Breast Cancer
R E S E A R C H

LETTER

COMPLEXO: identifying the missing heritability of breast cancer via next generation collaboration

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Linkage analysis, positional cloning, candidate gene mutation scanning and genome-wide association study approaches have all contributed significantly to our understanding of the underlying genetic architecture of breast cancer. Taken together, these approaches have identified genetic variation that explains approximately 30% of the overall familial risk of breast cancer, implying that more, and likely rarer, genetic susceptibility alleles remain to be discovered.

The application of massively parallel sequencing has further demonstrated the complexity of human genetic variation and has raised many challenges for computational and statistical methods for searching for additional breast cancer predisposition genes. Early findings are consistent with previous indications that no single gene is likely to account for a large proportion of the remaining unexplained genetic susceptibility [1,2].

Coordinated international collaboration offers great potential to advance the discovery of additional breast cancer susceptibility genes by increasing the likelihood of identifying functionally relevant genetic variants in the same genes in multiple families. A new consortium, COMPLEXO (a name chosen to reflect the complexity of the exome), has been formed to facilitate collaborations between researchers actively applying massively parallel

sequencing to understand the genetics of breast and ovarian cancer. The consortium has defined activities aimed at bringing together data and resources suitable for exome/genome sequencing initiatives and for large case-control-family study resources suitable for validation of candidate susceptibility genes in which rare mutations are associated with high to moderate risk of breast cancer. The aim of COMPLEXO is to bring to massively parallel sequencing the same power of large sample sets that have proven so successful in examining the role of common variants in cancer populations via the consortium model, such as the Breast Cancer Association Consortium (BCAC), the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), the Ovarian Cancer Association Consortium (OCAC) and the Collaborative Oncology Gene-environment Study (COGS) [3-5]. However, sequencing studies provide additional challenges in terms of defining specific modes of collaboration given differences in sequencing and targeted capture platforms, bioinformatics platforms, the need to integrate ongoing studies in many centers and socio-ethical-legal issues that are not as relevant to initiatives that are genotyping common genetic variation.

COMPLEXO invites collaboration from any researcher who would like to contribute to this consortium either by contributing data to the combined COMPLEXO data set, contributing resources for large-scale validation of candidate breast cancer predisposition genes or refining analytical and bioinformatic pipelines for massively parallel sequencing data filtering and prioritization. COMPLEXO also has interests in the critical assessment of current platforms and protocols and in developing and improving

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data filtering and gene prioritization strategies to enhance gene discovery initiatives. These approaches are relevant to all complex human diseases.

Interested researchers can engage with COMPLEXO via any local member or by contacting the corresponding author.

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3. [http://ccge.medschl.cam.ac.uk/consortia/bcac/index.html]
4. CIMBA (The Consortium of Investigators of Modifiers of BRCA1/2) [http://ccge.medschl.cam.ac.uk/consortia/cimba/index.html]
5. Collaborative Oncological Gene-environment Study [http://www.cogseu.org]