Published in final edited form as:
Schizophr Res. 2013 December ; 151(0): 226–228. doi:10.1016/j.schres.2013.10.016.

The genetic overlap between schizophrenia and height

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Abstract

Epidemiological studies suggest that height and schizophrenia risk are inversely correlated. These findings might arise because i) height and schizophrenia share genetic variants and ii) the effects of these shared variants are in opposite direction for the two traits. We use genome wide association data to empirically evaluate these hypotheses. We find that variants which impact on height and risk for schizophrenia are distributed across several genomic regions and the directions of effect vary, some consistent and others inconsistent with the direction expected from the phenotypic data. Moreover, signals that were in and not in accord with the phenotypic data aggregated in distinct biological pathways.

Keywords

Shrinkage; Suggestive signals; Network analysis

1. Introduction

Schizophrenia (SCZ) is a severe psychiatric disorder with largely unknown etiology and a lifetime prevalence of 4–5 per 1000 (McGrath et al., 2008). However, the characteristics of subjects with SCZ have been extensively studied. Clinical and epidemiological studies dating back to the beginning of the 20th century suggest that there is a link between height (H) and SCZ (Burchard, 1916; Gunnell et al., 2005; Kemali et al., 1976; Nopoulos et al., 1998; Perrin et al., 2007; Zammit et al., 2007). The largest investigation, a study of 720,000 Swedish men and women, found an inverse relationship between height (H) and SCZ (Gunnell et al., 2005). The reported hazard ratio is substantial: 0.8 for every 10cm height increase. These findings were later confirmed by the largest study to date to look at the relationship between risk to SCZ and H, i.e. a Swedish epidemiological study of 1.35 million males which included the males from the study described above (Zammit et al., 2007). Coupled with the high heritability of SCZ (Sullivan et al., 2003) and H (Yang et al., 2010), these epidemiological findings suggest that i) H and SCZ share common genetic variants and ii) genetic variants which increase H are likely to decrease SCZ risk, i.e. the effect of the variants on the two phenotypes is in opposite directions (i.e. discordant).

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Contributors
SAB, KSK and XC designed the study. SAB undertook the statistical analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors declare that they have no conflict of interests.

Role of funding source
The funding source was not involved in designing or interpreting the study.

To evaluate the discordance hypothesis for common genetic effects of H and SCZ, we need a statistical method to assess the genetic overlap between any two phenotypes. One possible approach is to look at the overlap of significant findings for genome-wide association studies (GWASs) of these phenotypes. However, GWASs often fail to provide many significant signals, even more so for psychiatric disorders (Ripke et al., 2011; Sklar et al., 2011; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2012). Thus, because, with current sample sizes, many positive signals are likely to exhibit p-values at only "suggestive" levels, we can increase the power to detect genetic overlap pathways by analyzing the shared suggestive signals. The definition for suggestive signals is subjective: it requires the p-values to fall below a reasonably small threshold. However, the findings from pathway analyses are sensitive to the choice of p-value threshold. For instance, in the paper describing ALIGATOR software (Holmans et al., 2009), authors noted that increasing the p-value threshold from 10^{-4} to 10^{-2} improved the significance of different bipolar disorder pathways. Consequently, an objective, data driven method to set the p-value threshold for suggestive signals would be a useful tool in uncovering causal pathways for any phenotype/overlap of phenotypes.

In this paper, we use available GWAS data to obtain the likely overlapping genetic variants/pathways of H and SCZ. This goal is achieved by i) using a novel data driven method to obtain suggestive signals for each phenotype, ii) establishing the existence of a statistically significant overlap between H and SCZ suggestive signals and iii) performing pathway analyses for these overlapping suggestive signals. We use pathway analysis results to make inferences regarding possible SCZ etiologies.

2. Methods

To estimate the genetic overlap between H and SCZ, we use the normally distributed summary statistics, i.e. Z-scores, from the largest meta-analyses available (see Web Resources) for these traits (characteristics of the two meta-analyses are detailed in the Supplementary Material, henceforth abbreviated SM). For SCZ, the meta-analyses were performed by the Psychiatric Genetic Consortium (Ripke et al., 2011). The H meta-analysis was performed by the GIANT consortium (Lango et al., 2010).

To obtain the genetic overlap between two phenotypes, e.g. H and SCZ, we retain SNPs which harbor suggestive GWAS signals for both phenotypes. To objectively select the suggestive signal SNPs for each trait, we use a novel data-driven method (Bacanu and Kendler, 2012). This method utilizes a two-step procedure. First, an original shrinkage method is employed to accurately estimate the means of the GWAS Z-scores (see SM). Second, for a desirable sensitivity–specificity profile, we select as suggestive only SNPs having an estimated (adjusted) mean (of the Z-scores) above a threshold of three. (Given that the estimated means are obtained by shrinking the GWAS Z-scores toward zero, the original Z-scores often have a magnitude much larger than three.) The genetic overlap of the two phenotypes consists of SNPs which are deemed suggestive for both traits (see Table S1 for relevant characteristics of these signals).

3. Results

The number of suggestive SNPs in the overlap of the two traits was 51 when the expected number under a random sharing was estimated to be 21.32. However, not all these overlap SNPs are independent. It is more useful to report the number of quasi-independent signals, e.g. similar to the "clumped" ($r^2 \leq 0.25$) SNPs from the PGC paper (Ripke et al., 2011). Assuming i) 117,000 clumped SNPs, as reported in Ripke et al. (2011) and ii) the fractions of suggestive signals for the two phenotypes being, as estimated from our data (Table S1), 0.006 (H) and 0.0029 (SCZ), the expected number of clumped SNPs under independence is

estimated to be 2.03. The number of clumped SNPs in the overlap, as obtained using NIEHS tag SNPs (see Web Resources), was estimated to be 9. Assuming a Poisson distribution for the number of overlap clumped SNPs, the observed number (9) is significantly larger ($p = 2.6 \times 10^{-4}$) than the number expected (2.03) under the assumption of a random sharing of suggestive signals between the two phenotypes. Thus, our results strongly suggest that most overlap signals are likely to be true positive associations rather than chance findings. The large fraction of the true positives makes it possible to uncover the relevant molecular pathways via a pathway analysis, as detailed later on.

There are 6 distinct genomic regions that contain variants that impact on both phenotypes (Table 1). For three of these regions, as predicted by the epidemiological studies, the directions of genetic effects on the two phenotypes are discordant. These regions appear to affect the overall functioning of individual cells or of the entire organism, e.g. transcription regulation and immune response. Perhaps surprisingly, the other three regions show positively correlated or concordant effects, i.e. genetic effects for H and risk for SCZ are in the same direction. In fact, one such region (chromosome 3) exhibited the strongest minimum signal for the two phenotypes. These concordant regions seem to change the balance between cell proliferation and cell upkeep/maintenance.

To uncover the underlying molecular mechanisms for these overlapping signals, we used both Grail and Ingenuity Pathway Analysis (IPA) (www.ingenuity.com) to perform separate pathway analyses for SNPs with concordant and discordant effects on H and SCZ. Signals of discordant effects seem to be enriched in immune and cell function pathways (Table S2 for Grail and Fig. S1 for IPA). Overlapping SNPs with concordant effects on the two phenotypes appear to aggregate in cell division/proliferation pathways (Table S3 and Fig. S2).

4. Discussion

Classic epidemiological studies have found that H and SCZ risk are negatively correlated. Based on this fact, and given the high heritability of both traits, H and SCZ are likely to have mostly overlapping genetic causes of discordant effect. Our analyses confirmed that H and SCZ are likely to have overlapping genetic causes. However, their overlapping genetic regions seem to be evenly divided between those which have discordant and concordant genetic effects.

Our analyses suggest that SNPs with discordant and concordant effects on H and SCZ belong to distinct pathways which, in turn, might point to different etiologic paths to SCZ. SNPs with discordant effects on SCZ and H fall into pathways affecting the organism/cell fitness, e.g. immune system and DNA/chromatin packing. SNPs with concordant effects on H and SCZ aggregate into pathways likely affecting the equilibrium between cell growth and maintenance, e.g. cell proliferation and tumor suppression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SAB is supported by MH039096-26 grant from NIH.

References

Bacanu SA, Kendler KS. Extracting actionable information from genome scans. Genet Epidemiol. 2012; 37:48–59. [PubMed: 22996309]

Burchard, E. Comprehensive Psychological Monographs. Vol. 73. John Hopkins Press; Baltimore: 1916. Physique and psychosis. An analysis of the postulated relationship between bodily constitution and mental disease syndrom. (Ref Type: Serial, Book, Monograph)

Gunnell D, Harrison G, Whitley E, Lewis G, Tynelius P, Rasmussen F. The association of fetal and childhood growth with risk of schizophrenia. Cohort study of 720,000 Swedish men and women. Schizophr Res. 2005; 79:315–322. [PubMed: 16125903]

Holmans P, Green EK, Pahwa JS, Ferreira MA, Purcell SM, Sklar P, Owen MJ, O'Donovan MC, Craddock N. Gene ontology analysis of GWA study data sets provides insights into the biology of bipolar disorder. Am J Hum Genet. 2009; 85:13–24. [PubMed: 19539887]

Kemali D, Polani N, Polani PE, Amati A. A dermatoglyphic study of 219 Italian schizophrenic males. Clin Genet. 1976; 9:51–60. [PubMed: 1248163]

Lango AH, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, Willer CJ, Jackson AU, Vedantam S, Raychaudhuri S, Ferreira T, Wood AR, Weyant RJ, Segre AV, Speliotes EK, Wheeler E, Soranzo N, Park JH, Yang J, Gudbjartsson D, Heard-Costa NL, Randall JC, Qi L, Vernon SA, Magi R, Pastinen T, Liang L, Heid IM, Luan J, Thorleifsson G, Winkler TW, Goddard ME, Sin LK, Palmer C, Workalemahu T, Aulchenko YS, Johansson A, Zillikens MC, Feitosa MF, Esko T, Johnson T, Ketkar S, Kraft P, Mangino M, Prokopenko I, Absher D, Albrecht E, Ernst F, Glazer NL, Hayward C, Hottenga JJ, Jacobs KB, Knowles JW, Kutalik Z, Monda KL, Polasek O, Preuss M, Rayner NW, Robertson NR, Steinthorsdottir V, Tyrer JP, Voight BF, Wiklund F, Xu J, Zhao JH, Nyholt DR, Pellikka N, Perola M, Perry JR, Surakka I, Tammesoo ML, Altmaier EL, Amin N, Aspelund T, Bhangale T, Boucher G, Chasman DI, Chen C, Coin L, Cooper MN, Dixon AL, Gibson Q, Grundberg E, Hao K, Juhani JM, Kaplan LM, Kettunen J, Konig IR, Kwan T, Lawrence RW, Levinson DF, Lorentzon M, McKnight B, Morris AP, Muller M, Suh NJ, Purcell S, Rafelt S, Salem RM, Salvi E, Sanna S, Shi J, Sovio U, Thompson JR, Turchin MC, Vandenput L, Verlaan DJ, Vitart V, White CC, Ziegler A, Almgren P, Balmforth AJ, Campbell H, Citterio L, De GA, Dominiczak A, Duan J, Elliott P, Elosua R, Eriksson JG, Freimer NB, Geus EJ, Glorioso N, Haiqing S, Hartikainen AL, Havulinna AS, Hicks AA, Hui J, Igl W, Illig T, Jula A, Kajantie E, Kilpelainen TO, Koiranen M, Kolcic I, Koskinen S, Kovacs P, Laitinen J, Liu J, Lokki ML, Marusic A, Maschio A, Meitinger T, Mulas A, Pare G, Parker AN, Peden JF, Petersmann A, Pichler I, Pietilainen KH, Pouta A, Ridderstrale M, Rotter JI, Sambrook JG, Sanders AR, Schmidt CO, Sinisalo J, Smit JH, Stringham HM, Bragi WG, Widen E, Wild SH, Willemsen G, Zagato L, Zgaga L, Zitting P, Alavere H, Farrall M, McArdle WL, Nelis M, Peters MJ, Ripatti S, van Meurs JB, Aben KK, Ardlie KG, Beckmann JS, Beilby JP, Bergman RN, Bergmann S, Collins FS, Cusi D, den HM, Eiriksdottir G, Gejman PV, Hall AS, Hamsten A, Huikuri HV, Iribarren C, Kahonen M, Kaprio J, Kathiresan S, Kiemeney L, Kocher T, Launer LJ, Lehtimaki T, Melander O, Mosley TH Jr, Musk AW, Nieminen MS, O'Donnell CJ, Ohlsson C, Oostra B, Palmer LJ, Raitakari O, Ridker PM, Rioux JD, Rissanen A, Rivolta C, Schunkert H, Shuldiner AR, Siscovick DS, Stumvoll M, Tonjes A, Tuomilehto J, van Ommen GJ, Viikari J, Heath AC, Martin NG, Montgomery GW, Province MA, Kayser M, Arnold AM, Atwood LD, Boerwinkle E, Chanock SJ, Deloukas P, Gieger C, Gronberg H, Hall P, Hattersley AT, Hengstenberg C, Hoffman W, Lathrop GM, Salomaa V, Schreiber S, Uda M, Waterworth D, Wright AF, Assimes TL, Barroso I, Hofman A, Mohlke KL, Boomsma DI, Caulfield MJ, Cupples LA, Erdmann J, Fox CS, Gudnason V, Gyllensten U, Harris TB, Hayes RB, Jarvelin MR, Mooser V, Munroe PB, Ouwehand WH. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010; 467:832–838. [PubMed: 20881960]

Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry. 2012; 18:497–511. [PubMed: 22472876]

McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008; 30:67–76. [PubMed: 18480098]

Nopoulos P, Flaum M, Arndt S, Andreasen N. Morphometry in schizophrenia revisited: height and its relationship to pre-morbid function. Psychol Med. 1998; 28:655–663. [PubMed: 9626721]

Perrin MA, Chen H, Sandberg DE, Malaspina D, Brown AS. Growth trajectory during early life and risk of adult schizophrenia. Br J Psychiatry. 2007; 191:512–520. [PubMed: 18055955]

Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, Lin DY, Duan J, Ophoff RA, Andreassen OA, Scolnick E, Cichon S, St CD, Corvin A, Gurling H, Werge T, Rujescu D, Blackwood DH, Pato CN, Malhotra AK, Purcell S, Dudbridge F, Neale BM, Rossin L, Visscher PM, Posthuma D, Ruderfer DM, Fanous A, Stefansson H, Steinberg S, Mowry BJ, Golimbet V, De HM, Jonsson EG, Bitter I, Pietilainen OP, Collier DA, Tosato S, Agartz I, Albus M, Alexander M, Amdur RL, Amin F, Bass N, Bergen SE, Black DW, Borglum AD, Brown MA, Bruggeman R, Buccola NG, Byerley WF, Cahn W, Cantor RM, Carr VJ, Catts SV, Choudhury K, Cloninger CR, Cormican P, Craddock N, Danoy PA, Datta S, de HL, Demontis D, Dikeos D, Djurovic S, Donnelly P, Donohoe G, Duong L, Dwyer S, Fink-Jensen A, Freedman R, Freimer NB, Friedl M, Georgieva L, Giegling I, Gill M, Glenthoj B, Godard S, Hamshere M, Hansen M, Hansen T, Hartmann AM, Henskens FA, Hougaard DM, Hultman CM, Ingason A, Jablensky AV, Jakobsen KD, Jay M, Jurgens G, Kahn RS, Keller MC, Kenis G, Kenny E, Kim Y, Kirov GK, Konnerth H, Konte B, Krabbendam L, Krasucki R, Lasseter VK, Laurent C, Lawrence J, Lencz T, Lerer FB, Liang KY, Lichtenstein P, Lieberman JA, Linszen DH, Lonnqvist J, Loughland CM, Maclean AW, Maher BS, Maier W, Mallet J, Malloy P, Mattheisen M, Mattingsdal M, McGhee KA, McGrath JJ, McIntosh A, McLean DE, McQuillin A, Melle I, Michie PT, Milanova V, Morris DW, Mors O, Mortensen PB, Moskvina V, Muglia P, Myin-Germeys I, Nertney DA, Nestadt G, Nielsen J, Nikolov I, Nordentoft M, Norton N, Nothen MM, O'Dushlaine CT, Olincy A, Olsen L, O'Neill FA, Orntoft TF, Owen MJ, Pantelis C, Papadimitriou G, Pato MT, Peltonen L, Petursson H, Pickard B, Pimm J, Pulver AE, Puri V, Quested D, Quinn EM, Rasmussen HB, Rethelyi JM, Ribble R, Rietschel M, Riley BP, Ruggeri M, Schall U, Schulze TG, Schwab SG, Scott RJ, Shi J, Sigurdsson E, Silverman JM, Spencer CC, Stefansson K, Strange A, Strengman E, Stroup TS, Suvisaari J, Terenius L, Thirumalai S, Thygesen JH, Timm S, Toncheva D, van den Oord E, van OJ, van WR, Veldink J, Walsh D, Wang AG, Wiersma D, Wildenauer DB, Williams HJ, Williams NM, Wormley B, Zammit S, Sullivan PF, O'Donovan MC, Daly MJ, Gejman PV. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011; 43:969–976. [PubMed: 21926974]

Sklar P, Ripke S, Scott LJ, Andreassen OA, Cichon S, Craddock N, Edenberg HJ, Nurnberger JI Jr, Rietschel M, Blackwood D, Corvin A, Flickinger M, Guan W, Mattingsdal M, McQuillin A, Kwan P, Wienker TF, Daly M, Dudbridge F, Holmans PA, Lin D, Burmeister M, Greenwood TA, Hamshere ML, Muglia P, Smith EN, Zandi PP, Nievergelt CM, McKinney R, Shilling PD, Schork NJ, Bloss CS, Foroud T, Koller DL, Gershon ES, Liu C, Badner JA, Scheftner WA, Lawson WB, Nwulia EA, Hipolito M, Coryell W, Rice J, Byerley W, McMahon FJ, Schulze TG, Berrettini W, Lohoff FW, Potash JB, Mahon PB, McInnis MG, Zollner S, Zhang P, Craig DW, Szelinger S, Barrett TB, Breuer R, Meier S, Strohmaier J, Witt SH, Tozzi F, Farmer A, McGuffin P, Strauss J, Xu W, Kennedy JL, Vincent JB, Matthews K, Day R, Ferreira MA, O'Dushlaine C, Perlis R, Raychaudhuri S, Ruderfer D, Hyoun PL, Smoller JW, Li J, Absher D, Thompson RC, Meng FG, Schatzberg AF, Bunney WE, Barchas JD, Jones EG, Watson SJ, Myers RM, Akil H, Boehnke M, Chambert K, Moran J, Scolnick E, Djurovic S, Melle I, Morken G, Gill M, Morris D, Quinn E, Muhleisen TW, Degenhardt FA, Mattheisen M, Schumacher J, Maier W, Steffens M, Propping P, Nothen MM, Anjorin A, Bass N, Gurling H, Kandaswamy R, Lawrence J, McGhee K, McIntosh A, McLean AW, Muir WJ, Pickard BS, Breen G, St CD, Caesar S, Gordon-Smith K, Jones L, Fraser C, Green EK, Grozeva D, Jones IR, Kirov G, Moskvina V, Nikolov I, O'Donovan MC, Owen MJ, Collier DA, Elkin A, Williamson R, Young AH, Ferrier IN, Stefansson K, Stefansson H, Thornorgeirsson T, Steinberg S, Gustafsson O, Bergen SE, Nimgaonkar V, Hultman C, Landen M, Lichtenstein P, Sullivan P, Schalling M, Osby U, Backlund L, Frisen L, Langstrom N, Jamain S, Leboyer M, Etain B, Bellivier F, Petursson H, Sigur SE, Muller-Mysok B, Lucae S, Schwarz M, Schofield PR, Martin N, Montgomery GW, Lathrop M, Oskarsson H, Bauer M, Wright A, Mitchell PB, Hautzinger M, Reif A, Kelsoe JR, Purcell SM. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet. 2011; 43:977–983. [PubMed: 21926972]

Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003; 60:1187–1192. [PubMed: 14662550]

Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large

proportion of the heritability for human height. Nat Genet. 2010; 42:565–569. [PubMed: 20562875]

Zammit S, Rasmussen F, Farahmand B, Gunnell D, Lewis G, Tynelius P, Brobert GP. Height and body mass index in young adulthood and risk of schizophrenia: a longitudinal study of 1 347 520 Swedish men. Acta Psychiatr Scand. 2007; 116:378–385. [PubMed: 17919157]

Web references

GeneCards. http://www.genecards.org

Grail. http://www.broadinstitute.org/mpg/grail/

Height meta-analysis. http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files

Ingenuity Pathway Analysis. http://www.ingenuity.com

NIEHS tag SNP selection. http://snpinfo.niehs.nih.gov/snpinfo/snptag.htm

Psychiatric Genetics Consortium. SCZ/BD/MDD GWAS results. https://pgc.unc.edu/Results.php#Results2Date

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.10.016.

Table 1

The regions of genetic overlap between height and psychiatric disorders. The function of the genes closest to the overlap regions was obtained from GeneCards (www.genecards.org). Concordant denotes that the genetic effects on risk to schizophrenia and height are in the same direction.

Chr	HG18 position (Mb)	No. SNPs	No. clumped SNPs ($r^2 < 0.25$)	Genes	Gene function	Concordant
2	24.546	1	1	NCOA1	Hormone dependent transcription	N
				ITSN2	Clathrin-mediated endocytosis	
2	233.130–233.146	5	1	EIF4E2	Translation initiation	Y
3	52.512–53.036	33	3	ITIH cluster	Hyaluronan carriers, involved in cell proliferation	Y
6	26.261–26.396	7	2	HIST cluster	Regulator of transcription	N
6	31.349–32.787	3	1	HLA cluster	Immune system	N
20	54.274–54.285	2	1	MC3R	Pigmentation, energy homeostasis	Y
				C20orf108 (FAM210B)	Not well known	