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# Association of a functional Claudin-5 variant with schizophrenia in female patients with the 22q11.2 deletion syndrome

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Contributors

Yiran Guo, Larry Singh, Yuankun Zhu, Stewart Anderson and Jorge Alvarez designed the study. Yiran Guo, Stewart Anderson and Jorge Alvarez wrote the manuscript. Yiran Guo and Larry Singh performed the analyses. Adam Resnick and Raquel Gur collected the data. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

The authors have no financial relationships with commercial interests to report.

## Letter to the editor:

There are currently hundreds of genetic variants associated with schizophrenia (SZ) through genome-wide association (Buniello et al., 2019) such that it is critical to consider SZ risk genetics in the context of brain developmental and mature functional properties as well as in molecular signaling pathways. One putative risk allele has been identified in the 3′ untranslated region of claudin-5 (*CLDN5* (Greene et al., 2018);), a tight junction protein that contributes to blood-brain barrier (BBB) integrity (Abbott et al., 2006). *CLDN5* is located in the region of hemizygous deletion in the 22q11.2 deletion syndrome (22qDS). SZ risk is greatly elevated in 22qDS; with most studies finding this risk increases roughly 25-fold to at least 25% (Gothelf et al., 1999; Hoeffding et al., 2017; Murphy et al., 1999; Schneider et al., 2014; Van et al., 2017) and see Vangkilde et al. (2016). The *CLDN5* variant rs10314 was associated with decreased claudin-5 expression, and was present in the remaining 22q11.2 region in 9 of 15 22qDS subjects with SZ, but only 8 of 44 22qDS subjects without SZ ($X^2$ P < 0.04) (Greene et al., 2018).

To determine whether this association stands with an independent and larger sample, we evaluated whole genome sequencing data of 490 22qDS patients from the 22q11 International Brain and Behavior Consortium (22q11-IBBC (Mlynarski et al., 2016);) aligned to Hg38. Genotyping at the *CLDN5* variant site had high depth (17.4 X in average). As expected no heterozygosity was detected within the 22q11.2 deleted region.

We performed Chi squared test on the entire dataset, and binned by sex. The Pearson two-sided $X^2$ P values are 0.273 (both), 0.797 (male) and **0.053** (female). The marginal p value for the female group suggests a potential sex bias of the rs10314 variant within this larger cohort ($n$ = 490) (see Table 1).

The 22qDS is one of the strongest risk factors for SZ (Schneider et al., 2014; Van et al., 2017), and clinical manifestations do not patently differ from non-syndromic SZ in terms of prodromal course, age of onset, symptoms, response to treatment or brain morphometry (Bassett et al., 2003; Butcher et al., 2015; Sun et al., n.d.). Our study suggests that a weak association of rs10314 with SZ in 22qDS is female sex dependent. In addition to the cited study (Greene et al., 2018), weak associations between rs10314 and non-syndromic SZ have been found in Han Chinese ($n$ = 176) (Sun et al., 2004), and Iranian populations ($n$ = 150) (Omidinia et al., 2014). None of those studies considered sex as a variable.

So how might a variant that decreases claudin-5 expression increase risk of SZ in females only? Such increase risk might result from reduced BBB integrity interacting with peripheral inflammation (Cheslow and Alvarez, 2016; Kipnis, 2016). Enhanced levels of inflammatory cytokines such as IL-6 have been reported in SZ (Frommberger et al., 1997; Upthegrove et al., 2014) as well as in 22qDS (Mekori-Domachevsky et al., 2017), and IL-6 itself can reduce claudin-5 expression (Cohen et al., 2013). Neuroimmune disorders such as multiple sclerosis, neuromyelitis optica and brain lupus are more common in women than men (Asgari et al., 2011; Cervera et al., 1993; Willer et al., 2003) suggesting that reduced BBB integrity could interact with a female predisposition for neuroinflammation resulting in psychosis. While SZ is a highly heterogenous disorder, neuroinflammatory contributions to

neuropathology in SZ have long been implicated (Muller, 2018). Based on our study, further evaluations of potential links between the BBB, mediators of neuroinflammation, and female sex are warranted.

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**Table 1**

Genotype counts in rs10314 in the 22q11-IBBC dataset.

| | Male | Female | Both sexes |
|---|---|---|---|
| | **rs10314/total/%** | **rs10314/total/%** | **rs10314/total/%** |
| Control | 12/90/13.3 | 15/148/10.1 | 27/238/11.3 |
| SZ-Case | 14/126/11.1 | 23/126/18.3 | 37/252/14.7 |