high-grade prostatic intraepithelial neoplasia (HGPIN) (23, 24, 25, 26, 27, 28, 29, 30). The minimal regions of some of the alterations have been defined by LOH and aCGH studies and include, for example, 8q21.13, 8q22.1, 8q22.2–3, 8q24.13, 8q24.21, 13q14, 13q21–22, 13q33, 16q21.1, and 16q24.3 (31, 32, 33, 34, 35, 36). Figure 1. depicts some of the minimal regions identified.

The superior resolution of aCGH compared to CGH has enabled the identification of smaller regions of copy number alterations, as has been demonstrated by

comparing the aCGH profiles of prostate tumors, xenografts and cell lines to CGH profiles of the same samples (27, 37, 38). On the whole, the findings have been about 90% concordant, although the aCGH has found more small aberrations than CGH. High-resolution aCGH analyses of chromosome arms 8q, 10q, and 16q have confirmed and refined the frequent copy number aberrations (CNAs) at these locations (Fig 1.) (34, 35, 36). aCGH has also identified novel recurrent copy number aberrations, for example gains of 2p25, 9p13-21, 11p15.4, 16p13.3 and 16p12.2-p11.2 (28, 37, 38).

As prostate cancer progresses to hormone-refractory disease and/or spreads to lymph nodes or distant organs, chromosomal aberrations become more abundant and additional recurrent aberrations appear. In addition to the alterations found already at early stages of the disease, losses in 10q, 15q, 17p, 19p/q, and 22q, as well as gains in 1q, 3q, and Xq are frequently found in locally recurrent hormone-refractory prostate cancer (23, 24, 26). Untreated lymph node metastases contain aberrations frequently in more or less the same regions as the locally recurrent hormone-refractory tumors, although the gain in Xq appears to be specific to hormone-refractory disease (23, 39).

The heterogeneity of prostate cancer has been addressed by comparing aCGH profiles of paired Gleason grade 3 and 4 samples from ten patients with organ confined prostate cancer of Gleason score 7 (29). The samples were not from separate foci, but from large lesions containing areas of differing Gleason grades. Losses were more often shared by the paired samples than gains (46% vs. 13%), indicating that losses occur earlier in prostate cancer development than gains. However, the majority of differences between the Gleason grades were single BAC copy number alterations, which may be due to poor quality hybridization and/or mismapped clones. Nupponen *et al*. (24) have shown that hormone-refractory tumors share a substantial proportion of the copy number alterations with the untreated tumors from the same patients in most cases of prostate cancer. In some cases, however, the hormone-refractory tumors may be derived from a clone that is genetically divergent from the bulk of the untreated primary tumor.

The prostate cancer cell lines and xenografts have been widely used as models for prostate cancer development. The xenografts resemble clinical prostate cancer in terms of chromosomal copy number alterations. Of the cell lines, however, only PC-3 carries the typical aberrations of clinical prostate cancer. Most of these models are derived from metastatic prostate cancer and hence represent advanced stages of the disease (40, 41). Thus it is not surprising that the most commonly found copy number alterations in cell lines and xenografts are the same as for advanced clinical samples (37, 42).

3.1.1. Candidate target genes of losses

Losses are more prevalent in early stage prostate cancer than gains (23, 43, 44). This implies that inactivation of tumor suppressor genes may be more important in prostate cancer initiation than oncogene activation. Attempts to identify target genes have been frustrating as somatic mutations in the remaining alleles have rarely been found. Therefore, it is now believed that haploinsufficiency, where the loss of a single gene copy is enough to cause an altered phenotype, or epigenetics, such as hypermethylation of promoter regions, play significant roles in prostate cancer (45, 46, 47).

3.1.1.1. 8p: *NKX3-1*

The most common chromosomal deletion in prostate cancer is the loss of 8p. This alteration is frequently found already in early stage prostate cancer and also in high-grade prostatic intraepithelial neoplasia (HGPIN) (23, 30). Independent loss of three separate regions in 8p has been identified: 8p23, 8p22, and 8p21.2 (28, 48).

NKX3-1 (NK3 transcription factor related, locus 1 (*Drosophila*), at 8p21.2) is an androgen-regulated homeobox gene that controls the development of the prostate during embryonic development and the differentiation of prostate epithelial cells in adulthood (49). In adults it is expressed mainly in the prostate. The loss of a single copy of *NKX3-1* has been shown to cause prostatic intraepithelial neoplasia (PIN) and dysplasia in mice, and its expression is decreased already in the early stages of disease (50). Further reduction in expression or mislocalisation of the protein happens during cancer progression (51). Haploinsufficiency of *Nkx3-1* has been demonstrated in *Nkx3-1* mutant mice by measuring the expression levels of Nkx3-1 target genes. Some of them were as much deregulated in the heterozygous mutants as they were in the homozygous mutants (52).

Apart from homozygous deletions, inactivating mutations of the *NKX3-1* coding sequence have not been detected in sporadic prostate cancer (53, 54). In hereditary prostate cancer, however, twenty-one germ-line variants of the gene have recently been identified in 159 probands, and some of them were shown to be linked to prostate cancer (55). One of these variants, a rare mutation, was shown to decrease the binding of the protein to its DNA recognition sequence and co-segregate completely with prostate cancer in a family with three affected brothers and one unaffected brother. Although three CpG sites in the promoter region of *NKX3-1* have been shown to be more methylated in cancer cells compared to adjacent normal cells, widespread methylation of the promoter has not been found (56). The expression of NKX3-1 may be regulated post-transcriptionally: protein levels in mice are low despite normal levels of mRNA (57).

3.1.1.2. 10q: *PTEN* and *MXI1*

A pattern of loss of distal 10p, gain of regions around the centromere, and loss of distal 10q (loss – gain – loss) has been identified in CGH and aCGH studies (24, 36, 42). Frequencies based on CGH studies usually range between 10 and 40% (23, 25, 29, 44). aCGH-studies, on the other hand, have consistently reported deletion frequencies around 30% (27, 37, 38).

The most studied candidate target gene for 10q is the *PTEN* (phosphatase and tensin homologue 1) tumor

suppressor gene at 10q23.3. In addition to frequent hemi- and homozygous deletions, mutations of the gene have been reported in aggressive late-stage prostate cancer, making *PTEN* a case of classical tumor suppressor gene (58). *PTEN* is essential in early development, since a double knock-out is embryonic lethal (59, 60). Haploinsufficiency of *PTEN* has been shown to promote prostate cancer progression in mice and shorten their survival (61, 62). *PTEN* is a rare case among putative target genes of chromosomal aberrations as its inactivation is relatively often mediated by homozygous deletion (17, 38, 63). These deletions of parts of 10q around the *PTEN* locus have been detected by aCGH in eleven prostate cancer xenografts and three cell lines (36). In addition to *PTEN* inactivation, *FLJ11218* and *PAPSS2* were significantly down-regulated and inactivating mutations or total loss of the remaining allele were found in *PAPSS2*. These findings suggest that *PTEN* may not be the only target gene of 10q23 deletions.

There is also evidence of independently deleted regions distal to *PTEN*, at 10q25–qter, implying additional tumor suppressor genes on 10q (64). A suggested candidate gene is *MXI1* (MAX interactor 1, isoform b, at 10q25.2), whose product is a transcription factor and an antagonist of *MYC* (v-myc myelocytomatosis viral oncogene homologue [avian]), (65, 66). Inactivating mutations of the remaining *MXI1* gene have been detected in prostate tumors with deletion at 10q24–25 (65). Forced expression of *MXI1* in DU145 has been shown to suppress their proliferation and colony forming potential (67).

3.1.1.3. 13q: *FOXO1A*

Although deletions at 13q are the most common (>60%) chromosomal aberrations in prostate cancer, candidate target genes have not been identified. The *BRCA2* and *RB1* genes at 13q13.1 and 13q14.2, respectively, do not seem to play significant roles in sporadic prostate cancer (68, 69, 70).

The transcription factor *FOXO1A* (forkhead box O1A, at 13q14.11) was recently identified as a candidate target gene for the deletion at 13q, where it was deleted significantly more often than the surrounding genes (71). Decreased expression in 11 of the 15 xenografts was determined by RT-PCR and in cell lines by Northern analysis. Re-introduction of *FOXO1A* into cell lines with reduced expression of the gene resulted in marked reduction of colony-formation. In addition, *FOXO1A* was shown to inhibit AR-signaling. However, the mechanism for the inactivation of the remaining allele does not seem to be either mutation or promoter hypermethylation. Instead, the protein is tightly regulated by the ubiquitine proteasome pathway (72).

3.1.1.4. 16q: *CDH1*, and *ATBF1*

LOH studies have defined at least four independently deleted regions in 16q: at 16q21.1, 16q22.1–22.3, 16q23.2–24.1, and 16q24.3–qter (31, 32, 73, 74). Loss at 16q24.3 is associated with progression of prostate cancer (74). A small deletion in 16q21 and 13 separate regions of frequent loss in 16q22.2–qter have been defined with a high-resolution chromosome 16q specific BAC/PAC/cosmid array of 326 clones from a pre-selected set of 16 samples with deletions in 16q (35). The regions were in agreement with the LOH studies, whose resolution is not as good. Six genes located in these regions – *FOXF1* (forkhead box F1), *MAF* (v-maf musculoaponeurotic fibrosarcoma oncogene homolog [avian]), *MVD* (mevalonate [diphospho] decarboxylase), *WFDC1* (WAP four-disulfide core domain 1), *WWOX* (WW domain containing oxidoreductase), and a predicted transcript *Q9H0B8* (now known as *CRISPLD2*, cysteine-rich secretory protein LCCL domain containing 2) – have also been shown to be consistently down-regulated in cancer compared to matched benign tissue, indicating them as putative tumor suppressor genes (35).

CDH1 (ECAD, E-cadherin) has been suggested as the target gene of 16q22.1. The encoded protein is a cell–cell adhesion molecule and it has been proposed that the gene could be a metastasis suppressor gene (75). Loss of *CDH1* expression is more frequent in advanced prostate cancer than in early stage disease and may contribute to tumor progression, rather than initiation (75). Decreased CDH1 protein expression could also be used as a prognostic marker for prostate cancer progression (76). Somatic mutations in the coding region of the remaining allele have not been detected and contradictory results on aberrant methylation at the promoter region in advanced prostate cancer have been published (73, 77, 78, 79). A polymorphism in the promoter region of *CDH1* has been shown to be associated with increased risk of prostate cancer (80).

The transcription factor *ATBF1* (AT-binding transcription factor 1) is located in a minimal commonly deleted region of about 860kb at 16q22.3 and mutations in it have been found in 24/66 of the samples studied (81). Inhibition of the gene by short interfering RNAs increased cell proliferation in an *ATBF1*-positive cell line and re-expression of the gene in an *ATBF1*-negative cell line decreased colony-forming efficiency. Germline mutations in the gene have been associated with increased risk of sporadic prostate cancer (82). *ATBF1* has been implicated in hepatoma and gastric cancer, and it has been shown to transactivate the CDKN1A cyclin-dependent kinase inhibitor (83, 84).

3.1.2. Candidate target genes of gains and amplifications

Gains or low-level amplifications are found in some of the early prostate cancers and in the majority of advanced prostate cancers. The most common gains, 7p/q and 8q, which are found in approximately 20% and 35% of untreated prostate cancers, respectively, have been found to be effective in predicting eventual progression in prostatectomy-treated patients (25, 85, 86).

High-level amplifications are found mainly in hormone-refractory prostate cancer (25, 26, 42). The most commonly observed amplifications are from the distal 8q (8q23–qter) and proximal Xq (Xq11–13). They are found at frequencies of 73% and 35%, respectively, by CGH (24).

3.1.2.1. 7q: *MCM7* and *EZH2*

Although gain of chromosome 7 is one of the earliest and most frequent genomic alterations in prostate cancer, only a few candidate target genes have been proposed. Several minimal regions of 7q gain have been identified in hormone-refractory prostate carcinoma, including 7q21, 7q31, and 7q36.1 (24, 37). The gain of chromosome 7 has been associated with early progression in radical prostatectomy treated patients (25).

MCM7 (minichromosome maintenance 7, at 7q21.3), was recently shown to be amplified (≥2 times as many copies as centromeres) in 45–50% untreated primary prostate cancers by FISH and quantitative real-time PCR (87). The cancers that were considered aggressive had a significantly higher copy number of *MCM7* than non-aggressive tumors. Overexpression of MCM7 was also shown in most of the tumors with amplification and increased protein levels have been shown to associate with higher tumor stage and Gleason score (87, Laitinen *et al*., unpublished data). MCM7 has been suggested a more accurate marker for proliferation than Ki67, as immunostaining by MCM7 antibodies can be seen not only in proliferating cells, but also in cells that are about to proliferate (88).

MCM7 is a component of the minichromosome maintenance (MCM) complex which binds DNA replication origins and prepares them for initiation of replication (89, 90). MCM proteins are not expressed in fully differentiated cells, which do not proliferate. Cancer cells and pre-malignant cells in the process of transformation, on the other hand, express MCM proteins at high levels, resulting in chromosomal defects. Given the role of *MCM7* in DNA replication licensing, its dysregulation is easy to accept as cancer-causing and -promoting.

We have recently shown that (enhancer of zeste homologue (*Drosophila*) 2) *EZH2* (at 7q36.1) is amplified in about 20% of locally recurrent hormone refractory prostate cancers (91). The 7q36.1 region has also been shown to be a minimal commonly gained or amplified region in 6/18 xenografts and cell lines (37). Expression of the gene is higher in localized prostate cancer and prostate cancer metastasis, as well as locally recurrent hormone-refractory prostate cancer, compared to BPH and normal prostate (91, 92).

EZH2 is essential for proliferation, as inhibition of *EZH2* by siRNA has been shown to result in a marked decrease in proliferation of the human papillomavirus 18-immortalised prostate cell line, RWPE, and PC-3 prostate cancer cells, with cell-cycle arrest in G_2 (92). An association between EZH2 overexpression and increased proliferation rate in prostate cancer has been shown by Bachmann *et al*. (93). EZH2 is a polycomb group protein and the histone methyltransferase component of polycomb repressive complexes 2, 3, and 4 (PRC2/3/4) (94, 95). These complexes play a crucial role in the maintenance of transcriptional repression of *Hox* genes, in X-chromosome inactivation, and in stem cell pluripotency (96). PRC2/3/4 methylate lysine 27, and possibly lysine 9, on histone H3, and lysine 26 on histone H1d (94, 95).

In addition to being overexpressed in (prostate) cancer, the substrate specificity of EZH2 may be altered through PTEN inactivation. PTEN inactivates AKT, which otherwise appears to phosphorylate EZH2, thus decreasing methylation of the primary substrate of EZH2, H3K27 (97). The preferred substrate, if any, of the phosphorylated EZH2, remains unknown. Since phosphorylation of EZH2 does not alter the critical composition of the PRC complex, it may well have targets relevant to tumorigenesis or metastasis.

3.1.2.2. 8q: *TCEB1*, *MYC* and *EIF3S3*

Gain of chromosome arm 8q is the most common copy number increase in prostate cancer and has been associated with poor outcome (23, 25, 86, 98). In many cases, the whole arm is affected, but sometimes smaller gains are observed. Two independent minimal regions of gain in 8q have been identified by CGH in hormone-refractory prostate cancer: 8q21 and 8q23–24 (24). van Duin *et al*. (34) identified five separate minimal regions of frequent copy number increase from 34 prostate cancer samples, including cell lines, xenografts, and clinical samples, with a chromosome 8q-specific array of 702 BACs. Based on previous CGH analysis, most of the samples were known to harbor 8q gains. The minimal regions ranged from 81 to 129Mb in size and were situated in bands 8q21.13, 8q22.1, 8q22.2–22.3, 8q24.13, and 8q24.21. A cDNA-microarray based CGH analysis of 5 cell lines and 13 prostate cancer xenografts identified four minimal regions of frequent copy number gain: 8q13.3-21.11, q22.3, q24.13-24.23 and q24.3 (37). This implies that there are more than one target genes in 8q. Suggested target genes for 8q amplification include *TCEB1* (transcription elongation factor B [SIII], polypeptide 1 [15kDa, elongin C], at 8q21.11), *TPD52* (tumor protein D52, at 8q21.13), *WWP1* (WW domain containing E3 ubiquitin protein ligase, at 8q21.3), *EIF3S3* (eukaryotic translation initiation factor 3, subunit 3, at 8q24.11), *RAD21* (RAD21 homologue [S. pombe], at 8q24.11), *PSCA* (prostate stem cell antigen, at 8q24.3), and *KIAA0196* (at 8q24.13) (99, 100, 101, 102, 103, 104, 105, 106).

TCEB1 (elongin C) has been shown to be gained in 34% of untreated prostate carcinomas and 54% of locally recurrent hormone refractory prostate tumors. In addition, 23% of the hormone refratory tumors had an amplification of the gene. In prostate cancer cell lines with the amplification, the gene has also been shown to overexpressed (99). TCEB1 is a component of the elongin (SIII) complex which activates transcription by RNA polymerase II. It is the regulatory unit of the elongin complex and may form a highly active, albeit relatively unstable complex with elongin A even in the absence of elongin B (107). TCEB1 also binds the Von Hippel-Lindau (VHL) tumor suppressor, and this binding inhibits the VHL from ubiquitinating HIF1A, a transcription factor, which is then stabilized and free to activate its target genes, such as the vascular endothelial growth factor (*VEGF*) (108).

The most obvious candidate target gene for 8q23–24 gain/amplification is the oncogene *MYC* at 8q24.21. MYC is a transcription factor with thousands of known and suspected target genes, including most RNA genes (109, 110). Overexpression of *MYC* has been shown to induce genomic instability, including amplification of some target genes and the gene for MYC itself (111). Expression of human MYC in transgenic mice has been shown to lead to murine PIN and adenocarcinoma in a dose-dependent manner (112). However, *MYC* overexpression has not been detected in clinical human prostate cancer (105).

EIF3S3 was identified as overexpressed by suppression subtractive hybridization in the breast cancer cell line, Sk-Br-3, which contains 8q amplification (104). The study subsequently showed that the gene was amplified and overexpressed in about 30% of hormone-refractory prostate cancers, thus making it a candidate target gene for 8q amplification in prostate cancer. A tissue microarray study has shown that the amplification is associated with advanced stage and Gleason score (113). In a cohort of incidentally found prostate carcinomas, patients with an increased copy number of *EIF3S3* had a statistically significantly shorter disease free survival time.

The protein encoded by *EIF3S3* is the 40kDa subunit of the eukaryotic translation initiation factor 3 (eIF3) which binds to the 40S ribosomal subunit and keeps it from associating inappropriately with the 60S ribosomal subunit. The location and function of EIF3S3 in the complex are not known (114).

Inhibition of *EIF3S3* expression in HeLa cells by siRNA has been shown to lead to cell death upon entry into mitosis (115). In contrast, *EIF3S3* overexpression in 3T3 cells has been shown to increase the proliferation rate and enhance the survival of the cells compared to control cells, although the cells were unable to form colonies in soft agar (116). Inhibition of *EIF3S3* expression by siRNA in cancer cell lines has been shown to reduce their growth rate. Since overexpression of *EIF3S3* does not transform cells, it is more likely to be involved in progression rather than initiation of prostate cancer.

3.1.2.3. Xq: *AR*

Androgen receptor (*AR*) is a nuclear steroid receptor and is expressed in normal and malignant prostate. It mediates the effects of androgens which are essential for normal development of the prostate and the differentiation of secretory epithelial cells. The removal of androgens from circulation (castration) is an effective treatment for prostate cancer (117). Although about 80% of prostate cancers initially regress after androgen withdrawal or antiandrogen treatment, patients eventually relapse and die (118).

The amplification of the *AR* gene at Xq12 is observed in 20–50% of hormone-refractory prostate cancers and it is also overexpressed (119, 120, 121, 122). Amplifications are never seen in hormone-naïve prostate cancer, but gains at the locus are have been detected in about 10% untreated prostate cancer (123). The cancers with *AR* amplification have been shown to respond better to second line maximal androgen blockade than tumors without the amplification, although only for a short period of time (124). The amplification at Xq12 explains the overexpression of *AR* in a subset (*ca* 30%) of hormone-refractory prostate cancers but the reason for the overexpression of the gene in the rest of the cases remains unknown. Mutations in the promoter and untranslated regions (UTR) of the transcript do not seem to play a part in *AR* overexpression (125).

Chen *et al*. (126) have shown that overexpression of AR is necessary and sufficient to restore hormone-refractory growth of androgen-sensitive prostate cancer xenografts derived from hormone-refractory tumours. It was also shown that the hormone-refractory growth is ligand-dependent and requires the nuclear action of AR. These findings may pave the way for new antiandrogen therapies, including blocking the nuclear localisation of the activated receptor. Importantly, the overexpression of *AR* in hormone-refractory clinical prostate cancer has been demonstrated by Linja *et al*. (121)

In addition to amplifications in hormone-refractory prostate cancer, polymorphisms and mutations of the *AR* gene have been found, and some of them have been linked to increased prostate cancer risk or failure of antiandrogen treatment (127). The mutations leading to failure of treatment with antiandrogens are most often located in the ligand-binding domain and alter the ligand-specificity of the protein. The mutant receptors may be stimulated by estradiol, progesterone, adrenal corticosteroids, glucocorticoids, or the antiandrogens flutamide or bicalutamide (128, 129, 130, 131, 132).

3.1.2.4. 9p

We recently described a frequent (>30%) gain at 9p13-q21 in 18 prostate cancer xenografts and cell lines (37). Two minimal regions, one at 9p13.3 and another at 9p13.1-q21, (Figure 2) were identified, and the smaller of the two has been confirmed by FISH. These gains may have been overlooked in CGH studies because they are located at or near the large heterochromatic region in proximal 9q, and such regions are usually omitted from CGH analyses due to difficulties in interpreting repetitive sequences and copy number variations between individuals (133). Also, the samples were mainly of metastatic origin and the gain may be restricted to advanced disease, which has not been extensively studied by aCGH. Indeed, Paris *et al*., (27) detected gains of 9p13 in two out of four metastatic samples and none in 16 primary cancers by aCGH.

No target genes for the amplification have yet been identified. The smaller gain, in 9p13.3, spans only about 3Mb. This stretch of the genome is gene-rich and harbors about 40 known genes and over 10 hypothetical genes or open reading frames. Of the known genes, at least *IL11RA* (interleukin 11 receptor alpha) and *VCP* (valosin containing protein), have been reported as overexpressed in prostate cancer (134, 135). We have also shown that *BAG1*,

Table 1. Common chromosomal aberrations in prostate cancer

Chromosomal region	Frequency (%), untreated prostate cancer	Frequency (%), hormone refractory	Known target(s)	References
Gains/amplifications				
7q	> 15	> 50		17, 23-27, 38, 42-44
8q	> 40	> 70		17, 23-27, 37-39, 42-43, 86, 113
9p13.3		> 30		27, 37
Xq12	< 10	> 30	*AR*	24-26, 42, 119-124
Losses				
8p	> 30	> 60		17, 23-29, 37-39, 42-44
10q	10-30	> 30	*PTEN*	17, 23-27, 36-37, 39, 44
13q	> 30	> 70		17, 23-27, 37-39, 42-43
16q	> 30	> 40		23-27, 37-39, 43-44
17p	> 30	> 40	*TP53*	24-26, 37-39
Rearrangement				
21q	>50	> 50	*TMPRSS2, ERG*	136, 138-140

AR: androgen receptor; *PTEN:* phosphatase and tensin homologue 1; *TP53*: tumor protein p53; *TMPRSS2*: transmembrane protease, serine 2; *ERG*: v-ets erythroblastosis virus E26 oncogene like (avian)

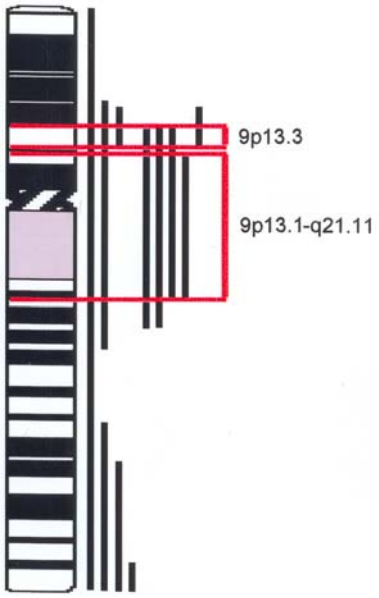

Figure 2. Frequent gain/amplification at 9p13.3 and 9p13.1-q21.11 (37). The minimal regions are shown by the red bars.

which is located slightly telomeric of the minimal common region of gain is amplified in 7% of hormone-refractory prostate cacner and the gene is also overexpressed (Mäki *et al*., unpublished data)

4. CHROMOSOMAL REARRANGEMENTS

To date, three translocations in prostate cancer have been described, all involving ETS transcription factors and *TMPRSS2*. Tomlins *et al*. (136) applied a bioinformatics method, cancer outlier profile analysis (COPA), to ONCOMINE, a cancer microarray database and data-mining platform, to initially identify genes that were overexpressed in a subset of prostate cancer cases instead of the majority of cases. Two related transcription factors, *ERG* (v-ets erythroblastosis virus E26 oncogene like (avian), at 21q22.3) and *ETV1* (ets variant gene 1, at 7p21.2), were found to be substantially overexpressed in a mutually exclusive way in a subset of cases, and ranked in the top 10 outlier genes in 6 out of 10 independent prostate cancer gene expression profiling studies. No consistent amplification of the genes was found in the cell lines and clinical samples overexpressing the genes, so further studies were conducted to see whether the genes were translocated. By exon-walking quantitative PCR, it was determined that the expression of the first exons of both ETS transcription factor genes was diminished compared to the overexpressed later exons, and RLM-RACE (RNA ligase-mediated rapid amplification of cDNA ends) revealed that the later exons of the genes were fused to the untranslated first exon of the *TMPRSS2* gene (transmembrane protease, serine 2, at 21q22.2).

Further confirmation of the translocations was obtained by FISH analysis. *ETV1* was confirmed to be translocated to *TMPRSS2* in 7/29 cases. The *ERG* gene was shown to split in 16/29 cases. Due to the proximity (*ca*. 3Mb) of *ERG* and *TMPRSS2*, the authors did not at this point prove that the FISH signal of *ERG* was translocated specifically to *TMPRSS2*. The translocation of *ERG* or *ETV1* to *TMPRSS2* was nevertheless reported in 79% (23/29) of prostate cancers and the event seems equally frequent in localized and metastatic disease. Another report by Tomlins *et al*. (137), identified a third ETS transcription factor, *ETV4* (at 17q21), as translocated to *TMPRSS2*, but this translocation was only found in one of the 98 prostate cancers studied.

Subsequent studies have confirmed the translocation of *ERG* to *TMPRSS2*, either by FISH or nested RT-PCR-amplification coupled with direct sequencing, in over 50% of prostate cancers (138, 139, 140, 141). It also seems that the fusion is associated with a deletion between the two genes (17, 139, 141).

Several variants of the fusion transcript have been identified. The fusion most commonly involves the first exon of *TMPRSS2* juxtaposed to exon 4 of *ERG* and this variant has been found by all the investigators in at least one sample (136, 137, 139, 140). Single cases of other variants have included as much as exons 1-5 from *TMPRSS2*, joined to exon 2, 3, 4, or 5 of *ERG*. The protein products of these fusion transcripts only include amino acids encoded by the *ERG* gene, as all in-frame translation initiation sites lie within it (138).

TMPRSS2 is androgen-induced and expressed in normal and neoplastic prostate (142) and the translocations render the ETS transcription factors androgen-inducible. Therefore the overexpression of translocated *ERG*, *ETV1* and *ETV4* should be limited to androgen receptor positive prostate cancers. The exact consequences of ETS transcription factor overexpression are not known, but both *ERG* and *ETV1* are known to participate in oncogenic translocations in Ewing's sarcoma and myeloid leukemias (143). ERG has been shown to regulate the expression of genes related to cell proliferation, differentiation, and apoptosis (144).

5. PERSPECTIVE

The most common large chromosomal aberrations in prostate cancer have already been reasonably well identified and some of the important target genes have been recognized (Table 1). As the methodologies to characterize chromosomal aberrations become more and more accurate, it will become easier to identify the true target genes of the copy number aberrations. Bioinformatics approaches, such as the one used to discover the activating translocations of the ETS transcription factors, may be also utilized to identify more recurrent translocations, not only in prostate cancer, but other solid cancers as well.

The identification of target genes of recurrent chromosomal aberrations is important, as it may lead to the development of new therapeutics in the future. Amplified oncogenes and genes activated by chromosomal rearrangement are attractive drug targets and success in targeting such genes has been seen in breast cancer and chronic myelomatous leukemia (145, 146).

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Abbreviations: CNA: Copy number alteration, FISH: fluorescence *in situ* hybridization, CGH: comparative genomic hybridization, aCGH: array-based comparative genomic hybridization, LOH: loss of heterozygosity, BAC: bacterial artificial chromosome

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