

Editorial

ENCODE and a new landscape
for psychiatric genetics

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**Summary**

Despite rigorous research into the genetics of neuropsychiatric disorders, the mechanism by which polygenic risk leads to complex clinical phenotypes remains unclear. The Encyclopedia of DNA Elements (ENCODE) project gives us new insight into gene regulation, and gene–gene and gene–environment interaction.

Better understanding of these key genomic mechanisms may provide the answers we have been searching for.

Declaration of interest

None.

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Neuropsychiatric disorders such as schizophrenia demonstrate a high degree of heritability.^{1,2} Understanding the genetic component of these disorders has driven decades of rigorous research in psychiatric genetics.^{3,4} Building on the success of earlier techniques such as linkage studies, recent genome-wide association studies (GWAS)^{5–7} have begun identifying risk variants that may give us important insight into disease mechanisms. There remains, however, significant 'missing heritability'⁸ in these complex diseases. Findings from GWAS have also demonstrated that many risk alleles do not necessarily code for amino acid changes in proteins, indicating a more regulatory function.⁹ The role of gene–gene and gene–environment interactions in the expression of disease phenotype and timing of illness onset have been suggested, but with the exception of some epigenetic phenomena¹⁰ we understand relatively little about these mechanisms.

The significance of non-coding regions

The Encyclopedia of DNA Elements (ENCODE) project has assigned biochemical functions to 80% of the genome and in doing so has laid to rest the idea that the vast areas of non-protein-coding DNA discovered by the Human Genome Project is 'junk DNA'.¹¹ It has emerged that non-coding regions are involved in a large number of regulatory processes including gene–gene regulation, gene–protein interaction and the transcription of non-translated RNA.

By highlighting the importance of non-coding functional DNA, ENCODE will allow researchers to re-evaluate the significance of existing psychiatric GWAS findings. We already know that certain regulatory sites harbour GWAS variants that are strongly correlated with the promoter regions of genes associated with schizophrenia.¹² Regulatory elements close to neuronal growth genes are highly preserved in the human lineage, indicating previously unsuspected functional importance.¹³

Mechanisms for gene regulation, and gene–gene and gene–environment interaction

ENCODE found that 95% of the genome was within 8 kb of a protein–gene interaction.¹¹ These findings may frame new hypotheses for mechanisms of gene–environment interactions, why disorders associated with similar genetic risk⁵ present with varied phenotypes and why so many disorders have onset at specific points in life.

Protein coding accounts for only 2% of the genome and a further 75% can be transcribed into non-translated RNA, with a likely regulatory role in at least some cell types.¹⁴ The fundamental concept of what a gene actually is may require some rethinking¹⁵ and the role of non-translated segments of RNA in disease will be a new focus for medical genetics.

Finally, ENCODE has demonstrated how distant genes interact to affect each other,¹⁶ revealing what has been termed a '3D puzzle' of gene regulation.¹⁷ This may explain how multiple distant and unrelated genes interact to produce complex clinical phenotypes.

Conclusions

Psychiatry has good cause to feel excitement over ENCODE. Following decades of research into psychiatric genetics, few conclusive findings have been translated into clinical practice. Alongside the recent successes of modern psychiatric genetics, ENCODE offers a much greater appreciation of the complexity of genomic biology. In this new scientific landscape psychiatrists should find some important answers to long-asked questions.

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