

Lessons learned from the DNA of individuals with psychiatric disorders

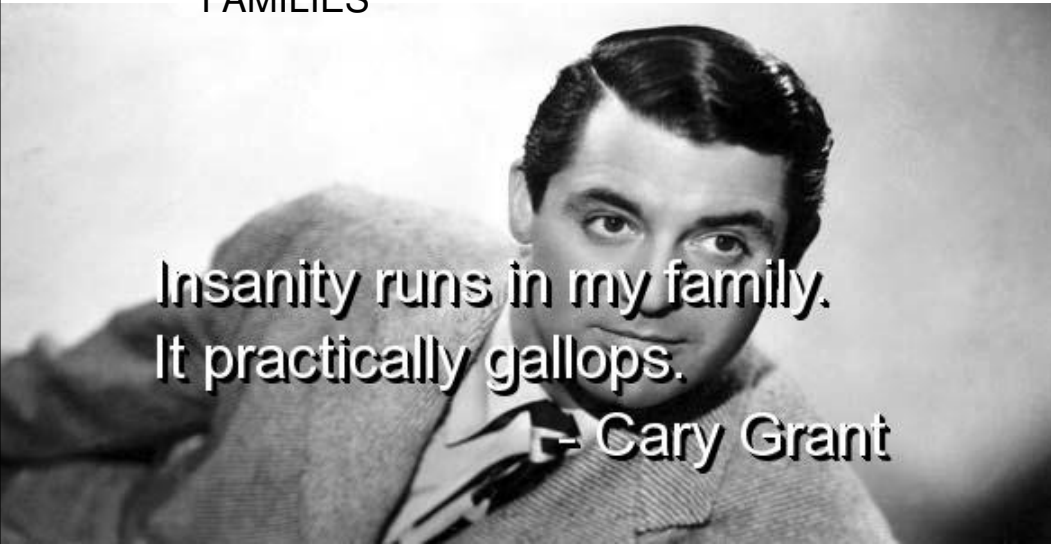
Daniel R. Weinberger, M.D.

Lieber Institute for Brain Development
Departments of Psychiatry, Neurology, Neuroscience,
and Genetic Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland 21205

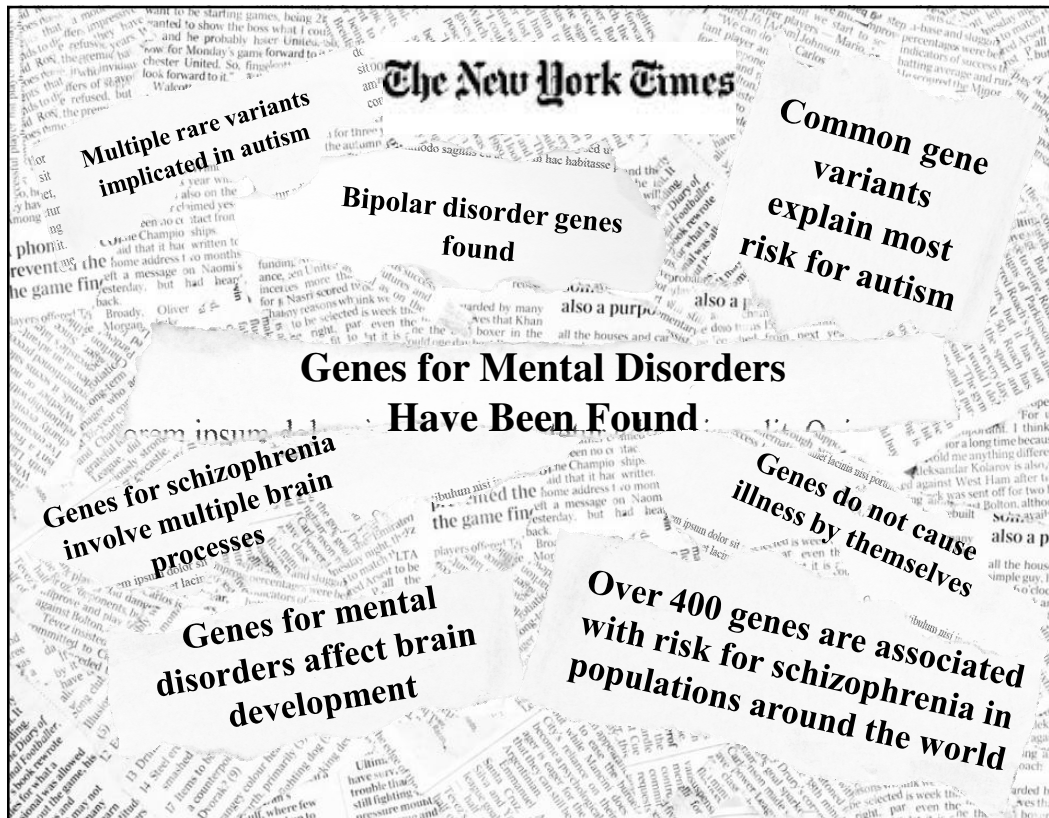
www.libd.org

LIEBER INSTITUTE *for*
BRAIN DEVELOPMENT
MALTZ RESEARCH LABORATORIES

WE'VE KNOWN FOR A LONG TIME
THAT PSYCHIATRIC ILLNESS RUNS IN
FAMILIES



Insanity runs in my family.
It practically gallops.
— Cary Grant



GENETICS AND MENTAL

GENES AND BEHAVIOR DISORDERS: WHY DO WE STUDY THEM?

- Most risk for psychiatric illness is related to inheritance
- Genes transcend phenomenological diagnosis
- Genes represent *mechanisms* of disease
- Genes clarify the environment
- Genes identify at risk individuals
- Genes identify biological pathways for development of new treatments

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

A *PEAK* AT SOME OF THE LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. The statistics are strong but the effects of individual genetic loci are very weak
3. Genetic risk does not respect DSM guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

A FEW DEFINITIONS:

Single nucleotide polymorphism "SNP": a common variation in DNA sequence at a single nucleotide

Allele: one of two or more variations in a DNA sequence at a specific site in the genome

Genotype: combination of variants at a locus in the genome

Genome wide association study (GWAS): comparisons of common allele frequencies in a sample of cases and a sample of controls

Pleiotropy: one gene affecting multiple seemingly unrelated traits

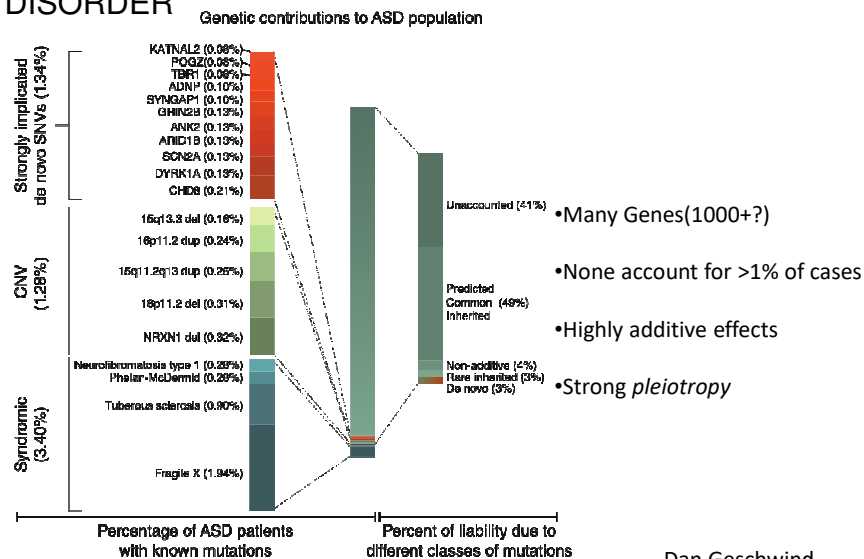
GENETICS OF BRAIN

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS: **Let's get started**

1. LITERALLY MANY HUNDREDS OF REGIONS OF THE GENOME THAT INCREASE RISK FOR MENTAL ILLNESS HAVE BEEN IDENTIFIED
2. The statistics are strong but the effects of individual genetic loci are very weak
3. Genetic risk does not respect DSM guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging.
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

GENETICS OF THE AUTISM SPECTRUM

GENETIC STUDIES OF AUTISM SPECTRUM DISORDER



GENOME WIDE ASSOCIATION STUDY (GWAS): THE WORK HORSE OF CLINICAL GENETICS OF COMMON DISORDERS



RECENT REPORTS HAVE IDENTIFIED MANY GENETIC LOCI ASSOCIATED WITH MANY HUMAN ILLNESSES AND TRAITS

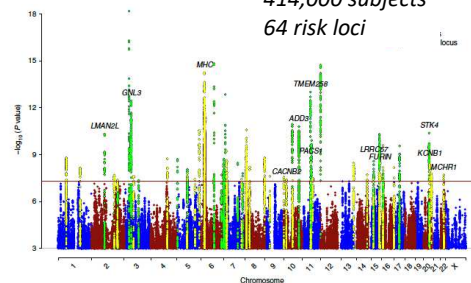
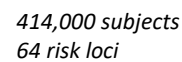
Mapping genomic loci implicates genes and synaptic biology in schizophrenia

<https://doi.org/10.1038/s41586-022-04434-5> A list of authors and their affiliations appears at the end of the paper.

<https://doi.org/10.1038/s41588-021-00857-4>

 Check for updates

Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology 2021



GENES AND PSYCHIATRIC DISORDERS

RECENT REPORTS HAVE IDENTIFIED MANY GENETIC LOCI ASSOCIATED WITH MANY HUMAN ILLNESSES AND TRAITS



Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions

Daniel F. Levey^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220,1221,1222,1223,1224,1225,1226,1227,1228,1229,1230,1231,1232,1233,1234,1235,1236,1237,1238,1239,1240,1241,1242,1243,1244,1245,1246,1247,1248,1249,1250,1251,1252,1253,1254,1255,1256,1257,1258,1259,1260,1261,1262,1263,1264,1265,1266,1267,1268,1269,1270,1271,1272,1273,1274,1275,1276,1277,1278,1279,1280,1281,1282,1283,1284,1285,1286,1287,1288,1289,1290,1291,1292,1293,1294,1295,1296,1297,1298,1299,1300,1301,1302,1303,1304,1305,1306,1307,1308,1309,1310,1311,1312,1313,1314,1315,1316,1317,1318,1319,1320,1321,1322,1323,1324,1325,1326,1327,1328,1329,1330,1331,1332,1333,1334,1335,1336,1337,1338,1339,1340,1341,1342,1343,1344,1345,1346,1347,1348,1349,1350,1351,1352,1353,1354,1355,1356,1357,1358,1359,1360,1361,1362,1363,1364,1365,1366,1367,1368,1369,1370,1371,1372,1373,1374,1375,1376,1377,1378,1379,1380,1381,1382,1383,1384,1385,1386,1387,1388,1389,1390,1391,1392,1393,1394,1395,1396,1397,1398,1399,1400,1401,1402,1403,1404,1405,1406,1407,1408,1409,1410,1411,1412,1413,1414,1415,1416,1417,1418,1419,1420,1421,1422,1423,1424,1425,1426,1427,1428,1429,1430,1431,1432,1433,1434,1435,1436,1437,1438,1439,1440,1441,1442,1443,1444,1445,1446,1447,1448,1449,1450,1451,1452,1453,1454,1455,1456,1457,1458,1459,1460,1461,1462,1463,1464,1465,1466,1467,1468,1469,1470,1471,1472,1473,1474,1475,1476,1477,1478,1479,1480,1481,1482,1483,1484,1485,1486,1487,1488,1489,1490,1491,1492,1493,1494,1495,1496,1497,1498,1499,1500,1501,1502,1503,1504,1505,1506,1507,1508,1509,1510,1511,1512,1513,1514,1515,1516,1517,1518,1519,1520,1521,1522,1523,1524,1525,1526,1527,1528,1529,1530,1531,1532,1533,1534,1535,1536,1537,1538,1539,1540,1541,1542,1543,1544,1545,1546,1547,1548,1549,1550,1551,1552,1553,1554,1555,1556,1557,1558,1559,1560,1561,1562,1563,1564,1565,1566,1567,1568,1569,1570,1571,1572,1573,1574,1575,1576,1577,1578,1579,1580,1581,1582,1583,1584,1585,1586,1587,1588,1589,1590,1591,1592,1593,1594,1595,1596,1597,1598,1599,1600,1601,1602,1603,1604,1605,1606,1607,1608,1609,1610,1611,1612,1613,1614,1615,1616,1617,1618,1619,1620,1621,1622,1623,1624,1625,1626,1627,1628,1629,1630,1631,1632,1633,1634,1635,1636,1637,1638,1639,1640,1641,1642,1643,1644,1645,1646,1647,1648,1649,1650,1651,1652,1653,1654,1655,1656,1657,1658,1659,1660,1661,1662,1663,1664,1665,1666,1667,1668,1669,1670,1671,1672,1673,1674,1675,1676,1677,1678,1679,1680,1681,1682,1683,1684,1685,1686,1687,1688,1689,1690,1691,1692,1693,1694,1695,1696,1697,1698,1699,1700,1701,1702,1703,1704,1705,1706,1707,1708,1709,1710,1711,1712,1713,1714,1715,1716,1717,1718,1719,1720,1721,1722,1723,1724,1725,1726,1727,1728,1729,1730,1731,1732,1733,1734,1735,1736,1737,1738,1739,1740,1741,1742,1743,1744,1745,1746,1747,1748,1749,1750,1751,1752,1753,1754,1755,1756,1757,1758,1759,1760,1761,1762,1763,1764,1765,1766,1767,1768,1769,1770,1771,1772,1773,1774,1775,1776,1777,1778,1779,1780,1781,1782,1783,1784,1785,1786,1787,1788,1789,1790,1791,1792,1793,1794,1795,1796,1797,1798,1799,1800,1801,1802,1803,1804,1805,1806,1807,1808,1809,1810,1811,1812,1813,1814,1815,1816,1817,1818,1819,1820,1821,1822,1823,1824,1825,1826,1827,1828,1829,1830,1831,1832,1833,1834,1835,1836,1837,1838,1839,1840,1841,1842,1843,1844,1845,1846,1847,1848,1849,1850,1851,1852,1853,1854,1855,1856,1857,1858,1859,1860,1861,1862,1863,1864,1865,1866,1867,1868,1869,1870,1871,1872,1873,1874,1875,1876,1877,1878,1879,1880,1881,1882,1883,1884,1885,1886,1887,1888,1889,1890,1891,1892,1893,1894,1895,1896,1897,1898,1899,1900,1901,1902,1903,1904,1905,1906,1907,1908,1909,1910,1911,1912,1913,1914,1915,1916,1917,1918,1919,1920,1921,1922,1923,1924,1925,1926,1927,1928,1929,1930,1931,1932,1933,1934,1935,1936,1937,1938,1939,1940,1941,1942,1943,1944,1945,1946,1947,1948,1949,1950,1951,1952,1953,1954,1955,1956,1957,1958,1959,1960,1961,1962,1963,1964,1965,1966,1967,1968,1969,1970,1971,1972,1973,1974,1975,1976,1977,1978,1979,1980,1981,1982,1983,1984,1985,1986,1987,1988,1989,1990,1991,1992,1993,1994,1995,1996,1997,1998,1999,2000,2001,2002,2003,2004,2005,2006,2007,2008,2009,2010,2011,2012,2013,2014,2015,2016,2017,2018,2019,2020,2021,2022,2023,2024,2025,2026,2027,2028,2029,2030,2031,2032,2033,2034,2035,2036,2037,2038,2039,2040,2041,2042,2043,2044,2045,2046,2047,2048,2049,2050,2051,2052,2053,2054,2055,2056,2057,2058,2059,2060,2061,2062,2063,2064,2065,2066,2067,2068,2069,2070,2071,2072,2073,2074,2075,2076,2077,2078,2079,2080,2081,2082,2083,2084,2085,2086,2087,2088,2089,2090,2091,2092,2093,2094,2095,2096,2097,2098,2099,2100,2101,2102,2103,2104,2105,2106,2107,2108,2109,2110,2111,2112,2113,2114,2115,2116,2117,2118,2119,2120,2121,2122,2123,2124,2125,2126,2127,2128,2129,2130,2131,2132,2133,2134,2135,2136,2137,2138,2139,2140,2141,2142,2143,2144,2145,2146,2147,2148,2149,2150,2151,2152,2153,2154,2155,2156,2157,2158,2159,2160,2161,2162,2163,2164,2165,2166,2167,2168,2169,2170,2171,2172,2173,2174,2175,2176,2177,2178,2179,2180,2181,2182,2183,2184,2185,2186,2187,2188,2189,2190,2191,2192,2193,2194,2195,2196,2197,2198,2199,2200,2201,2202,2203,2204,2205,2206,2207,2208,2209,2210,2211,2212,2213,2214,2215,2216,2217,2218,2219,2220,2221,2222,2223,2224,2225,2226,2227,2228,2229,2230,2231,2232,2233,2234,2235,2236,2237,2238,2239,2240,2241,2242,2243,2244,2245,2246,2247,2248,2249,2250,2251,2252,2253,2254,2255,2256,2257,2258,2259,2260,2261,2262,2263,2264,2265,2266,2267,2268,2269,2270,2271,2272,2273,2274,2275,2276,2277,2278,2279,2280,2281,2282,2283,2284,2285,2286,2287,2288,2289,2290,2291,2292,2293,2294,2295,2296,2297,2298,2299,2300,2301,2302,2303,2304,2305,2306,2307,2308,2309,2310,2311,2312,2313,2314,2315,2316,2317,2318,2319,2320,2321,2322,2323,2324,2325,2326,2327,2328,2329,2330,2331,2332,2333,2334,2335,2336,2337,2338,2339,2340,2341,2342,2343,2344,2345,2346,2347,2348,2349,2350,2351,2352,2353,2354,2355,2356,2357,2358,2359,2360,2361,2362,2363,2364,2365,2366,2367,2368,2369,2370,2371,2372,2373,2374,2375,2376,2377,2378,2379,2380,2381,2382,2383,2384,2385,2386,2387,2388,2389,2390,2391,2392,2393,2394,2395,2396,2397,2398,2399,2400,2401,2402,2403,2404,2405,2406,2407,2408,2409,2410,2411,2412,2413,2414,2415,2416,2417,2418,2419,2420,2421,2422,2423,2424,2425,2426,2427,2428,2429,2430,2431,2432,2433,2434,2435,2436,2437,2438,2439,2440,2441,2442,2443,2444,2445,2446,2447,2448,2449,2450,2451,2452,2453,2454,2455,2456,2457,2458,2459,2460,2461,2462,2463,2464,2465,2466,2467,2468,2469,2470,2471,2472,2473,2474,2475,2476,2477,2478,2479,2480,2481,2482,2483,2484,2485,2486,2487,2488,2489,2490,2491,2492,2493,2494,2495,2496,2497,2498,2499,2500,2501,2502,2503,2504,2505,2506,2507,2508,2509,2510,2511,2512,2513,2514,2515,2516,2517,2518,2519,2520,2521,2522,2523,2524,2525,2526,2527,2528,2529,2530,2531,2532,2533,2534,2535,2536,2537,2538,2539,2540,2541,2542,2543,2544,2545,2546,2547,2548,2549,2550,2551,2552,2553,2554,2555,2556,2557,2558,2559,2560,2561,2562,2563,2564,2565,2566,2567,2568,2569,2570,2571,2572,2573,2574,2575,2576,2577,2578,2579,2580,2581,2582,2583,2584,2585,2586,2587,2588,2589,2590,2591,2592,2593,2594,2595,2596,2597,2598,2599,2600,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2611,2612,2613,2614,2615,2616,2617,2618,2619,2620,2621,2622,2623,2624,2625,2626,2627,2628,2629,2630,2631,2632,2633,2634,2635,2636,2637,2638,2639,264}

GENETICS OF BRAIN

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. THE STATISTICS ARE STRONG, BUT THE EFFECTS OF INDIVIDUAL GENETIC LOCI ARE VERY WEAK
3. Genetic risk does not respect DSM guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging.
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

GENETICS OF PSYCHIATRIC ILLNESS

THE STATISTICS ARE STRONG....BUT THE EFFECTS ARE WEAK

Schizophrenia

SNP	CHR	BP	P	OR	SE	A1A2	FRQ A 74776	FRQ U 101023
rs140365013	6	27523869	1.205E-39	1.22838	0.0156	G/A	0.931	0.944
rs58120505	7	2029867	6.265E-28	1.086	0.0075	T/C	0.582	0.557
rs1790135	12	12366923	6.908E-24	1.08785	0.0084	C/T	0.32	0.281
rs12571643	10	10452027	1.246E-23	1.12019	0.0113	G/A	0.863	0.856
rs4702	15	9142650	1.797E-23	1.0822	0.0079	G/A	0.436	0.432
rs2710323	3	5281590	3.175E-22	1.07433	0.0074	T/C	0.525	0.512
rs4298967	12	240819	1.279E-21	1.086	0.0086	A/G	0.279	0.282
rs13107325	4	103188709	1.919E-21	0.85496	0.0165	C/T	0.925	0.936
rs2139054	2	58156583	1.045E-20	0.9309	0.0077	A/C	0.35	0.379
rs7779548	7	137074540	1.821E-19	1.0779	0.0079	G/A	0.686	0.66

Bipolar Disorder

Table 1 | Genome-wide significant loci for BD from meta-analysis of 41,917 cases and 371,549 controls

Locus	CHR	BP	SNP	P	OR	s.e.	A1/A2	frq. controls	Previous report* for BD (citation)	Name for novel locus*	Previous report* for psychiatric disorders
1	1	6105668	rs2126180	1.6x10 ⁻⁹	1.058	0.009	A/G	0.457		LINC01748	
2	1	163745389	rs1073749	7.2x10 ⁻⁹	1.056	0.009	C/T	0.444		NUP2	CDG
3*	2	9741653	rs461965	4.8x10 ⁻¹¹	1.068	0.010	G/A	0.670		MAN2L1 (PGC2)	CDG
4	2	166152389	rs1718381	2.7x10 ⁻⁸	1.108	0.019	G/A	0.924		MAN2A (PGC2)	
5	2	169481837	rs1341726	2.1x10 ⁻⁸	1.064	0.011	C/G	0.758		CERS6	
6	2	193738336	rs2011302	4.3x10 ⁻⁸	1.055	0.010	A/T	0.377		PCGEM1	CDG
7	2	194437889	rs2779164	4.9x10 ⁻⁸	1.053	0.010	A/G	0.564		Intergenic (PGC2)	CDG
8*	3	36856030	rs9834970	1x10 ⁻⁸	1.087	0.009	C/T	0.48		TRANK1 (PGC2)	SCZ, CDG
9*	3	52626443	rs2335147	3.6x10 ⁻⁸	1.070	0.009	T/C	0.58		ITIH1 (PGC2)	SCZ, CDG
10	3	70488788	rs15694474	2.4x10 ⁻⁸	1.068	0.012	T/A	0.799		MDR1C2	

GENETICS OF PSYCHIATRIC ILLNESS

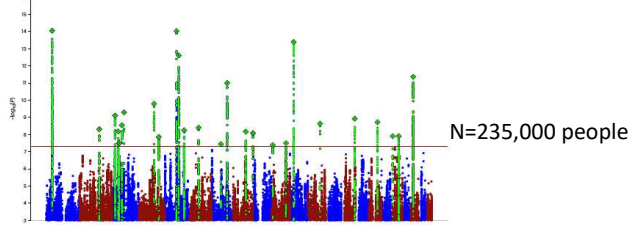
nature genetics

Article

<https://doi.org/10.1038/s41588-022-01285-8>

Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains

Nature 2023



Genomic locus	Chr.	Position (bp)	rs ID	A1	A2	Neighb. genes	Freq. cases	Freq. controls	OR	s.d.	P-value	New
1	1	44076469	rs549845	G	A	PTPRF, KDMA4	0.321	0.326	1.082	0.01	9.03×10^{-4}	No
2	2	145714354	rs1438898	A	C		0.762	0.769	1.065	0.01	4.88×10^{-4}	Yes
3	3	20724204	rs2986697	G	A		0.634	0.643	1.061	0.01	7.90×10^{-5}	No
4	3	43691501	rs9877066	G	A	SNRK, ANO10, ABHD5	0.944	0.951	0.888	1.02	6.60×10^{-4}	Yes
5	3	49916710	rs7613360	C	T	TRAP, CAMK1V, MSTR, CTD-233K9.3, MON1A	0.598	0.614	0.948	1.01	3.18×10^{-4}	Yes
6	3	51884072	rs2310569	G	A	IQCF3, IQCF2, IQCF5, IQCF1	0.314	0.308	0.944	1.01	3.16×10^{-4}	Yes
7	3	71499401	rs7778444	C	T	FOXP1	0.695	0.660	1.063	1.01	2.67×10^{-4}	Yes
8	3	87015142	rs114142727	C	G	VGLL3	0.988	0.988	1.285	1.04	5.13×10^{-5}	Yes
9	4	11217523	rs7576773	C	T		0.888	0.880	1.101	0.02	1.63×10^{-5}	Yes
10	4	147099654	rs6537401	G	A	LSM6, RPH1-GLB2, SLC10A7	0.660	0.655	0.945	0.01	1.40×10^{-4}	Yes

LIBD

GENETICS OF BRAIN

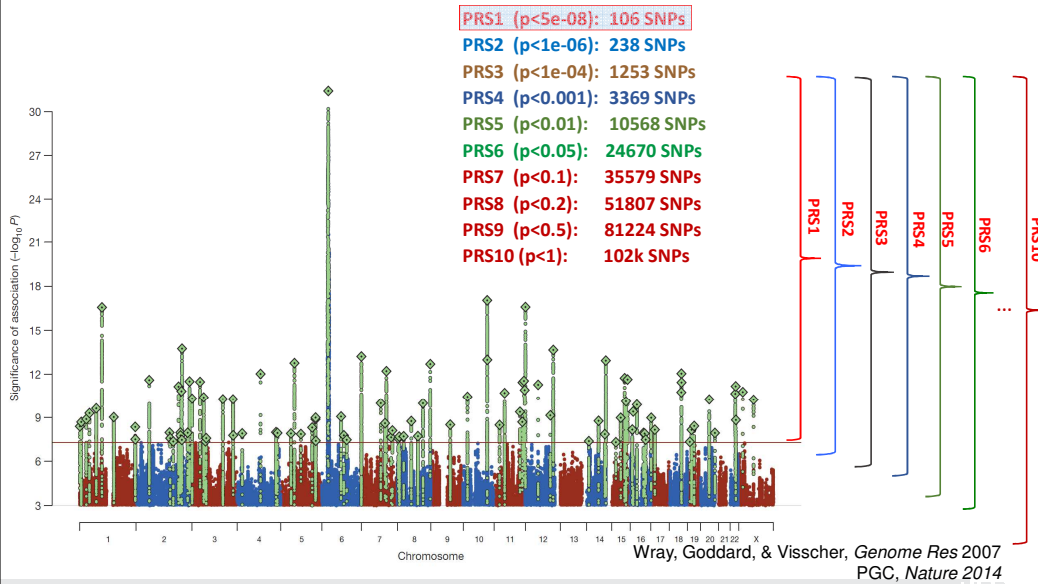
LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. THE STATISTICS ARE STRONG, BUT THE EFFECTS OF INDIVIDUAL GENETIC LOCI ARE VERY WEAK
3. Genetic risk does not respect DSM guidelines
4. PREDICTION OF INDIVIDUAL ILLNESS LIABILITY BASED ON GENOMIC RISK IS SO FAR NOT OF CLINICAL VALUE
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging.
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

METHODS: GENOMIC RISK CALCULATION

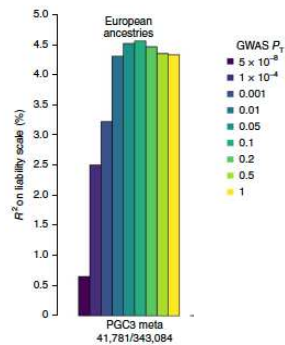
POLYGENIC RISK SCORES (PRS): ADDING UP ALL THE RISK ALLELES



POLYGENIC RISK PREDICTION



Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology

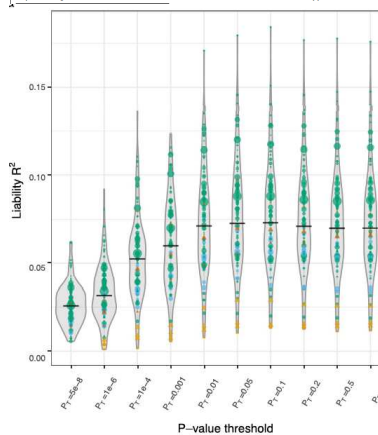


Article

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

Nature 2022

<https://doi.org/10.1038/s41586-022-04434-5> A list of authors and their affiliations appears at the end of the paper.



LESSONS LEARNED FROM DNA

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. The statistics are strong, but the effects of individual genetic loci are very weak
3. **GENETIC RISK DOES NOT RESPECT DSM GUIDELINES**
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging.
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

PLEOTROPY IS THE RULE

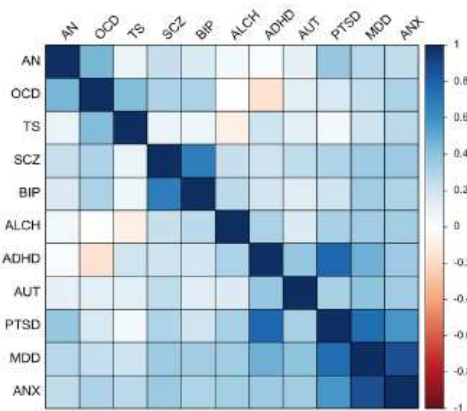
medRxiv preprint doi: <https://doi.org/10.1101/2020.09.22.20196069>; this version posted September 23, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-NC-ND 4.0 International license.

Stratified Genomic SEM

1

1 Genetic Architecture of 11 Major Psychiatric Disorders at Biobehavioral, Functional
2 Genomic, and Molecular Genetic Levels of Analysis
3

Andrew D. Grotzinger,^{1,2} Travis T. Mallard,¹ Woniola A. Akingbuwa,² Hill F. Ip,² Mark J. Adams,² Cathryn M. Lewis,⁴ Andrew M. McIntosh,² Jakob Grove,² Søren Dalsgaard,⁴ Klaus-Peter Lesch,^{7,9} Nora Strom,^{10,12} Sandra M. Meier,^{13,14} Manuel Mattheisen,^{1,3,15} Anders D.



Correlational structure of risk genes for psychiatric diagnoses

LESSONS LEARNED FROM DNA

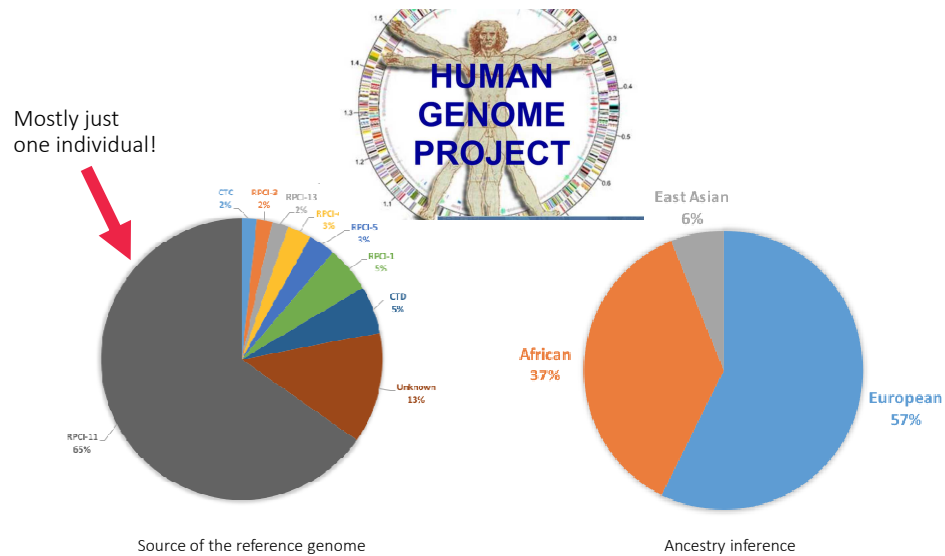
LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. The statistics are strong, but the effects of individual genetic loci are very weak
3. Genetic risk does not respect dsm guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. ANCESTRY MATTERS
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging.
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

HUMAN REFERENCE GENOME

WHO IS THE HUMAN REFERENCE GENOME?



Green et al (2010). *Science*.

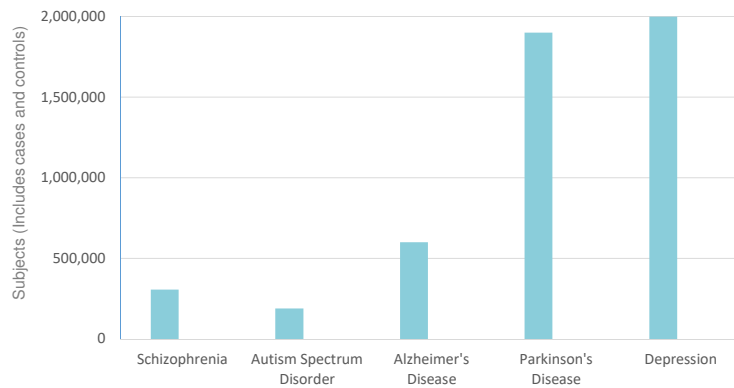
RESEARCH DISPARITIES

4.9+ MILLION research subjects worldwide

ZERO Individuals of African Ancestry

Until 2021, genome-wide association studies (GWAS) for schizophrenia, autism, Alzheimer's, Parkinson's, and depression.

Ancestry Representation in Latest GWAS:
African ancestry cohort = N of ZERO

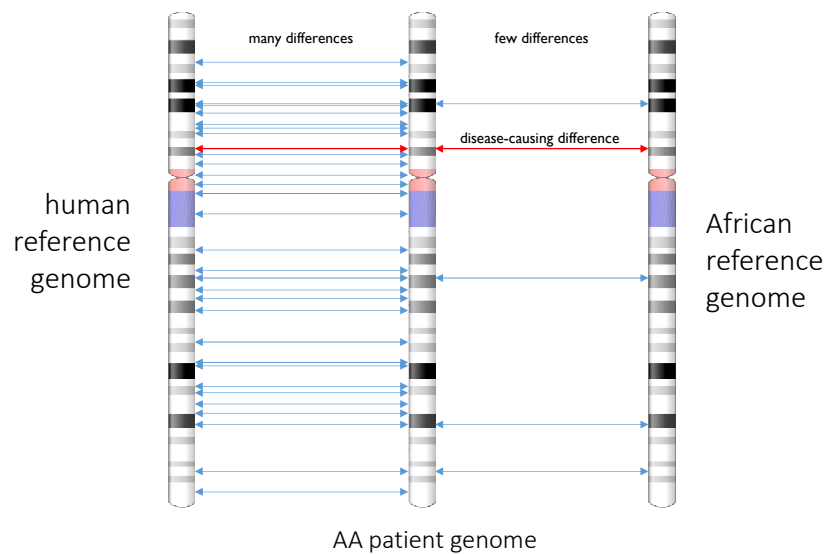


Neuron

Weinberger, Dzirasa,
Crompton-Young.
August 5, 2020

HUMAN REFERENCE GENOME

WHY IS THE REFERENCE GENOME A PROBLEM?



ANCESTRY MATTERS

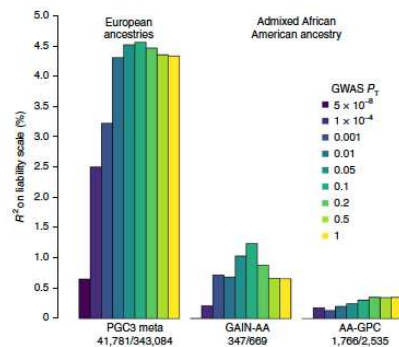
nature
genetics

ARTICLES

<https://doi.org/10.1038/s41588-020-06821-4>

Check for updates

Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology



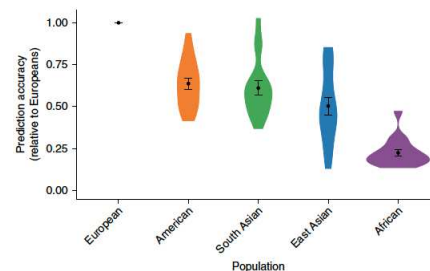
PERSPECTIVE

nature
genetics

Clinical use of current polygenic risk scores may exacerbate health disparities

Alicia R. Martin^{1,2,3,4*}, Masahiro Kana^{1,2,3,4,5}, Yoichiro Kamatani^{1,2,3,4,5}, Yukinori Okada^{1,2,3,4,5}, Benjamin M. Neale^{1,2,3,4,5} and Mark J. Daly^{1,2,3,4,5}

2019



25

LIBD

LESSONS LEARNED FROM DNA

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

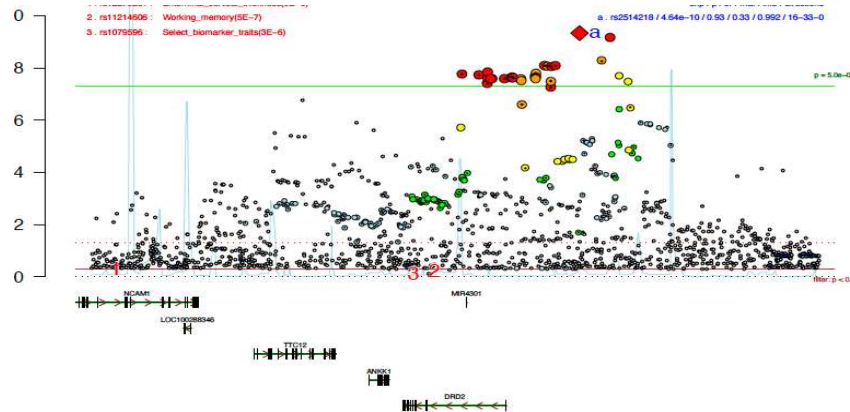
1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. The statistics are strong, but the effects of individual genetic loci are very weak
3. Genetic risk does not respect dsm guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS IS A TREASURE MAP, BUT TO FIND THE TREASURE (I.E. THE GENES) REQUIRES A LOT MORE DIGGING.
7. The environment still matters
8. Genetic discoveries provide biological insights into brain mechanisms of illness and potential strategies for treatment and prevention

26

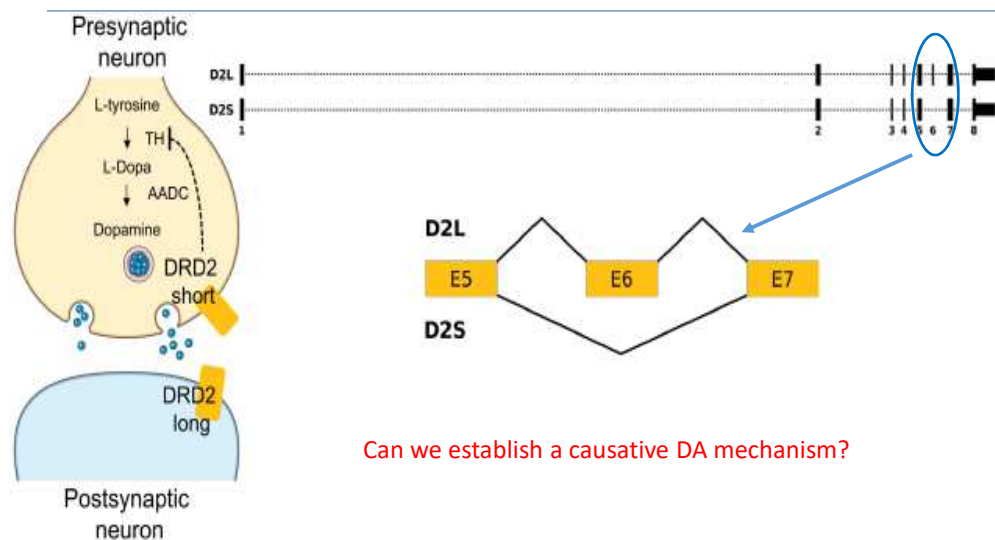
LIBD

WHITHER THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA?

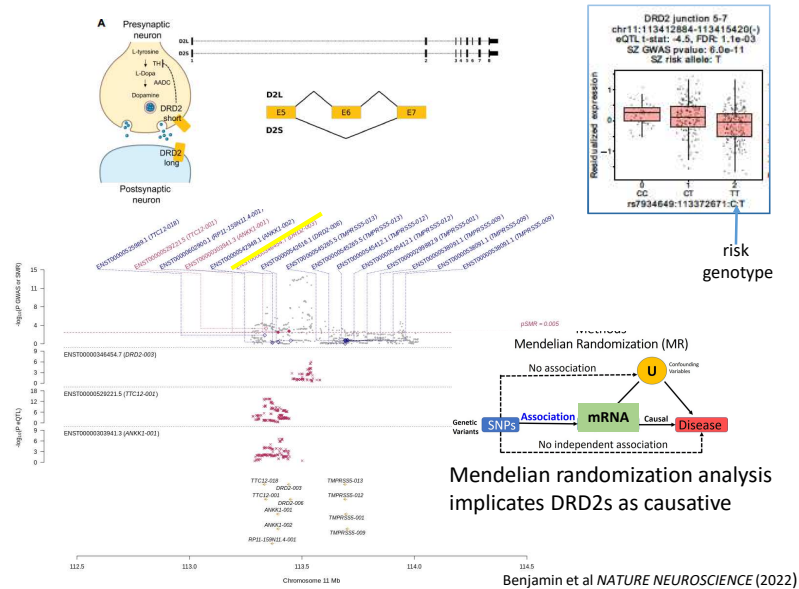
DRD2 is in one of the GWAS risk regions!!!



DIGGING DEEPER INTO *DRD2* IN BRAIN



THE MECHANISM OF THE DOPAMINE (DA) LINK TO RISK FOR PSYCHOSIS?
It's diminished control of presynaptic DA release!



LESSONS LEARNED FROM DNA

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. The statistics are strong, but the effects of individual genetic loci are very weak
3. Genetic risk does not respect dsm guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging
7. **The environment still matters**
8. **GENETIC DISCOVERIES PROVIDE BIOLOGICAL INSIGHTS INTO BRAIN MECHANISMS OF ILLNESS AND POTENTIAL STRATEGIES FOR TREATMENT AND PREVENTION**

GENE x ENVIRONMENT

ALL VERY INTERESTING BIOLOGY.....BUT THAT ELUSIVE ENVIRONMENTAL COMPONENT IS THE ...



How about GxE?

GENETIC RISK X EARLY LIFE COMPLICATION

nature
medicine

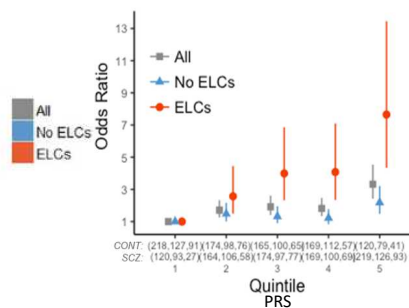
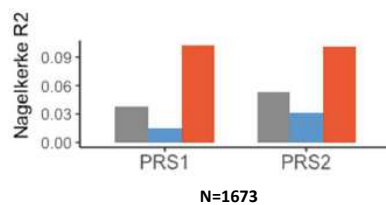
ARTICLES

<https://doi.org/10.1038/s41591-018-0021-y>

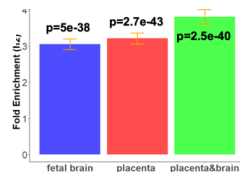
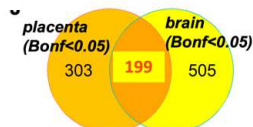
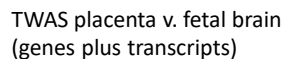
Convergence of placenta biology and genetic risk for schizophrenia

Gianluca Ursini^{1,2,3}, Giovanna Punzi^{1,2}, Qiang Chen¹, Stefano Marengo^{4,5}, Joshua F. Robinson⁶, Annamaria Porcell⁷, Emily G. Hamilton⁸, Marina Mitjans⁹, Giancarlo Maddalena², Martin Begemann⁷, Jan Seidel⁷, Hidenaga Yanamori⁸, Andrew E. Jaffe¹⁰, Karen F. Berman⁴, Michael F. Egan¹⁰, Richard E. Straub¹, Carlo Colantuoni^{11,12,13}, Giuseppe Blasi¹⁴, Ryota Hashimoto^{15,16}, Dan Rujescu¹⁵, Hannelore Ehrenreich¹, Alessandro Bertolino² and Daniel R. Weinberger^{1,3,17,18,19}

2018



PRIORITIZATION OF POTENTIAL CAUSATIVE GENES FOR SCHIZOPHRENIA IN PLACENTA

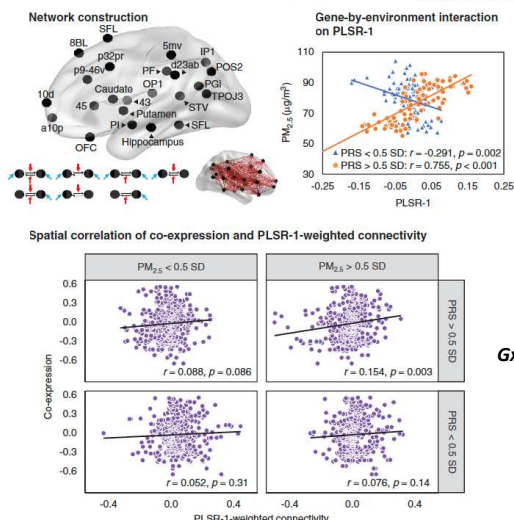


Enrichment fold for heritability

Ursini et al *Nature Comm* 2023

AS Air pollution interacts with genetic risk to influence cortical networks implicated in depression

PNAS 2021 Vol. 118 No. 46 e2109310118

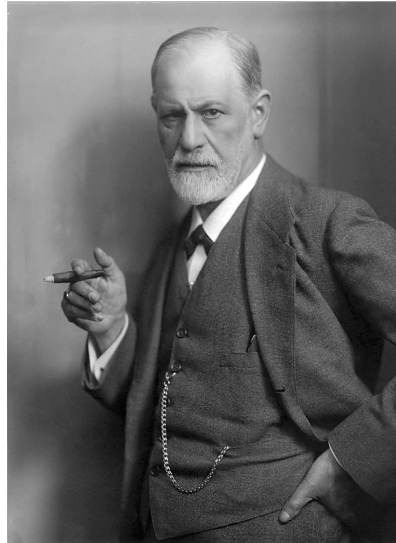


Dynamic causal
model of fMRI network
during social stress

GxE in network coexpression
of depression risk
(GWAS) genes in brain

EARLY LIFE EXPERIENCE

DOES EARLY CHILDHOOD MATTER?



LIBD

GxE: CHILDHOOD TRAUMA AND RISK FOR DEPRESSION

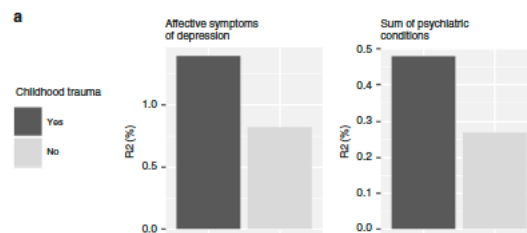
nature COMMUNICATIONS

ARTICLE <https://doi.org/10.1038/s41467-020-18400-9> OPEN [Check for updates](#)

A phenome-wide association and Mendelian Randomisation study of polygenic risk for depression in UK Biobank

Xueyi Shen¹, David M. Howard^{1,2}, Mark J. Adams¹, W. David Hill^{3,4}, Toni-Kim Clarke¹, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium⁵, Ian J. Deary^{1,6}, Heather C. Whalley^{1,10,11} & Andrew M. McIntosh^{1,3,4,12,13}

2020

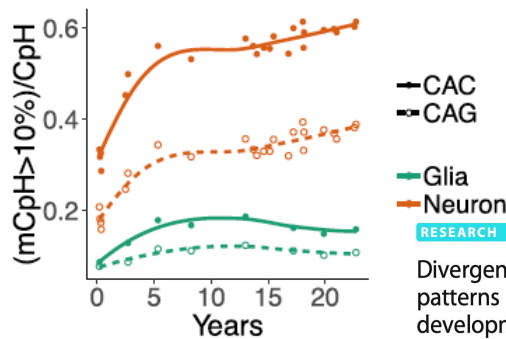


History of childhood trauma doubles the risk related to genes for depression

URGENT NEED

EARLY CHILDHOOD EXPERIENCE LEAVES ITS MARK IN THE GENOME

The human genome is most sensitive to environmental experience during the first five years of life, more than any other time. These findings highlight the potential biological impact of early childhood adversity.



RESEARCH

Open Access

Divergent neuronal DNA methylation patterns across human cortical development reveal critical periods and a unique role of CpH methylation

Amanda J. Price^{1,2†}, Leonardo Collado-Torres^{1,3†}, Nikolay A. Ivanov¹, Wei Xia¹, Emily E. Burke¹, Joo Heon Shin¹, Ran Tao¹, Liang Ma¹, Yankai Jia¹, Thomas M. Hyde^{1,4,5}, Joel E. Kleinman^{1,5}, Daniel R. Weinberger^{1,2,4,5,6} and Andrew E. Jaffe^{1,2,3,5,6,7,8*}

Price et al. *Genome Biology* (2019) 20:196
<https://doi.org/10.1186/s13059-019-1805-1>

LESSONS LEARNED FROM DNA

LESSONS LEARNED FROM THE DNA OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS

LESSONS LEARNED:

1. Literally many hundreds of regions of the genome that increase risk for mental illness have been identified
2. The statistics are strong, but the effects of individual genetic loci are very weak
3. Genetic risk does not respect dsm guidelines
4. Prediction of individual illness liability based on genomic risk is so far not of clinical value
5. Ancestry matters
6. GWAS is a treasure map, but to find the treasure (i.e. the genes) requires a lot more digging
7. The environment still matters
8. GENETIC DISCOVERIES PROVIDE BIOLOGICAL INSIGHTS INTO BRAIN MECHANISMS OF ILLNESS AND POTENTIAL STRATEGIES FOR TREATMENT AND PREVENTION

GENES ARE CLUES TO CAUSATIVE MECHANISMS

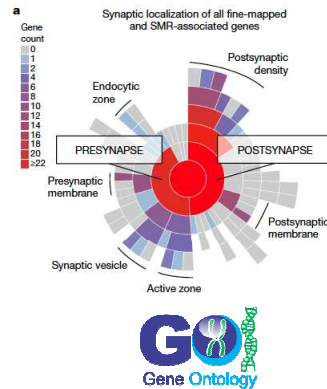
GENES OFFER INSIGHTS TO MOLECULAR PROCESSES

Article

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

Nature 2022

<https://doi.org/10.1038/s41586-022-04434-5> A list of authors and their affiliations appears at the end of the paper.



39

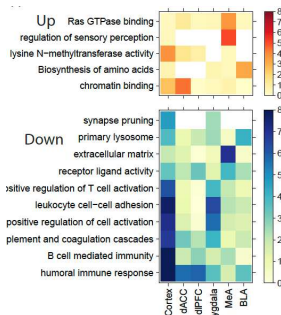
LIBD

INFORMATICS OF GENE EXPRESSION

GENES OFFER INSIGHTS TO MOLECULAR PROCESSES

Decoding shared versus divergent transcriptomic signatures across cortico-amygdala circuitry in PTSD and depressive disorders

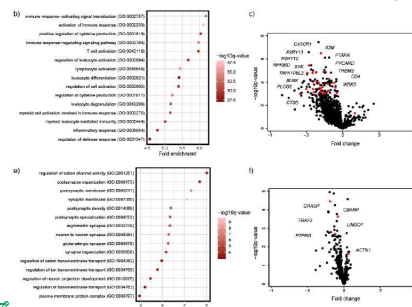
Andrew E. Jaffe, Ran Tao¹, Stephanie C. Page¹, Kristen R. Maynard¹, Elizabeth A. Pattie¹, Claudia V. Nguyen¹, Amy Deep-Soboslay¹, Rahul Bharadwaj, Keith A. Young, Matthew J. Friedman, Douglas E. Williamson¹, Traumatic Stress Brain Research Group, Joo Heon Shin¹, Thomas M. Hyde¹, Keri Martinowich, and Joel E. Kleinman¹
American Journal of Psychiatry 2022



RESOURCE

Amygdala and anterior cingulate transcriptomes from individuals with bipolar disorder reveal downregulated neuroimmune and synaptic pathways

Peter P. Zandi^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Andrew E. Jaffe^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Fernando S. Goes^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Emily E. Burke^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Leonardo Colado-Torres^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Louie Husk-Myers^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Arta Seyedian^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Yan Lin^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Fayaz Seifuddin^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Mehdi Pirooznia^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Christopher A. Ross^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Joel E. Kleinman^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, Daniel R. Weinberger^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}, and Thomas M. Hyde^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}
2022

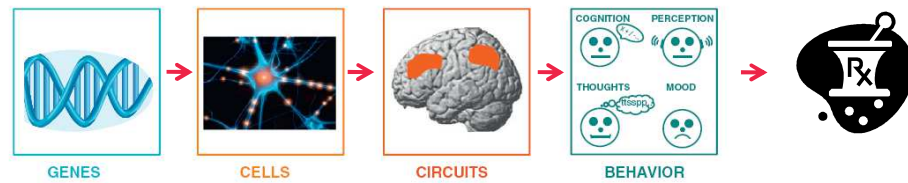


40

LIBD

THE SCIENTIFIC FRONTIER

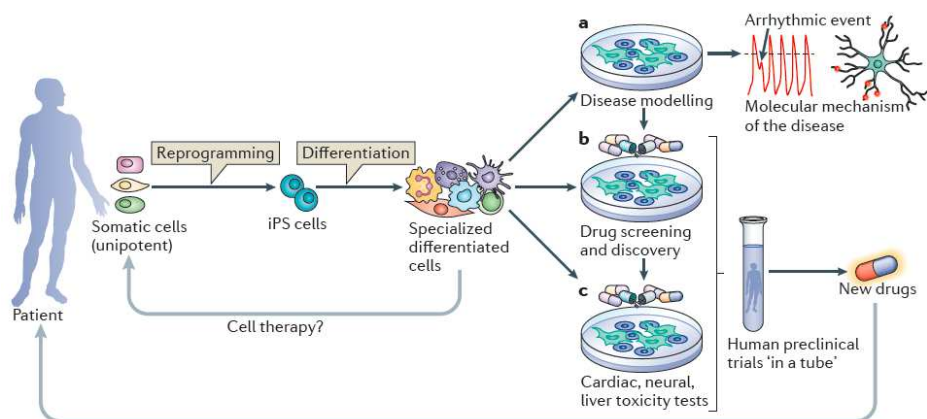
FINALLY: HOW DO WE TRANSLATE ANY OF THIS INTO IMPROVED LIVES?



We have to build high fidelity models

MODELING HUMAN DISEASE IN A DISH

THE HUMAN STEM CELL REVOLUTION

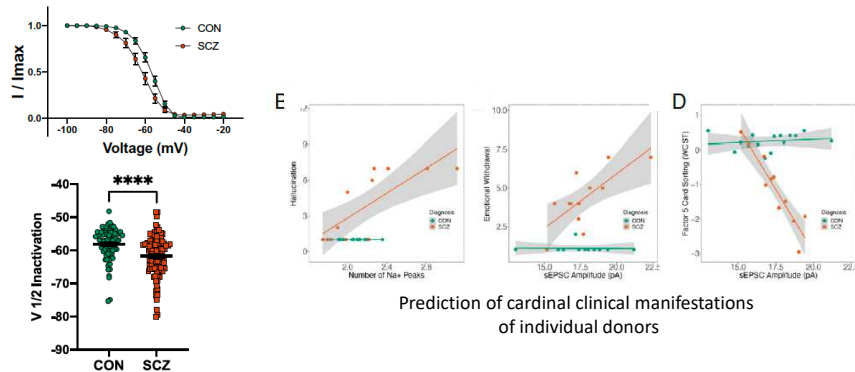


The problem for modeling psychiatric illness is knowing what cell phenotype actually matters

Electrophysiological measures from human iPSC-derived neurons are associated with schizophrenia clinical status and predict individual cognitive performance

Stephanie Cerce Page^{a,1}, Srinidhi Rao Sripathy^{a,1}, Federica Farinelli^{a,1}, Zengyou Ye^{a,1}, Yanhong Wang^{a,1}, Daniel J. Hiler^a, Elizabeth A. Pattie^a, Claudia V. Nguyen^a, Madhavi Tippi^a, Rebecca L. Moses^a, Hui-Ying Chen^a, Matthew Nguyen Tran^{a,b}, Nicholas J. Eagles^a, Joshua M. Stolz^a, Joseph L. Catallini II^{a,c}, Olivia R. Soudry^a, Dwight Dickinson^d, Karen F. Berman^a, Jose A. Apud^d, Daniel R. Weinberger^{a,b,e,f,g}, Keri Martinowich^{a,e,f,2}, Andrew E. Jaffe^{a,c,e,f,h,2}, Richard E. Straub^{a,2}, and Brady J. Maher^{a,e,f,2,3}

PNAS 2022 Vol. 119 No. 3 e2109395119



Prediction of cardinal clinical manifestations of individual donors

RESEARCH

HOW FAR WILL THE GENOMIC ERA TAKE US IN PSYCHIATRY?

- Genetics is *the* game changer in psychiatry research
- Genetic insights mark a path for identifying causative mechanisms and new therapeutic targets
- Genetic insights will help clarify the role of the environment
- Genetic insights have proven Freud right that there are early developmental signatures of psychiatric disorders
- Genes will guide the development of cell and animal model systems to validate mechanisms and test new therapeutic agents
- There are currently no clinical applications, either for diagnosis or treatment