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Male-pattern baldness susceptibility locus at 20p11

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Abstract

We conducted a genome-wide association study for androgenic alopecia in 1,125 men and identified a newly associated locus at chromosome 20p11.22, confirmed in three independent cohorts (n = 1,650; OR = 1.60, $P = 1.1 \times 10^{-14}$ for rs1160312). The one man in seven who harbors risk alleles at both 20p11.22 and *AR* (encoding the androgen receptor) has a sevenfold-increased odds of androgenic alopecia (OR = 7.12, $P = 3.7 \times 10^{-15}$).

Androgenic alopecia is a common disorder affecting 40% of adult men and women1. Men and women with hair loss experience negative body-image perceptions2. Moreover, the mechanisms involved in androgenic alopecia may influence common medical disorders, such as coronary heart disease and metabolic syndrome3. Underscoring the social

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AUTHOR CONTRIBUTIONS
V.M., P.V., G.W. and D.W. designed and implemented the CoLaus Study and the primary nested male-pattern baldness study. J.B.R., F.G., L.A.K., H.S., K. Stefansson, T.D.S. and V.M. designed the final study with appropriate replication datasets. J.B.R., X.Y., F.G., D.W., K. Song and V.M. analyzed the data. J.B.R., V.B., D.G., G.W., P.V., D.W., K.K.H.A., L.A.K., B.W., U.T., A.K., T.R., P.S., T.D.S. and V.M. contributed to data collection and phenotype definitions. V.B., G.W., T.D.S. and V.M. obtained funding. N.S. and P.D. performed genotyping for the women from the TwinsUK cohort. J.B.R. wrote the first draft of the paper and all authors made important contributions to the final version of the paper.

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implications of baldness, global annual sales of a medical therapy for male-pattern baldness recently surpassed $405 million (Merck Financial Disclosures, Fourth Quarter 2007).

Androgenic alopecia is a highly heritable condition, with heritability estimates of over 80%4. Genetic variants in, or in proximity to, the *AR* (androgen receptor) gene have been previously associated with male-pattern baldness5-9. However, as the inheritance pattern of this trait seems to be polygenic, we undertook a two-stage genome-wide association (GWA) study for androgenic alopecia.

We carried out an extreme discordant case-control GWA scan for androgenic alopecia nested within the CoLaus population-based study in Lausanne, Switzerland10. A total of 578 male individuals with early-onset alopecia were compared with 547 male control individuals without alopecia (**Supplementary Methods** online). In the second stage, we sought replication in independent samples from the UK, Iceland and The Netherlands. The UK cohort comprised 453 men (176 affected individuals) from a population-based sample of British twins; 1,308 women (95 affected individuals) from this sample were also assessed for hair loss. The Dutch cohort comprised 463 men (147 affected individuals) previously diagnosed with prostate cancer and also assessed for androgenic alopecia. The Icelandic study included 734 Icelandic men (536 affected individuals) and 878 Icelandic women (397 affected individuals). The overall sample size thus comprised 4,961 individuals.

The GWA study (Supplementary Fig. 1 online) was done using the Affymetrix GeneChip Human Mapping 500K array in the CoLaus cohort. All SNPs from this GWA study with a P value $\leq 10^{-5}$ were from two loci (Supplementary Fig. 2 online). We confirmed the importance of the previously described *AR* gene5-9 (OR for lead SNP rs6625163[A] = 3.30 (2.31-4.71), $P = 5.0 \times 10^{-11}$). We also located a new susceptibility locus on chromosome 20p11.22 (OR = 1.79 (1.49-2.15), $P = 3.2 \times 10^{-10}$ for rs1160312[A] and OR = 1.80 (1.49-2.16), $P = 3.5 \times 10^{-10}$ for rs913063[T]; the r^2 between rs1160312 and rs913063 was 1.0; Table 1). These SNPs are located over 350 kb distant to the nearest annotated gene, *PAX1*.

This same risk allele at rs1160312, rs1160312[A], was associated with an increased risk of androgenic alopecia in the TwinsUK cohort (OR = 1.68 (1.22-2.33), $P = 2.0 \times 10^{-3}$), hair loss in men in the Icelandic cohort (OR = 1.41 (1.10-1.79), $P = 6.1 \times 10^{-3}$) and androgenic alopecia in the Dutch cohort (OR = 1.40 (1.06-1.85), $P = 0.018$). In a combined analysis of all male cases and controls, the risk allele was strongly associated with hair loss (OR = 1.60 (1.42-1.80), $P = 1.1 \times 10^{-14}$). In addition, the same risk allele was associated with hair loss in women (OR = 1.24 (1.05-1.47), $P = 0.012$) for combined data from Icelandic and TwinsUK women (OR = 1.29 (1.05-1.57), $P = 0.01$ for Icelandic women; OR = 1.13 (0.82-1.56), $P = 0.45$ for women from the TwinsUK cohort).

We found that 14% of men harbored at least one risk allele at both 20p11.22 and the *AR* gene and that this was associated with a markedly increased risk of androgenic alopecia (OR = 7.12 (4.34-11.68), $P = 3.7 \times 10^{-15}$) in the CoLaus cohort. We observed no significant statistical interaction between the two loci. The variance in androgenic alopecia explained by the presence of at least one risk allele at both loci was 13.7%. Using all men from the population-based CoLaus study who did not meet case or control definitions and who were not included in the GWA scan ($n = 940$), we found that the ability of these two risk alleles to exclude the development of androgenic alopecia was high, but lacked specificity (negative predictive value = 96.5%, positive predictive value = 12.2%, sensitivity = 98.2%, specificity = 6.6%).

The rs1160312 SNP lies between *PAX1* and *FOXA2* on chromosome 20. It is not immediately clear how this gene might affect androgenic alopecia. Although rs1160312 is over 350 kb away from both genes, it remains possible that this SNP (or another variant in linkage disequilibrium with it) may influence the expression of either transcript through long-range control, as has been demonstrated for other genes involved in development11. How these variants affect disease outcomes deserves further investigation.

The fact that, despite a relatively small number of subjects, rs1160312 had a genome-wide significant association with androgenic alopecia in the discovery cohort alone and several other SNPs within the LD block bearing rs1160312 were associated with androgenic alopecia (Fig. 1) reflects the strength of the extreme discordant age-based case-control definitions. The phenotype from the Icelandic and the female TwinsUK cohorts was derived from self-reported hair loss, without the use of matching diagrams. Although this phenotype definition is less precise than that derived using diagram-matching techniques, which have been previously validated12, the association for males was replicated in Iceland and the results for females are consistent between the cohorts. However, it is necessary to investigate the association for female hair loss in larger and carefully phenotyped cohorts.

Even though the definition of hair loss and the method of sampling differed between the four study groups, the fact that the association was observed in all groups underscores the generalizability of our findings to other European populations. We also note that, as in any GWA study, the identified variant is likely to be in linkage disequilibrium with the causal SNP.

These results may have clinical significance. Androgenic alopecia is a disease of considerable social concern and the scalp is one of the few areas that are directly accessible by liposome–DNA mixtures13; this method has been demonstrated to result in hair-follicle transfection14. Therefore, if a variant at 20p11.22 influences expression of a transcript, such as *PAX1* or *FOXA2*, then manipulation of this pathway may lead to a target for gene therapy. However, demonstration of an influence of the chromosome 20p11.22 locus on transcription of either gene requires further investigation. The relatively high prevalence and magnitude of risk attributed to the risk alleles at both *AR* and 20p11.22 loci suggests that these markers may assist in the identification of groups of men at high risk for androgenic alopecia, and the absence of these risk alleles can be helpful in excluding its development.

In summary, we report a replicated GWA study for androgenic alopecia providing evidence from four distinct European populations for a newly associated locus that influences a common disorder of social importance. The risk alleles at this newly identified locus and *AR* are common in Europeans and impart a relatively large risk for androgenic alopecia. Given the feasibility of gene therapy in human follicles, our results may point to an intriguing new potential target for the treatment of hair loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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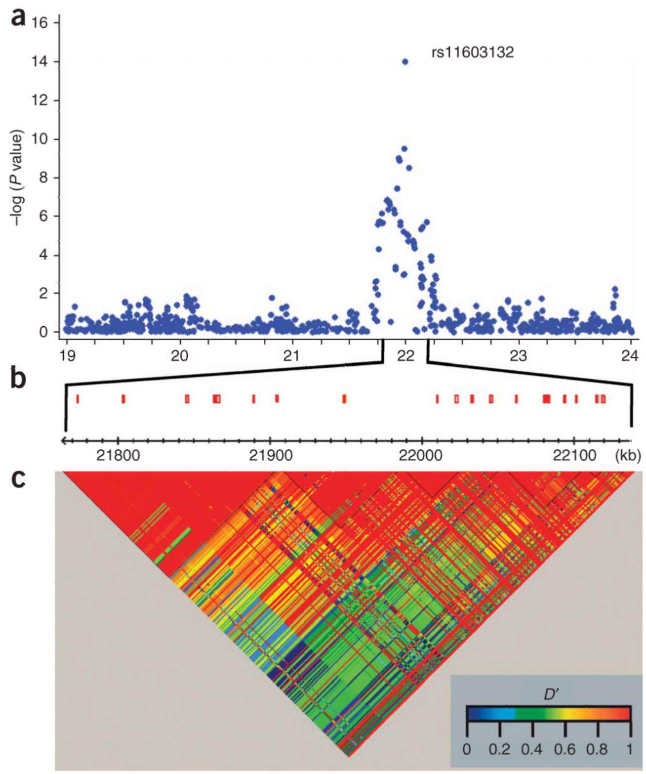

Figure 1.

Association between SNPs near chromosome 20p11.22 and androgenic alopecia. (**a**) −log (*P* value) measures for association between SNPs and chromosomal position. (**b**) Recombination hot spots (HapMap CEPH population, NCBI build 36). (**c**) Linkage disequilibrium in GOLD heat map Haploview 4.0 color scheme, CEPH population. The *x* axis represents genomic position in Mb (**a**) and in kb (**b,c**). All *P* values are derived from the CoLaus cohort, except that for the lead SNP, rs11603132, which is derived from the combined *P* value from the CoLaus, TwinsUK, Icelandic and Dutch cohorts.

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Table 1

Summary results for the lead SNP from the 20p11.22 locus for androgenic alopecia in men

			Sample size		Risk-allele frequency				
Marker	**Chr.**	**Cohort**	**Controls**	**Cases**	**Controls**	**Cases**	**OR per risk allele (95% CI)**	P	$P_{combined}$
rs1160312	20	CoLaus	547	578	0.43	0.57	1.79 (1.49-2.15)	3.2×10^{-10}	
A/G		TwinsUK	277	176	0.45	0.58	1.68 (1.22-2.33)	2.0×10^{-3}	
		Icelandic	198	536	0.56	0.64	1.41 (1.10-1.79)	6.1×10^{-3}	
		Dutch	316	147	0.52	0.60	1.40 (1.06-1.85)	0.018	
		All men	1,338	1,437			1.60 (1.42-1.80)		1.1×10^{-14}