Recurrent CYP2C19 deletion allele is associated with triple-negative breast cancer

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Abstract

Background: Using a genome-wide approach, we have previously observed an increase in the frequency of rare copy number variants (CNVs) in familial and early-onset breast cancer cases when compared to controls. Moreover, the biological networks of the CNV disrupted genes differed between the two groups. Here, six of the previously observed CNVs were selected for further investigation. Four of these were singletons and disturbed the following genes: DCLRE1C, CASP3, DAB2IP and ITGA9, encoding proteins that are part of the TP53 and β-estradiol centered network. The two others were recurrent alleles and disrupted CDH19 and CYP2C19 genes. Of these, CDH19 encodes a cadherin functioning as a cell-cell adhesion receptor and CYP2C19 a CYP450 enzyme with a major function in estrogen catabolism.

Methods: The exact breakpoints of the six previously observed CNV deletion alleles were defined by using qPCR, nested PCR and sequencing. The prevalence of these CNVs was investigated in 842 Northern Finnish breast cancer cases, unselected for family history of cancer and age at disease onset, as well as in 497 healthy female controls by using multiplex PCR. Also the association of the relatively common CDH19 and CYP2C19 deletion alleles with different clinical parameters was studied.

Results: No significant differences in the carrier frequencies between cases and controls were found for any of the studied CNVs. However, the deletion in CYP2C19 showed a significant association with triple-negative breast cancer (p = 0.021).

Conclusion: Our results indicate that inherited changes in CYP2C19 gene participating in estrogen catabolism have an influence on the molecular subtype of breast cancer.

Keywords: Copy number variation, CYP2C19, Triple-negative breast cancer

Background

Copy number variants (CNVs) are genomic microduplications or microdeletions which can affect gene function and predispose to various diseases [1], including breast cancer. Although no evidence for the association of common CNVs with breast cancer susceptibility has been reported [2], recent genome-wide studies suggest that rare CNVs represent an alternative source of genetic variation influencing hereditary breast cancer risk [3,4]. In our previous study, we observed a consistent increase in the frequency of rare CNVs in familial and early-onset breast cancer cases when compared to controls. Furthermore, the biological networks of the disrupted genes differed between the two groups: the disrupted genes in breast cancer cases were shown to be closely related to estrogen signalling and TP53 centered tumor suppressor network [4].

Based on their biological functions and recurrence, two of the previously identified deletion alleles disrupting CYP2C19 and CDH19 genes, respectively, were hypothesized to play a role in breast cancer predisposition also in the general population. Of these, CYP2C19 encodes a CYP450 enzyme with a major function in estrogen catabolism: it catalyzes 17β-hydroxy dehydrogenation and 16α-hydroxylation of estradiol [5,6]. CYP2C19 has also been reported to participate in tamoxifen metabolism during
matchings among the tumor biology. CDH19 encodes a cadherin, which is a cell-cell adhesion receptor establishing and maintaining intercellular connections. Loss of function of cadherins may be connected to cancer formation [8]. In our previous study, the CYP2C19 deletion allele was found twice as frequent in familial breast cancer cases (5.8%) as in controls (2.3%), whereas CDH19 was observed once in both familial (1.0%) and control cohorts (0.8%) [4], implicating the need for a larger dataset for the evaluation of their disease relatedness. Besides the breast cancer risk itself, both changes could also have an effect on tumor biology.

Although a majority of the previously observed CNV alleles, which disrupted genes from the TP53 and β-estradiol centered network, were singletons [4], some could represent founder mutations typical for the Finnish population. Thus, based on their biological functions, four singleton deletion alleles disrupting CASP3, DAB2IP, DCLRE1C and ITGA9 genes, respectively, were included in the study. Of these CASP3 functions in apoptosis, failure of which can lead to cancer [9]. DAB2IP encodes a member of the RAS GTPase-activating gene family and has been reported to act as a tumor suppressor: its inactivation by promoter methylation occurs in several malignancies, including prostate and breast cancer [10]. DCLRE1C operates in the DNA double-strand break repair pathway, defect of which has been strongly associated with breast cancer predisposition [11], and ITGA9 encodes α-integrin, which participates in the control of cell division, differentiation and migration [12-14]. The chromosomal region harboring ITGA9 has been reported to be deleted in several epithelial malignancies, including breast carcinoma [15].

Here we have defined the exact breakpoints of six previously identified deletion alleles disrupting the CYP2C19, CDH19, CASP3, DCLRE1C, DAB2IP and ITGA9 genes, respectively, and evaluated their association with breast cancer risk and disease subtype using a Northern Finnish case-control cohort. As a result, we provide evidence suggestive of the CYP2C19 deletion allele being associated particularly with susceptibility to triple-negative breast cancer.

Genotyping of the deletion alleles

The exact breakpoints of CYP2C19, CDH19, CASP3, DCLRE1C, DAB2IP and ITGA9 genes disrupting deletion CNVs were defined by performing qPCR (BioRad CFX96, BioRad, Hercules, CA, USA) and nested PCR (GeneAmp High Fidelity PCR System, Applied Biosystems, Foster City, CA, USA) with the primers surrounding the breakpoint coordinates received from Illumina HumanOmni-Quad BeadChips, analyzed with GenomeStudio Genotyping module (Illumina Inc., San Diego, CA, USA) and Nexus Copy Number Discovery Edition 5.1 software (BioDiscovery Inc. El Segundo, CA, USA) [4]. The breakpoints were verified by direct sequencing (ABI3130xl Genetic Analyzer, Applied Biosystems, Foster City, CA, USA).
Nested allele-specific PCR for the detection of the deletion alleles was designed in a multiplex format, containing control primers to monitor PCR success. Deletion CNV-containing samples were used as positive controls. Primers to amplify the deletion alleles are presented in Additional file 1: Table S1. The obtained PCR amplicons were analyzed with Bioanalyzer (Agilent Technologies, Waldbronn, Germany). All the observed deletion carrier samples were verified by direct sequencing. The heterozygosity of the CYP2C19 and CDH19 deletion alleles was confirmed by second, wild type allele specific PCR. For CYP2C19, the same forward primer as in multiplex reaction was used, reverse (ACTTGACGATGGAGGATGAA) resided on genomic region present only in wild type allele. For CDH19, the reverse primer was the same as in multiplex reaction, whereas the forward primer (TCTGAATCTGGTGAGGAGGGTGA) was wild type specific.

Genotyping for other CYP2C19 metabolizer alleles in CYP2C19 deletion carriers

The status of the remaining CYP2C19 allele both in carriers with breast cancer and those remaining healthy was investigated by genotyping for the three literature described metabolizer types: CYP2C19*2 (c.681G > A, rs4244285, poor metabolizer), CYP2C19*3 (c.636G > A, rs57081121, poor metabolizer) and CYP2C19*17 (-806C > T, rs12248560, ultra-rapid metabolizer) [18-21]. Genotyping was performed with direct sequencing (ABI3130xl Genetic Analyzer) using primers in Additional file 1: Table S2 [22-24].

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY, USA). P-values for comparisons between cases and controls and for the evaluation of the differences in tumor characteristics were obtained using Pearson’s chi-squared or Fisher’s exact test. Fisher’s exact test was used if any of the cross-tab cells had expected count less than 5. P-values were not corrected for multiple testing in order not to eliminate potentially significant findings obtained with small number of CNV carriers. All p-values were two-sided.

Table 1 Genomic coordinates, sizes and carrier frequencies of the studied deletion alleles

| Disrupted gene | Location of deletion | Deletion size | Carrier frequency, n/N (%) | P-value | OR (95% CI) |
|----------------|----------------------|---------------|----------------------------|---------|------------|
| DCLRE1C        | Chr10: 14,983,925−15,065,676 | 82 kb         | 0/842 (−)                  | 0/497 (−) | NA         | NA         |
| CASP3          | Chr4: 185,506,876−185,841,468 | 335 kb        | 0/842 (−)                  | 0/497 (−) | NA         | NA         |
| DAB2IP         | Chr9: 124,201,774−124,361,084 | 159 kb        | 0/842 (−)                  | 0/497 (−) | NA         | NA         |
| ITG9           | Chr3: 37,750,166−37,810,925 | 61 kb         | 1/842 (0.1%)               | 1/497 (0.2%) | 1.000 | 0.590 (0.037 − 9.450) |
| CDH19          | Chr18: 64,082,045−64,335,669 | 254 kb        | 12/842 (1.4%)              | 3/497 (0.6%) | 0.168 | 2.381 (0.669 − 8.478) |
| CYP2C19        | Chr10: 96,497,324−96,559,110 | 62 kb         | 31/842 (3.7%)              | 17/497 (3.4%) | 0.804 | 1.079 (0.591 − 1.971) |

NA = not available, OR = odds ratio, CI = confidence interval. Genomic coordinates according to human genome assembly 19 (February 2009).
Table 2 Tumor characteristics of CYP2C19 deletion allele carriers compared with the tumors of non-carrier unselected breast cancer cases

| Category       | CYP2C19 deletion | Wild type | P-value* | OR  | 95% CI  |
|----------------|------------------|-----------|----------|-----|---------|
|                | %                | %         |          |     |         |
| T              |                  |           |          |     |         |
| 1              | 18               | 304       | 58.3%    |     |         |
| 2              | 10               | 188       | 36.1%    | 0.692 | 1.17   | 0.54-2.52 |
| 3              | 1                | 16        | 3.1%     | 1 vs. 2,3,4 |     |         |
| 4              | 0                | 13        | 2.5%     |     |         |
| N              |                  |           |          |     |         |
| Neg            | 20               | 293       | 56.0%    | 0.354 | 1.43   | 0.67-3.04 |
| Pos            | 11               | 230       | 44.0%    |     |         |
| M              |                  |           |          |     |         |
| Neg            | 31               | 500       | 95.6%    | 0.632 | NA     |         |
| Pos            | 0                | 23        | 4.4%     |     |         |
| ER             |                  |           |          |     |         |
| Neg            | 10               | 101       | 19.3%    | 0.048 | 2.19   | 0.99-4.86 |
| Pos            | 19               | 421       | 80.7%    |     |         |
| PR             |                  |           |          |     |         |
| Neg            | 13               | 153       | 29.4%    | 0.078 | 1.95   | 0.92-4.16 |
| Pos            | 16               | 368       | 70.6%    |     |         |
| HER2           |                  |           |          |     |         |
| Neg            | 24               | 447       | 85.6%    | 0.595 | 0.81   | 0.30-2.18 |
| Pos            | 5                | 75        | 14.4%    |     |         |
| Grade          |                  |           |          |     |         |
| 1              | 4                | 86        | 17.1%    |     |         |
| 2              | 14               | 226       | 44.9%    | 0.659 | 0.85   | 0.41-1.77 |
| 3              | 13               | 191       | 38.0%    | 1 and 2 vs. 3 |     |         |
| Tumor histology|                  |           |          |     |         |
| Ductal         | 23               | 395       | 75.7%    |     |         |
| Lobular        | 3                | 90        | 17.2%    | 0.656 | 1.23   | 0.49-3.09 |
| Medullary      | 0                | 2         | 0.4%     | Ductal vs. all other |     |         |
| Other          | 3                | 35        | 6.7%     |     |         |
| Type           |                  |           |          |     |         |
| LumA           | 16               | 385       | 73.8%    |     |         |
| LumB           | 3                | 43        | 8.2%     | 0.021 | 2.83   | 1.20-6.66 |
| HER2           | 2                | 32        | 6.1%     | Triple-neg vs. other |     |         |
| Triple-neg     | 8                | 62        | 11.9%    |     |         |
| Ki67           |                  |           |          |     |         |
| 0              | 1                | 71        | 13.7%    |     |         |
| 1              | 13               | 231       | 44.5%    | 0.393 | 0.72   | 0.34-1.54 |
| 2              | 7                | 112       | 21.6%    | 0 and 1 vs. 2 and 3 |     |         |
| 3              | 7                | 105       | 20.2%    |     |         |

*T = tumor size, N = nodal status, M = primary metastasis, ER = estrogen receptor, PR = progesterone receptor, LumA = luminalA, LumB = luminalB, Neg = negative, Pos = positive.

*not corrected for multiple testing.
6.66). Altogether, these results indicate that the tumor characteristics of CYP2C19 deletion carriers are related to estrogen responsiveness. As the known biological function of CYP2C19 is related to estrogen catabolism, and as the studied deletion allele is expected to be a null allele, we further defined the status of the remaining CYP2C19 allele in relation to literature described metabolizer genotypes both in carriers with breast cancer and those remaining healthy. No CYP2C19*3 poor metabolizers were identified, whereas four CYP2C19*2 poor metabolizers were identified in patients (4/31, 12.9%) and one in controls (1/17, 5.9%). There was no difference in the frequency of CYP2C19*17 ultra-rapid metabolizer genotypes (7/31, 22.6% in patients vs. 3/17, 17.6% in healthy controls), indicating that the disease risk of individual with CYP2C19 deletion was not significantly affected by the metabolizer status of the remaining allele. Furthermore, in a majority (7/10) of the deletion carriers with ER negative cancer the second allele was found to be wild type, whereas one (1/10) had a poor-metabolizer CYP2C19*2 allele and the rest (2/10) an ultra-rapid metabolizer CYP2C19*17 allele.

**Discussion**

Inherited genomic alterations are expected to have an effect on individual’s risk of getting cancer. However, these alterations may affect not only the risk but also the pattern of somatically acquired mutations and thereby tumor biology. Much of the work in this field has been concentrating on single nucleotide polymorphisms (SNPs) whereas the role of CNVs has remained poorly defined, partially because their detection with Sanger or even with sophisticated Next-Generation sequencing is hard or even impossible, and the fast and cost-efficient investigation of CNV alleles requires the characterization of their breakpoints in exact detail. Of the currently studied rare CNV alleles, the breakpoints of five out of six were adequately well described by the used analysis software, indicating that high-resolution microarrays can predict fairly well the genuine genomic coordinates of the aberrations. The singleton CNVs previously identified in familial or early-onset cases [4] were absent from, or remained extremely rare in the unselected breast cancer cases, but the two recurrent alleles were observed at higher frequency. The carrier frequency of the CDH19 deletion was twice as high in unselected breast cancer cases as in controls but remained below statistical significance, indicating the need for larger case–control cohorts to demonstrate its association with breast cancer. The other recurrent CNV allele, CYP2C19 deletion, had surprisingly high prevalence both in the studied cases and controls (>3%), particularly when considering that deletion CNVs have rarely been reported in CYP genes, despite the numerous studies performed. This can be explained by the poor detection of CNV alleles by conventional genotyping methods, but also by the fact that our study was performed with samples from Finnish founder population. Founder populations are known to harbor unique mutations and some of the mutations rare in other populations can also show enrichment in them. In regard to cancer predisposition, the effect of the CYP2C19 deletion was reminiscent to that of a low-penetrance allele. However, it was found to be associated specifically with the triple-negative molecular subtype of the breast cancer.

There are multiple lines of evidence for the profound role of estrogen in breast cancer development: disruptions in estrogen signalling and metabolism have long been considered to affect breast cancer risk. This can result from different reproductive and hormonal factors [25], but could also be due to variations in the enzymatic machinery responsible for estrogen metabolism. Indeed, the currently studied CYP2C19 deletion CNV is expected to result in a null allele of a gene encoding an enzyme involved in estrogen catabolism [5,6]. All currently identified mutation positive individuals were heterozygous for the CYP2C19 deletion, and the genotype of the remaining allele seemed not to play a role in the observed association with tumor triple-negativity. This could be explained by a genuine haploinsufficient situation, in which single allele is unable to sustain full functionality when compared to the protein levels produced by two wild type alleles. Alternatively, as the CYP2C19 deletion allele extends over 60 kb, starting only 1377 bp from the 3’ end of the adjacent CYP2C18 gene, it could change the genomic landscape of this region in a way that leads to aberrant expression of both genes. It is also possible that large genomic deletions disturb the communication between the homologous alleles required for their full function by deleting regulatory elements required for this process [26].

Another CYP2C19 allele, CYP2C19*17, defining an ultra-rapid metabolizer phenotype, has previously been associated with a decreased risk for breast cancer. This suggests that increased catabolism of estrogens by CYP2C19 may lead to decreased estrogen levels and therefore reduced breast cancer risk [27]. Correspondingly, our initial hypothesis was that CYP2C19 deletion allele effects are mediated through life-long increased estrogen levels. Why this would predispose particularly to ER negative breast cancer is currently, however, puzzling and the mechanism through which the CYP2C19 deletion operates remains unclear. However, any perturbations in estrogen metabolism are still among the possible explanations. Curiously, there are also reports linking obesity with triple-negative breast cancer [28]. Although obesity-related insulin resistance and chronic inflammatory could be possible explanations for this phenomenon, increased body mass index is known to cause changes in the hormonal cycles and result in excessive adipose tissue [29,30]. This can increase the estrogen production and availability, leading
again to the unexpected association with receptor negative breast cancer. Nevertheless, as triple-negative breast cancer is a tumor subtype with unique characteristics not only in its pathological presentation but also in prognosis and response to therapy, identification of additional risk factors specifically associated with this subgroup of breast cancer could help to understand its etiology.

Conclusion
Our results indicate that an inherited defect in the CYP2C19 gene with a role in estrogen catabolism has an influence on the molecular subtype of breast cancer and is significantly associated with triple-negative tumors. The role of the CYP2C19 deletion allele, as well as that of the CDH19 deletion, in breast cancer predisposition warrants further studies and the obtained results should be replicated with larger and independent case–control cohorts.

Additional files

Additional file 1: Table S1. Primers used in multiplex PCR. Table S2. Primers used for the detection of other metabolizer phenotypes described in CYP2C19. Table S3. Correspondence of microarray based and sequencing confirmed genomic coordinates for the breakpoints. Table S4. Tumor characteristics of CDH19 deletion allele carriers compared with the tumors of non-carrier unselected breast cancer cases.

Additional file 2: Figure S1. Sequence of the CYP2C19 deletion breakpoint.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
KP and RW conceived the study. KP and AT performed the breakpoint mapping, AT multiplex analysis and CYP2C19 genotyping. AJV provided the clinical information for the patients. KP and AT analyzed the statistics and drafted the manuscript. All authors read and approved the final manuscript.

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