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Developmental perspective on the role of genes in smoking risk

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Numerous risk genes for nicotine dependence (ND) have been identified. Prior to the GWAS era, chromosomal risk regions were identified by linkage (1) and risk genes by association, including, for example, DOPA decarboxylase (*DDC*) and *ANKK1/TTC12* discussed below. Genomewide association studies (GWAS) have demonstrated highly significant and consistently (remarkably so) replicable associations between variation in the chromosome 15 nicotinic receptor gene cluster *CHRNA5-CHRNA3-CHRNB4* and ND and related traits.

As more risk genes for psychiatric disorders are identified, we draw closer to an understanding of the genetic part (at least) of the risk for these traits. This understanding is composed of several elements. First, we attain a clearer view of the pathophysiology of the disorder; and second, we improve our comprehension of what exactly the gene does and what its variation influences. It would be absurdly reductionist to approach this work with the expectation of finding that a certain allele is enough to cause a DSM-IV diagnosis; diagnostic constructs are valuable but they are estimates and, as we are reminded every decade or so by revisions of the DSM, they are subject to substantial change.

Gene effects on complex traits are often conceptualized as having effects on endophenotypes or intermediate phenotypes, which are related to risk for the diagnostic trait, but are not wholly deterministic of them. No specific risk allele at a genetic locus would be expected to lead to the full syndrome of ND (for example), but it is easy enough to picture variants that influence risk by, say, influencing an individual's positive or negative cognitive response or his hedonic response to nicotine, his physiological sensations of nausea or lightheadedness, his characterological propensity to light a tube of leaves and put it in his mouth to inhale the products of combustion, even his propensity to experience painful eye irritation from cigarette smoke. It is reasonable to expect that genes that affect some, maybe all, of these individual components of the nicotine dependence phenotype, and many others, could be identified.

The situation is similar across complex traits, and there are some very well worked-out examples. The effect of *ALDH2* on alcohol dependence risk is a well-known intermediate phenotype with a clear mechanism of action. A null allele at the *ALDH2* locus interferes with the metabolism of acetaldehyde, the first metabolic product of ethanol in the major metabolic pathway. Acetaldehyde is toxic and at high levels produces the "flushing

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reaction," which is physically uncomfortable. People with one or two inactive *ALDH2* alleles clear acetaldehyde slowly. When they drink ethanol they experience a dysphoric flushing reaction and therefore they are at decreased risk for alcohol dependence. So, this variant affects a person's physical response to ethanol, as opposed to anything that has to do with ethanol's reinforcing effects, directly. Presumably the affected individual learns the lesson of the flushing reaction early in his history of exposure to ethanol.

Some gene effects for nicotine dependence (ND) have been similarly unpacked, that is, we know more about them than that they influence risk of ND – we know something about the nature of the influence. We also know that separate genetic factors account for different aspects of ND (e.g., initiation and cessation), based on genetic epidemiology studies. A single nucleotide polymorphism (SNP) variant, rs1051730, that maps to *CHRNA3* in the chromosome 15 cluster, has been associated to ND *per se*, but more specifically, it associated strongly to smoking quantity (2), (3) with an estimated effect size of about 0.8 cigarettes per day (3). The variant is associated to how many cigarettes are consumed, rather than a DSM diagnosis or any other related trait such as smoking initiation. Further research might demonstrate a more basic, direct relationship with a specific phenotypic trait even than that. There is now strong evidence that multiple loci mapped to this nicotinic receptor cluster affect smoking risk (4).

The relationship of the chromosome 15 nicotinic receptor cluster to ND risk is one of the newest stories in substance dependence genetics; the relationship of genetic variation at the D_2 dopamine receptor gene *DRD2* and its possible relation to risk is one of the oldest of the molecular era. Twenty years ago, the hypothesis that genetic variation at *DRD2* could affect risk for drug and alcohol dependence made a huge splash in the field of biological psychiatry. Here, all at once, was a ringing confirmation of the importance of the D_2 receptor in reward pathways, and of the importance of those pathways in substance dependence risk; a dramatic demonstration of the value of genetic association studies, which, unlike the linkage studies that were the most prevalent design to that point, are gene- rather than region-based; and eventually, a way to unify a series of related phenotypes under the same genetic influence. Whatever euphoria resulted from this discovery was short lived, as numerous failures-to-replicate were published. But replications were published too, and while they all showed much weaker effects than the first positive studies, a complex picture emerged. Something was happening in the genetic neighborhood of *DRD2*. But what was it? A few functional variants at *DRD2* were identified, but it was shown that they could not account for the observed associations. In 2006, another possible explanation was proposed: that the origin of the association signals was not *DRD2*, but a nearby gene or genes (*ANKK1* and/or *TTC12*), close enough to *DRD2* to be in linkage disequilibrium with it (5). We still lack a really good understanding of the exact functional importance of these two genes, and it is possible that although the best (i.e., most statistically significant) association signals map outside of *DRD2*, these variants could play a role in regulating the adjacent *DRD2* locus.

Ducci et al. (6) report data regarding both the *CHRNA5-CHRNA3-CHRNB4* cluster and *TTC12-ANKK1-DRD2* in the present issue of this journal. The investigated the effects of these variants on smoking behavior at different developmental stages. Their study has several noteworthy positive features. First of all it is quite large, with 4762 subjects. Second, assessments at different ages (14 and 31) are available, and this permitted a developmental approach. (But unfortunately the assessments do not provide much detail about tobacco use traits.) Third, the sample is relatively homogeneous, genetically and environmentally, a sample of Finns collected and ascertained in Finland. This latter feature cuts two ways though; the Finns are a genetically distinct population with a unique genetic heritage; findings don't necessarily generalize (cf ref. (7)). A further advantage is the restricted

chronological range of recruitment – the study group is a 1966 birth cohort -- which can decrease the effects of secular trends, increasing power to detect genetic effects. This is especially advantageous for a trait such as cigarette smoking, which has seen enormous changes in prevalence over recent decades owing to differing societal views of smoking and changes in governmental regulation.

Ducci et al. (6) found significant associations between SNPs in both regions and smoking-related phenotypes, including rs1051730 at *CHRNA3* and rs10502172 at *TTC12*. Their findings were consistent with previous work; rs1051730 was, in particular, associated with heavy smoking. However, they were able to draw additional conclusions: *CHRNA3* was associated equivalently at ages 14 and 31, whereas *TTC12*'s effects on adult smoking were mediated by its effects on adolescent smoking, and on a personality measure, novelty seeking. Subjects with 3+ risk alleles (at the two loci) were found to have about triple the odds of regular smoking than subjects with no risk alleles, which is quite a large effect for a complex trait.

Different genes act to modulate risk for ND in different ways, through different mechanisms and via different physiology that exerts risk via alternative behavioral mechanisms. Ducci et al. (6) report data consistent with what is already known about the chromosome 15 cluster in terms of specific phenotypes affected, and add new information suggesting that *TTC12-ANKK1-DRD2* acts in part via a novelty seeking mechanism. The latter set of loci have also been shown to affect alcohol dependence risk and this mechanism could clearly translate in a way that could account for effects on other substance-dependence-related traits; and predicts (testibly) effects on additional novelty seeking-related traits, such as pathological gambling. Moreover, they show both effects acting in different ways in the same population. This is by no means surprising, but it is only by virtue of a study design that incorporates valuable longitudinal data in a large population sample that these relationships could be demonstrated.

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References

1. Li MD. Identifying susceptibility loci for nicotine dependence: 2008 update based on recent genome-wide linkage analyses. Hum Genet. 2008; 123:119–131. [PubMed: 18205015]
2. Liu JZ, Tozzi F, Waterworth DM, Pillai SG, Muglia P, Middleton L, et al. Wellcome Trust Case Control Consortium, Mooser V, Francks C, Marchini J. Meta-analysis and imputation refines the association of 15q25 with smoking quantity. Nat Genet. 2010; 42(5):436–40. Epub 2010 Apr 25. [PubMed: 20418889]
3. Thorgeirsson TE, Gudbjartsson DF, Surakka I, Vink JM, Amin N, Geller F, et al. Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. Nat Genet. 2010 May; 42(5):448–53. Epub 2010 Apr 25. [PubMed: 20418888]
4. Saccone NL, Culverhouse RC, Schwantes-An T-H, Cannon DS, Chen X, et al. Multiple Independent Loci at Chromosome 15q25.1 Affect Smoking Quantity: a Meta-Analysis and Comparison with Lung Cancer and COPD. PLoS Genet. 2010; 6(8):e1001053.10.1371/journal.pgen.1001053
5. Gelernter J, Yu Y, Weiss R, Brady K, Panhuysen C, Yang BZ, Kranzler HR, Farrer L. Haplotype Spanning TTC12 and ANKK1, Flanked By the DRD2 and NCAM1 Loci, is Strongly Associated to Nicotine Dependence in Two Distinct American Populations. Hum Mol Genet. 2006; 15(24):3498–3507 d.10.1093/hmg/ddl426 [PubMed: 17085484]

6. Ducci F, Kaakinen M, Pouta A, Hartikainen A-L, Veijola J, Isohanni M, et al. TTC12-ANKK1-DRD2 and CHRNA5-CHRNA3-CHRNB4 Influence Different Pathways Leading to Smoking Behavior from Adolescence to Mid-Adulthood. Biol Psych. In Press, Corrected Proof, Available online 17 December 2010 (Present issue) [Epub ahead of print].

7. Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T, et al. A population-specific HTR2B stop codon predisposes to severe impulsivity. Nature. 2010; 468(7327):1061–6. [PubMed: 21179162]