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## *Review*

# Chromosome 16q loss– a genetic key to the understanding of breast carcinogenesis

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**Summary.** In the last decade the concepts of breast cancer dedifferentiation and progression have undergone a significant and substantial change. In the past it was widely believed that the detailed associations between genetic and morphological changes defined in the Vogelstein model of colorectal cancer pathogenesis could be transferred to breast carcinogenesis. A multitude of studies seemed to verify this a priori hypothesis. However, with the introduction of global screening techniques, predominantly at the DNA level, it became obvious that this linear model might be oversimplified for breast cancer.

It is now widely accepted that losses of chromosomal 16q characterize in-situ and invasive breast cancer tumours with predominantly low tumour grade and estrogen receptor (ER) positivity (luminal breast cancers). In contrast, high grade breast cancers of the HER2, the basal or the non expressor phenotype with 16q-losses are rarely seen and in consequence a concept of multiple, parallel pathways with defined precursor lesions emerged.

As a consequence, it became obvious that the hunt for oncogenes/tumour suppressor genes in invasive breast cancer is pathway specific. Whereas high grade breast cancers have been relatively well characterized by several recurrent changes in oncogenes/tumour suppressor genes located on various chromosomal regions (e.g. *egfr*, p53, HER2), the characterization of a 16q-specific tumour suppressor gene in ER-positive breast cancer is still a tremendous challenge.

This review will focus on the role of 16q in breast cancer and aims to give insights into actual research efforts, e.g. alternative explanations in order to unravel the central role of 16q in breast cancer.

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### Chromosome 16 in breast cancer

Chromosome 16 belongs to the small group of metacentric chromosomes. It is characterized by large centromeric heterochromatin. Alterations of chromosome 16 belong to the most frequent and most extensively characterized genetic alterations in invasive breast cancer. Two major genetic changes involving chromosome 16 have been described. The loss of the long arm, or at least large parts of 16q, was first demonstrated by classical cytogenetics, and later confirmed by microsatellite analysis and comparative genomic hybridization, but more recently also amplifications of 16p have been described.

The repeated detection of 16q-losses initiated intense research on putative tumour suppressor genes residing on 16q, but so far no convincing single candidate gene or group of candidate genes have been described which would convincingly fulfil the requirements in the sense of the Knudson postulate.

Interestingly, the described clinical significance of 16q-losses varied over time. At first glance this might question the general importance of 16q-losses, but when looking deeper into these contradictory results, the interpretation of 16q-losses seems to be heavily influenced by the varying methods over time (Buerger and Boecker, 2006).

### Chromosome 16q losses in invasive breast cancer

The earliest descriptions of 16q losses were based on G-banding of metaphase chromosomes. The loss of 16q was often, but not exclusively, due to an unbalanced chromosomal translocation t(1;16) (Pandis et al., 1994, 1995; Tsuda et al., 1997; Adeyinka et al., 2003) and was associated with a decreased rate of lymph node

metastases, increased expression of estrogen (ER) and progesterone receptor (PR), low tumour proliferation rate and improved overall survival (Adeyinka et al., 1999, 2003; Tsuda et al., 1999a; Hislop et al., 2002). In a few cases t(1;16) was the sole cytogenetic abnormality (Pandis et al., 1992), underlining the importance of 16q-losses. Since the breakpoint of the recurrent t(1;16) was located in the centromeric heterochromatin of chromosome 16, no specific genetic gene fusion transcript resulted from this chromosomal alteration. It was speculated by Tsuda et al, that hypomethylation of specific chromosomal regions in the pericentromeric regions on 16q could be associated with the pathogenesis of an unbalanced chromosomal translocation t(1;16) (Tsuda et al., 2002). Further studies using fluorescence *in situ* hybridization (FISH) also demonstrated the presence of this chromosomal alteration predominantly in Grade 1 (G1) and Grade 2 (G2) invasive breast cancer cases (Tsuda et al., 1999b). In parallel, loss of heterozygosity analysis (LOH) with microsatellite markers covering the whole 16q-arm narrowed 16q losses down to 3 different shortest regions (SOR) of overlap.

Interestingly, different studies revealed partially different, partially overlapping results (Whitmore et al., 1998; Cleton-Jansen et al., 2001; Callen et al., 2002). Part of these discrepant results might be explained by the limited number of cases that could be analysed by classical cytogenetics, and the limited statements about the overall chromosome 16q-status that can be made by LOH analysis as discussed more extensively below. In line with this, correlations between cytogenetic findings on the one hand and histopathological features and prognosis on the other have varied as well (Tsuda et al., 1994a; Caligo et al., 1998; Hansen et al., 1998). With the introduction of conventional (chromosome) Comparative Genomic Hybridization (CGH) and array CGH that yield a global overview of unbalanced chromosomal alterations in paraffin-embedded tissue, these limitations could be overcome (Ried et al., 1995; Pinkel et al., 1998).

In further studies it could be shown that this grade dependent distribution of 16q-losses was maintained in different invasive carcinomas. Especially tubular, tubulo-lobular, lobular, papillary and ductal invasive grade 1 breast cancers were characterized by 16q-losses, whereas ductal invasive grade 3 carcinomas usually lack this alteration (Buerger et al., 1999a; Roylance et al., 1999; Waldman et al., 2001; Reis-Filho et al., 2005). More detailed studies in ductal invasive grade 3 carcinomas could further show that 16q loss is also very uncommon in HER2-overexpressing/amplified carcinomas (Isola et al., 1999) and in basal, triple-negative breast carcinomas of various subtypes (Korsching et al., 2002, 2005; Reis-Filho et al., 2006; Vincent-Salomon et al., 2007; Lae et al., 2009). In general, 16q loss was associated with prognostically favourable features such as a low proliferation rate, ER/PR expression and axillary lymph node negativity (Zudaire et al., 2002; Farabegoli et al., 2004; Loo et al., 2004; Fang et al., 2011). Noteworthy, even though the background and the biological rationale of these findings are unclear, synchronous multifocal unilateral and bilateral breast cancers also displayed 16q-losses in a significant percentage (Agelopoulos et al., 2003; Ghazani et al., 2007).

The explanation for 16q-losses in grade 3 breast cancers could be twofold. On one hand it might be that this subgroup has evolved from grade 1 through grade 2 carcinomas (Roylance et al., 2006), but could on the other hand reflect cytogenetic instability in different subclones within a tumour. The latter hypothesis is further substantiated by the finding of 16q-losses in poorly-differentiated DCIS and the lack of an identical alteration in the synchronous ipsilateral invasive breast cancer within the same patient (Buerger et al., 2000b).

Noteworthy, the underlying mechanisms of 16q-losses in grade 1 and grade 3 ductal invasive breast cancer cases seem to differ significantly. Several studies showed no differences in the frequency of LOH at 16q between invasive tumours of different histological grade. Combining data from LOH, FISH with chromosome

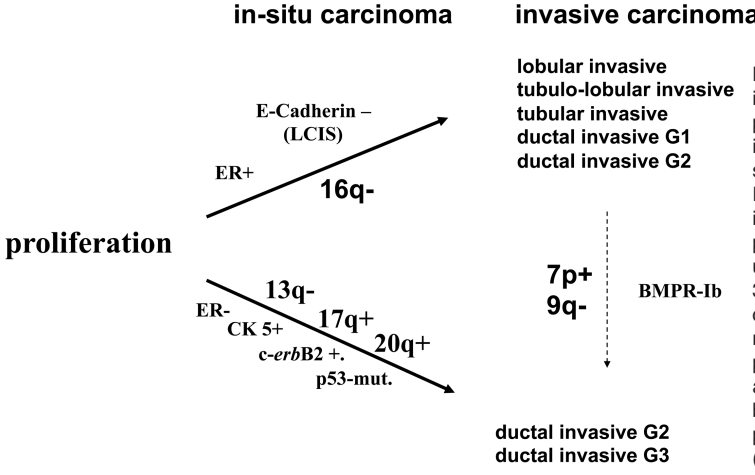


**Fig. 1.** Morphological and cytogenetic progression model of invasive breast cancer and associated *in situ* carcinoma. The presence of multiple, at least two different progression pathways in invasive breast cancer is nowadays undoubted and substantiated by RNA expression profiling (Sorlie et al., 2001). From a genetic point of view the loss of chromosome 16q-material is the most significant distinguisher between these different pathways and is associated with the expression of ER. It seems unlikely that poorly-diffferentiated DCIS/poorly differentiated grade 3 breast cancers generally evolve out of this low-grade pathway due to the distribution of 16q. These are characterized by a multitude of different genetic alterations and protein expression patterns, including c-erbB2 overexpressing breast cancers, as well as the "basal" carcinoma subgroup. For a subgroup of luminal breast cancers a "progression through grade" has been postulated, even though the exact mechanisms remain unclear (Korsching et al., 2004; Helms et al., 2005; Natrajan et al., 2009a).

16–specific probes and CGH, it could be demonstrated that physical losses of chromosome 16q could be preferentially demonstrated in well-differentiated grade I carcinomas, whereas in poorly differentiated grade III tumours, LOH was accompanied by mitotic recombination. These results clarified the discrepancies between CGH and LOH for 16q in breast cancer (Cleton-Jansen et al., 2004) and further point towards the existence of different, independent pathways. More recent studies also revealed that in low-grade carcinomas the whole arm of 16q was usually lost, whereas in less differentiated carcinomas only small parts/regions of the respective arm seem to be lost (Natrajan et al., 2009b).

### Chromosome 16q losses in ductal *in situ* carcinomas of the breast

An important finding was the demonstration of 16q losses as rather early events in breast carcinogenesis in ductal (DCIS) and lobular carcinoma *in situ* (LCIS) (Tsuda et al., 1994b, 1995; Lakhni et al., 1995a; Stratton et al., 1995). The first studies dealing with genetic changes in DCIS using conventional CGH demonstrated that 16q losses are, besides gains of 1q, the most frequent changes in DCIS. This established the presence of 16q loss in the precursor stage of breast cancer. Loss of 16q was predominantly detected in G1 and G2 DCIS, whereas other cytogenetic alterations were more frequent in G3 DCIS (Buerger et al., 1999b; Vos et al., 2000; Waldman et al., 2000). Articles also demonstrated that 16q-loss is associated with absence of intraductal necrosis, low proliferation rate (Buerger et al., 2000a) and the lack of identical alterations in poorly differentiated DCIS and synchronous ipsilateral invasive breast cancer (Buerger et al., 2000b).

### Chromosome 16q losses in lobular neoplasia of the breast

In lobular neoplasia (atypical lobular hyperplasia and LCIS) 16q loss was frequently seen using conventional CGH (Lu et al., 1998b; Etzell et al., 2001) and array CGH (Mastracci et al., 2006a; Green et al., 2009). Usually there was loss of the complete arm of 16q (Etzell et al., 2001). There was no difference in frequency between 16q loss between atypical lobular hyperplasia and LCIS (Lu et al., 1998a,b; Mastracci et al., 2006a,b). Also, a similar frequency of 16q loss in lobular neoplasia was found compared with invasive lobular carcinoma (Etzell et al., 2001; Hwang et al., 2004). There were some indications that 16q loss in LCIS is associated with t(1;16) (Flagiello et al., 1998a,b; Buerger et al., 2000b; Chen et al., 2009a,b). On the other hand, some articles reported a significantly higher frequency of 1q gain in invasive lobular carcinomas, compared with lobular neoplasia (Lu et al., 1998b; Etzell et al., 2001).

With regard to the relation between lobular neoplasia and DCIS, similar chromosomal changes were found between lobular neoplasia compared to DCIS and

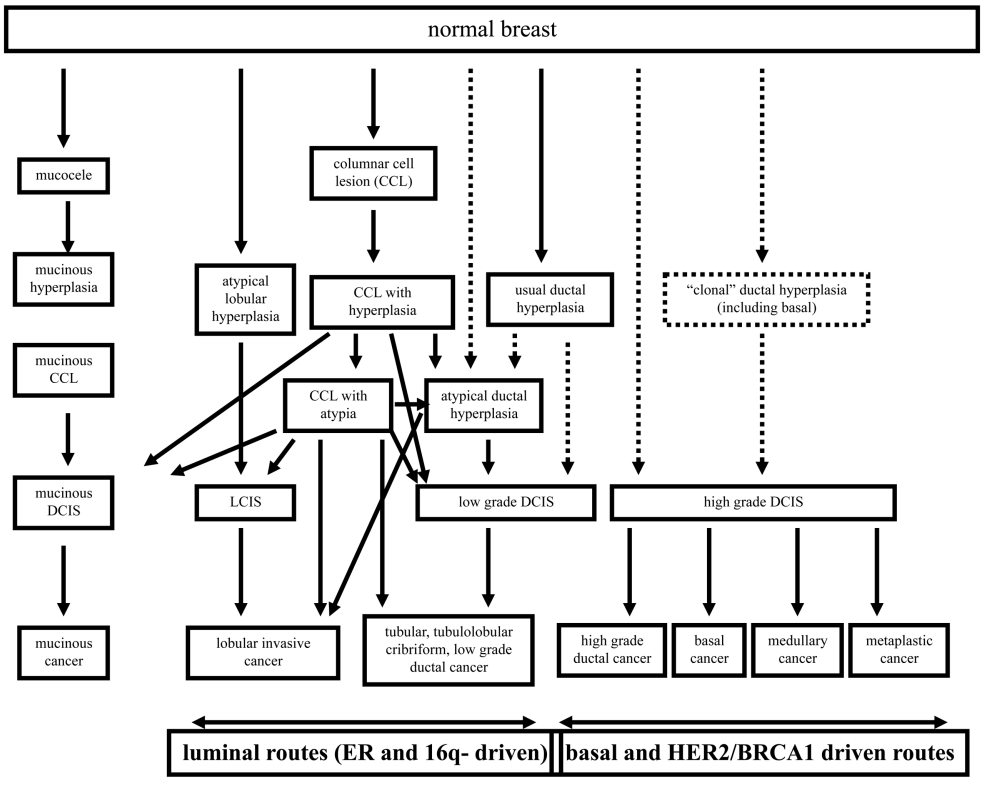


**Fig. 2.** The detection of 16q-losses in breast lesions discussed as precursor lesions of in-situ carcinomas and invasive breast cancer further support the presence of a low and a high grade pathway in breast carcinogenesis. Even though the number of genetic investigations is rather low, the available genetic and morphological observations support a direct relationship between cylinder cell lesions (cylinder cell change and cylinder cell hyperplasia), flat epithelial atypia, atypical ductal hyperplasia and well-differentiated DCIS. More recent studies showed that mucinous carcinomas represent their own subgroup of cancers within the spectrum of the low-grade breast cancers.

invasive ductal carcinoma, which suggests a common genetic pathway (Lu et al., 1998b).

In search of tumour suppressor genes, several gene targets located on chromosome 16q were tested with real-time PCR in LCIS and normal lobular epithelium (Green et al., 2009). LCIS had a significantly lower gene expression of DPEP1 (dipeptidase 1), CDH1 and CTCF (CCCTC-binding factor). Also, CTCF immunohistochemistry expression was significantly lower in LCIS. This low expression indicates these genes are potential tumour suppressor genes in breast cancer.

### Chromosome 16q losses in atypical ductal hyperplasia

LOH analysis and CGH of 16q in atypical ductal hyperplasia (ADH) demonstrated variability ranging from 10 to 58% (Lakhani et al., 1995b). Some articles revealed that the loss of 16q was similar in ADH to DCIS and invasive ductal carcinoma (Gao et al., 2009; Larson et al., 2006). Because of frequent concordant LOH patterns between ADH and coexisting invasive cancer, the precursor role of ADH was corroborated (Larson et al., 2006). Not all studies could confirm this (Tsuda et al., 2001a), probably explained by the high tumour grade (G2-3) of the (metachronous) invasive carcinomas. O'Connell et al. tested 16q loss in several lesions (UDH, ADH and DCIS) in cancerous and non-cancerous breasts (O'Connell et al., 1998). There was no significant difference between the frequency of 16q loss between the cancerous group and the non-cancerous group. This was in contrast with the findings of Ellsworth et al., who described a low frequency of 16q loss of pure ADH (not accompanied by more advanced lesions). Pure ADH only had significantly more frequent allelic imbalance at chromosome 8q24 compared with normal breast, while the frequency of 16q loss was similar to normal epithelium (Ellsworth et al., 2010).

To conclude, 16q loss is often present in ADH which underlines its role in breast carcinogenesis, with progression potential to both low nuclear grade ductal and lobular (pre)invasive lesions.

### Chromosome 16q losses in columnar cell lesions

Recently, atypical columnar cell lesions (CCL, characterized by the presence of columnar epithelial cells lining the terminal duct lobular units of the breast, either with atypical nuclei or early ("clinging") architectural atypia, also known as flat epithelial atypia or DIN1a), have been proposed as the earliest possible neoplastic alterations of the breast. LOH and CGH analysis demonstrated relatively frequent 16q loss in atypical CCL (Moinfar et al., 2000; Simpson et al., 2005), which suggests a precursor role in low grade early breast carcinogenesis. Other frequent chromosomal changes were LOH of chromosome 11q and 3p (Moinfar et al., 2000). A gain of 1q was variably observed in CCL. A high frequency of 1q gain was found in CCLs associated with lobular neoplasia (Simpson et al., 2005; Stacher et al., 2011). Schmidt et al. showed a high concordance between 16q loss in atypical CCL and the adjacent invasive carcinoma or *in situ* carcinoma (Schmidt et al., 2008).

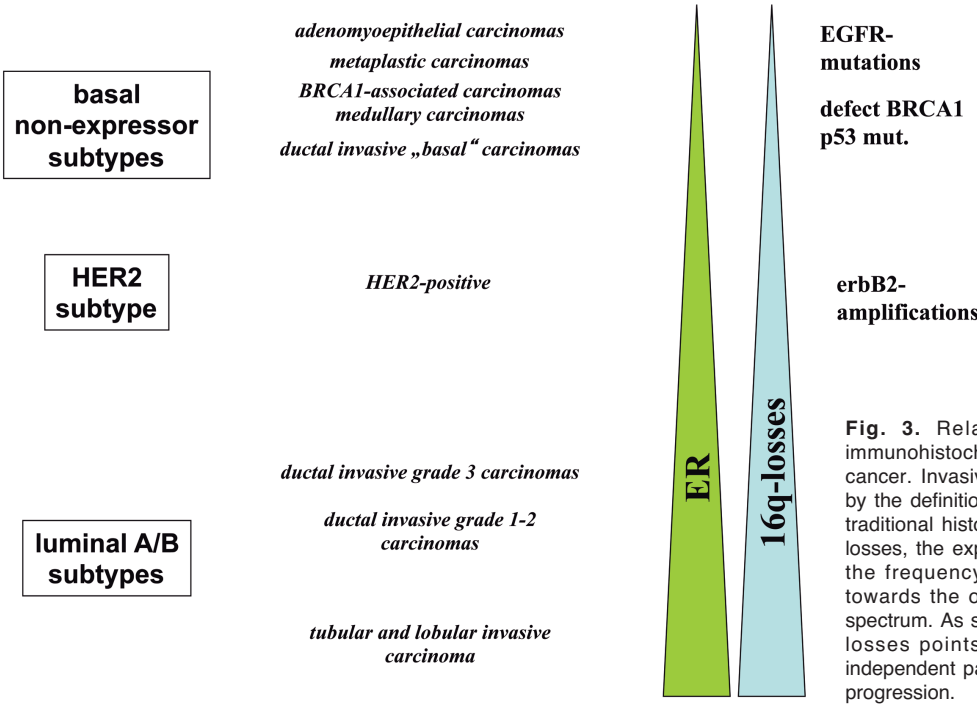


**Fig. 3.** Relationship between morphological, immunohistochemical and genetic findings in breast cancer. Invasive breast cancer can be characterized by the definition of molecular subtypes as well as the traditional histological typing. The distribution of 16q-losses, the expression of estrogen receptor (ER) and the frequency of other genetic alterations points towards the obvious existence of a breast cancer spectrum. As shown in the text, the distribution of 16q losses points towards the existence of multiple independent pathways, rather than a stepwise tumour progression.

Moinfair et al. found that pure atypical CCL (not associated with invasive ductal carcinoma) showed the same frequency of 16q loss as in cancerous breasts (Moinfar et al., 2000). This is in contrast with the findings of Ellsworth et al., who tested pure CCL by LOH and revealed a significantly lower frequency of 16q loss compared with CCL of cancerous breasts. They also demonstrated that pure CCL did not show a

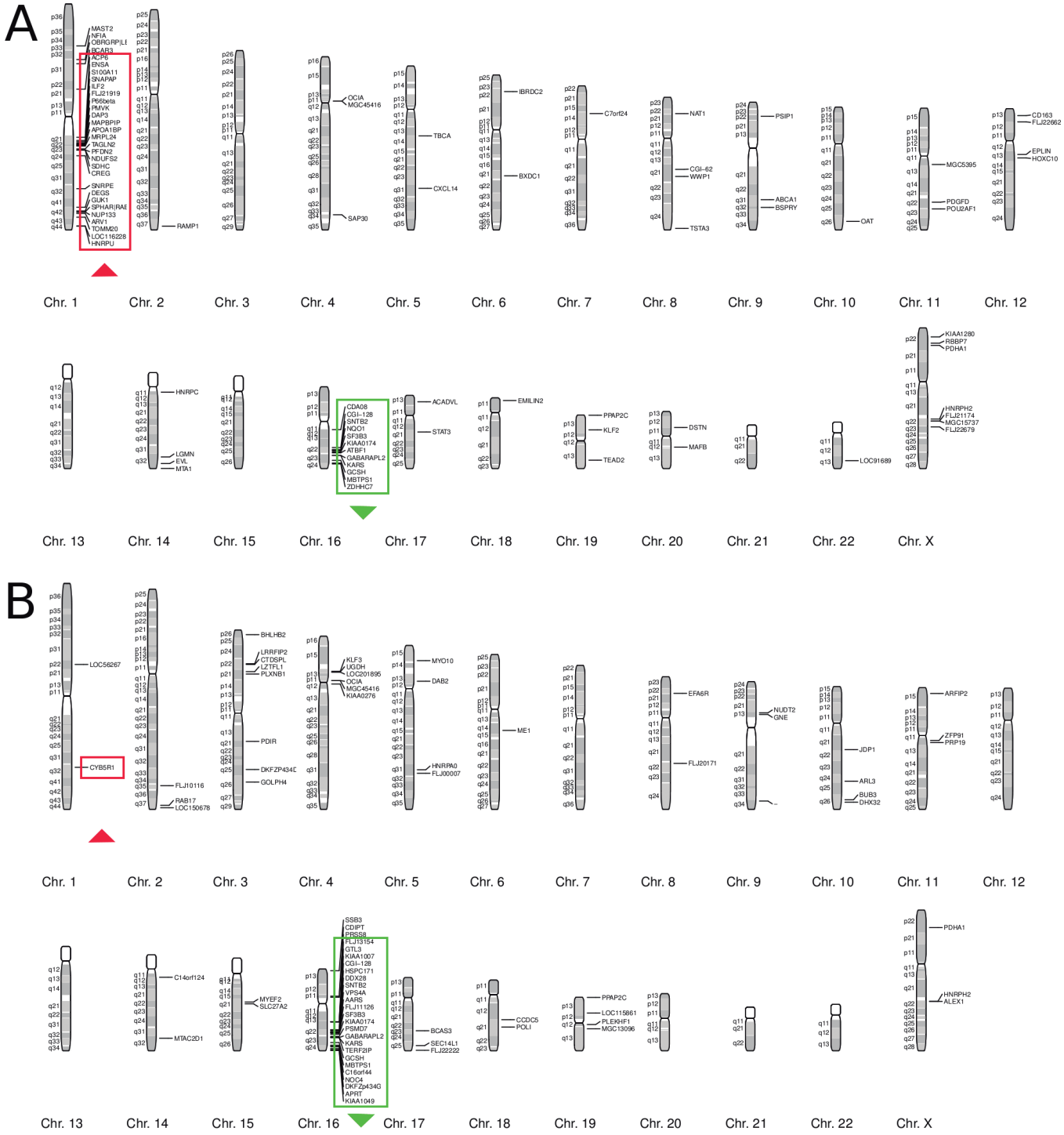


**Fig. 4.** Overview of all differentially expressed genes in regard to their chromosomal location. The genome is displayed as a panel of ordered metaphase ideograms of the human chromosomes 1 to 22 and X. The differentially expressed genes are mapped to their genomic location. On 16q and 1q a significant accumulation of differentially expressed genes can be seen. All the 16q genes revealed a decreased expression, while 1q genes showed an increased expression.

significantly higher loss of 16q than normal tissue. However, no distinction between non-atypical and atypical CCL was made. Ellsworth et al. suggested that pure CCLs have different molecular changes from CCL with more advanced synchronous lesions (Ellsworth et al., 2010).

Different types of CCL (metaplasia, hyperplasia, hyperplasia with architectural atypia, hyperplasia with cytologic atypia, hyperplasia with architectural and cytologic atypia and metaplasia with cytologic atypia) were compared by Simpson et al. (2005). A remarkable finding of the CGH analysis was the relatively high 16q loss in columnar cell metaplasia and hyperplasia, respectively 29% and 36%. CCL with atypia (architectural or cytologic) showed 16q loss in 47%. They concluded that all these CCL categories exhibit loss of 16q, and that the morphologic classification of CCL closely mirrors the level of genetic instability (Simpson et al., 2005).

To conclude, it appears that 16q loss is common in CCL, possibly most common in atypical CCL. Studying the progression risk of 16q loss would be interesting.

### Chromosome 16q losses in usual ductal hyperplasia and normal epithelium

Although usual ductal hyperplasia (UDH) is generally regarded as a polyclonal carcinogenetic dead end, Gong et al. suggested a precursor role of UDH, based on a high frequency of 16q loss (56%) in UDH adjacent to ADH (Gong et al., 2001). However, pure UDH (not related to ADH) demonstrated lower frequency of 16q loss (11%). Other studies revealed low frequencies of 16q loss in UDH (O'Connell et al., 1998; Tsuda et al., 2001b; Larson et al., 2006; Gao et al., 2009). This may imply that a subset of lesions morphologically appear as UDH yet harbour clonal cell populations with progression potential.

Also, morphologically normal epithelium from cancerous breasts was analysed for 16q losses, and normal epithelium with mildly atypical nuclear features at high magnification demonstrated loss of 16q with a frequency of 44%, equal to the rate in atypical CCLs (Moinfar et al., 2000). In contrast, normal epithelium from women without breast disease did not show any LOH at the tested loci (Moinfar et al., 2000). Normal epithelium in cancerous breasts tested by Larson et al. revealed that 16q loss was one of the most frequent LOH, although significantly less frequent compared to carcinoma *in situ* and invasive carcinoma (Larson et al., 2002). This suggests that even morphologically normal breast epithelium may harbour aberrant clones that may progress and contribute to tumorgenesis.

### Correlation between chromosomal 16q-status and gene expression patterns

As nicely reviewed by Rakha et al., the classical hunt for "the" 16q-specific tumour suppressor gene seemed to fail in the past, since somatic mutations (in view of the Knudson hypothesis) of the respective genes could not be observed (van Wezel et al., 2005; Rakha et al., 2006). Consequently, other mechanisms seem to contribute to the 16q-specific effect in breast carcinogenesis. One mechanism, even though hard to prove for a long time, was haploinsufficiency as a result of a loss of chromosomal material in the sense of a gene dosage effect. Consequently, the loss of chromosomal material at a distinct genetic region would be associated with a decreased expression of the affected genes.

Global gene expression has been proven to be of high value in the gene based subclassification of invasive breast cancer. According to Perou et al. invasive breast cancer can be divided into luminal, basal and HER2 driven cancers (Perou et al., 2000). The luminal group is composed of luminal A and luminal B breast cancers, both characterized by the expression of ER and/or PR, but differing in the expression of HER2 and/or the rate of tumour proliferation (Kornegoor et al., 2012). The studies of Wennmalm et al. and Nordgard et al. demonstrated a clear correlation between 16q-specific gene expression and intrinsic breast cancer subgroup as previously described (Sorlie et al., 2001), as well as the overall survival in breast cancer patients (Nordgard et al., 2008). A decreased expression of genes located on 16q was associated with an improved prognosis (Wennmalm et al., 2007). Interestingly, the expression based classification of Sorlie et al. (2001) agreed better with 16q expression than stratification according to grade.

Similar findings were observed by Wang et al. using combined genome-wide single nucleotide polymorphism analysis and expression analysis. 16q-losses have not been detected in basal breast cancers, but in ER-positive luminal breast cancers (Wang et al., 2004), as already seen in a series of breast cancers characterized by immunohistochemistry (Korsching et al., 2002).

DCIS studies with global screening techniques demonstrated that DCIS can be classified into different intrinsic subtypes like invasive breast cancer (Tamimi et al., 2008). On the genomic and the transcriptomic level invasive carcinomas and DCIS revealed similar pheno- and genotypic relationships, demonstrating that the molecular heterogeneity of breast cancers is already detectable at the *in situ* level. Furthermore, a gene dosage effect could be shown for 16q in DCIS (Vincent-Salomon et al., 2008).

Against this background it has been speculated that 16q-losses will mediate their effect by a simple gene dosage effect, mainly in luminal, ER-positive breast cancer. In a recently published study of Hungermann et al. this hypothesis was further substantiated. Whole-arm chromosome 16q losses were associated with decreased expression of a number of candidate genes located on 16q in breast carcinomas with a low degree of genetic instability. The differential expression of the candidate genes according to the chromosomal 16q-status vanished in genetically advanced breast cancer cases and negative ER status. These results corroborate previous reports about the importance of whole-arm loss of chromosome

16q in breast carcinogenesis and give evidence that haploinsufficiency, in the sense of a gene dosage effect, might be an important contributing factor in the early steps of breast carcinogenesis (Hungermann et al., 2011). Haploinsufficiency is associated with the loss of one allele of a specific gene in a tumour cell, whereas the other allele maintains gene expression, leading to a decreased overall expression (gene dosage) in the tumour cell. Dosage sensitivity has been implicated in tumourigenesis especially for cell-cycle regulatory genes, such as p53 and p27, but also for other genes (Santarosa and Ashworth, 2004). However, a recurrent feature of haploinsufficient genes is that tumours generated via this mechanism are of later onset and lower aggressiveness. In addition, haploinsufficiency has been associated with an early stage of disease. For some genes also a pathway specific haploinsufficiency effect has been described. The parallels between these observations and the findings in breast cancer are compelling. 16q-losses belong to the earliest events in breast cancer and are generally associated with favourable prognostic features in breast cancer.

The relationship between 16q-losses and the expression of ER will focus further research on the interaction between ER and 16q-losses in ER-positive carcinomas (Habashy et al., 2012).

## Consequences for progression and classification schemes of breast cancer and its precursor lesions

Integrating all these data into a unifying model of breast carcinogenesis it becomes evident that a simple linear model like the one proposed for colorectal carcinogenesis does not apply to breast cancer. Rather, the distribution of 16q-loss in preinvasive or invasive breast lesions clearly points towards the existence of different pathways, associated with different malignancy grades. One could therefore propose a low-grade and a high-grade pathway in breast carcinogenesis (van-Diest, 1999). The latter is characterized by a multitude of different genetic alterations and protein expression patterns (p53, HER2, Ck5) in invasive breast cancer and its associated DCIS. In contrast, hallmarks of the low-grade pathway are the loss of 16q, the expression of ER and a likewise lower degree of genetic instability (Korsching et al., 2008). Lobular and ductal breast lesions might therefore be regarded as two different morphological patterns with a unique underlying genetic alteration pattern as shown in figure 1.

These observations are therefore not only of tumour-biological interest, but also significantly influence our understanding of the classification of early breast lesions and invasive breast cancer. The modified DIN (ductal intraepithelial neoplasia) concept, highly analogous to a multitude of other "intraepithelial neoplasia" classification systems, such as in the cervix or squamous epithelium, suggest a linear progression of grade 1 to grade 3 and finally to invasive carcinoma. However, as discussed above, this simple concept transferred from other tumour entities does not to seem hold for breast cancer and the DIN classification scheme therefore insufficiently reflects the underlying biology. Since the distribution of 16q-losses changes significantly with grade, it is unlikely that well-differentiated DCIS progresses towards poorly-differentiated DCIS in high frequency. The morphological association of G1 DCIS with tubular, tubulo-lobular, lobular and ductal invasive grade 1 carcinomas, in contrast to the poorly-differentiated DCIS/ductal invasive grade 3 carcinoma pathway, is also a plea against this hypothesis. Consequently, our current understanding of breast cancer has to incorporate the presence of multiple genetic pathways in the progression of *in situ* and invasive breast cancer as recently reviewed.

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